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Research Article

Microwave Synthesis, Characterization, and Antimicrobial Activity of Some Novel Isatin Derivatives

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Three series of isatin derivatives [3-hydrazino, 3-thiosemicarbazino, and 3-imino carboxylic acid derivatives] were synthesized employing microwave irradiation. The prepared compounds were characterized by FT-IR, NMR, elemental analysis, and X-ray crystallography for derivatives **5b**. The synthesized compounds were screened for antimicrobial activity against selected bacteria and fungi. The results revealed that the *N*-alkyl isatin derivatives were biologically active with different spectrums activity. Most of the 3-hydrazino and 3-thiosemicarbazino isatin derivatives were biologically inactive and generally the active derivatives showed weak to moderate activity mainly against Gram-positive bacteria. The imino isatin carboxylic acid derivatives (2-[4-(1-benzyl-5-bromo-2-oxoindolin-3-ylideneamino) phenyl]acetic acid, **5d**) showed promising activity against all tested Gram-positive bacteria and against fungal pathogens.

1. Introduction

The development of new therapeutic agents is one of the essential goals in medicinal chemistry. In the recent years there has been a spectacular increase in the use of microwave heating within the pharmaceutical industry, because it facilitates the synthesis of new chemical entities with reduced reaction time [1]. Microwave irradiation is considered as an alternate source of heating and it has been proven recently that microwave heating improves the efficiency of the reaction and reduces the reaction time [2–7].

It was reported that the biological properties of isatin derivatives include different effects on the brain and offer protection against some types of infections [8–11]. Isatin is considered as important class of bioactive compounds exhibiting caspase inhibitor [12, 13], antibacterial, and antiproliferative activity [14]. Schiff bases of isatin analogous have anti smallpox [15] and GAL3 receptor antagonist capabilities [16]. Isatin derivatives reported to show antiviral [17], anti-inflammatory, analgesic [18], and anticonvulsant activities [19]. Isatin-β-thiosemicarbazone derivatives were found to demonstrate a range of chemotherapeutic activities [20–26]. The literature survey revealed that thiocarbohydrazide is an irreversible inhibitor of catalase, which inhibits the degradation of serotonin and also possesses anticonvulsant activity [27].

We report here the synthesis of three different series of isatin derivatives (hydrazone, thiosemicarbazone, and imino carboxylic acid derivatives) employing microwave irradiation. The prepared compounds were subjected to *in vitro* screening for their antimicrobial activities against representatives of pathogenic Gram-positive and Gram-negative bacteria and fungi.

2. Experimental Section

2.1. Chemistry

2.1.1. Materials. The solvents used were of HPLC reagent grade. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Fourier transform infrared spectroscopy (FTIR) spectra were recorded on a Nicolet 560 spectrometer. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a JEOL 400 MHz spectrometer with chemical shift values reported in ppm (δ units) relative to an internal standard. The microwave irradiation was conducted using a multimode reactor (Synthos 3000, Anton Paar GmbH, and 1400 W maximum magnetron). Reactions were performed in teflon vessels (capacity 10 mL). The target temperature was set and fixed during the irradiation. Settings and readings for power (W) and pressure were taken from the instrument. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzers, and the values found were within ±0.3% of the theoretical values. Follow-up of the reactions and checks of the purity of the compounds were done by thin layer chromatography (TLC) on silica gel-protected aluminum sheets (GF254, Merck), and the spots were detected by exposure to UV-lamp at λ 254 nm for a few seconds. The compounds were named using Chem. Draw Ultra version 11, Cambridge Soft Corporation. The X-ray diffraction measurements of compound **5b** were performed using Bruker APEX-II D8 Venture diffractometer.

*2.1.2. Synthesis of Isatin Derivatives (**1b–1f**)* . A mixture of isatin (5 mmol) and potassium carbonate (8 mmol) in DMF (10 mL) was stirred for 10 minutes at room temperature. Alkyl halides (6 mmol; benzyl bromide for preparation of **1c**, **1d,** and **1e**; CH_3I for preparation of **1b**; and 1,3-dibromoethane for preparation of **1f**) were added dropwise to the reaction mixture and then the reaction was microwave irradiated using a multimode reactor (Synthos 3000, Anton Paar GmbH, Graz, Austria) (1,400 W maximum magnetron). The vessels were heated for 5 minutes at 80°C and held at the same temperature for a further 5 minutes (400 W). Cooling was accomplished by a fan (5 minutes). The final product was dried and recrystallized from ethanol. All the spectral data for the products obtained were in good agreement with the reported data.

*(1) 1-Methylisatin (**1b**)*. The product was obtained as orange red crystals in 90% yield; mp 126-127°C [Lit. [28] mp 126-127°C; in 73% yield]. ^{1}H NMR ($CDCl_3$): δ = 3.36 (s, 3H, CH_3), 6.78 (d, J = 7.8 Hz, 1H, Ar), 7.12 (t, J = 7.4 Hz, 1H, Ar), 7.47 (t, J = 8.1 Hz, 1H, Ar), 7.61 (d, J = 8.1 Hz, 1H, Ar) ppm.

*(2) 1-Benzylisatin (**1c**)*. The product was obtained as orange red crystals in 88% yield; mp 134–136°C. [Lit. [28] mp 134–136°C; 88% yield]. ^{1}H NMR ($CDCl_3$): δ = 4.93 (s, 2H, $C_6H_5\underline{CH_2}$), 6.77 (d, J = 7.7 Hz, 1H, Ar), 7.08 (t, J = 7.4 Hz, 1H, Ar), 7.33 (s, 5H, Ar), 7.47 (t, J = 8.1, 1H), 7.61 (d, J = 8.1, 1H, Ar) ppm.

