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Research Article

Microwave-Assisted Synthesis, Characterization, Antimicrobial and Antioxidant Activity of Some New Isatin Derivatives

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A series of β-Isatin aldehyde-N,N′-thiocarbohydrazone derivatives were synthesized and assayed for their *in vitro* antimicrobial and antioxidant activity. The new compounds were characterized based on spectral (FT-IR, NMR, MS) analyses. All the test compounds possessed a broad spectrum of activity having MIC values rangeing from 12.5 to 400 μg/ml against the tested microorganisms. Among the compounds **3e**, **3j** and **3n** show highest significant antimicrobial activity. The free radical scavenging effects of the test compounds against stable free radical DPPH (α,α-diphenyl-β-picryl hydrazyl) and H_2O_2 were measured spectrophotometrically. Compounds **3j**, **3n**, **3l**, and **3e**, respectively, had the most effective antioxidant activity against DPPH and H_2O_2 scavenging activity.

1. Introduction

The development of new therapeutic agents is one of the fundamental goals in medicinal chemistry. In the past five years there has been a dramatic upsurge in the use of microwave heating within the pharmaceutical industry to facilitate the chemical synthesis of new chemical entities [1]. Medicinal chemists were among the first to fully realize the true power of this enabling technology. Microwave (MW) synthesis has since been shown to be an invaluable tool for medicinal chemistry and drug discovery applications since it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds [2].

Isatin is an endogenous compound identified in humans. Biological properties of isatin include a range of actions in the brain and offer protection against certain types of infections [3]. Isatin constitutes an important class of bioactive compounds exhibiting caspase inhibitor [4, 5], antibacterial and antiproliferative activity [6]. Schiff bases of the isatin analogs have antismall pox [7] and GAL3 receptor antagonist capabilities [8]. Additional analogs have displayed inhibitory activity against eLF2 kinase activator [9], TNF-α, CDK2 [10], and SARS protease [11]. Isatin displays antiviral [12], anti-inflammatory, analgesic [13], and anticonvulsant [14] activities. Isatin-β-thiosemicarbazone derivatives were found to demonstrate a range of chemotherapeutic activities [15, 16]. The literature survey revealed that, thiocarbohydrazide is an irreversible inhibitor of catalase and the degradation of serotonin is also inhibited and also possess anticonvulsant activity [17]. Many biochemical reactions involve the generation of reactive oxygen species (ROS) and is controlled by the antioxidant defense system in the body. ROS are associated with incidence of heart diseases, thrombosis [18], hypertension [19], Alzheimer's and Parkinson's diseases [20] and cancer over the radical-induced DNA double-strand breaks [21]. In order to protect against ROS and to suppress the cell damage, synthetic antioxidants have been used in recent years.

Our present investigation was an attempt to develop some β-Isatin aldehyde-N,N′thiocarbohydrazone (**3a–n**) derivatives under MW irradiation taking minimum solvent or almost solvent-free conditions as depicted in Scheme 1, which upholds the motto of green chemistry. This series of compounds was than subjected to *in vitro* antimicrobial and antioxidant activity.

2. Experimental

The IR spectra: thermo Nicolet Nexus 670S series. ^{1}H NMR: Avance-300 MHz instrument, Mass spectra: LC-MSD-Trap-SL using ESI(+) method. Microwave-assisted reactions were carried out on household LG model : MS-1947C maximum 12,000 Watts. Melting points (m.p) were determined in open capillaries, using Toshniwal melting point apparatus, expressed in $^\circ$C, and are uncorrected. All the solvents were of AR grade and were distilled before use. Isatin was purchased from Himedia (Mumbai, India). Indole-3-carboxyaldehyde and H_2O_2 were obtained from Merck (India). All substituted aldehydes were purchased from Sd. Fine Chemicals. The standard cultures of test microorganisms were obtained from Department of Microbiology, Kakatiya University, Warangal.

3. Chemistry

3.1. Synthesis of Isatin Derivatives. Isatin derivatives were prepared using a modified Sandmeyer methodology [22]. N-methyl isatin is prepared by microwave method as reported in the literature [23]. All the isatin derivatives exhibit same physical properties as reported in the literature.

3.2. Synthesis of Thiocarbohydrazide. The syntheses of thiocarbohydrazide were prepared by Taguchi method. The physical data of the synthesized compound are comparable and show m.p 170–172°C similar to that as reported in the literature [24].

