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Heterocyclization of Aromatic Amino Acids: Novel Syntheses and Antibacterial Activity of Fused, Non-fused, and Spiro Polyheterocyclic Derivatives

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Abstract—Commercially available *p*-aminobenzoic acid was used as a precursor for the synthesis of novel fused, non-fused, and spiro polyheterocyclic derivatives bearing indene, imidazole, pyrazole, and/or triazine nucleus via addition to simple and accessible reagents such as ninhydrin, *o*-phenylenediamine, and carbon disulfide. The experimental procedures were straightforward and simple, the products were isolated in 15–86% yields, and. their structure was confirmed by spectroscopic data. The synthesized compounds were evaluated for their antibacterial activity against some Gram-positive and Gram-negative bacteria.

Keywords: amino acid, imidazole, spiro compounds, indenopyrrole, thiazole, antibacterial activity

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INTRODUCTION

In recent years, indeno-fused heterocycles have attracted considerable attention because of their therapeutic and synthetic importance and broad spectrum of biological activity [13]. Like indenopyrrole derivative (Fig. 1) [4], many spiroheterocyclic systems have shown good biological activities [5, 6]. Thiazoles have been used in improvement of drugs for the treatment of allergies [7], hypertension [8], inflammation [9], schizophrenia [10], bacterial [11] and HIV infections [12], as hypnotics [13], and more recently for the treatment of pain [14]. 1,2,4-Triazines possess a broad spectrum of biological properties, including antifungal [15], anti-HIV [16], antitumor [17], neuroprotective [18], antimalarial [19], antibacterial [20], antiproliferative [21], and CRF1 receptor antagonistic [22] activities. This invigorated our enthusiasm for the synthesis of novel polyheterocyclic derivatives in continuation of our past work [23].

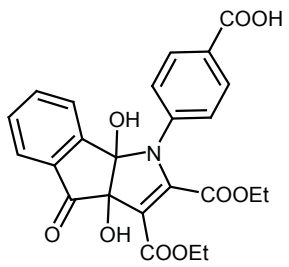


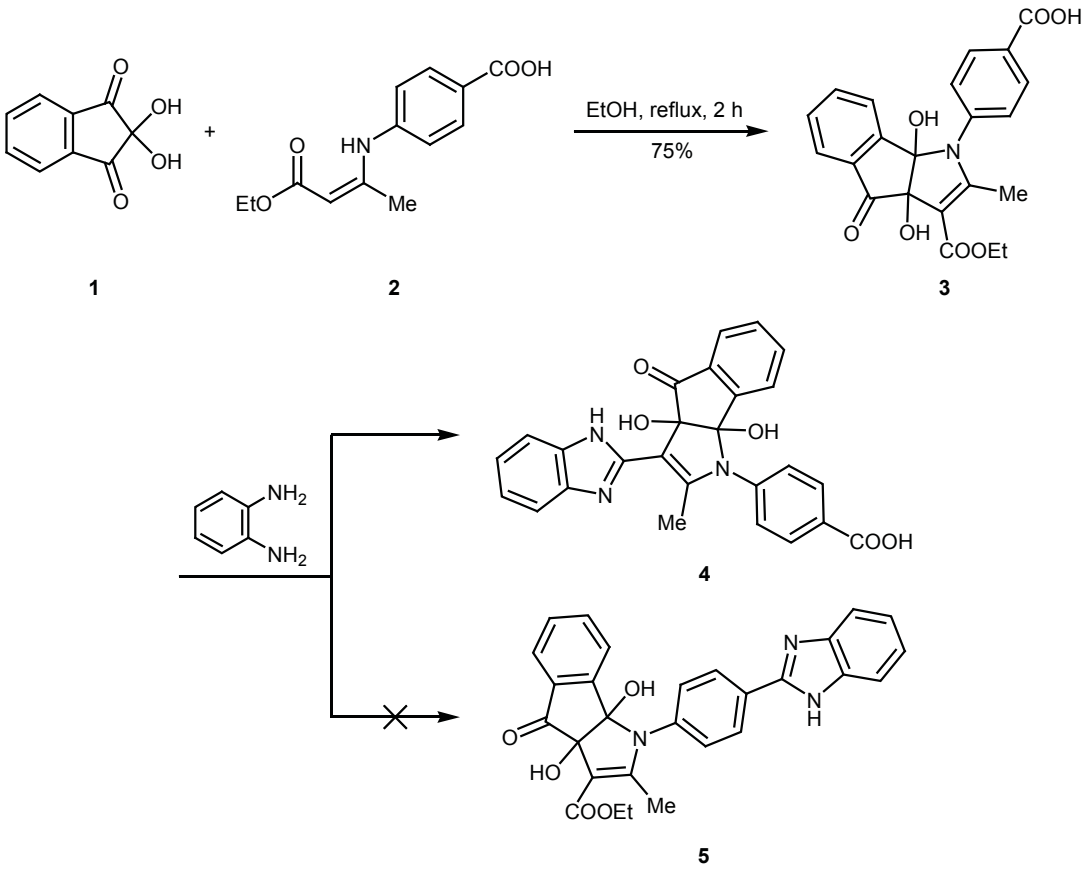
Fig. 1. An example of biologically active indenopyrrole derivative.