*(3) 1-Benzyl-5-bromoisatin (**1d**; Supporting Information Page 2 in Supplementary Material Available Online at* http://dx.doi.org/10.1155/2015/716987*)*. The product was obtained as red orange crystals in 93% yield; mp 149–151°C [Lit. [29] mp 152-153°C, in 95% yield]. ^{1}H NMR ($CDCl_3$): δ = 4.91 (s, 2H, $C_6H_5\underline{CH_2}$), 6.69 (d, J = 8.1 Hz, 1H, Ar), 7.24–7.32 (m, 5H, Ar), 7.45 (dd, 1H, J = 8.1 Hz, 2.2 Hz, Ar), 7.56 (d, 1H, J = 2.2 Hz, Ar) ppm.

*(4) 1-Benzyl-5-chloroisatin (**1e**; Supporting Information Page 3)*. The product was obtained as orange crystals in 86% yield; mp 136°C (Lit. [29] mp 134°C, in 65% yield]. ^{1}H NMR ($CDCl_3$): δ = 4.94 (s, 2H, $C_6H_5\underline{CH_2}$), 6.69 (d, J = 8.1 Hz, 1H, Ar), 7.28–7.34 (m, 5H, Ar), 7.45 (dd, 1H, J = 8.1 Hz, 2.3 Hz, Ar), 7.56 (d, 1H, J = 2.3 Hz, Ar) ppm.

*(5) 1-(2-Bromoethyl)isatin (**1f**; Supporting Information Page 4)*. The product was obtained as red orange crystals in 89% yield; mp 130-131°C (Lit. [29] mp 131-132°C; in 80% yield). ^{1}H NMR ($CDCl_3$): δ = 3.60 (t, 2H, J = 6.6 Hz, CH_2), 4.16 (t, 2H, J = 6.6 Hz, CH_2), 7.00 (d, 1H, J = 8.1 Hz, Ar), 7.16 (t, 1H, J = 7.3 Hz, Ar), 7.60–7.63 (m, 2H, Ar) ppm.

*2.1.3. Microwave Method for the Synthesis of (**3a–3n**)*. A multimode reactor (Synthos 3000 Anton Paar, GmbH, 1400 W maximum magnetron) was used. The initial step was conducted with 4-Teflon vessels rotor (MF 100) that allows the reactions to process under the same conditions. Isatin derivatives **1a–1f** and hydrazine hydrate **2a**, thiosemicarbazide **2b,** or 4-aminobenzamide **2c** were mixed together in a small portion of ethanol and then subjected to microwave irradiation (400 watt). The vessels were heated for 5 min at 100°C and held at the same temperature for another 5 min. cooling was accomplished by a fan (5 min). The final product was washed with cold ethanol and then dried under vacuum to afford the products **3a–3n** in high yield and purity.

*(1) 3-Hydrazinoisatin (**3a**; Supporting Information Pages 5 and 6)*. The product was obtained as yellow crystals from ethanol, in 91% yield; mp 240–242°C (Lit. [30] 242°C). ^{1}H NMR (d_6-DMSO): δ = 6.86 (d, J = 8.1 Hz, 1H, Ar), 6.98 (t, J = 7.3 Hz, 1H, Ar), 7.14 (t, J = 7.3 Hz, 1H, Ar), 7.35 (d, J = 8.1 Hz, 1H, Ar), 9.55 (d, J = 14.0 Hz, 1H, NH), 10.54 (d, J = 14.0 Hz, 1H, NH), 10.75 (brs, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO): δ = 110.5, 118.01, 121.9, 122.8, 126.8, 127.6, 139.2, 163.3 ppm.

*(2) 1-Methyl-3-hydrazinoisatin (**3b**; Supporting Information Pages 7 and 8)*. The product was obtained as yellow crystals from ethanol in 93% yield, mp 95–97°C. ^{1}H NMR (d_6-DMSO): δ = 3.66 (s, 3H, CH_3), 6.96–7.05 (m, 2H, Ar), 7.23 (t, J = 8.0 Hz, 1H, Ar), 7.41 (d, J = 7.3 Hz, 1H, Ar), 9.64 (d, J = 8.8 Hz, 1H, NH), 10.58 (d, J = 10.3 Hz, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO): δ = 25.7, 109.8, 117.7, 121.9, 122.4, 125.9, 127.6, 140.5, 161.3 ppm. $C_9H_9N_3O$ (175.19): Calcd. C, 61.70; H, 5.18; N, 23.99; found: C, 61.87; H, 5.33; N, 24.19.

*(3) 1-Benzyl-3-hydrazinoisatin (**3c**; Supporting Information Pages 9 and 10)*. The product was obtained as yellow crystals from ethanol in 93% yield; mp 114-115°C (Lit. [30] 114-115°C).

^{1}H NMR (d_6-DMSO): δ = 4.97 (s, 2H, CH_2), 6.96 (d, J = 8.0 Hz, 1H, Ar), 7.02 (t, J = 7.3 Hz, 1H, Ar), 7.17 (t, J = 8.0 Hz, 1H, Ar), 7.32 (s, 5H, Ar), 7.43 (d, J = 7.3 Hz, 1H, Ar), 9.77 (d, J = 14.0 Hz, 1H, NH), 10.58 (d, J = 14.0 Hz, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO): δ = 42.8, 109.8, 117.9, 122.13, 122.6, 125.6, 127.5, 127.8, 127.9, 129.2, 137.3, 139.5, 161.3 ppm.