3.3. Microwave-Assisted Synthesis of Monothiocarbohydrazones **(2a–n)** . A mixture of thiocarbohydrazide (0.01 mol) and substituted aldehyde with catalytic amount of glacial acetic acid was taken in 30 mL of ethanol in 250 mL conical flask. The resulting mixture was irradiated under microwave for 10 cycles for 10 sec (2 mins) at 160 W. Then the reaction mixture was cooled on overnight and the precipitate was collected by filtration. Further it was purified by recrystallization by ethanol. The synthesized compounds were comparable with the reported literature [25].

3.4. Microwave Synthesis of β-Isatin Aldehyde-N,N′-thiocarbohydrazones **(3a–n)**. A mixture of monothiocarbohydrazone (0.01 mol) and substituted Isatin(0.01 mol) with a catalytic amount of glacial acetic acid (15 mL) was taken in 30 mL of ethanol in 250 mL conical flask. Then the reaction mixture was subjected for microwave irradiation for 10 cycles for 10 sec (2 min) at 160 W. Then the reaction mixture was cooled on overnight and the precipitate was collected by filtration. The solid was purified by column chromatography and subsequently by recrystallization with ethanol. The synthesis of all compounds can also be carried out by One-Pot rapid synthesis by taking an equimolar amount of aldehydes, thiocarbohydrazide, and substituted Isatin derivatives and the compounds showing same physical data of the proposed mechanism.

3.5. Spectral Data of All Synthesized Compounds

3.5.1. 1-Benzylidene-5-(2-oxoindoline-3-ylidene) Thiocarbohydrazones **(3a)**. IR ($\overline{\nu}$ cm^{-1}): 3210 (–NH), 3186 (C–H, Ar), 1709 (s, C=O, lactam), 1360 (s, C=S), 1520 (s, C=N), 1482 (s, C=C, Ar). ^{1}H-NMR (DMSO) δ ppm: 13.1 (s, 1H, NH), 11.9 (s, 1H, NH), 11.3 (s, 1H, NH), 8.39 (1H, N=CH), 8.30–8.24 (m, 2H), 8.00–7.91 (m, 3H), 7.68 (dd, J = 7.4, 1.5 Hz, 1H), 7.59 (dd, J = 7.5, 1.5 Hz, 1H), 7.47 (td, J = 7.5, 1.5 Hz, 1H), 7.27–7.20 (m, 1H); mass (ESI-MS): m/z 324 (M + 1, 100%), 346 (M + Na, 50%).

3.5.2. 1-((1H-Indol-4-yl)methylene)-5-(2-oxoindolin-3-ylidene) Thiocarbohydrazone) **(3b)**. IR ($\overline{\nu}$ cm^{-1}): 3228(br, N–H, lactam), 3138 (w, C–H, Ar), 1706 (s, C=O, lactam), 13371 (s, C=S), 1538 (s, C=N), 1463 (s, C=C). ^{1}H-NMR (DMSO) δ ppm: 14.1 (s, 1H, NH), 12.2 (s, 1H, NH), 11.7 (s, 1H, NH), 11.3 (s, 1H, NH), 8.67 (1H, =CH–), 8.47 (1H, N=CH), 7.87 (dd, J = 7.4, 1.6 Hz, 1H), 7.64–7.52 (m, 3H), 7.49–7.40 (m, 2H), 7.34 (td, J = 7.4, 1.5 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H). ^{13}C NMR (DMSO δ ppm): 173.9 (C=S), 162 (C=O), 143 (C=N), 110–137 (Ar–C); mass (ESI-MS): m/z 363 (M + 1, 100%), 385 (M + Na, 80%)

