Research Article

Synthesis of Isoxazolopyridines and Spirooxindoles under Ultrasonic Irradiation and Evaluation of Their Antioxidant Activity

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New polycyclic-fused isoxazolo[4,5-e]pyridines and spirooxindoles were obtained via multicomponent reaction of 5-amino-3-methylisoxazole, indan-1,3-dione, and aromatic aldehydes and reaction of 5-amino-3-methylisoxazole, isatin, and β-diketones in the presence of ($\pm$)-camphor-10-sulfonic acid as an effective and nontoxic organocatalyst under ultrasound-promoted conditions. The antioxidant activity of the novel synthesized compounds was studied.

1. Introduction

Multicomponent reactions allow the building of several new bonds in a single step and therefore these one-pot reactions are one of the most attractive topics in synthetic chemistry [1]. These reactions have enormous effectiveness, particularly for the construction of heterocyclic compounds which exhibit a wide range of biological activities [2–5]. Multicomponent reactions proceed in accordance with green chemistry principles in terms of a high degree of atom economy, easier progress of reactions, decreased reaction times, lack of waste products, and low power consumption [6, 7].

Isoxazole and spirooxindole compounds have exhibited many biological properties such as antibacterial [8], anti-inflammatory [9], anticonvulsant [10], muscle relaxant [11], anti-HIV and anticancer activity [12–16], and significant activity in hypertension and Alzheimer's disease [17, 18]. Consequently, several protocols for the synthesis of isoxazoles and spirooxindoles have been reported [19–28].

($\pm$)-Camphor-10-sulfonic acid (CSA) is an effective, safe, water-soluble, and reusable organocatalyst for various organic reactions, for instance, Friedel-Crafts reactions [29], synthesis of dioxabicyclo[3.3.1]nonane and β-amino naphthol compounds [30, 31], and synthesis of spirocyclic compounds [32], and is also frequently used in the optical resolution of amines [33].

It is important to develop new synthetic processes that provide better environmental performance in synthetic organic chemistry [34]. Numerous organic reactions can be effectively achieved in higher yields, shorter reaction times, and milder reaction conditions under ultrasonic irradiation due to cavitational collapse [35–40].

This work aims to study the synthesis of isoxazolopyridines and spirooxindoles under ultrasonic irradiation in the presence of ($\pm$)-CSA as an organocatalyst. Antioxidants are being increasingly noticed for the prevention of the damaging influence of free radicals in the human body [41]. Hence, to expand biological curiosity to isoxazolopyridine and spirooxindole compounds, the new synthesized compounds were tested for their free radical scavenging activity (determined for DPPH), reducing activity (reduction of the Fe^{3+}/ferricyanide complex to its ferrous form), metal chelating (chelating activity capacity of ferrous ions) activity, superoxide scavenging activity, and total antioxidant activity.

2. Experimental

2.1. Materials and Methods. NMR spectra were determined on a Bruker Avance III-500 MHz NMR. Chemical shifts are given in ppm downfield from Me_4Si in DMSO-d_6 solution. Coupling constants are given in Hz. The FTIR spectra were
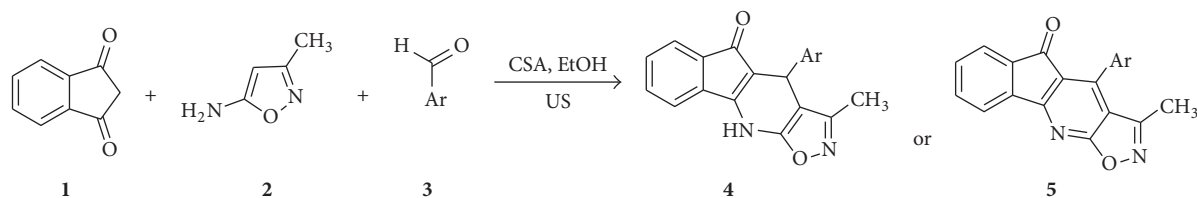
SCHEME 1: Three-component synthesis of isoxazolopyridine derivatives.
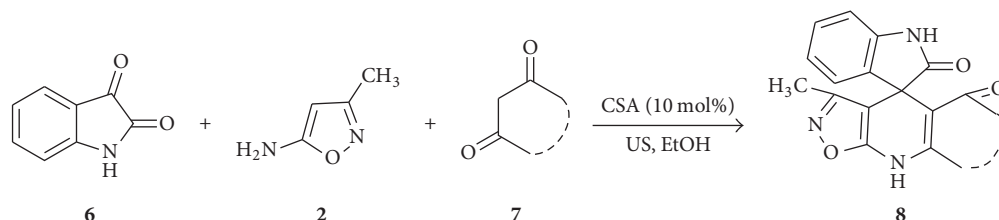
SCHEME 2: Three-component synthesis of spirooxindole derivatives.

recorded on a Perkin-Elmer FT-IR spectrometer (ATR) and absorption frequencies are reported in cm^{-1}. MS spectra were recorded on an AB Sciex 3200 QTRAP LC-MS/MS. Elemental analyses were measured with CHNS-932 LECO apparatus and were in good agreement (±0.2%) with the calculated values. Ultrasonication was performed in an Alex Ultrasonic Bath with a frequency of 32 kHz and a power of 230 W. The internal dimensions of the ultrasonic cleaner tank were $240 \times 140 \times 100$ mm with liquid holding capacity of 3 L. The reactor was a 100 mL Pyrex round-bottom flask. The reaction flasks were suspended in the center of the bath, and the addition or removal of water controlled the temperature of the water bath. Melting points were measured on a Gallenkamp melting-point apparatus. TLC was conducted on standard conversion aluminum sheets precoated with a 0.2 mm layer of silica gel. All reagents were commercially available.