*(4) 1-Benzyl-5-bromo-3-hydrazinoisatin (**3d**; Supporting Information Pages 11 and 12)*. The product was obtained as yellow crystals from ethanol in 95% yield; mp 134–136°C. ^{1}H NMR (d_6-DMSO): δ = 4.97 (s, 2H, CH_2), 6.96 (d, 1H, J = 8.1 Hz, Ar), 7.19 (d, 1H, J = 8.1 Hz, Ar), 7.24–7.33 (m, 5H, Ar), 8.15 (s, 1H, Ar), 9.98 (brs, 1H, 1NH), 10.35 (brs, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO): δ = 40.3, 111.3, 117.4, 123.9, 126.7, 127.0, 127.8, 128.0, 129.2, 136.9, 138.0, 161.1 ppm. $C_{15}H_{12}BrN_3O$ (329.02): Calcd. C, 54.56; H, 3.66; N, 12.73; found: C, 54.78; H, 3.54; N, 12.98.

*(5) 1-Benzyl-5-chloro-3-hydrazinoisatin (**3e**)*. The product was obtained as yellow crystals from ethanol in 93% yield; mp 105–107°C. ^{1}H NMR (d_6-DMSO-): δ = 4.97 (s, 2H, CH_2), 6.96 (d, J = 8.1 Hz, 1H, Ar), 7.19 (d, J = 8.1 Hz, 1H), 7.24–7.33 (m, 5H, C_6H_5), 8.15 (s, 1H, Ar), 9.98 (brs, 1H, 1NH), 10.35 (brs, 1H, NH) ppm; ^{13}C NMR (d_6-DMSO): δ = 40.2, 111.3, 117.4, 123.9, 127.0, 127.8, 128.0, 129.2, 137.0, 138.0, 161.1 ppm. $C_{15}H_{12}ClN_3O$ (285.73): Calcd. C, 63.05; H, 4.23; N, 14.71; found: C, 63.31; H, 4.44; N, 14.98.

*(6) Isatin-3-thiosemicarbazone (**3f**)*. The product was obtained as yellow crystals in 89% yield; mp 246°C (dec) (Lit. [29] 245-246°C). ^{1}H NMR (d_6-DMSO): δ = 6.85–7.00 (m, 2H, Ar), 7.10 (brs, 2H, Ar), 7.50 (brs, 2H, NH_2), 8.05 (s, 1H, NH), 12.65 (brs, 1H, NH) ppm.

*(7) 1-Benzyl isatin-3-thiosemicarbazone (**3g**; Supporting Information Pages 13 and 14)*. The product was obtained as yellow solid from ethanol in 93% yield; mp 246-247°C. ^{1}H NMR (d_6-DMSO): δ = 4.98 (s, 2H, CH_2), 7.02 (d, J = 8.1 Hz, 1H, Ar), 7.19 (t, J = 8.1 Hz, 1H, Ar), 7.24–7.39 (m, 5H, Ar), 7.72 (d, J = 8.1 Hz, 1H, Ar), 8.77 (s, 1H, 1NH), 9.12 (s, 1H, NH), 12.42 (s, 1H, 1NH) ppm. ^{13}CNMR (d_6-DMSO): δ = 43.1, 110.9, 120.1, 121.4, 123.6, 128.0, 128.2, 129.3, 131.5, 131.6, 136.3, 143.2, 161.4, 179.3 ppm. $C_{16}H_{14}N_4OS$ (310.37): Calcd. C, 61.92; H, 4.55; N, 18.05; found: C, 62.13; H, 4.68; N, 18.31.

*(8) 1-Benzyl-5-bromoisatin-3-thiosemicarbazone (**3h**; Supporting Information Pages 15 and 16)*. The product was obtained as yellow solid from ethanol in 91% yield; mp 246-247°C. ^{1}H NMR (d_6-DMSO): δ = 4.98 (s, 2H, CH_2), 6.98 (d, J = 8.0 Hz, 1H, Ar), 7.24–7.38 (m, 5H, Ar), 7.52 (d, J = 8.0 Hz, 1H), 7.96 (s, 1H, Ar), 8.90 (s, 1H, 1NH), 9.18 (s, 1H, NH), 12.23 (s, 1H, 1NH) ppm. ^{13}C NMR (d_6-DMSO): δ = 43.2, 112.9, 115.5, 122.4, 123.9, 122.4, 123.9, 128.0, 128.2, 129.3, 130.1, 133.5, 136.0, 142.1, 161.0, 179.3 ppm. $C_{16}H_{13}BrN_4OS$ (389.27): Calcd. C, 49.37; H, 3.37; N, 14.39; found: C, 49.53; H, 3.61; N, 14.66.

*(9) 1-Benzyl-5-chloroisatin-3-thiosemicarbazone (**3i**; Supporting Information Pages 17 and 18)*. The product was obtained as yellow solid from ethanol in 91% yield; mp 242°C (dec). ^{1}H NMR (d_6-DMSO): δ = 4.98 (s, 2H, CH_2), 7.02 (d, J = 8.1 Hz, 1H, Ar), 7.20–7.50 (m, 5H, Ar), 7.82 (s, 1H, Ar), 8.89 (s, 1H, 1NH), 9.19 (s, 1H, NH), 12.25 (s, 1H, 1NH) ppm. ^{13}C NMR (d_6-DMSO) δ = 43.2, 112.4, 121.1, 122.0, 127.9, 128.0, 128.2, 129.3, 130.3, 130.8, 136.0, 141.7, 161.1, 179.3 ppm. $C_{16}H_{13}ClN_4OS$ (344.82): Calcd. C, 55.73; H, 3.80; N, 16.25; found: C, 56.00; H, 3.89; N, 16.01.