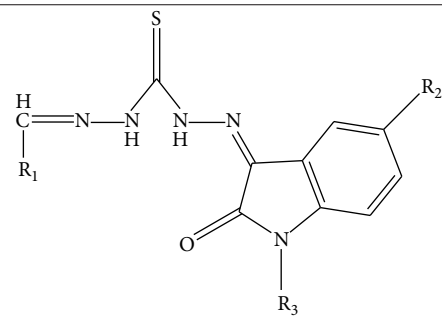
3.5.3. 1-(2-Oxoindolin-3-ylidene)-5-(thiophen-3-yl) Methylene) Thiocarbohydrazone **(3c)**. IR ($\overline{\nu}$ cm^{-1}): 3316 (N–H), 3026 (w, C-H, Ar), 1708 (s, C=O, lactam), 1368 (s, C=S), 1395 (s, C=N), 1528 (s, CH=N). ^{1}H-NMR (DMSO) δ ppm: 14.7 (s, 1H, NH), 13.3 (s, 1H, –NH), 11.9 (s, 1H, –NH), 8.90 (s, 1H), 7.65–7.59 (m, 2H), 7.57–7.45 (m, 2H), 7.31 (dd, J = 7.5, 2.8 Hz, 1H), 7.27–7.20 (m, 1H), 6.96 (dd, J = 7.5, 1.5 Hz, 1H); mass (ESI-MS): m/z 330 (M+1, 100%).

3.5.4. 1-(4-(Dimethylamino)benzylidene)-5-(2-oxoindolin-3-ylidene) Thiocarbohydrazone **(3d)**. IR ($\overline{\nu}$ cm^{-1}): 3218 (–NH), 3016 (w, C–H, Ar), 2700 (C–H, *str*), 1702 (s, C=O, lactam), 1358 (s, C=S), 1528 (s, C=N), 1528 (s, CH=N). ^{1}H-NMR (DMSO) δ ppm: 14.9 (s, 1H, –NH), 14.5 (s, 1H, –NH), 13.0(s, 1H, –NH), 8.06 (s, 1H), 7.76 (dd, J = 7.5, 1.5 Hz, 1H), 7.61 (dd, J = 7.5, 1.7 Hz, 1H), 7.53–7.46 (m, 3H), 7.28–7.20 (m, 1H), 6.85–6.79 (m, 2H), 3.02 (s, 6H); mass (ESI-MS): m/z 367(M + 1, 100%), 389 (M + Na, 40%).

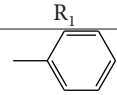
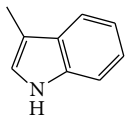
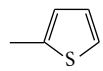
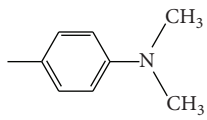
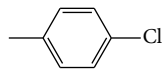
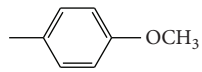
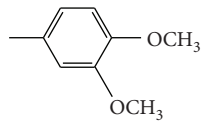
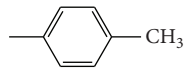
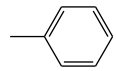
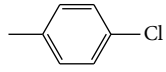
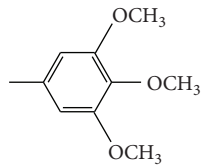
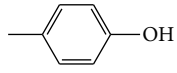
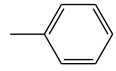
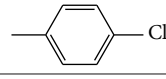
3.5.5. 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) Thiocarbohydrazone **(3e)**. IR ($\overline{\nu}$ cm^{-1}): 3345 (N–H), 3050 (C–H, Ar), 1630 (C=O, lactam), 900–690 (Ar, oop); 785(C–Cl); ^{1}H-NMR (DMSO) δ ppm; 14.7 (s, 1H), 13.6 (s, 1H), δ 11.2 (s, 1H), 7.93 (s, 1H), 7.85–7.79 (m, 2H), 7.68 (dd, J = 7.5, 1.6 Hz, 1H), 7.60 (dd, J = 7.4, 1.6 Hz, 1H), 7.48 (td, J = 7.4, 1.5 Hz, 3H), 7.27–7.20 (m, 1H); mass (ESI-MS): m/z 357 (M+ , 100%), 359 (M+2, 38%).

