



New 5-methylisatin including thiocarbohydrazones: preparation, structure elucidation and antimicrobial activity

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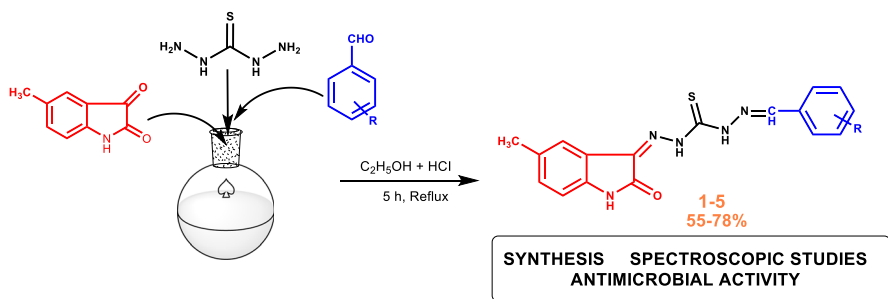
Abstract

New 5-methylisatin including thiocarbohydrazones (**1–5**) have been synthesized. The chemical structure of synthesized compounds was elucidated with IR, ¹H NMR, ¹³C NMR spectroscopic methods, and elemental analysis. Moreover, the synthesized compounds have been screened for antimicrobial activity. Their antibacterial activities were tested against Gram-positive (*Bacillus subtilis* ATCC 6623, *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212), Gram-negative (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 70060, *Pseudomonas aeruginosa* ATCC 27853), and fungal (*Candida albicans* ATCC 10231, *Aspergillus niger* ATCC 16404) microbial strains using the microdilution method. In the isatin series, particularly the compound **2** showed the best antimicrobial activity against *E. faecalis* strain with MIC values of 64 µg/mL compared to other compounds. This high activity of compound **2** is due to the presence of two electron-donating methoxy groups in its structure. The remaining substituted compounds have shown good and moderate antimicrobial activity compared to standard drugs. The results may provide insights into the target compounds' structure–activity relationships, which may facilitate the development of pharmacological and biological applications for the target compounds.

Graphical abstract

New isatins bearing thiocarbohydrazone were synthesized. Structures of all compounds were elucidated with spectroscopic approaches. The antimicrobial activities

of the tested compounds presented promising antimicrobial activity against the eight tested microorganisms.



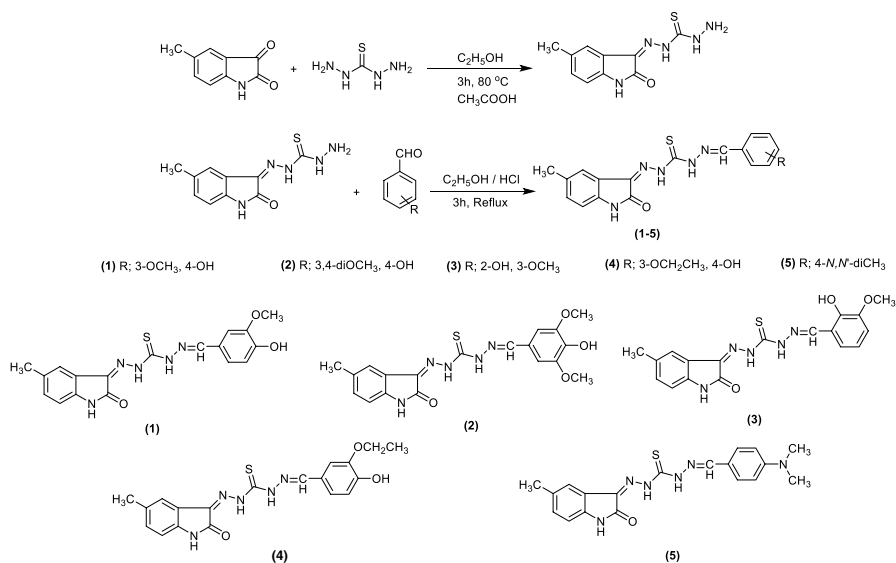
Keywords Isatin · Thiocarbohydrazones · Schiff bases · Antimicrobial activity · Spectroscopic studies · Minimum inhibitory concentration (MIC)

Introduction

Isatin and its derivatives (1H-indole-2,3-dione) are an important class of aromatic heterocyclic compounds. Isatin nucleus can be regarded a significant skeleton for the design of biologically active and drug discovery compounds. Numerous biological and medicinal activities can be performed by modifying the isatin scaffold, such as anti-oxidant [1–3], anti-fungal [4–6], anti-bacterial [4, 7–9], anti-cancer [10, 11], thymidine phosphorylase activity [12], enzyme inhibitory [4, 13–15], anti-viral [16, 17], anti-tubercular [18], anti-convulsant [19], and analgesic [20].