*(10) 1-(2-Bromoethyl)isatin-3-thiosemicarbazone (**3j**; Supporting Information Pages 19 and 20)*. The product was obtained as yellow crystals from ethanol in 88% yield; mp 246°C (dec). ^{1}H NMR (d_6-DMSO): δ = 3.77 (t, 2H, J = 6.4 Hz, CH_2), 4.21 (t, 2H, J = 6.4 Hz, CH_2), 7.18 (t, 1H, J = 7.3 Hz, Ar), 7.28 (d, 1H, J = 8.0 Hz, Ar), 7.43 (t, 1H, J = 7.3 Hz, Ar), 7.21 (d, 1H, J = 7.3 Hz, Ar), 8.77 (s, 1H, NH), 9.12 (s, 1H, NH), 12.36 (s, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO) δ = 30.1, 40.5, 110.9, 119.8, 121.3, 131.3, 131.8, 142.9, 161.3, 179.2 ppm. $C_{11}H_{11}BrN_4OS$ (327.20): Calcd. C, 40.38; H, 3.39; N, 17.12; found: C, 40.66; H, 3.54; N, 17.40.

*(11) 4-Amino-N′-(2-oxoindolin-3-ylidene)benzohydrazide (**3k**; Supporting Information Pages 21 and 22)*. The product was obtained as a yellowish brown solid in 82% yield; mp > 250°C. ^{1}H NMR (d_6-DMSO): δ = 6.00 (brs, 2H, NH_2), 6.64 (d, 2H, J = 8.8 Hz, Ar), 6.92 (d, 1H, J = 8.8 Hz, Ar), 7.11 (t, 1H, J = 8.1 Hz, Ar), 7.38 (t, 1H, J = 8.1 Hz, Ar), 7.76 (d, 2H, J = 8.1 Hz, Ar), 7.88 (d, 1H, J = 7.3 Hz, Ar), 10.80 (s, 1H, NH), 11.33 (s, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO): δ = 111.1, 113.3, 116.5, 118.9, 122.4, 127.0, 131.0, 132.8, 142.2, 144.1, 153.7, 165.5 ppm. $C_{15}H_{12}N_4O_2$ (280.28): Calcd. C, 64.28; H, 4.32; N, 19.99; found: C, 64.13; H, 4.19; N, 20.14.

*(12) 4-Amino-N′-(1-methyl-2-oxoindolin-3-ylidene)benzohydrazide (**3l**; Supporting Information Pages 23 and 24)*. The product was obtained as a yellow powder from ethyl acetate in 88% yield; mp > 250°C. ^{1}H NMR (d_6-DMSO): δ = 3.26 (s, 3H, CH_3), 6.01 (brs, 2H, NH_2), 6.64 (d, 2H, J = 8.4 Hz, Ar), 7.12 (d, 1H, J = 8.0 Hz, Ar), 7.16 (d, 1H, J = 7.6 Hz, Ar), 7.38 (t, 1H, J = 7.6 Hz, Ar), 7.74 (d, 2H, J = 8.8 Hz, Ar), 7.88 (d, 1H, J = 7.6 Hz Ar), 11.34 (s, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO): δ = 26.0, 109.2, 112.7, 113.1, 115.2, 118.3, 122.2, 126.1, 131.1, 132.2, 139.1, 144.5, 153.7, 163.6 ppm. $C_{16}H_{14}N_4O_2$ (294.31): Calcd. C, 65.30; H, 4.79; N, 19.04; found: C, 65.45; H, 4.85; N, 19.31.

*(13) 4-Amino-N′-(1-benzyl-2-oxoindolin-3-ylidene)benzohydrazide (**3m**; Supporting Information Pages 25 and 26)*. The product was obtained as yellowish brown solid in 87% yield; mp 198–200°C. ^{1}H NMR (d_6-DMSO): δ = 4.99 (s, 2H, CH_2), 6.04 (brs, 2H, NH_2), 6.67 (d, 2H, J = 8.0 Hz, Ar), 7.00 (d, 1H, J = 7.3 Hz, Ar), 7.14 (t, 1H, J = 7.3 Hz, Ar), 7.27–7.41 (m, 5H, Ar), 7.65 (d, 1H, J = 8.8 Hz, Ar), 7.76 (d, 2H, J = 8.0 Hz, Ar), 7.95 (d, 1H, J = 7.3 Hz, Ar), 11.39 (s, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO) δ = 43.9, 110.3, 113.3, 113.7, 116.0, 123.0, 126.9, 127.7, 128.0, 128.1, 128.2, 129.3, 130.0, 131.2, 132.6, 142.3, 144.0, 153.8, 164.3 ppm. $C_{22}H_{18}N_4O_2$ (370.41): Calcd. C, 71.34; H, 4.90; N, 15.13; found: C, 71.60; H, 5.01; N, 15.41.