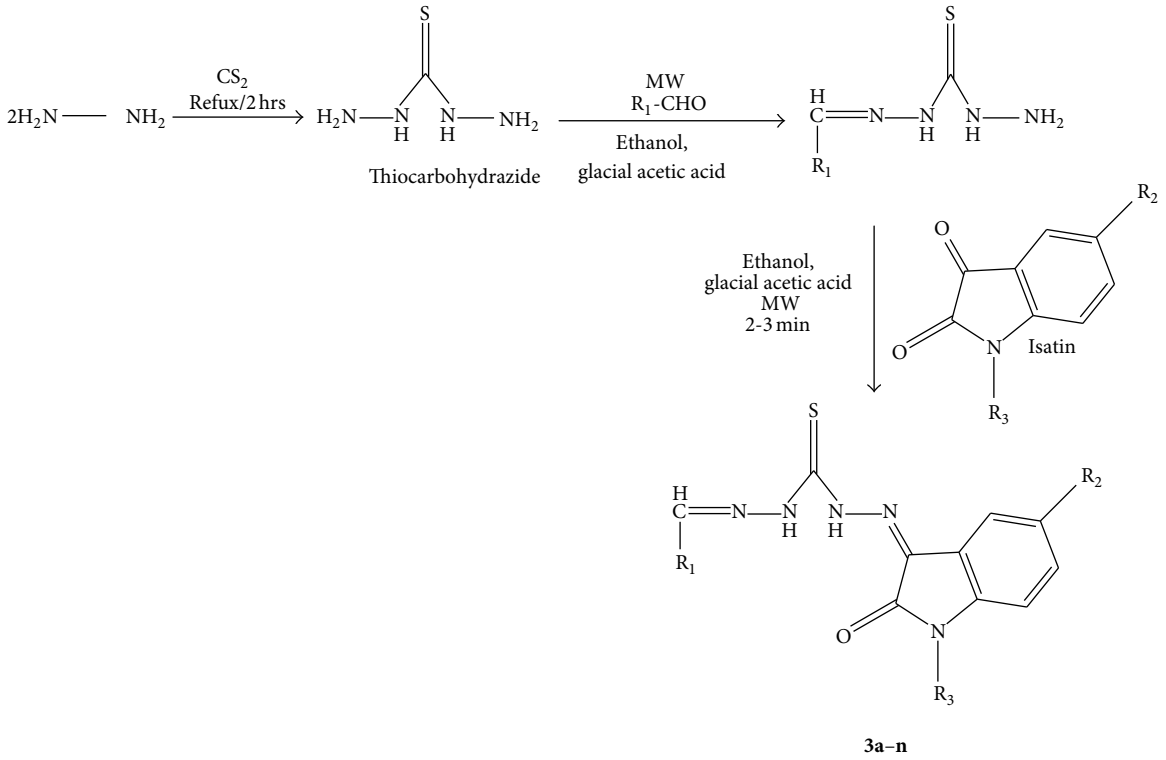
3.5.6. 1-(4-Methoxybenzylidene)-5-(2-oxoindolin-3-ylidene) Thiocarbohydrazone **(3f)**. IR ($\overline{\nu}$ cm^{-1}): 3348 (N–H), 3020 (C–H, Ar), 1648 (C=O), 1313 (C=S); ^{1}H-NMR (DMSO) δ ppm; 14.7 (s, 1H), 13.1 (s, 1H), δ 10.9 (s, 1H), 7.93 (s, 1H), 7.71–7.57 (m, 4H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.27–7.20

Table 1: Physical data of all synthesized test compounds **(3a–n)**.



3a–n

Entry	Comp.	R_1	R_2	R_3	MF	MW	MP	%YIELD
1	**3a**		H	H	$C_{16}H_{13}N_5OS$	323	230–232	66
2	**3b**		H	H	$C_{18}H_{14}N_6OS$	362	184–186	80
3	**3c**		H	H	$C_{14}H_{11}N_5OS_2$	329	152–156	84
4	**3d**		H	H	$C_{18}H_{18}N_6OS$	366	240–242	72
5	**3e**		H	H	$C_{16}H_{12}ClN_5OS$	357	138–140	54
6	**3f**		H	H	$C_{17}H_{15}N_5O_2S$	353	228–231	52
7	**3g**		H	H	$C_{18}H_{17}N_5O_3S$	383	222–225	68
8	**3h**		H	H	$C_{18}H_{17}N_5OS$	351	133–136	72
9	**3i**		CH_3	H	$C_{17}H_{15}N_5OS$	337	210–212	82
10	**3j**		CH_3	H	$C_{17}H_{14}ClN_5OS$	371	235–238	64
11	**3k**		CH_3	H	$C_{20}H_{21}N_5O_4S$	427	152–154	52
12	**3l**		H	CH_3	$C_{17}H_{15}N_5O_2S$	353	242–245	78
13	**3m**		H	CH_3	$C_{17}H_{15}N_5OS$	337	242–245	74
14	**3n**		H	CH_3	$C_{17}H_{14}ClN_5OS$	371	178–180	62