2.2. General Procedure for the Synthesis of Isoxazolopyridine Derivatives (4a–e and 5f–h) under Ultrasonic Irradiation. A mixture of CSA (34.8 mg, 0.15 mmol), 5-amino-3-methylisoxazole, (1.00 mmol), indan-1,3-dione (1.00 mmol), and aromatic aldehydes (1.00 mmol) in 5 mL EtOH was irradiated with ultrasound of low power at 70°C for the period of time indicated in Scheme 1 and Table 2. After completion of the reaction, as indicated by TLC monitoring, the resultant solid was washed with water and crystallized from ethanol to give products **4a–e** and **5f–h**.

2.3. General Procedure for the Synthesis of Spirooxindole Derivatives (8a–d) under Ultrasonic Irradiation. A mixture of CSA (23.2 mg, 0.10 mmol), 5-amino-3-methylisoxazole, (1.00 mmol), isatin (1.00 mmol), and β-diketones (1.00 mmol) in 5 mL EtOH was irradiated with ultrasound of low power at 70°C for the period of time indicated in Scheme 2 and Table 3. After completion of the reaction, as indicated by TLC monitoring, the resultant solid was washed with water and crystallized from ethanol to give products **8a–d**.

2.4. Free Radical Scavenging Activity. The free radical scavenging activity was determined by 1,1-diphenyl-2-picryl-hydrazyl (DPPH•). The activity was assayed according to the methodology described by Brand-Williams et al. [42]. 20 mg/L DPPH• in methanol was prepared and 1.5 mL of this solution was added to 0.75 mL of isoxazolopyridine or spirooxindole compounds solution in water at various concentrations (25–400 μg/mL). After 30 minutes the absorbance was measured at 517 nm. The inhibition activity percentage was calculated according to the following equation:

$$\text{Free radical scavenging effect}\% = \left[\frac{(A_0 - A_1)}{A_0} \right] \cdot 100 \quad (1)$$

(A_0 is the control absorbance and A_1 is the sample solution absorbance).

2.5. The Reducing Power Assay. The reducing power of newly synthesized compounds was assayed according to the methodology of Oyaizu [43]. Various concentrations of compounds (25–400 μg/mL) in 1 mL of distilled water were mixed with 0.2 M phosphate buffer and 2.5 mL of potassium ferricyanide $[K_3Fe(CN)_6]$. This mixture was incubated at 50°C for 30 minutes and trichloroacetic acid (2.5 mL, 10%, w/v) was added to the mixture and then centrifuged at 3000 rpm for 10 min. Lastly, 2.5 mL of solution was mixed with 0.5 mL $FeCl_3$ and distilled water (2.5 mL) and then the absorbance was measured at 700 nm.

2.6. Metal Chelating Activity. The ferrous ions' (Fe^{2+}) chelating activities of the isoxazolopyridines, spirooxindoles, and standards were investigated according to the methodology described by Decker and Welch [44]. 1 mL of various concentrations (25–400 μg/mL) of the newly synthesized compounds was mixed with 3.7 mL of water. This mixture was incubated for 30 minutes with 2 mM $FeCl_2$. Afterward, 5 mM ferrozine was added and left standing at room temperature

for 10 min. The absorbance of the resulting solution was measured at 562 nm.

$$\text{Metal chelating activity} \,(\%) = \left[\frac{(A_0 - A_1)}{A_0}\right] \cdot 100. \quad (2)$$

2.7. Superoxide Scavenging Activity.

The superoxide anion scavenging activity of isoxazolopyridine and spirooxindole compounds was done according to the methodology described by Liu et al. [45]. The superoxide radicals were formed in 3 mL of 16 mM *Tris*-HCl buffer which contained 1 mL of 50 μM NBT solution, 1 mL of 78 μM NADH solution, and a sample solution of the newly synthesized compounds (25–400 μg/mL) in water. 1 mL of 10 μM phenazine methosulphate (PMS) solution was added to the mixture. Then the mixture was incubated at 25°C for 5 min and the absorbance at 560 nm was measured.

$$\% \text{ Inhibition} = \left[\frac{(A_0 - A_1)}{A_0}\right] \cdot 100. \quad (3)$$

2.8. Total Antioxidant Activity Assay.

The total antioxidant activity of isoxazolopyridine and spirooxindole compounds was assayed according to the thiocyanate method described by Mitsuda et al. [46]. The solution of isoxazolopyridine and spirooxindole compounds (150 μg/mL) in 2.5 mL of 0.04 M potassium phosphate buffer was added to 2.5 mL of linoleic acid emulsion in 0.04 M potassium phosphate buffer. This mixed solution (5 mL) was incubated at 37°C. For the period of incubation, 0.1 mL of the mixture was diluted with 3.7 mL of methanol at regular terms, and then 0.1 mL of 30% ammonium thiocyanate and 0.1 mL of 20 mM ferrous chloride in 3.5% hydrochloric acid were added. The absorbance was measured at 500 nm. This step was repeated every 10 h until the control reached its maximum absorbance value.

$$\text{Inhibition of lipid peroxidation} \,(\%)$$
$$= \left[\frac{(A_0 - A_1)}{A_0}\right] \cdot 100. \quad (4)$$