*(14) 4-Amino-N′-(1-benzyl-3-bromo-2-oxoindolin-3-ylidene)benzohydrazide (**3n**; Supporting Information Pages 27 and 28)*. The product was obtained as brown solid in 83% yield; mp 260–263°C. ^{1}H NMR (d_6-DMSO): δ = 4.99 (s, 2H, CH_2),

6.04 (brs, 2H, NH_2), 6.67 (d, 2H, J = 8.04 Hz, Ar), 7.00 (d, 1H, J = 7.3 Hz, Ar), 7.14 (t, 1H, J = 7.3 Hz, Ar), 7.27–7.41 (m, 5H, Ar), 7.65 (d, 1H, J = 8.8 Hz, Ar), 7.76 (d, 2H, J = 8.1 Hz, Ar), 7.95 (d, 1H, J = 7.3 Hz, Ar), 11.39 (s, 1H, NH), 11.33 (s, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO): δ = 43.9, 110.3, 113.3, 113.7, 116.0, 123.0, 126.9, 127.7, 128.0, 128.1, 128.2, 129.3, 130.0, 131.2, 132.6, 142.3, 144.0, 153.8, 164.3 ppm. $C_{22}H_{18}N_4O_2$ (449.30): Calcd. C, 71.34; H, 4.90; N, 15.13; found: C, 71.60; H, 5.01; N, 15.41.

*2.1.4. Microwave Method for the Synthesis of (**5a–5d**).* Isatin derivatives **1a–1d** and 4-aminophenyl acetic acid **4** were mixed in small amount of ethanol as a solvent in the presence of glacial acetic acid (2-3 drops). The individual vessels were heated for 5 min at 100°C and held at the same temperature for another 5 min; cooling was accomplished by a fan (5 min). The final product was washed with cold methanol and then dried under vacuum to afford products **5a–5d** in a pure state, as observed from their spectral data.

*(1) 2-[4-(2-Oxoindolin-3-ylideneamino)phenyl]acetic Acid (**5a**; Supporting Information Pages 29 and 30).* The product was obtained as brown crystals from ethyl acetate in 88% yield; mp: 210–212°C. ^{1}H NMR (d_6-DMSO): δ = 3.63 (s, 2H, CH_2), 6.43 (d, 1H, J = 7.3 Hz, Ar), 6.72 (t, 1H, J = 7.3 Hz, Ar), 6.90 (d, 1H, J = 8.1 Hz, Ar), 6.98 (d, 2H, J = 8.1 Hz, Ar), 7.32–7.40 (m, 3H, Ar), 10.88 (s, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO): δ = 40.2, 112.1, 116.3, 117.9, 119.9, 122.2, 125.8, 129.8, 131.1, 132.3, 135.0, 147.5, 149.5, 155.4, 164.0, 173.3 ppm. $C_{16}H_{12}N_2O_3$ (280.28): Calcd. C, 68.56; H, 4.32; N, 9.99; found: C, 68.78; H, 4.49; N, 10.08.

*(2) 2-[4-(1-Methyl-2-oxoindolin-3-ylideneamino)phenyl]acetic Acid (**5b**; Supporting Information Pages 31 and 32).* The product was obtained as brown crystals from ethyl acetate in 88% yield; mp 198–200°C. ^{1}H NMR (d_6-DMSO): δ = 3.19 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 6.45 (d, 1H, J = 8.0 Hz, Ar), 6.78 (t, 1H, J = 8.0 Hz, Ar), 6.92 (d, 2H, J = 8.0 Hz, Ar), 7.08 (d, 1H, J = 8.0 Hz, Ar), 7.34 (d, 2H, J = 8.0 Hz, Ar), 7.43 (t, 1H, J = 8.0 Hz, Ar) ppm. ^{13}C NMR (d_6-DMSO) δ = 26.1, 40.0, 110.2, 115.1, 117.3, 119.4, 122.2, 124.9, 130.6, 131.9, 134.4, 147.9, 148.8, 154.1, 162.2, 172.8 ppm. $C_{17}H_{14}N_2O_3$(294.30): Calcd. C, 69.38; H, 4.79; N, 9.52; found: C, 69.54; H, 4.86; N, 9.78.

*(3) 2-[4-(1-Benzyl-2-oxoindolin-3-ylideneamino)phenyl]acetic Acid (**5c**; Supporting Information Pages 33 and 34).* The product was obtained as reddish brown crystals from ethyl acetate in 86% yield; mp 180–182°C. ^{1}H NMR (d_6-DMSO): δ = 3.64 (s, 2H, CH_2), 4.99 (s, 2H, CH_2), 6.50 (d, 1H, J = 7.3 Hz, Ar), 6.78 (t, 1H, J = 8.0 Hz, Ar), 6.96–7.07 (m, 3H, Ar), 7.29–7.46 (m, 8H, Ar) ppm. ^{13}C NMR (d_6-DMSO): δ = 40.3, 43.4, 111.2, 114.3, 115.9, 117.9, 122.9, 125.7, 127.9, 128.1, 129.2, 130.3, 131.2, 132.5, 134.8, 136.4, 147.4, 149.3, 154.4, 162.9, 173.3 ppm. $C_{23}H_{18}N_2O_3$ (370.40): Calcd. C, 74.58; H, 4.90; N, 7.56; found: C, 74.74; H, 5.05; N, 7.42.