Aromatic amino acids are precursors for reactive intermediates that are utilized for further heterocyclization resulting in organic systems of potential biological activity. Ninhydrin also bears suitable functionalities for further cyclization [24–27]. The present article reports the synthesis of non-fused and fused polyheterocyclic systems containing indene, imidazole, pyrazole, and/or triazine rings from amino acid and simple and available laboratory reagents [23, 28, 29].

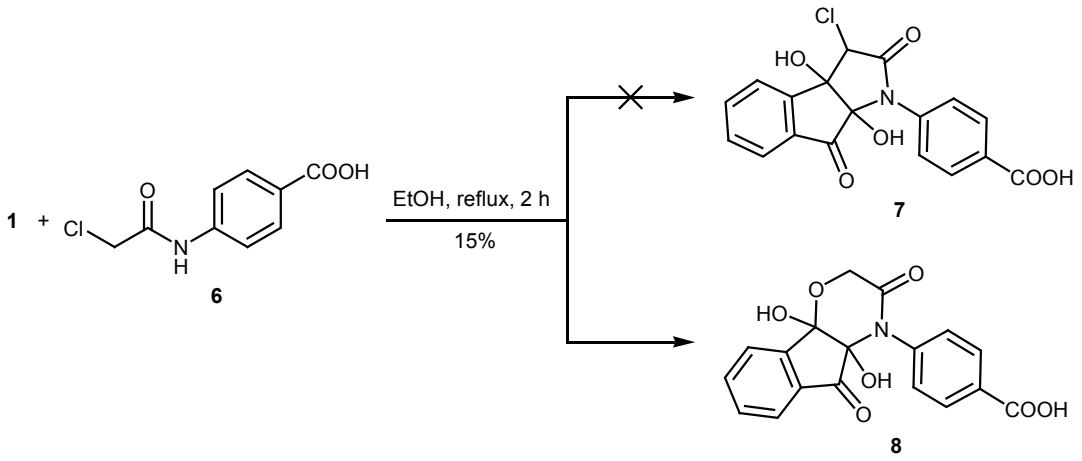
RESULTS AND DISCUSSION

The condensation of ninhydrin (**1**) with enaminone **2**, followed by intramolecular addition of the enamino carbon atom to the carbonyl group produced pyrroloindene **3** (Scheme 1). The structure assigned for **3** was established from analytical and spectral data. The IR spectrum of **3** showed a characteristic peak around 3380 cm^{-1} due to OH group and a broad band around 1691 cm^{-1} for C=O function. The ^1H NMR spectrum

Scheme 1.