Scheme 1

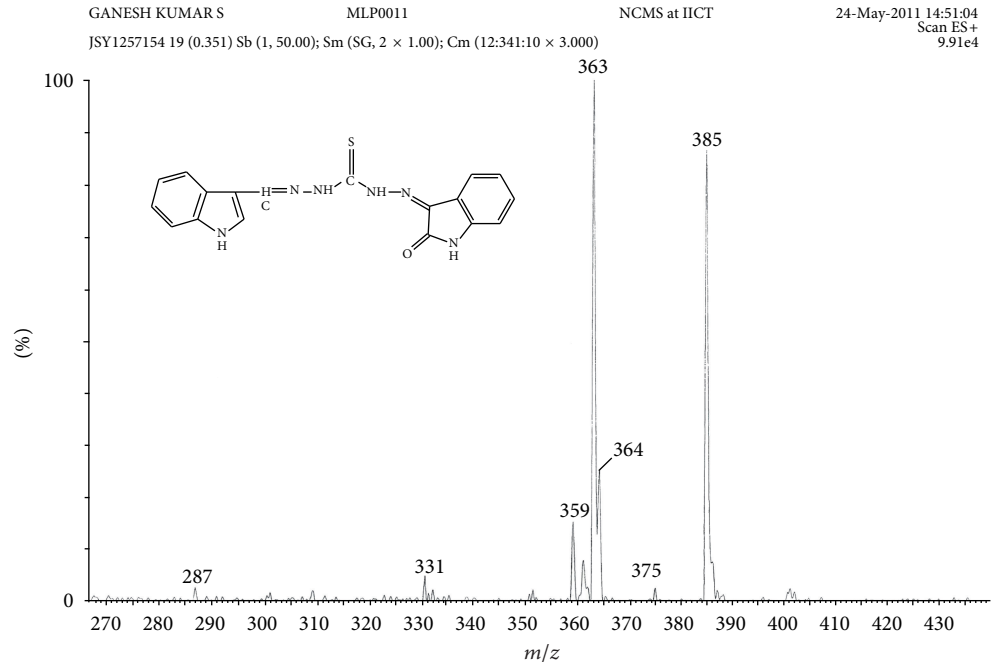


Figure 1: Mass spectra of compound **3b** showing a base Peak M+1 peak and M+Na peak recorded on ES+ mode.

(m, 1H), 7.14–7.08 (m, 2H), 3.79 (s, 3H); mass (ESI-MS): m/z 354 (M+1, 100%).

3.5.7. 1-(4-Methylbenzylidene)-5-(2-oxoindolin-3-ylidene) Thiocarbohydrazone **(3h)**. IR ($\overline{\nu}$ cm^{-1}): 3248 (N–H), 3010 (C–H, Ar), 1628 (C=O), 1306 (C=S); ^{1}H-NMR (DMSO) δ ppm; 13.4 (s, 1H), 12.3 (s, 1H), δ 10.1 (s, 1H), 7.95–7.88 (m, 3H), 7.68 (dd, J = 7.5, 1.6 Hz, 1H), 7.60 (dd, J = 7.5, 1.6 Hz, 1H), 7.48 (td, J = 7.5, 1.6 Hz, 1H), 7.43–7.37 (m, 2H), 7.27–7.20 (m, 1H), 2.41 (s,3H).; mass (ESI-MS): m/z 338 (M+1, 100%).

Table 2: The *in vitro* antimicrobial activity of the synthesized β-Isatin aldehyde-N,N′-thiocarbohydrazone derivatives.

Comp. no.	Gram positive		Gram negative		Fungi		
	B. Subtilis	*S.aureus*	*E. coli*	*P.aeruginosa*	*C.albicans*	*P. notatum*	*A. niger*
3a	50	100	100	100	200	50	200
3b	75	50	25	200	100	100	100
3c	50	50	200	400	400	50	400
3d	25	100	100	200	100	100	100
3e	25	50	25	100	25	50	25
3f	50	100	200	400	200	400	200
3g	50	50	25	100	100	25	100
3h	50	50	—	50	50	100	50
3i	50	—	100	100	50	200	50
3j	12.5	6.25	50	50	25	50	12.5
3k	100	100	100	—	50	50	100
3l	25	50	50	100	50	50	50
3m	50	100	200	—	100	200	100
3n	12.5	25	25	50	12.5	25	12.5
Ciproflaxin	3.12	3.12	6.25	6.25	—	—	—
Miconazole	—	—	—	—	6.25	6.25	3.12

Table 3: Antioxidant activity of synthesized compounds.