*(4) 2-[4-(1-Benzyl-5-bromo-2-oxoindolin-3-ylideneamino)phenyl]acetic Acid (**5d**).* The product was obtained as reddish brown crystals from ethylacetate in 89% yield; mp 179-180°C. ^{1}H NMR (d_6-DMSO): δ = 3.65 (s, 2H, CH_2), 4.99 (s, 2H, CH_2), 6.64 (d, 1H, J = 7.3 Hz, Ar), 6.90–7.11 (m, 3H, Ar), 7.29–7.48 (m, 8H, Ar) ppm. ^{13}C NMR (d_6-DMSO): δ = 40.3, 43.4, 114.3, 117.7, 117.9, 127.9, 128.0, 128.1, 129.2, 129.3, 131.2, 136.1, 136.8, 146.5, 148.9, 154.6, 162.9, 173.2 ppm. $C_{23}H_{17}BrN_2O_3$ (449.30): Calcd. C, 61.48; H, 3.81; N, 6.23; found: C, 61.73; H, 3.99; N, 6.51.

2.2. Biology

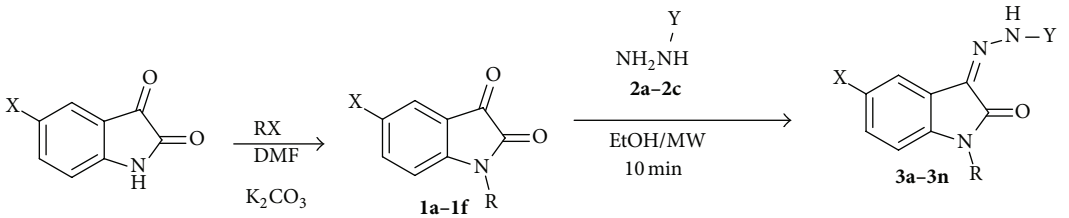
2.2.1. Antimicrobial Activities of the Prepared Compounds. The antimicrobial activities of the prepared compounds were tested against representative pathogenic Gram-positive, Gram-negative, and filamentous fungus test strains by using the paper disc diffusion method [31]. In this method, three agar media, nutrient agar [32] for bacteria, Sabouraud agar [33] for the yeast strain, and Czapek Dox agar for the fungus strain [34], were prepared and sterilized by autoclaving at 120°C and 1.5 atm for 20 min. The agar plates were poured, left to cool down and after solidification they were inoculated with the bacterial and fungal strains by streaking. The synthesized compounds were dissolved in dimethylsulfoxide (DMSO) at a final concentration of 10 mg/mL and 5 μL of each compound was loaded on a sterile filter paper disc (5 mm diameter; 50 μg per disc). The filter paper disc was then transferred aseptically into the inoculated agar plates along with commercially available tetracycline and erythromycin discs as positive controls and DMSO as the negative control for comparison. The plates were then incubated at 37°C for 24 h for bacteria and at 30°C for 48–72 h for fungi. After incubation, diameters of the inhibition zones around the paper discs were measured in mm as an indication of the antimicrobial activities of the compounds.

3. Results and Discussion

3.1. Chemistry. *N*-alkyl isatin derivatives **1b–1f** were prepared from isatin derivatives according to the reported method employing microwave irradiation [30]. The spectral data of **1b–1f** were in good agreement with the reported data [28–30, 35–38]. Isatin derivatives **3a–3n** were prepared by condensation of **1a–1f** either with hydrazine hydrate **2a**, thiosemicarbazide **2b**, or 4-aminobenzhydrazide **2c** following the reported procedure using microwave irradiation (Scheme 1) [30]. The products **3a–3n** were obtained in excellent yields (85–95%; Section 2) and their spectral data were in good agreement with their proposed structures.

The IR spectra of **3a–3e** showed absorption bands in the regions 3398 to 3217 cm^{-1} corresponding to (NH), a band at 1688 cm^{-1} corresponding to the C=O group, and a peak around 1584 cm^{-1} that reveals the formation of the C=N bond. The NMR spectra of all the products **3a–3e** are in a good agreement with their structures [28–30].

The IR spectra of the series **3f–3j** showed absorption bands in the region 3453 cm^{-1} related to the asymmetric (N–H) vibration of the terminal NH_2 group. The other bands at 3336 and 3256 cm^{-1} may be due to the symmetric (N–H) vibrations of the amide and amino groups. The peaks at 1680 and 1588 cm^{-1} correspond to C=O and C=N group,

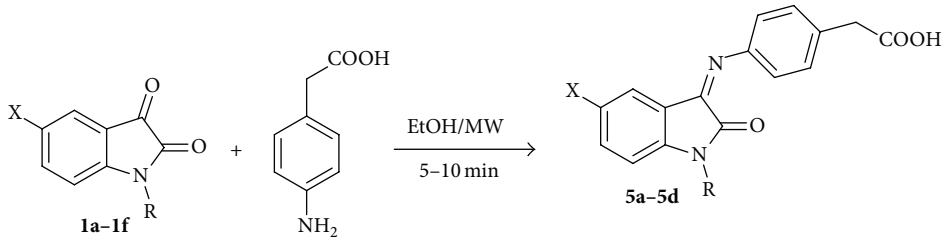


X = H; **1a**
X = Br, or Cl

X = R = H; **1a**
X = H, R = CH_3; **1b**
X = H, R = Bn; **1c**
X = Br, R = Bn; **1d**
X = Cl, R = Bn, **1e**
X = H, R = CH_2CH_2Br, **1f**