Thiocarbohydrazones consist of a significant class of dyes and pigments presenting the anti-microbial [21–23], anti-bacterial [24], anti-fungal [25], anti-oxidant [26, 27], anti-leishmanial [28], cytotoxic [29], anti-viral [30], and anti-tumoral activity [31]. Furthermore, substituted isatin-thiocarbohydrazones based on Schiff Base are usually called as β -isatin aldehyde-*N,N'*-thiocarbohydrazones [32]. Thiocarbohydrazones have also reported as corrosion inhibitors in the literature [33–35].

In this work, isatins based thiocarbohydrazone and Schiff bases are important not only in possessing medicinal activities, but also in biological properties. We reported that new isatin derivatives were achieved by reaction of isatin-thiocarbohydrazide with various aromatic aldehydes. The chemical structures of the compounds were clarified by using IR, ^1H NMR and ^{13}C NMR spectroscopic approaches, and elemental analysis. Moreover, the antimicrobial activities of the compounds were tested against selected strains using the microdilution method.



Scheme 1 The structures and synthetic route for new isatin derivatives (1–5)

Experimental section

Measurement and reagents

All reagents and solvents were bought from Aldrich, Sigma, or Merck Chemical Company and were used without further purification. The solvents were spectroscopic grade. Melting points were recorded using Stuart Melting Point 30 apparatus and are uncorrected. The elemental analysis was measured on Eurovector EA3000-Single. IR spectra were recorded on a Bruker Vertex 80v spectrophotometer. ¹H NMR and ¹³C NMR spectra were determined in dimethyl sulfoxide-*d*₆ (DMSO-*d*₆) a Bruker Avance DPX-400 (400 MHz) spectrophotometer using TMS as the internal standard.

Synthesis of new 5-methylisatin including thiocarbohydrazones

A mixture of 5-methylisatin (8.0 mmol) and thiocarbonylhydrazide (8.0 mmol) in ethanol (20 mL) and four drops of acetic acid was refluxed for 3 h. The reaction mixture was cooled, and the precipitate formed was filtered and washed with ethanol (96%) to give isatin-β-thiocarbohydrazone. A mixture of isatin-β-thiocarbohydrazone (4.0 mmol), various aromatic aldehydes (4.0 mmol) and two drops of hydrochloric acid in ethanol (20 mL) was refluxed for 5 h. The colour precipitate formed was filtered and washed with ethanol (96%) to give a product. The reaction route is given in Scheme 1. They were obtained according to an earlier procedure [36].

Antimicrobial activity assay

The in vitro antimicrobial activities were observed and the minimal inhibitory concentration (MIC) values were determined [37, 38] by microdilution method using bacterial strains listed in Table 6. The synthesized compounds in this study were dissolved in in dimethyl sulfoxide (DMSO) at the proper concentration. Amoxicillin and Tetracycline were used as the reference standard for antibacterial activity while Ketoconazole was used as the reference standard for antifungal activity.

The cultures were obtained from nutrient broth for all the bacterial strains after 24 h of incubation at 37 °C. Fungal strains were maintained in nutrient broth after incubation for 24 h at 28 °C. Bacterial and fungal microorganisms were suspended in nutrient broth. The turbidity of bacterial and fungi suspensions was set at a concentration of approximately 10^6 cells/ml. DMSO, pure microorganisms and pure media were used as control wells. 100 μ L suspension of each microorganism and 100 μ L suspension of compounds were tested in the 96 well microplates. The MIC value of the tested compounds and the standards are presented in Table 6.

Results and discussion

Physical properties

The structure names, melting points, yields and basic analysis data of the synthesized compounds are presented in Tables 1 and 2.