Scheme 2.



showed a downfield carboxylic proton signal at δ 13.22 ppm, aromatic multiplet at δ 7.35–7.98 ppm, and two OH signals at δ 6.56 and 5.86 ppm; signals from the ester ethyl and methyl protons were also present. The ^{13}C NMR spectrum of **3** showed three downfield signals at δ_C 198.57, 167.33, and 165.63 ppm for the three carbonyl carbons. The condensation of **3** with *o*-phenylenediamine selectively involved the ester group to furnish compound **4**, whereas the carboxy group remained intact (no alternative product **5** was detected; Scheme 1). The structure of **4** was supported by the presence of carboxylic proton signal and the absence of ethoxy protons; the NH signal of the imidazole ring was located at a low field. The ^{13}C NMR spectrum of **4** contained two downfield signals at δ_C 189.71 and 167.21 ppm for two carbonyl carbons.

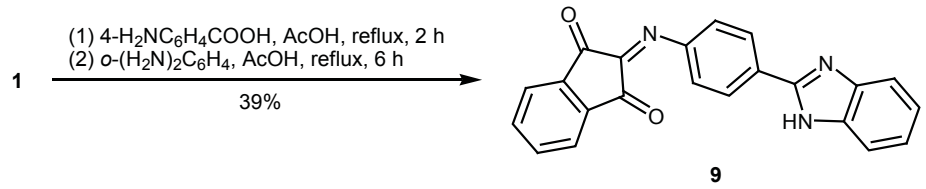
Chloroacetamide **6** underwent oxazine cyclization with compound **1** via alkylation followed by addition of the imino group to carbonyl carbon affording indenooxazine **8**, but no cycloaddition product **7** was detected (Scheme 2). The IR spectrum of **8** displayed peaks at 3401 (broadened) and 1685 cm^{-1} for OH and C=O groups, respectively. The ^1H NMR spectrum of **8** contained downfield signals at δ 12.76 and 10.41 ppm for COOH and OH, and three carbonyl carbon signals were observed in its ^{13}C NMR spectrum at δ_C 189.71, 167.3, and 165.59 ppm.

p-Aminobenzoic acid reacted with ninhydrin through elimination of two water molecules, and the subsequent acid-catalyzed intermolecular cyclocondensation with *o*-phenylenediamine afforded 2-iminoindandione **9** (Scheme 3). Compound **9** showed stretching frequencies at 3435, 1727 and 1603 cm^{-1} due to NH, C=O and C=N groups, respectively. The ^1H NMR spectrum of **9** lacked signals for COOH and OH groups but contained a downfield D_2O-exchangeable signal at δ 7.71 ppm for imidazole NH. The ^{13}C NMR spectrum of compound **9** displayed one carbonyl carbon signal at δ_C 189.77 ppm due to its symmetric structure.