3-Methyl-4-phenyl-4H-indeno[1,2-b]isoxazolo[4,5-e]pyridin-5(10H)-one (4a). Red powder (EtOH), Yield (71%), m.p. 242–244°C; IR (ATR), v_{max}/cm^{-1}: 3432 (NH), 3164, 3068 (arom. CH), 2857 (aliph. CH), 1699 (C=O); ^{1}H NMR (DMSO-d_6) δ/ppm: 1.86 (s, 3H, Me), 5.11 (s, 1H, CH), 7.21 (d, 1H, J = 7.00 Hz, Ar-H), 7.29–7.46 (m, 4H, Ar-H), 7.50–7.75 (m, 4H, Ar-H), 12.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ/ppm 190.36 (C=O), 160.32 (Ar-C), 159.08 (Ar-C), 155.19 (Ar-C), 144.27 (Ar-C), 140.72 (Ar-C), 136.05 (Ar-CH), 133.39 (Ar-CH), 130.34 (Ar-CH), 129.58 (Ar-CH), 128.28 (Ar-CH), 127.84 (Ar-CH), 126.59 (Ar-CH), 123.59 (Ar-CH), 120.49 (Ar-CH), 119.22 (Ar-C), 108.28 (Ar-C), 97.40 (Ar-C), 34.48 (CH), 9.90 (Me); MS: m/z (ESI) 316.4 [M++2], 314.1 [M+]$^+$, 298.4 [M+−16], 106.0 [M+−208]. Anal. Calcd for C$_{20}$H$_{14}$N$_2$O$_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.50; H, 4.53; N, 8.86.

4-(3-Methyl-5-oxo-5,10-dihydro-4H-indeno[1,2-b]isoxazolo[4,5-e]pyridin-4-yl)benzonitrile (4b). Red powder (EtOH), Yield (76%), m.p. 257–259°C; IR (ATR) v_{max}/cm^{-1}: 3432 (NH), 3151, 3106 (arom. CH), 2997, 2920 (aliph. CH), 2231 (C≡N), 1713 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm 1.82 (s, 3H, Me), 5.09 (s, 1H, CH), 7.25 (d, 1H, J = 7.00 Hz, Ar-H), 7.36–7.56 (m, 4H, Ar-CH), 7.77–7.82 (m, 3H, Ar-H), 12.18 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ/ppm 190.20 (C=O), 160.64 (Ar-C), 158.96 (Ar-C), 155.71 (C≡N), 149.47 (Ar-C), 135.84 (Ar-C), 133.27 (Ar-C), 132.36 (Ar-CH), 132.01 (Ar-CH), 131.81 (Ar-CH), 130.52 (Ar-CH), 130.09 (Ar-CH), 129.02 (Ar-CH), 120.60 (Ar-CH), 119.43 (Ar-CH), 118.76 (Ar-C), 109.52 (Ar-C), 107.18 (Ar-C), 96.51 (Ar-C), 34.62 (CH), 9.88 (Me); MS: m/z (ESI) 338.0 [M+−1], 321.8 [M+−18], 296.6 [M+−43], 221.3 [M+−118], 138.2 [M+−201], 126.3 [M+−213]. Anal. Calcd for C$_{21}$H$_{13}$N$_3$O$_2$: C, 74.33; H, 3.86; N, 12.38. Found: C, 74.40; H, 5.82; N, 12.43.

4-(4-(Benzyloxy)phenyl)-3-metyl-4H-indeno[1,2-b]isoxazolo[4,5-e]pyridin-5(10H)-one (4c). Red powder (EtOH), Yield (78%), m.p. 285–287°C; IR (ATR) v_{max}/cm^{-1}: 3322 (NH), 3106, 3040 (arom. CH), 2985 (aliph. CH), 1704 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm 2.07 (s, 3H, Me), 4.96 (s, 1H, CH), 5.22 (s, 2H, CH$_2$), 7.17–7.44 (m, 5H, Ar-H), 7.52–7.67 (m, 4H, Ar-H), 7.75–7.97 (m, 4H, Ar-H), 12.00 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ/ppm 189.75 (C=O), 167.28 (Ar-C), 159.60 (Ar-C), 157.21 (Ar-C), 147.12 (Ar-C), 145.64 (Ar-CH), 140.67 (Ar-C), 136.95 (Ar-C), 136.27 (Ar-C), 135.89 (Ar-C), 132.68 (Ar-CH), 131.08 (Ar-CH), 130.17 (Ar-CH), 128.46 (Ar-CH), 127.92 (Ar-CH), 127.65 (Ar-CH), 123.57 (Ar-CH), 122.65 (Ar-CH), 121.59 (Ar-CH), 115.24 (Ar-CH), 114.34 (Ar-CH), 113.99 (Ar-CH), 111.89 (Ar-C), 97.54 (Ar-C), 69.45 (CH$_2$), 33.61 (CH), 12.64 (Me); MS: m/z (ESI) 421.5 [M++1], 404.2 [M+−16], 314.0 [M+−106]. Anal. Calcd for C$_{27}$H$_{20}$N$_2$O$_3$: C, 77.13; H, 4.79; N, 6.66. Found: C, 77.21; H, 4.73; N, 6.69.