Vibrational frequencies

In the FT-IR spectra of the compounds, the signal of the aldehyde group ($-\text{CHO}$, two bands) of the starting material was not observed at $2830\text{--}2680\text{ cm}^{-1}$. Moreover, the symmetric and asymmetric stretching vibrations of the amino group ($-\text{NH}_2$) did not show at $3400\text{--}3150\text{ cm}^{-1}$. Instead, new $-\text{C}=\text{N}$ stretching vibrations of imine group were observed at $1631\text{--}1541\text{ cm}^{-1}$. These data showed that the intended reaction took place successfully, as expected.

For compounds **1–4**, the O–H signals of phenolic region were observed at $3669\text{--}3667\text{ cm}^{-1}$; the $-\text{C}-\text{O}$ stretching vibrations originating from the methoxy/ethoxy and hydroxy groups were detected in the range $1159\text{--}1073\text{ cm}^{-1}$.

For all compounds (**1–5**), while the $-\text{NH}$ vibrations of isatin moiety were observed at $3524\text{--}3310\text{ cm}^{-1}$, the $-\text{NH}$ vibrations of thiocarbohydrazone region were observed in the range $3312\text{--}3104\text{ cm}^{-1}$, the $-\text{C}=\text{O}$ signals of isatin region were observed at $1699\text{--}1688\text{ cm}^{-1}$, the $-\text{C}=\text{S}$ signals of thiocarbohydrazone region were observed at $1386\text{--}1362\text{ cm}^{-1}$, the $-\text{C}-\text{N}$ group vibrations were observed at $1254\text{--}1200\text{ cm}^{-1}$. These frequency values of the compounds are in agreement with those of similar compounds in the literature [1, 39–41]. IR vibrations for the

Table 1 Physical data, melting points, and yields for the compounds (1–5)

Comp.	Compounds name	R	Yield %	M. P. (°C)	Colour	Solubility
1	<i>N'</i> -(4-hydroxy-3-methoxybenzylidene)-2-((<i>Z</i>)-5-methyl-2-oxoindolin-3-ylidene)hydrazine-1-carbothiohydrazide	3-OCH ₃ -4-OH	78	261–262	Light Orange	DMSO (+)
2	<i>N'</i> -(4-hydroxy-3,5-dimethoxybenzylidene)-2-((<i>Z</i>)-5-methyl-2-oxoindolin-3-ylidene)hydrazine-1-carbothiohydrazide	3,5-diOCH ₃ -4-OH	75	242–243	Brown	DMSO (+)
3	<i>N'</i> -(2-hydroxy-3-methoxybenzylidene)-2-((<i>Z</i>)-5-methyl-2-oxoindolin-3-ylidene)hydrazine-1-carbothiohydrazide	2-OH-3-OCH ₃	55	254–255	Dark Orange	DMSO (+)
4	<i>N'</i> -(3-ethoxy-4-hydroxybenzylidene)-2-((<i>Z</i>)-5-methyl-2-oxoindolin-3-ylidene)hydrazine-1-carbothiohydrazide	3-OC ₂ H ₅ -4-OH	77	246–247	Yellow	DMSO (+)
5	<i>N'</i> -(4-(dimethylamino)benzylidene)-2-((<i>Z</i>)-5-methyl-2-oxoindolin-3-ylidene)hydrazine-1-carbothiohydrazide	- <i>N,N'</i> -diCH ₃	62	246–247	Orange	DMSO (+)

Table 2 Elemental analysis results of the compounds

Comp.	Mol. mass (g/mol)	Molecular formula	Calculated			Experimental		
			C%	H%	N%	(C) %	(H) %	(N) %
1	383.43	C ₁₈ H ₁₇ N ₅ O ₃ S	56.39	4.47	18.27	56.46	4.45	18.31
2	413.45	C ₁₉ H ₁₉ N ₅ O ₄ S	55.20	4.63	16.94	55.27	4.59	16.90
3	383.43	C ₁₈ H ₁₇ N ₅ O ₃ S	56.39	4.47	18.27	56.45	4.51	18.32
4	397.45	C ₁₉ H ₁₉ N ₅ O ₃ S	57.42	4.82	17.62	57.37	4.77	17.66
5	380.47	C ₁₉ H ₂₀ N ₆ OS	59.98	5.30	22.09	60.06	5.26	22.11