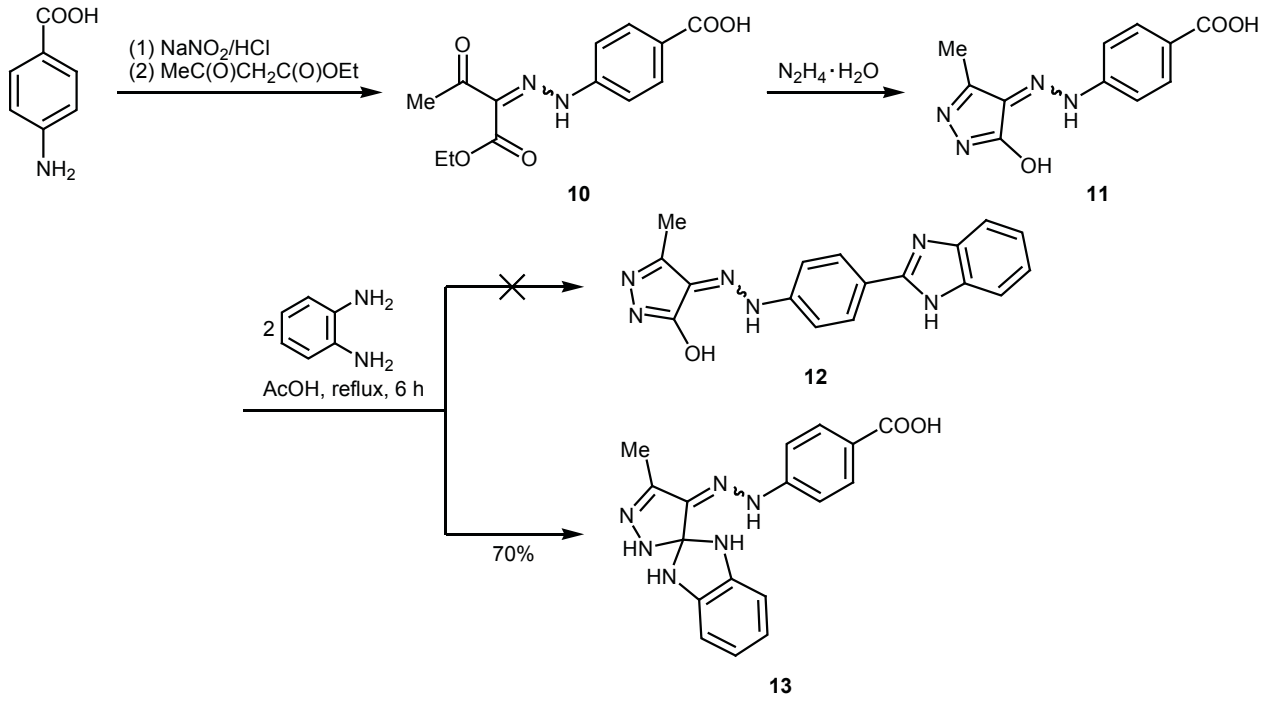
Coupling of ethyl acetoacetate with the diazonium salt derived from *p*-aminobenzoic acid (**2**) resulted in hydrazone **10**. The 1,3-bielectophilic system of **10** underwent pyrazole cyclization with hydrazine to give 3-hydroxypyrazole **11**. Acid-catalyzed condensation of **11** with 2 equiv of *o*-phenylenediamine yielded spiro compound **13** while no reaction at the carboxy group to form **12** was observed (Scheme 4). The structure of **13** was supported by the presence of D_2O exchangable signals of COOH and four NH groups at δ 13.30, 8.09, 8.07, 4.37, and 3.49 ppm. The carbonyl carbon signal of **13** was located at δ_C 167.21 ppm in the ^{13}C NMR spectrum.

Treatment of potassium dithiocarbamate **14** with chloroacetic acid resulted in alkylation of the sulfur atom, and subsequent intramolecular nucleophilic attack of the nitrogen atom on the electrophilic carbonyl carbon with elimination of water afforded dihydro-

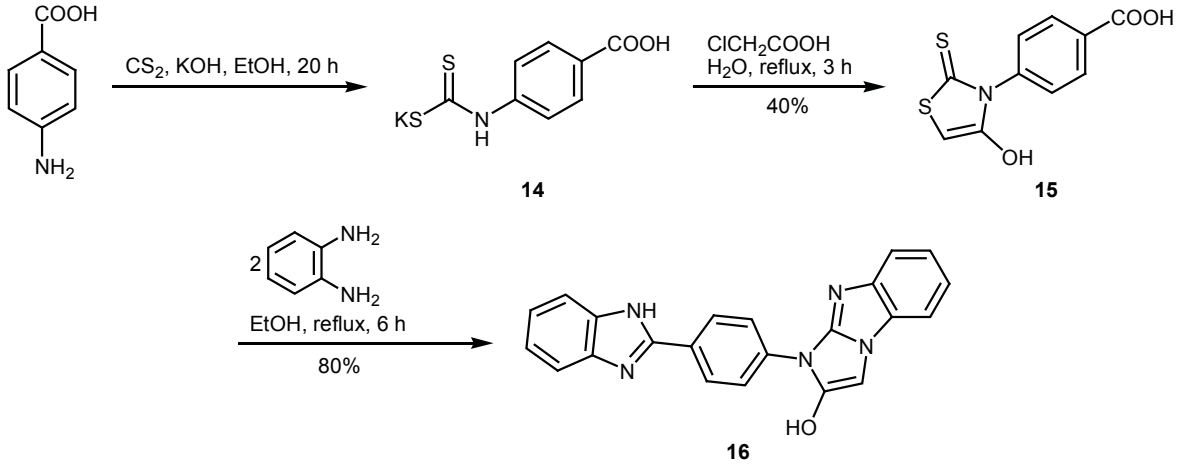
Scheme 3.