X = R = Y = H; **3a**
X = H, R = CH_3, Y = H; **3b**
X = H, R = Bn, Y = H; **3c**
X = Br, R = Bn, Y = H; **3d**
X = Cl, R = Bn, Y = H; **3e**
X = R = H, Y = -CS-NH_2; **3f**
X = H, R = Bn, Y = -CS-NH_2; **3g**
X = Br, R = Bn, Y = -CS-NH_2; **3h**
X = Cl, R = Bn, Y = -CS-NH_2; **3i**
X = H, R = CH_2CH_2Br, Y = -CS-NH_2; **3j**
X = R = H, Y = 4-NH_2-C_6H_4-CO-; **3k**
X = H, R = CH_3, Y = 4-NH_2-C_6H_4-CO-; **3l**
X = H, R = Bn, Y = 4-NH_2-C_6H_4-CO-; **3m**
X = Br, R = Bn, Y = 4-NH_2-C_6H_4-CO-; **3n**

Scheme 1: Synthesis of 3-hydrazino and 3-thiosemicarbazino isatin derivatives.



X = Y = H; **1a**
X = H, R = CH_3; **1b**
X = H, R = Bn; **1c**
X = Br, R = Bn; **1d**

X = Y = H; **5a**
X = H, R = CH_3, **5b**
X = H, R = Bn, **5c**
X = Br, R = Bn, **5d**

Scheme 2: Synthesis of isatin-3-iminocarboxylic acid derivatives.

respectively. The NMR of all the products **3f–3j** are in good agreement with their proposed structures (Section 2).

The IR spectra of **3k–3n** reveal absorption bands in the regions 3406, 3325, and 3225 cm^{-1} which can be assigned to the asymmetric (N–H) vibration of the terminal NH_2 group and the amide groups. The peaks at 1712, 1642, and 1592 cm^{-1} correspond to two C=O and C=N groups, respectively. NMR spectra of all the obtained products **3k–3n** are in good agreement with their proposed structures (Section 2).

The imino isatin carboxylic acid derivatives **5a–5d** were prepared by condensation of isatin derivatives **1a–1d** with 4-aminophenylacetic acid **4** using microwave irradiation and ethanol as a solvent (Scheme 2).

The IR spectra of the compounds derived from 4-aminophenylacetic acid **5a–5d** reveal broad absorption bands in the region 3432-2632 cm^{-1} which can be assigned to the hydroxyl group of the carboxylic group. The peaks at 1729, 1645, and 1602 cm^{-1} are related to the (C=O) of the carboxylic, carbonyl, and imino groups, respectively. The ^1H NMR and ^{13}C-NMR spectra of the products **5a–5d** are also in good agreement with their structures. The ^1H NMR spectrum of compound **5b** as a prototype displayed two singlet peaks at δ 3.19 and δ 3.62 corresponding to CH_3 and the benzylic protons ($C_6H_5CH_2$), respectively. Six peaks corresponding to the 8 aromatic protons were observed at δ = 6.45, 6.78, 6.92, 7.08, 7.34, and 7.43 ppm. The ^{13}C-NMR spectrum confirmed

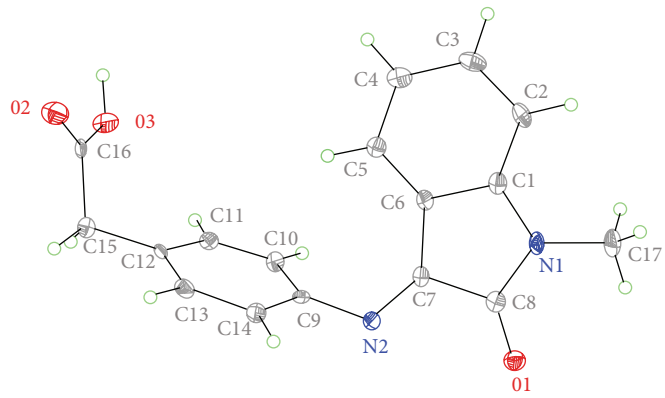


Figure 1: ORTEP diagram of compound **5b** (CCDC-1004251) drawn at 50% ellipsoids for nonhydrogen atoms.

its structure, where two signal were observed at δ = 26.1 and 40.0 ppm assigned to the methyl and benzylic protons, respectively. The observed peak at δ = 154.1, 162.2, and 172.8 ppm is related to the C=N, C=O, and the carbonyl of the carboxylic groups, respectively.

Single crystal X-ray crystallography is without doubt a decisive analytical tool which confirms the configuration of the imine double bond in the target compounds **5a–5d**. Fortunately, we have succeeded in getting single crystals of compound **5b** that was suitable for X-ray crystallography. The solved structure is a representative example for the synthesized target compounds **5a–5d**. The assigned (*E*)-configuration of compound **5b** was established via its single crystal X-ray structure (Figure 1).

Molecular formula of **5b** is as follows: $C_{17}H_{14}N_2O_3$, Molecular weight: 294.30, Monoclinic, P21/*c*, a = 10.3860 (8) Å, b = 8.5519 (7) Å, c = 16.0149 (11) Å, β = 96.604 (2)°, V = 1413.01 (19) Å^3, *D*calc = 1.383 Mg m^{-3}, orange plate with 0.69 × 0.35 × 0.08 mm. A total of 28282 reflections were measured, of which 3241 were independent. *R*int = 0.163, dataset (h; k; l) = −13, 13; −11, 11; −20, 20. Refinement of F^2 against all reflections, led to [$F^2 > 2(F^2)$] = 0.073, $wR(F^2)$ = 0.204, and S = 1.07.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (supplementary publication number CCDC-1004251). Copies of the data may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, UK.