Table 3 IR vibration values for the synthesized compounds

Comp.	OH	-NH (ist)	-NH (tcrb)	Ar CH	Aliph CH	C=O	C=S	C=N	C-N	C-O
1	3668	3310	3272	2980	2906	1699	1376	1592	1248	1146
			3144					1541	1204	1119
2	3667	3524	3312	2980	2911	1693	1386	1625	1246	1159
			3149					1550	1211	1113
3	3669	3426	3243	2980	2904	1688	1383	1625	1237	1113
			3131					1200	1073	
4	3668	3316	3218	2982	2927	1695	1362	1631	1245	1158
			3154					1603	1206	1117
5	-	3426	3227	2960	2904	1691	1366	1628	1254	-
			3104					1603	1231	

ist isatin; *tcrb* thiocarbohydrazide

compounds are presented in Table 3. IR spectra of all compounds are given in supplementary material (Fig. S1–S4 in Supplementary information).

For compound **1**, the O–H signal of phenolic region was observed at 3668 cm⁻¹; the –NH vibrations of thiocarbohydrazide and isatin moiety were observed at 3272, 3144, and 3310 cm⁻¹ as shown in Fig. 1. The C=O signal of isatin ring was observed at 1699 cm⁻¹; the –C=N stretching vibration was appeared at 1592 and 1541 cm⁻¹; the C=S signal of thiocarbohydrazide region was observed at 1376 cm⁻¹; the –C–N stretching vibration was appeared at 1248 and 1204 cm⁻¹; the –C–O signal of aryl ring were observed at 1146 and 1119 cm⁻¹.

¹H NMR interpretations

The ¹H NMR spectra of all compounds were detected in DMSO-*d*₆ solvent. DMSO-*d*₆ and water in DMSO (HOD, H₂O) signals are shown around at 2.00, 2.50 (quintet) and 3.30 ppm (variable, based on the solvent and its concentration), respectively [42]. The chemical shifts of all compounds are given in Table 4.

For compounds **1–5**, the proton signals of imine (–CH=N) were detected as a singlet in the ranges 8.59–8.06 ppm. The amino signals (N²H and –N¹H) of

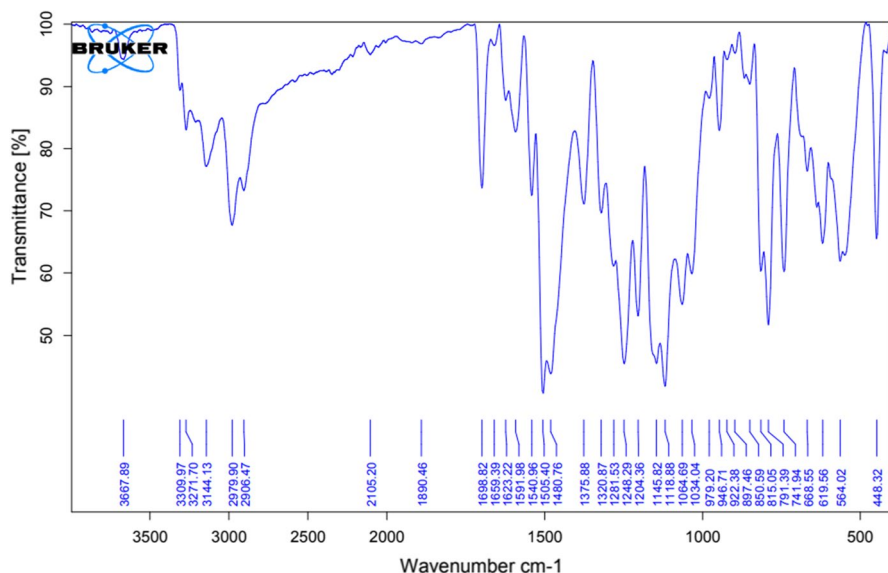


Fig. 1 IR spectrum of compound 1

thiocarbohydrazone moiety were observed as a singlet in the ranges 14.62–14.50 and 12.56–12.36 ppm, respectively. The –NH signals of the isatin region were observed as a singlet at 11.17–11.11 ppm. The aromatic proton signals of phenolic region (H4–H8) were observed between 7.71 and 6.74 ppm. The aromatic proton (H1–H3) signals of the isatin ring were detected in the ranges 7.41 and 6.83 ppm. The methyl (–CH₃) proton signals were resonated as a singlet at 3.35 and 3.31 ppm (Fig. S5–S8 in Supplementary information).