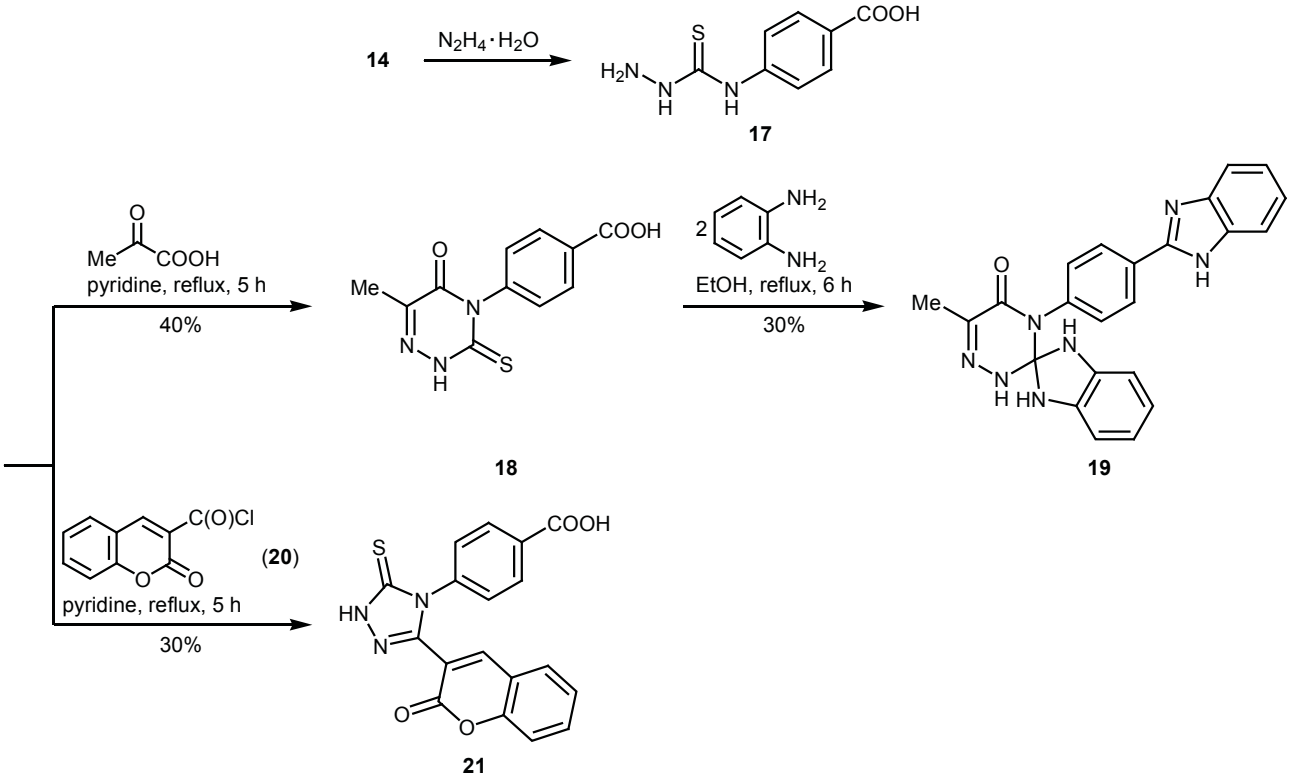
Scheme 4.