S. No	Compound	IC_{50} (μg/mL)* DPPH	IC_{50} (μg/mL) H_2O_2
1.	**3a**	57.40 ± 0.11	66.35 ± 0.08
2.	**3b**	39.62 ± 0.06	48.43 ± 0.12
3.	**3c**	41.66 ± 0.33	40.1 ± 0.05
4.	**3d**	50.67 ± 0.05	56.3 ± 0.05
5.	**3e**	32.43 ± 0.12	32.56 ± 0.03
6.	**3f**	56.8 ± 0.05	62.4 ± 0.05
7.	**3g**	58.7 ± 0.08	68.16 ± 0.08
8.	**3h**	38.7 ± 0.15	37.4 ± 0.15
9.	**3i**	47.6 ± 0.14	51.85 ± 0.31
10.	**3j**	20.31 ± 0.06	24.42 ± 0.06
11.	**3k**	53.0 ± 0.57	61.33 ± 0.08
12.	**3l**	30.62 ± 0.21	31.30 ± 0.05
13.	**3m**	32.24 ± 0.11	31.36 ± 0.08
14.	**3n**	26.56 ± 0.12	26.62 ± 0.11
15.	Ascorbic acid	18.55 ± 0.05	21.83 ± 0.08

*n = 3 values are expressed in mean ± S.E.M.

3.5.8. (1-Benzylidene-5-(5-methyl-2-oxoindolin-3-ylidene) Thiocarbohydrazone **(3i)**. IR ($\overline{\nu}\,cm^{-1}$): 3455 (N–H), 3140 (N–H), 3028 (C–H, Ar), 2989 (–CH3, *Str*), 1693 (C=O), 1319 (C=S); ^{1}H-NMR (DMSO) δ ppm; 13.1 (s, 1H), 11.8 (s, 1H), δ 9.8 (s, 1H), 7.83–7.67 (m, 3H), 7.48 (dd, J = 7.5, 1.6 Hz, 1H), 7.56 (dd, J = 7.5, 1.6 Hz, 1H), 7.48 (td, J = 7.5, 1.6 Hz, 1H), 7.43–7.37 (m, 2H), 7.27–7.20 (m, 1H), 2.61 (s, 3H).; mass (ESI-MS): m/z 338 (M+1, 100%), 360 (M + Na, 50%).

3.6. Biological Activity

3.6.1. Antimicrobial Activity. All the synthesized compounds were screened for their *in vitro* antibacterial and antifungal activities by the twofold serial dilution technique using the principles of Clinical and Laboratory Standards Institute (CLSI) [26]. Test compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1 mg/mL. Further dilutions of the test compounds and standard drug were

prepared test medium to provide concentrations are in which 400, 200, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 μg/mL. Minimal inhibitory concentrations for each compound were investigated against standard bacterial strains; *E. coli* and *P.aeruginosa* (gram negative); *B. subtilis, Staphylococcus aureus* (gram positive); *C. albicans, P.notatum* and *A. niger* (fungal strain). Ciprofloxacin was used as reference for antibacterial activity and miconazole used as reference for antifungal activity. The MIC values for all test compounds and reference drug are shown in Table 2.

3.7. Antioxidant Activity

3.7.1. DPPH Radical Scavenging Method. Blois [27] showed that α,α-diphenyl-β-picryl hydrazyl radical (DPPH) can be used for determining antioxidant activity. DPPH in ethanol shows a strong absorption band at 517 nm (independent of pH from 5.0 to 6.5), and the solution appears to be deep violet in color. As the DPPH radical is scavenged by the donated hydrogen from the antioxidant, the absorbance is diminished according to the stoichiometry. Briefly, 0.5 mL of DPPH solution (0.2 mM) was mixed with 0.1 mL of various concentrations of test compounds and 1.5 mL ethanol was added. The mixture was kept at room temperature for 30 min, and then the absorbance (OD) was read at 517 nm against blank. The % reduction of free radical concentration (OD) with different concentration of test compounds was calculated and was compared with standard, ascorbic acid. The results were expressed as IC_{50} values (the concentration of test required to scavenge 50% free radicals).