For compounds 1–4, the hydroxyl (–OH) proton signals were detected as a singlet at in the ranges 9.68–9.01 ppm. For compounds 1–3, the methoxy (–OCH₃) proton signals were resonated as a singlet in the range of 3.93, 3.88, and 3.84 ppm, respectively. In Fig. 2, the methyl (CH₃) and methoxy (OCH₃) proton peaks of compound 1 were observed as a singlet at 3.55 and 3.93 ppm.

For compound 4, the proton signal of the methylene group (–CH₂) was observed as a quartet at 4.22–4.17 ppm (*q*, *J*=6.9 Hz, 2H); the –CH₃ proton signal was detected as a triplet at 1.44–1.41 ppm (*t*, *J*=6.9 Hz, 3H). For compound 5, the proton signal of the amino group (N(CH₃)₂) was detected as a singlet at 3.03 ppm. These data consistent with the values of earlier reported for similar compounds [1, 16, 43, 44].

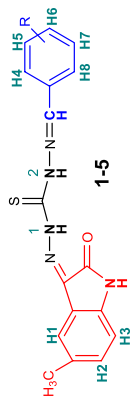
¹³C NMR interpretations

The ¹³C NMR spectra of all compounds were obtained in DMSO-*d*₆ a solvent. The carbon chemical shift of all compounds are presented in Table 5. For compounds 1–5, the characteristic –C=S peaks of the thiocarbohydrazone moiety were detected

Table 4 ^1H NMR (δ , ppm, in DMSO- d_6) values of synthesized compounds

Comp.	1st NH	N ² H	N ¹ H	OH	CH=N	OCH ₃ /OCH ₂	CH ₃	1st H1–H3	Ar H4–H8
1	11.17	14.61	12.48	9.68	8.08	3.93	3.35	7.41(s, 1H, H1) 7.20–7.18 (d, $J=8.0$ Hz, 1H, H3) 6.84–6.83 (d, $J=7.8$ Hz, 1H, H2)	7.69 (s, 1H, H4) 7.16–7.14 (d, $J=8.1$ Hz, 1H, H8) 6.86–6.84 (d, $J=7.7$ Hz, 1H, H7) 7.24 (s, 2H, H4, H8)
2	11.16	14.62	12.56	9.01	8.06	3.88	3.35	7.41(s, 1H, H1) 7.20–7.18 (d, $J=8.0$ Hz, 1H, H3) 6.87–6.84 (dd, $J=7.9, 4.9$ Hz, 1H, H2)	7.71–7.69 (d, $J=8.0$ Hz, 1H, H6) 7.21–7.18 (t, $J=7.6$ Hz, 1H, H7) 7.03–7.01 (d, $J=7.8$ Hz, 1H, H8)
3	11.15	14.53	12.48	9.33	8.59	3.84	3.31	7.41–7.39 (d, $J=8.6$ Hz, 1H, H1) 6.86–6.83 (dd, $J=7.9, 4.3$ Hz, 2H, H2, H3)	7.66 (s, 1H, H4) 7.14–7.12 (d, $J=8.1$ Hz, 1H, H8) 6.88–6.86 (d, $J=8.0$ Hz, 1H, H7)
4	11.11	14.59	12.47	9.60	8.06	4.22–4.17 (q, $J=6.9$ Hz, 2H)	3.35, 1.44–1.41 (t, $J=6.9$ Hz, 3H)	7.41(s, 1H, H1) 7.20–7.18 (d, $J=8.0$ Hz, 1H, H3) 6.85–6.83 (d, $J=7.9$ Hz, 1H, H2)	7.71–7.69 (d, $J=8.9$ Hz, 2H, H4, H8), 6.76–6.74 (d, $J=9.0$ Hz, 2H, H5, H7)
5	11.13	14.50	12.36	–	8.06	–	3.35, 3.03 (N(CH ₃) ₂)	7.40 (s, 1H, H1) 7.22–7.17 (d, $J=9.7$ Hz, 1H, H3) 6.87–6.84 (dd, $J=7.9, 5.9$ Hz, 1H, H2)	