4-(2,4-Difluorophenyl)-3-methyl-4H-indeno[1,2-b]isoxazolo[4,5-e]pyridin-5(10H)-one (4d). Red powder (EtOH), Yield (73%), m.p. 292–294°C; IR (ATR) v_{max}/cm^{-1}: 3377 (NH), 3101, 3052 (arom. CH), 2924 (aliph. CH), 1727 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm 1.84 (s, 3H, Me), 5.19 (s, 1H, CH), 6.98–7.02 (m, 2H, Ar-H), 7.15–7.27 (m, 2H, Ar-H), 7.33–7.57 (m, 3H, Ar-H), 12.15 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ/ppm 190.08 (C=O), 160.62 (Ar-C), 158.75 (Ar-C), 155.81 (Ar-C), 135.94 (Ar-C), 133.33 (Ar-C), 131.99 (Ar-CH), 131.55 (Ar-CH), 130.48 (Ar-CH), 127.01 (Ar-CH), 123.81 (Ar-CH), 120.58 (Ar-CH), 119.34 (Ar-CH), 111.83 (Ar-C), 111.66 (Ar-C), 106.69 (Ar-C), 103.61 (Ar-C), 96.27 (Ar-C), 27.45 (CH), 9.53 (Me); MS: m/z (ESI) 351.4 [M++1], 335.0 [M+−15], 221.1 [M+−129]. Anal. Calcd for C$_{20}$H$_{12}$F$_2$N$_2$O$_2$: C, 68.57; H, 3.45; N, 8.00. Found: C, 68.64; H, 3.48; N, 8.07.

3-Methyl-4-(thiophen-2-yl)-4H-indeno[1,2-b]isoxazolo[4,5-e]pyridin-5(10H)-one (4e). Red powder (EtOH), Yield (78%), m.p. 281–283°C; IR (ATR) v_{max}/cm^{-1}: 3336 (NH), 3120, 3047 (arom. CH), 2928 (aliph. CH), 1706 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm 1.86 (s, 3H, Me), 5.11 (s, 1H, CH), 7.20–7.27 (m, 2H, Ar-H), 7.35–7.56 (m, 3H, Ar-H), 7.65–7.83 (m, 2H, Ar-H), 12.13 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ/ppm 190.40 (C=O), 161.94 (Ar-C), 159.11 (Ar-C), 149.09 (Ar-C), 136.66 (Ar-C), 136.14 (Ar-C), 131.97 (Ar-CH), 130.40

(Ar-CH), 125.65 (Ar-CH), 123.80 (Ar-CH), 122.45 (Ar-CH), 121.98 (Ar-CH), 120.55 (Ar-CH), 119.20 (Ar-C), 107.42 (Ar-C), 96.92 (Ar-C), 37.00 (CH), 10.02 (Me); MS: m/z (ESI) 321.2 [M++1], 305.0 [M+−15], 222.0 [M+−98]. Anal. Calcd for $C_{18}H_{12}N_2O_2S$: C, 67.48; H, 3.78; N, 8.74. Found: C, 67.53; H, 3.83; N, 8.79.

3-Methyl-4-(3-phenoxyphenyl)-5H-indeno[1,2-b]isoxazolo[4, 5-e]pyridin-5-one (5f). Red powder (EtOH), Yield (72%), m.p. 279–281°C; IR (ATR) v_{max}/cm^{-1}: 3105, 3025 (arom. CH), 2986 (aliph. CH), 1709 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm 2.04 (s, 3H, Me), 7.06–7.18 (m, 3H, Ar-H), 7.20–7.61 (m, 8H, Ar-H), 7.76–7.94 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ/ppm 188.27 (C=O), 167.12 (Ar-C), 157.11 (Ar-C), 156.59 (Ar-C), 155.90 (Ar-C), 145.66 (Ar-C), 140.70 (Ar-C), 136.24 (Ar-C), 135.75 (Ar-C), 132.78 (Ar-CH), 130.08 (Ar-CH), 129.76 (Ar-CH), 124.17 (Ar-CH), 123.69 (Ar-CH), 123.55 (Ar-CH), 122.01 (Ar-CH), 121.67 (Ar-CH), 120.02 (Ar-CH), 119.53 (Ar-CH), 118.50 (Ar-CH), 111.76 (Ar-C), 12.32 (Me); MS: m/z (ESI) 405.2 [M++1], 376.2 [M+−28], 361.0 [M+−43], 312.2 [M+−92], 284.2 [M+−120]. Anal. Calcd for $C_{26}H_{16}N_2O_3$: C, 77.22; H, 3.99; N, 6.93. Found: C, 77.30; H, 3.92; N, 6.97.

4-(Furan-2-yl)-3-methyl-5H-indeno[1,2-b]isoxazolo[4,5-e]pyr-idin-5-one (5g). Red powder (EtOH), Yield (80%), m.p. 272–274°C; IR (ATR) v_{max}/cm^{-1}: 3136, 3059, 3014 (arom. CH), 2921, 2874 (aliph. CH), 1725 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm 1.84 (s, 3H, Me), 6.93–6.95 (m, 1H, Ar-H), 7.57–7.97 (m, 4H, Ar-H), 8.26–8.46 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ/ppm 189.16 (C=O), 150.75 (Ar-C), 150.46 (Ar-C), 141.69 (Ar-C), 135.82 (Ar-C), 135.55 (Ar-CH), 132.79 (Ar-CH), 124.57 (Ar-CH), 124.51 (Ar-CH), 123.69 (Ar-CH), 122.86 (Ar-CH), 122.79 (Ar-CH), 121.52 (Ar-CH), 119.37 (Ar-CH), 115.00 (Ar-C), 112.98 (Ar-C), 14.04 (Me); MS: m/z (ESI) 303.2 [M++1], 275.0 [M+−27], 220.0 [M+−82]. Anal. Calcd for $C_{18}H_{10}N_2O_3$: C, 71.52; H, 3.33; N, 9.27. Found: C, 71.58; H, 3.36; N, 9.23.