3.2. Biology. The antimicrobial activities of the prepared compounds against a panel of pathogenic tested organisms are collected in Table 1. The results revealed that all the *N*-alkyl isatin derivatives **1b–1f** were biologically active with different spectrum activity. The isatin itself **1a** exhibited average antibacterial activities against the Gram-negative test organisms only, but the activity decreased with the presence of the methyl group in **1b**. On the other hand, the introduction of a benzyl group in **1c** decreased the activity against Gram-negative bacteria and confers activity against Gram-positive bacteria, namely, *Bacillus subtilis*. However, the presence of ethyl bromide group in **1f** expands the spectrum activity to be active against *Bacillus subtilis* and two Gram-negative tested bacteria and against the fungal pathogens in study.

Differently, most of the 3-hydrazino and 3-thiosemicarbazino isatin derivatives **3a–3n** were biologically inactive and generally the active derivatives showed weak to moderate activity against at least two of the tested Gram-positive test bacteria. Interestingly, the activity was associated with the presence of the bromine or chlorine in the isatin moieties **3d**, **3e,** and **3n**; however, their effect cannot be confirmed in the activity of **3h** and **3i** because **3f** was originally active.

Among the imino isatin carboxylic acid derivatives, **5d** which has bromine at position 5 showed good to high antimicrobial activity compared to the positive control (erythromycin and tetracycline) against the Gram-positive and fungal test organisms. The presence of the methyl group in **5b** was associated with the activity against the Gram-negative bacteria and, similarly as in the *N*-alkyl isatin derivatives, compound **5c**, having a benzyl group, showed antimicrobial activity against *Bacillus subtilis* and Candida albicans. These results obtained are similar to the reported results by Singh et al. and Patel et al. [28, 39].

4. Conclusions

Three series of isatin derivatives (3-hydrazino, 3-thiosemicarbazino, and 3-imino carboxylic acid derivatives) were synthesized by employing microwave irradiation in good yields and purities. The prepared compounds were evaluated for their antimicrobial activity against Gram-positive and Gram-negative bacteria and fungal pathogenic organisms. In general, the *N*-alkyl isatin derivatives were biologically active, while some of the 3-hydrazino and 3-thiosemicarbazino isatin derivatives were active against at least two of the three used Gram-positive test organisms. It was found that the activity was associated with the presence of the bromine or chlorine in the isatin moiety of the prepared compounds. The highest activity was achieved with one of the imino isatin carboxylic acid derivatives that showed good to high activity towards the three Gram-positive bacteria and the two fungal tested microorganisms.

Table 1: The antimicrobial activities of the synthesized isatin derivatives expressed as inhibition zones of growth in mm against the tested pathogenic organisms.

Compound	Test organism[a]							
	B.s.	*M.l.*	*M.p.*	*E.c.*	*P.v.*	*S.t.*	*C.a.*	*Ph.i.*
1a	—	—	—	14 ± 0.33	14 ± 0.66	15 ± 0.33[b]	—	—
1b	—	—	—	9 ± 0.33	9 ± 0.33	9 ± 0.33	—	—
1c	7 ± 0.33	—	—	—	—	—	—	—
1f	8 ± 0.66	—	—	10 ± 0.33	10 ± 0.66	—	8 ± 0.66	8 ± 0.33
3a	—	—	—	—	—	—	—	—
3b	—	—	—	—	—	—	—	—
3c	—	—	—	—	—	—	—	—
3d	9 ± 0.66	—	15 ± 0.33	—	—	—	—	—
3e	9 ± 0.33	—	15 ± 0.66	—	—	—	—	—
3f	7 ± 0.66	10 ± 0.33	15 ± 0.33	—	—	—	—	—
3g	—	—	—	—	—	—	—	—
3h	9 ± 0.66	—	10 ± 0.66	—	—	—	—	—
3i	7 ± 0.66	—	10 ± 0.33	—	—	—	—	—
3j	—	—	—	—	—	—	—	—
3k	—	—	—	—	—	—	—	—
3l	—	—	—	—	—	—	—	—
3m	—	—	—	—	—	—	—	—
3n	11 ± 0.33	13 ± 0.66	17 ± 0.33	—	—	—	—	—
5a	—	—	—	—	—	—	—	—
5b	—	—	—	17 ± 0.66	—	11 ± 0.33	—	—
5c	10 ± 0.66	—	—	—	—	—	10 ± 0.33	—
5d	18 ± 0.33	20 ± 0.66	23 ± 0.66	—	—	—	18 ± 0.33	15 ± 0.66
Erythromycin[c]	28 ± 0.33	18 ± 0.33	16 ± 0.66	13 ± 0.33	14 ± 0.33	11 ± 0.66	—	—
Tetracycline[d]	24 ± 0.66	20 ± 0.33	15 ± 0.66	22 ± 0.33	18 ± 0.66	20 ± 0.66	—	—

[a]All the results were obtained in DMSO; "—", no activity; *B.s.*, *Bacillus subtilis*; *M.l.*, *Micrococcus luteus*; *M.p.*, *Mycobacterium phlei*; *E.c.*, *Escherichia coli*; *P.v.*, *Proteus vulgaris*; *S.t.*, *Salmonella Typhi*; *C.a.*, *Candida albicans*; and *Ph.i.*, *Phytophthora infestans*. [b]Zone of inhibition in mm (mean ± S.D., $n = 3$). [c]The concentration was 15 μg. [d]The concentration was 30 μg.

Conflict of Interests

The authors declare no conflict of interests.

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