Scheme 5.



Scheme 6.



thiazole **15** (Scheme 5). Compound **15** showed stretching frequencies at 3311, 1671, and 1605 cm^{-1} for OH, C=O, and C=S groups, respectively. The ^1H NMR spectrum of **15** displayed downfield signals at δ 12.8 and 10.22 ppm for COOH and OH protons. The reaction of **15** with 2 equiv of *o*-penylenediamine involved both condensation at the carboxy group and recyclization of the dihydrothiazole ring to furnish imidazobenzimidazole derivative **16**. Compound **16** displayed IR frequencies at 3441 and 1608 cm^{-1} for NH and C=N, respectively. The OH and NH protons of **16** resonated in the ^1H NMR spectrum at δ 6.98 and 6.97 ppm (D_2O exchangeable).

Treatment of compound **14** with hydrazine hydrate gave thiosemicarbazide **17** which reacted with pyruvic acid to produce 1,2,4-triazine **18** (Scheme 6) which displayed IR bands at 3437 (OH), 1673 (C=O), 1600 (C=O), and 1292 cm^{-1} (C=S). The ^1H NMR spectrum of **18** showed two downfield signals at δ 12.65 and 10.20 ppm for COOH and NH protons. The reaction of

18 with 2 equiv of *o*-phenylenediamine involved both the thione and carboxylic acid functionality, leading to spiro triazine derivative **19**. Compound **19** showed peaks at 3434, 1692, and 1610 cm^{-1} for NH, C=O, and C=N stretchings, respectively, in the IR spectrum. Four NH protons of **19** resonated in the ^1H NMR spectrum of **19** at δ 8.62, 8.33, 8.03, 6.85 ppm (D_2O exchangeable), and the C=O signal was located at δ_C 167.21 ppm in the ^{13}C NMR spectrum.

2-Oxochromene-3-carbonyl chloride (**20**) reacted with thiosemicarbazide **17** via hydrazinolysis followed by intramolecular cyclodehydration to form triazole derivative **21** (Scheme 6). The OH, NH, C=O, and C=S groups of **21** gave rise to IR absorption bands at 3457, 3309, 1698, 1246 cm^{-1} respectively. The COOH and NH proton signals of **21** were observed at δ 12.39 and 10.86 ppm, respectively, in the ^1H NMR spectrum. The ^{13}C NMR spectrum showed signals at δ_C 167.31, 163.03, 160.55 ppm due to C=S and two C=O groups, respectively.

Compounds **8, 9, 13, 16** and **19** were investigated in vitro for antibacterial activity against Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) utilizing the disc diffusion method [30] at a concentration of 1 mg/mL. DMSO was used as solvent, and ciprofloxacin was used as standard antibacterial agent. The results are given in Table 1 (zone of inhibition of bacterial growth). Compounds **8**, **16**, and **19** showed a high antibacterial activity and, while compounds **9** and **13** were moderately active against the tested bacteria.

EXPERIMENTAL

The melting points were measured using an Electrothermal IA 9100 apparatus with open capillary tubes and are uncorrected. All experiments were carried out using dry solvents. Thin-layer chromatography (TLC) was performed on Silica gel 60 F254 plates (Merck) with detection by UV light. The products were purified by crystallization. The IR spectra (KBr disc) were recorded on a Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded at a Varian Mercury VX-300 spectrometer at 300 and 75.4 MHz, respectively, using DMSO-d_6 as a solvent and TMS as an internal standard. The analytical data and in vitro antimicrobial activities were obtained from the Microanalysis Center at the Cairo University, Giza, Egypt.

Compounds **2, 6, 10, 11** and **17** were prepared by the procedures described in the literature [23, 28, 29].