3-Methyl-4-(pyridin-2-yl)-5H-indeno[1,2-b]isoxazolo[4,5-e]pyridin-5-one (5h). Red powder (EtOH), Yield (73%), m.p. 276–278°C; IR (ATR) v_{max}/cm^{-1}: 3106, 3033 (arom. CH), 2920 (aliph. CH), 1716 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm 2.02 (s, 3H, Me), 7.60–7.72 (m, 3H, Ar-H), 7.78–7.86 (m, 2H, Ar-H), 7.99–8.80 (m, 3H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 188.27 (C=O), 167.22 (Ar-C), 157.20 (Ar-C), 149.57 (Ar-C), 149.16 (Ar-C), 144.68 (Ar-C), 140.81 (Ar-C), 136.26 (Ar-C), 136.23 (Ar-CH), 135.91 (Ar-CH), 132.89 (Ar-CH), 125.67 (Ar-CH), 124.68 (Ar-CH), 123.83 (Ar-CH), 121.89 (Ar-CH), 121.81 (Ar-CH), 111.49 (Ar-C), 12.42 (Me); MS: m/z (ESI) 314.3 [M++1], 286.0 [M+−27], 229.0 [M+−84], 216.0 [M+−97]. Anal. Calcd for $C_{19}H_{11}N_3O_2$: C, 72.84; H, 3.54; N, 13.41. Found: C, 72.91; H, 3.60; N, 13.35.

3′-Methyl-7′,8′-dihydro-5′H-spiro[indoline-3,4′-isoxazolo[5, 4-b]quinoline]-2,5′(6′H,9′H)-dione (8a) Lit. [22]. White powder (EtOH), Yield (80%), m.p. 221–223°C; IR (ATR) v_{max}/cm^{-1}: 3337, 3222 (NH), 3127, 3028 (arom. CH), 2955, 2934, 2887 (aliph. CH), 1732 (C=O), 1686 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm 1.53 (s, 3H, Me), 1.90 (dd,

2H, J_1 = 13.00 Hz, J_2 = 7.00 Hz, CH$_2$), 2.17 (ddd, 2H, J_1 = 11.00 Hz, J_2 = 6.90 Hz, J_3 = 2.70 Hz, CH$_2$), 2.64 (t, 2H, J = 6.10 Hz, CH$_2$), 6.80 (d, 1H, J = 7.70 Hz, Ar-H), 6.87 (dtd, 2H, J_1 = 8.20 Hz, J_2 = 7.30 Hz, J_3 = 1.00 Hz, Ar-H), 7.13 (td, 1H, J_1 = 7.50 Hz, J_2 = 1.50 Hz, Ar-H), 10.39 (s, 1H, NH), 11.08 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 193.70 (C=O), 178.86 (C=O), 159.51 (Ar-C), 157.08 (Ar-C), 154.15 (Ar-C), 141.40 (Ar-C), 135.99 (Ar-C), 127.73 (Ar-CH), 123.28 (Ar-CH), 121.65 (Ar-CH), 109.83 (Ar-C), 108.67 (Ar-CH), 93.80 (Ar-C), 48.73 (C), 36.79 (CH$_2$), 27.39 (CH$_2$), 20.89 (CH$_2$), 8.78 (Me); MS: m/z (ESI) 322.5 [M++1], 279.0 [M+−43], 251.0 [M+−71]. Anal. Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.36; H, 4.65; N, 13.12.

3-Methylspiro[indeno[2,1-e]isoxazolo[5,4-b]pyridine-4,3′-in-doline]-2′,5(10H)-dione (8b). Orange powder (EtOH), Yield (88%), m.p. 242–244°C; IR (ATR) v_{max}/cm^{-1}: 3434, 3349 (NH), 3149, 3115, 3085 (arom. CH), 2912 (aliph. CH), 1741 (C=O), 1710 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm ^{1}H NMR (DMSO-d_6): δ/ppm 1.57 (s, 3H, Me), 6.70–7.10 (m, 4H, Ar-H), 7.25–7.93 (m, 4H, Ar-H), 10.63 (s, 1H, NH), 12.53 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ/ppm 189.18 (C=O), 175.68 (C=O), 161.52 (Ar-C), 157.71 (Ar-C), 156.41 (Ar-C), 142.71 (Ar-C), 142.06 (Ar-C), 136.14 (Ar-CH), 132.31 (Ar-C), 130.83 (Ar-CH), 128.78 (Ar-CH), 128.13 (Ar-C), 122.67 (Ar-CH), 121.49 (Ar-CH), 120.85 (Ar-CH), 119.69 (Ar-CH), 109.85 (Ar-CH), 106.19 (Ar-C), 95.65 (Ar-C), 52.42 (C), 8.90 (Me); MS: m/z (ESI) 354.1 [M+−1], 311.08 [M+−43], 284.4 [M+−71]. Anal. Calcd for $C_{21}H_{13}N_3O_3$: C, 70.98; H, 3.69; N, 11.83. Found: C, 71.05; H, 3.75; N, 11.87.

3-Methyl-5H-spiro[benzo[g]isoxazolo[5,4-b]quinoline-4,3′-indoline]-2′,5,10(11H)-trione (8c). Dark purple powder (EtOH), Yield (90%), m.p. 250–252°C; IR (ATR) v_{max}/cm^{-1}: 3376, 3280 (NH), 3178, 3072, 3014 (arom. CH), 2922 (aliph. CH), 1736 (C=O), 1699 (C=O), 1672 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm 1.62 (s, 3H, Me), 6.89–7.24 (m, 4H, Ar-H), 7.49–7.84 (m, 4H, Ar-H), 10.74 (s, 1H, NH), 11.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ/ppm 180.99 (C=O), 179.12 (C=O), 178.32 (C=O), 169.42 (Ar-C), 159.74 (Ar-C), 157.09 (Ar-C), 155.32 (Ar-C), 141.10 (Ar-C), 135.97 (Ar-C), 135.08 (Ar-CH), 133.44 (Ar-CH), 130.02 (Ar-C), 128.55 (Ar-CH), 126.11 (Ar-CH), 125.83 (Ar-CH), 124.22 (Ar-CH), 122.08 (Ar-CH), 116.06 (Ar-C), 109.17 (Ar-CH), 93.90 (Ar-C), 49.80 (C), 8.86 (Me); MS: m/z (ESI) 384.1 [M++1], 341.0 [M+−43], 325.0 [M+−58], 312.0 [M+−71], 297.2 [M+−86]. Anal. Calcd for $C_{22}H_{13}N_3O_4$: C, 68.93; H, 3.42; N, 10.96. Found: C, 69.05; H, 3.53; N, 11.85.