1st Isatin



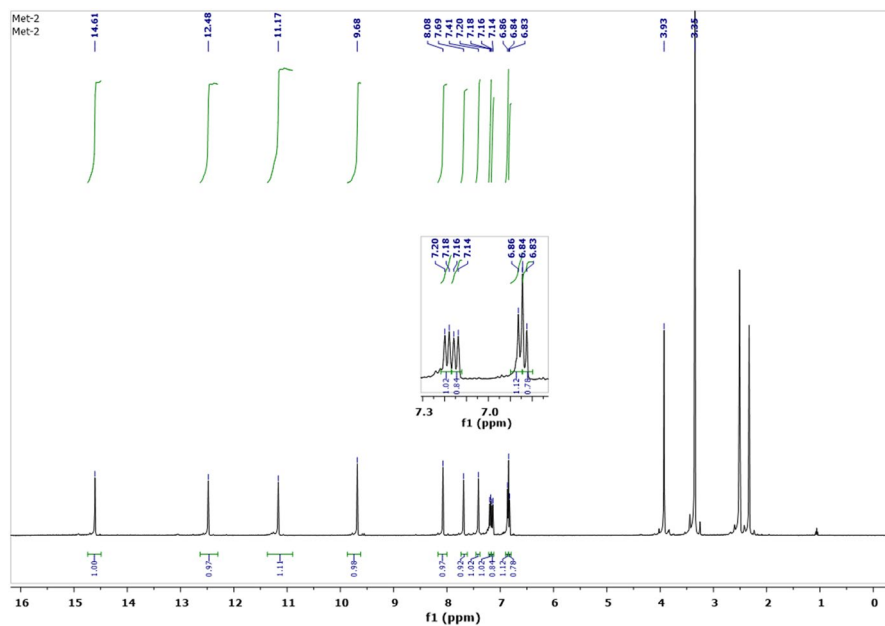
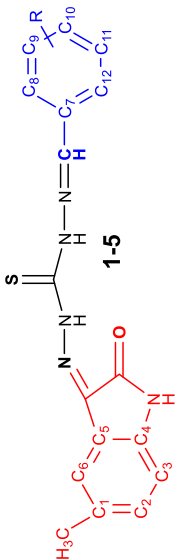


Fig. 2 ^1H NMR spectrum of compound **1**

at 175.5–174.8 ppm. The characteristic $-\text{C}=\text{O}$ and $-\text{C}=\text{N}$ of isatin region peaks were observed at 163.3–163.1 and 152.3–148.6 ppm, respectively. The other characteristic $-\text{CH}=\text{N}$ (imin) peaks were detected in the ranges 145.8–140.3 ppm. The carbon signals of the $-\text{CH}_3$ group were observed at 21.0 and 20.9 ppm (Fig. S9–S12 in supplementary information).

The aromatic carbon signals (C1–C6) of isatin region were observed at between 138.1 and 111.3 ppm. The aromatic carbon atoms (C7–C12) of phenolic region were detected in the ranges 148.8–105.6 ppm. For compounds **1**, **2**, and **4**, the resonance of the C9 and C10 carbon atoms shifted down-field due to the presence of electron-withdrawing group of $-\text{OCH}_3$ / $-\text{OC}_2\text{H}_5$ and $-\text{OH}$ as shown in Fig. 3. For compound **3**, the resonance of the C8 (147.3) and C9 (140.4) carbon atoms shifted down-field due to the presence of electron-withdrawing group of $-\text{OCH}_3$ and $-\text{OH}$.

For compounds **1–3**, the methoxy ($-\text{OCH}_3$) carbon signals were resonated at 56.2, 56.6, and 56.4 ppm, respectively. For compound **4**, the carbon signal of the methylene ($-\text{CH}_2$) and methyl ($-\text{CH}_3$) groups were observed at 64.4 and 15.2 ppm, respectively. For compound **5**, the carbon signal of the $(\text{N}(\text{CH}_3)_2)$ was detected as a singlet at 41.3 ppm. These spectroscopic data are consistent with the values of previously reported similar compounds and the literature [2, 26, 36, 45].