4-[3-(Ethoxycarbonyl)-3a,8b-dihydroxy-2-methyl-4-oxo-3a,4-dihydroindeno[1,2-*b*]pyrrol-1(8b*H*)-yl]benzoic acid (3). A mixture of ninhydrin (**1**, 4.0 mmol) and compound (**2**, 4.0 mmol) in 10 mL of ethanol was refluxed for 2 h. The mixture was cooled and poured into ice-cold water, and the product was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 1.26 g (75%), pink crystals, mp 160–164°C. IR spectrum, ν, cm^{-1}: 3654 (OH), 3380 (OH), 3257 (OH), 1691 (C=O), 1593 (C=O), 1526 (C=O). ^1H NMR spectrum, δ, ppm: 13.22 s (1H, COOH), 7.35–7.98 m (8H, H_{arom}), 6.56 s (1H, OH), 5.86 s (1H, OH), 4.02 q (2H, CH_2, J = 4.5 Hz), 2.01 s (3H, CH_3), 1.01 t (3H, CH_3, J = 4.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 198.57, 167.33, 165.63 (C=O); 158.91, 130.65, 125.27, 123.68 (C_6H_4); 147.67, 135.44, 135.25, 130.34, 130.28, 130.23, 98.82, 84.76 (indene); 141.18, 96.01 (pyrrole); 58.74, 14.99 (CH_2CH_3); 14.83 (CH_3). Found, %: C 64.41; H 4.60; N 3.35. $C_{22}H_{19}NO_7$. Calculated, %: C 64.54; H 4.68; N 3.42.

4-[3-(1*H*-benzimidazol-2-yl)-3a,8b-dihydroxy-2-methyl-4-oxo-3a,4-dihydroindeno[1,2-*b*]pyrrol-1(8b*H*)-yl]benzoic acid (4). A mixture of compound **3** (1.0 mmol) and *o*-phenylene diamine (1.0 mmol) in 10 mL of ethanol was refluxed for 6 h. The mixture

Table 1. In vitro antibacterial activity of compounds **8**, **9**, **13**, **16**, and **19** (inhibition zone diameter, mm/mg sample)

Compound no.	*Bacillus subtilis*	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
8	22	24	23	28
9	13	14	15	12
13	11	12	10	11
16	21	22	23	21
19	20	21	23	20
Control (DMSO)	–	–	–	–
Ciprofloxacin (reference drug)	19	22	28	24

was cooled and poured into ice-cold water, and the product was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 0.23 g (86%), black powder, mp 178–180°C. IR spectrum, ν, cm^{-1}: 3758 (OH), 3429 (OH, NH), 3058 (OH), 1685 (C=O), 1605 (C=O), 1548 (C=N). ^1H NMR spectrum, δ, ppm: 12.43 s (1H, COOH), 8.65 s (1H, NH), 7.81–8.10 m (12H, H_{arom}), 7.11 s (1H, OH), 3.46 s (1H, OH), 1.22 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 189.71 (C=O), 167.21 (C=O); 156.85, 131.39, 124.64, 120.51 (C_6H_4); 150.19, 133.21, 132.87, 137.38, 129.79, 122.70, 121.42, 117.84 (indene); 142.55, 118.92 (pyrrole); 142.26, 141.36, 137.02, 130.79 (imidazole); 14.66 (CH_3). Found, %: C 68.69; H 4.14; N 9.18. $C_{26}H_{19}N_3O_5$. Calculated, %: C 68.87; H 4.22; N 9.27.

4-[4a,9b-Dihydroxy-3,5-dioxo-2,3,4a,5-tetrahydroindeno[1,2-*b*][1,4]oxazin-4(9b*H*)-yl]benzoic acid (8). A mixture of ninhydrin (**1**, 7.0 mmol) and compound **6** (7.0 mmol) in 10 mL of ethanol was refluxed for 2 h. The mixture was cooled and poured into ice-cold water, and the product was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 0.5 g (15%), pink crystals, mp 218–222°C. IR spectrum, ν, cm^{-1}: 3401 (OH), 3278 (OH), 3206 (OH), 1685 (C=O), 1603 (C=O). ^1H NMR spectrum, δ, ppm: 12.76 s (1H, COOH), 10.41 s (1H, OH), 7.66–7.89 m (8H, H_{arom}), 4.26 s (1H, OH), 3.32 s (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.71 (C=O), 167.30 (C=O), 165.59 (C=O); 150.28, 141.18, 135.44, 135.25, 130.65, 130.23, 123.68, 113.03 (indene); 142.93, 130.34, 130.28, 125.27 (C_6H_4); 44.05 (OCH_2). Found, %: C 60.76; H 3.58; N 3.86. $C_{18}H_{13}NO_7$. Calculated, %: C 60.85; H 3.69; N 3.94.