3-Methyl-6,7-dihydrospiro[cyclopenta[e]isoxazolo[5,4-b]pyr-idine-4,3′-indoline]-2′,5(8H)-dione (8d). White powder (EtOH), Yield (76%), m.p. 216–218°C; IR (ATR) v_{max}/cm^{-1}: 3340, 3220 (NH), 3125, 3025 (arom. CH), 2967, 2936, 2883 (aliph. CH), 1735 (C=O), 1689 (C=O); ^{1}H NMR (DMSO-d_6): δ/ppm 1.52 (s, 3H, Me), 2.33 (d, 2H, J = 4.90 Hz, CH$_2$), 2.77 (br s, 2H, CH$_2$), 6.83–7.00 (m, 3H, Ar-H), 7.20 (t, 1H, J = 7.30 Hz, Ar-H), 10.58 (s, 1H, NH), 11.69 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ/ppm 199.32 (C=O), 177.45 (C=O), 166.86 (Ar-C), 161.74 (Ar-C), 157.46 (Ar-C), 141.44 (Ar-C),

Table 1: Optimization of (±)-CSA catalyst loading in the synthesis of compound **4a**.

(±)-CSA (mol%)	Temperature (°C)	Conditions	Time (min)	Yield (%)[a]
—	40	US	300	35
5	40	US	180	52
5	70	US	120	58
10	70	US	120	65
15	70	US	120	71
20	70	US	120	72
20	78	Δ/reflux	360	51

[a]Isolated yield.

Table 2: Synthesis of isoxazolopyridine derivatives in the presence of catalytic amount of (±)-CSA.

Product	Ar	Time (min)	Yield (%)[a]
4a	Phenyl	120	71
4b	4-Cyanophenyl	120	76
4c	4-Benzyloxyphenyl	120	78
4d	2,4-Difluorophenyl	120	73
4e	Thiophen-2-yl	120	78
5f	3-Phenoxyphenyl	120	72
5g	Furan-2-yl	120	80
5h	Pyridine-2-yl	120	73

[a]Isolated yield.

133.79 (Ar-C), 128.44 (Ar-CH), 124.24 (Ar-CH), 122.03 (Ar-CH), 114.12 (Ar-C), 109.16 (Ar-CH), 94.37 (Ar-C), 46.85 (C), 33.55 (CH_2), 24.12 (CH_2), 8.84 (Me); MS: m/z (ESI) 308.3 [M++1], 265.0 [M+−43], 238.0 [M+−70]. Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.52; H, 4.32; N, 13.70.

3. Results and Discussion

Initially, the three-component reaction of benzaldehyde (1.00 mmol), indan-1,3-dione (1.00 mmol), and 5-amino-3-methylisoxazole (1.00 mmol) was examined under ultrasonic irradiation without a catalyst at 40°C in 5 mL EtOH. The formation of compound **4a** was completed in 300 minutes with a yield of 35%. When the same reaction was examined in the presence of 5 mol% (±)-CSA at 40°C under ultrasound irradiation, the product was obtained with a yield of 52% in 180 minutes (Table 1). Increasing the temperature to 70°C increased the yield to 58% and the reaction was completed in 120 minutes. In order to observe the effect of the amount of (±)-CSA on the reaction, experiments using different amounts of catalyst were performed (Table 1). The best result was obtained by carrying out the reaction using 15 mol% of (±)-CSA at 70°C under ultrasonic irradiation.

Using the best optimized conditions, several isoxazolopyridine derivatives were synthesized at 70°C in the presence of 15 mol% (±)-CSA catalyst in EtOH under ultrasonic irradiation (Scheme 1). The results are summarized in Table 2.

It is important to point out the fact that for some unknown reasons the reaction involving 5-amino-3-methylisoxazole, indan-1,3-dione, and aromatic aldehydes gave isoxazolopyridines **5** or their dihydro derivatives **4** independently of the substituent carried by the aldehydes.

Then the spirooxindole derivatives were synthesized via multicomponent reaction of 5-amino-3-methylisoxazole, isatin, and β-diketones in the presence of (±)-CSA catalyst under ultrasonic irradiation (Scheme 2). The best yields were observed in the presence of 10 mol% (±)-CSA in EtOH under ultrasonic irradiation at 70°C (Table 3).

The structure of the novel generated compounds was confirmed by Fourier transform-infrared (FTIR), ^{1}H, ^{13}C, APT NMR techniques, and mass spectroscopy. In the [1]H

NMR spectra of the isoxazolopyridines **4a–e**, benzilic C-H proton resonated near δ 5.06–5.30 and in the ^{13}C NMR spectra, the benzilic C-H carbon resonated near δ 27–37. The mass spectra of all novel compounds exhibited the expected molecular ion peak.