Table 5 ^{13}C NMR data of compounds **1–5**, (δ/ppm)


	C=S	Ist C=O	Ist C=N	CH=N	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	CH ₃	Subs.
1	175.3	163.2	150.0	145.1	132.2	132.1	121.6	138.0	111.3	125.5	120.6	109.4	148.8	140.3	115.8	123.7	20.9	56.2 ^a
2	175.2	163.2	148.7	145.0	132.2	132.1	121.6	138.1	111.3	124.3	120.6	105.6	140.3	138.9	140.3	105.6	20.9	56.6 ^a
3	175.5	163.3	148.6	141.5	132.1	120.9	121.6	138.1	111.4	120.0	120.6	147.3	140.4	113.9	117.7	119.7	20.9	56.4 ^a
4	175.3	163.1	150.2	140.3	132.2	132.1	121.6	138.0	111.4	125.4	120.6	110.3	147.9	145.2	115.8	123.6	20.9	64.4 ^b 15.2 ^c
5	174.8	163.2	152.3	145.8	132.1	129.5	121.1	137.6	111.3	129.4	120.7	121.5	112.2	140.3	112.2	121.5	21.0	41.3 ^c

Subs. Substituents

^aOCH₃, ^bOCH₂, ^cCH₃

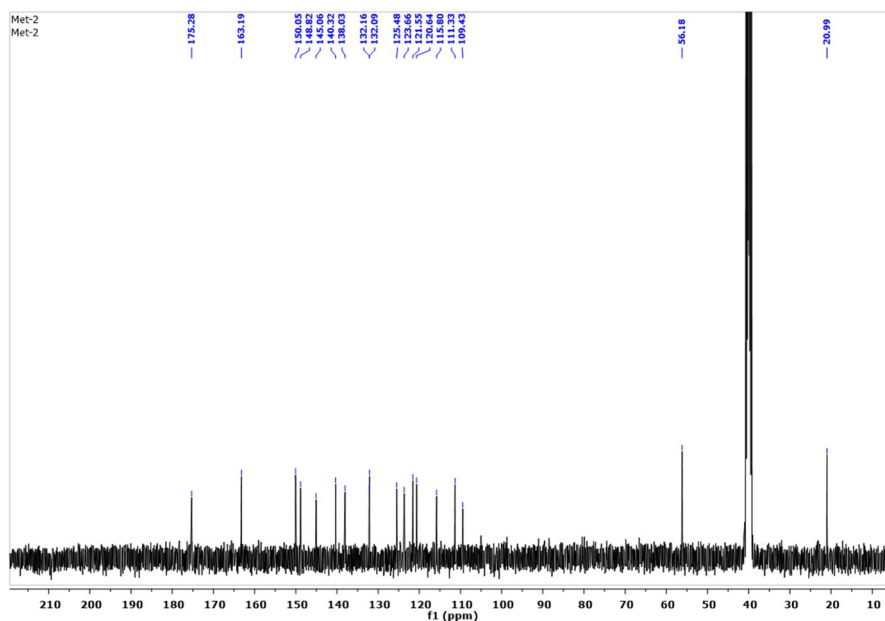


Fig. 3 ^{13}C NMR spectrum of compound 1

Evaluation of antimicrobial activities

The compound **2** among all compounds showed the highest antimicrobial activity against all strains tested while the compound **5** exhibited the lowest that. The 3,5-diOCH₃-4-OH substituted possessed compound **2** had the highest activity against *E. faecalis* strain (64 $\mu\text{g}/\text{mL}$) of Gram-positive and Gram-negative bacteria species compared with other derivatives. For this compound, introduction of an extra methoxy group to the aromatic ring dramatically increased the antimicrobial activity. The 3-OCH₃-4-OH substituted compound **1** and the 2-OH-3-OCH₃ substituted compound **3**, this two compound bearing the same groups on the ring showed high activity against *B. subtilis* (128 $\mu\text{g}/\text{mL}$) and the compound **3** was also showed the same value activity against *E. faecalis* (128 $\mu\text{g}/\text{mL}$) microorganism. The 3-OCH₂CH₃-4-OH substituted compound **4**, which carrying an ethoxy and hydroxy group on the ring, demonstrated the same activity value of compound **3** against *E. faecalis* (128 $\mu\text{g}/\text{mL}$) microorganism. This result showed that the binding of the ethoxy group in compound **4** at the same position instead of the methoxy group in compound **3** did not change the activity against *E. faecalis* microorganism. The *N,N'*-diCH₃ substituted compound **5** of the isatins based thiocarbohydrazone series showed a significant reduction in activity compared to the other compounds. Among all microorganisms, this compound showed the highest activity only against *K. pneumoniae* against with MIC values of 256 $\mu\text{g}/\text{mL}$. All of the compounds exhibited lower activity against fungi than the *Ketoconazole* standard. Considering all tested compounds, compound **2** had the highest antifungal activity against *A. niger*

Table 6 The minimum inhibition concentrations (MIC's) of the tested molecules

Comp. Std.	Minimum inhibition concentration ($\mu\text{g}/\text{mL}$)							
	<i>B. subtilis</i>	<i>S. aureus</i>	<i>E. faecalis</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>A. niger</i>	<i>C. albicans</i>
1	128	128	256	512	512	256	1024	1024