3.7.2. Hydrogen Peroxide Scavenging Activity. The ability of test compounds to scavenge hydrogen peroxide was determined according to the method of Sanchez [28] and Famey [29]. The solution of hydrogen peroxide (20 mM) was prepared in PBS (pH 7.4). Various concentrations of 1 mL of test compounds and standard were added to 2 mL of H_2O_2. Absorbance of hydrogen peroxide at 230 nm was determined 10 min later against the blank. Ascorbic acid was used as reference standard.

4. Results and Discussion

A series of 1-substituted-5-((1,5-disubstituted)-2-oxoindolin-3-ylidene) thiocarbohydrazide derivatives **(3a–n)** were synthesized by using a two-step procedure as depicted in Scheme 1. The synthesized compounds were purified by column chromatography. All of the derivatives were supported by spectral data. The IR, ^{1}H NMR, and mass spectra are in agreement with the proposed structures. Physical data of all the synthesized compounds are shown in Table 1.

The IR spectra of the compounds **3a–3n** reveal absorption bands in the region 1509–1610 cm^{-1} corresponding to C=N stretching bands. Absence of carbonyl (C=O) peak around 1715 cm^{-1} reveals the formation of Schiff bases. Mass spectra the base peak are shown as M+1 peak and also characteristic of all the remaining derivatives. From the Figure 1 of the mass spectra the base peak is shown as M+1 peak and also characteristic of the remaining derivatives.

4.1. In Vitro Antimicrobial Activity. Antimicrobial activity was investigated on all synthesized test compounds using two strains of Gram-positive and Gram-negative bacteria and against three strains of fungal species by twofold serial dilution technique. All the biological results of the test compounds are given in Table 2. The synthesized compounds showed a significant and broad spectrum of antimicrobial activity. Among the compounds tested **3j**, **3n** were found to be more active at an MIC value of 12.5 μg/mL for *Bacillus subtilis*. All the derivatives showed antibacterial activity against *Staphylococcus aureus* at MIC values between 25 and 100 μg/mL. For *E. coli* and *P.aeruginosa* the MIC values are between 25 and 400 μg/mL. All compounds show significant antifungal activity between MIC values 12.5 and 200 μg/mL. Among the tested compounds **3e**, **3j**, **3n** shows highest activity against three strains of fungal organisms. The N-substituted isatin derivatives exhibits more potent antimicrobial activity compared to simple isatins.

4.2. In Vitro Antioxidant Activity. The antioxidant activity of all the synthesized compounds performed using DPPH and H_2O_2 method and the results given in Table 3. The values are expressed in IC_{50} that is, ability of the test compound required to decrease the concentration of test free radical by 50%. All the synthetic compounds produced a concentration-dependent scavenging of free radical. The IC_{50} values of all the synthetic test compounds were found between 20 and 60 μg/mL. Among all the test compounds, compounds **3e**, **3j**, **3m**, **3l**, **3n** had more potent antioxidant activity against DPPH and H_2O_2 free radicals. It is proposed that DPPH may be scavenged by an antioxidant through donation of hydrogen ($H^{\cdot}$) to form a stable DPPH-H molecule which does not absorb at 517 nm.

Thus the results show that synthesized compounds possess antioxidant activity. It was observed that the test compounds with electron withdrawing groups (halogens) on the aromatic ring favors anti-oxidant activity. In a biological system, an antioxidant is defined as "any substance that when present at low concentrations compared to that of an oxidizable substrate would delay or prevent oxidation of the substrate." The compounds exhibit antioxidant activity as chelators for prooxidant or catalyst metal ions, provide H for primary oxidant, decompose hydroperoxide, deactivate singlet oxygen, absorb ultraviolet radiation, or act as oxygen scavengers [30].

5. Conclusions

A series of Schiff bases has been synthesized as shown in Scheme 1. These synthesized compounds were subjected to antimicrobial and antioxidant activity, amongst the compounds tested substituent with an electron withdrawing group on the aromatic ring showing significant activity than the unsubstituted compounds.

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