Generally, efficient HAT agents are the compounds which show high hydrogen atom donating ability, and they usually have low heteroatom-H bond dissociation energies. Abstraction of hydrogen from these compounds leads to C-centered radicals which are stabilized by resonance or the generation of sterically hindered radicals [47]. In this study, the antioxidant activity of the synthesized compounds **4a–e**, **5f-g**, and **8a–d** was examined for free radical scavenging activity, reducing activity, metal chelating activity, superoxide scavenging activity, and total antioxidant activity.
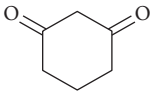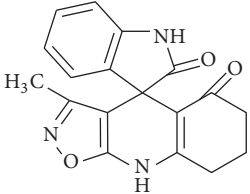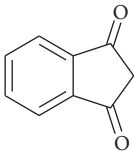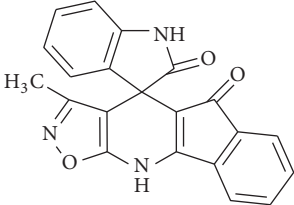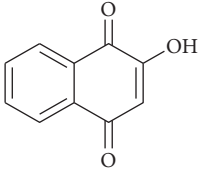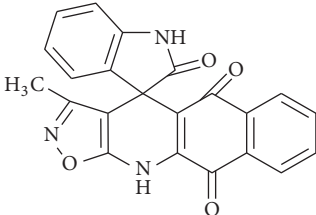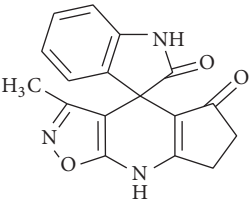
The DPPH• scavenging effect of isoxazolopyridine and spirooxindole compounds (**4a–e**, **5f–h**, and **8a–d**) and standards (BHA, BHT, Trolox, and Resorcinol) was studied and compounds **4a** and **8a** were found to be the ones with the most potential activity (Figure 1). These results indicate that the new synthesized compound had a moderate effect on the scavenging free radical. A higher DPPH radical scavenging activity is associated with a lower EC_{50} value.

As indicated in Figure 2, the reducing power of compounds **5f**, **4c**, **8a**, and **4b** at 400 μg/mL concentration is higher than the other synthesized compounds and the reducing power was increased by increasing the concentration.

The metal chelating activity for the ferrous ion of the new synthesized compounds was assayed by the inhibition of the red-colored ferrozine/$FeCl_2$ complex. EDTA, Trolox, and BHT were used as standard compounds. The isoxazolopyridine and spirooxindole compounds showed moderate to good metal chelating activities at 25, 50, 100, 200, and 400 μg/mL concentrations (Figure 3). Compound **4b** exhibited the highest chelating activity among the tested compounds at 400 μg/mL.

The superoxide scavenging activity of isoxazolopyridine and spirooxindole compounds was compared with the same concentrations of BHT, Trolox, and BHA. None of the compounds showed greater antioxidant activity than the standards. However, compounds **5g**, **5h**, **4e**, and **4b** exhibited higher inhibition than the other synthesized compounds (Figure 4).

TABLE 3: Synthesis of spirooxindole derivatives in the presence of catalytic amount of (±)-CSA.

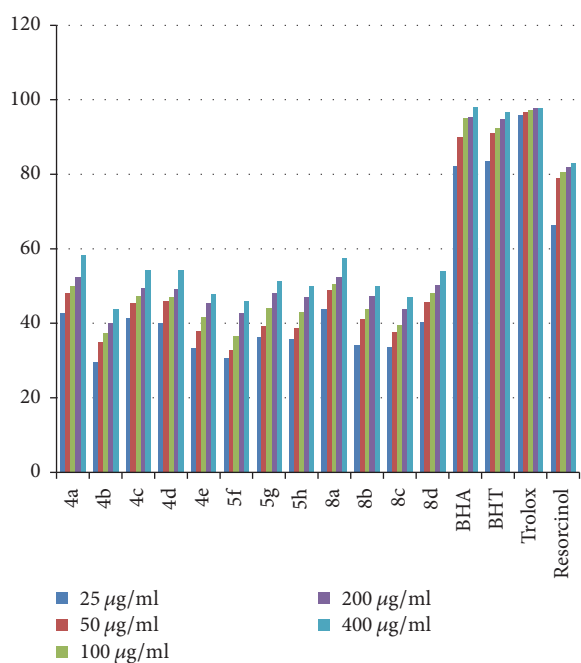| Entry	β-Diketone	Product	Time (min)	Yield (%)[a]
a			30	80 [22]
b			30	88
c			30	90
d			30	76

[a]Isolated yield.

FIGURE 1: DPPH radical scavenging activity of isoxazolopyridine and spirooxindole compounds. BHA, BHT, Trolox, and Resorcinol were used as reference.
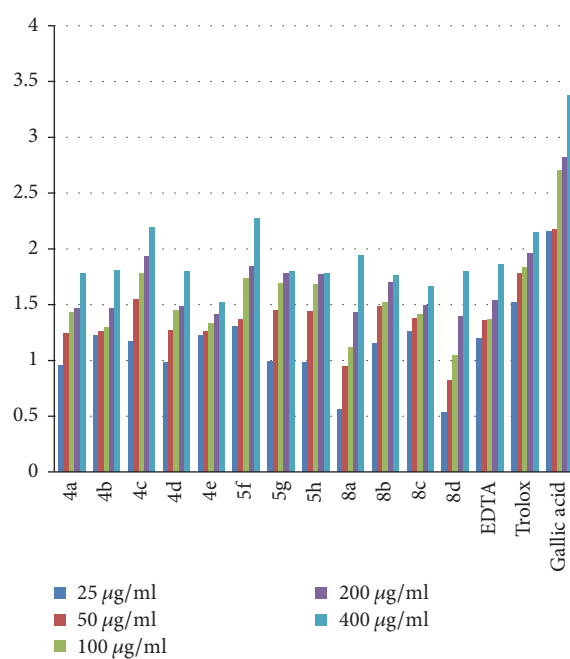