2	256	128	64	128	128	128	128	256
3	128	256	128	512	256	512	1024	1024
4	512	512	128	256	256	512	256	512
5	1024	512	512	512	256	512	1024	1024
Amoxicillin	<2	> 1024	> 1024	1024	> 1024	> 1024	–	–
Tetracycline	<2	64	64	<2	64	64	–	–
Ketoconazole	–	–	–	–	–	–	1	2

(128 $\mu\text{g}/\text{mL}$). The 3,5-diOCH₃-4-OH substituted compound **2** showed the best activity against *C. albicans* with MIC values of 256 $\mu\text{g}/\text{mL}$, while the 3-OCH₂CH₃-4-OH substituted compound **4**, exhibited the same value activity against *A. niger* (256 $\mu\text{g}/\text{mL}$). These results revealed that the excellent potency of these compounds is probably due to the presence of electron donating groups such as –OH, –OCH₃, –OC₂H₅ on the phenyl rings attached to the azomethine group (–CH=N), eliciting enhanced antimicrobial activity against certain strains [29, 45–48] (Table 6).

Conclusions

New isatin derivatives based on thiocarbohydrazone have been synthesized and isolated in acceptable yields with 55–78%. IR, ¹H NMR and ¹³C NMR spectroscopic approaches, and elemental analysis were used to elucidate the chemical structures of all compounds. Moreover, the antimicrobial activities of the newly synthesized compounds were tested. Among the tested compounds, the compound **2** exhibited exceptionally good antimicrobial activities compared to other derivatives against *E. faecalis* with MIC values of 64 $\mu\text{g}/\text{mL}$. The good microbial activity of this compound due to the presence of two methoxy group at C3 and C5 and an additional of a hydroxyl group at C4 in the phenyl ring. Compounds **1** and **3**, which have a methoxy group and a hydroxyl group in the *ortho* position on the phenyl ring, showed the same activity against *B. subtilis* with MIC values of 128 $\mu\text{g}/\text{mL}$. The compound **2** showed good antimicrobial activity against *E. faecalis* compared to other strains, with MIC values of 64 $\mu\text{g}/\text{mL}$. Compound **5** of the isatin-based thiocarbohydrazone series showed a significant reduction in activity compared to other compounds. All of the compounds showed lower activity against fungi than the Ketoconazole standard. The obtained results revealed that the presence of electron donating groups such

as a hydroxyl group or methoxy group in the structures of the compounds can provide better activity.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11164-022-04799-2>.

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Author contributions HY contributed to spectroscopic characterization, writing—review, visualization and editing, supervision. ŞÇ contributed to spectroscopic characterization, biological studies, writing—review. OB contributed to synthesis, spectroscopic characterization. AV contributed to biological studies, writing—review. HM contributed to synthesis methodology, writing—review. NTK contributed to synthesis methodology, review, editing.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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