FIGURE 2: Reducing power of isoxazolopyridine and spirooxindole compounds. EDTA, Trolox, and Gallic acid were used as reference.
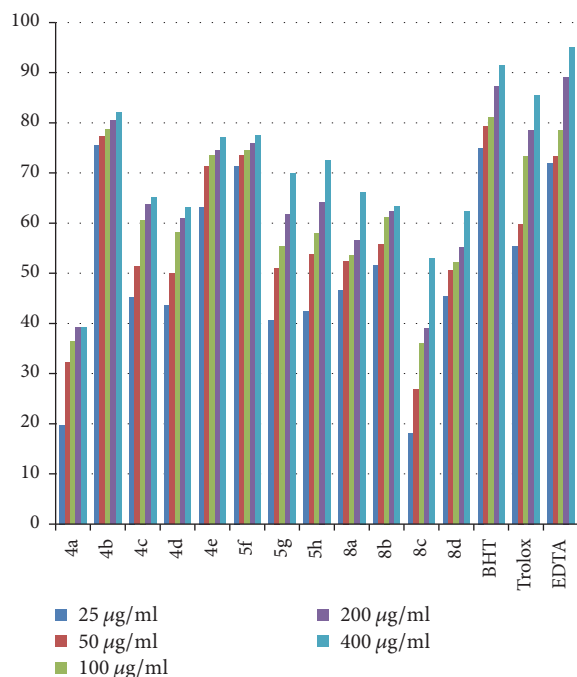
FIGURE 3: Metal chelating activity of isoxazolopyridine and spirooxindole compounds. BHT, Trolox, and EDTA were used as reference.
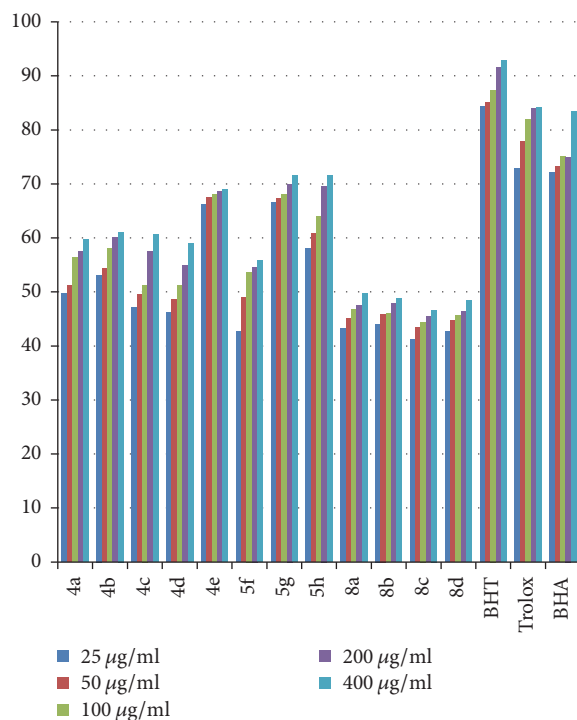

FIGURE 4: Superoxide scavenging activity of isoxazolopyridine and spirooxindole compounds. BHT, Trolox, and BHA were used as reference.

Total antioxidant activity of the isoxazolopyridine and spirooxindole compounds was assayed by thiocyanate methodology. Compounds **4b** and **8a** showed effectual
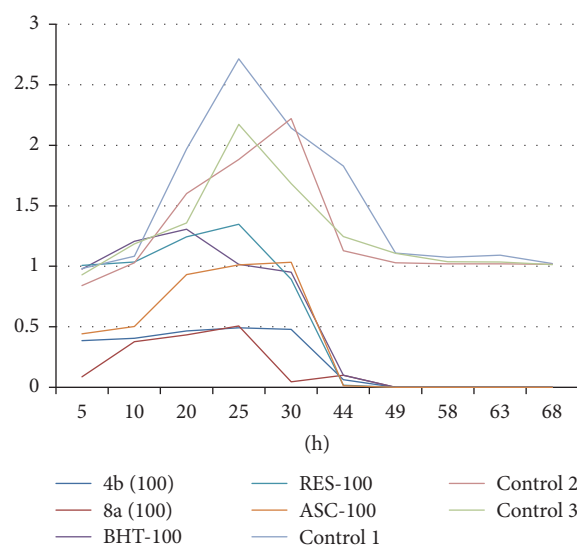
FIGURE 5: Total antioxidant activities of isoxazolopyridine and spirooxindole compounds. BHT, Resorcinol, and Ascorbic acid were used as reference.

antioxidant activity (Figure 5). The results indicated that compound **4b** had stronger total antioxidant activity than BHT, Resorcinol, and Ascorbic acid at the same concentration (100 μg/mL).

4. Conclusions

In conclusion, new isoxazolopyridine and spirooxindole compounds were synthesized via one-pot three-component reaction of 5-amino-3-methylisoxazole, indan-1,3-dione, and aromatic aldehydes and reaction of 5-amino-3-methylisoxazole, isatin, and β-diketones in the presence of ($\pm$)-camphor-10-sulfonic acid under ultrasound-promoted conditions. This procedure provided a practical, simple, and efficient way to obtain isoxazolopyridines and spirooxindoles in moderate to high yields. The antioxidant activities of these compounds were determined. Compounds **4b**, **4e**, **5f**, **5g**, **5h**, and **8a** exhibited higher activities.

Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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