2-{[4-(1*H*-benzimidazol-2-yl)phenyl]imino}-1*H*-indene-1,3(2*H*)-dione (9). A mixture of ninhydrin (**1**, 1.5 mmol) and 4-aminobenzoic acid (1.5 mmol) in 10 mL of acetic acid was refluxed for 2 h. *o*-Phenylenediamine (1.5 mmol) was then added, and the mixture was refluxed for 6 h, cooled, and poured into ice-cold water. The product was filtered off, washed with water, dried, and recrystallized from acetic acid. Yield 0.19 g (39%), green crystals, mp 210–212°C. IR spectrum, ν, cm^{-1}: 3435 (NH), 1727 (C=O), 1603 (C=N). ^1H NMR spectrum, δ, ppm: 7.72–8.06 m (12H, H_{arom}), 7.71 s (1H, NH, D_2O-exchangeable). ^{13}C NMR spectrum, δ_C, ppm: 189.77 (2C, C=O); 156.92, 141.42, 132.91, 131.43 (imidazole); 150.28, 137.42, 137.10, 129.83 (C_6H_4); 142.60, 142.30, 133.24, 130.83 (indene). Found, %: C 75.09; H 3.65; N 11.87. $C_{22}H_{13}N_3O_2$. Calculated, %: C 75.20; H 3.73; N 11.96.

4-{2-[5′-Methyl-1,3-dihydrospiro[benzimidazole-2,3′-pyrazol]-4′(2′*H*)-ylidene]hydrazinyl}benzoic acid (13). A mixture of compound **11** (1.0 mmol) and *o*-phenylenediamine (1.0 mmol) in 10 mL of acetic acid was refluxed for 6 h. The mixture was cooled and poured into ice-cold water, and the product was filtered off, washed with water, dried, and recrystallized from acetic acid. Yield 0.03 g (70%), yellow crystals, mp 288–290°C. IR spectrum, ν, cm^{-1}: 3767 (OH), 3435 (NH), 1671 (C=O), 1606 (C=N). ^1H NMR spectrum, δ, ppm: 13.30 s (1H, COOH, D_2O exchangeable), 8.09 s (1H, NH, D_2O exchangeable), 8.07 s (1H, NH, D_2O exchangeable), 7.25–7.42 m (8H, H_{arom}), 4.37 s (1H, NH, D_2O exchangeable), 3.49 s (1H, NH, D_2O exchangeable), 1.24 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 167.21 (C=O); 147.45, 61.07 (pyrazole); 145.50, 130.21, 127.04, 115.69 (C_6H_4); 131.46, 126.03, 115.76 (imidazole); 14.66 (CH_3). Found, %: C 60.63; H 4.69; N 24.91. $C_{17}H_{16}N_6O_2$. Calculated, %: C 60.71; H 4.79; N 24.99.

4-[4-Hydroxy-2-sulfanylidene-1,3-thiazol-3(2*H*)-yl]benzoic acid (15). Carbon disulfide (14.0 mmol) was added dropwise to an ice-cold solution of KOH (14.0 mmol) in 20 mL of absolute ethanol containing *p*-aminobenzoic acid (14.0 mmol). The mixture was stirred at room temperature for 20 h, chloroacetic acid (14.0 mmol) and 5 mL of water were added to the resulting suspension of potassium salt **14**, and the mixture was refluxed for ~3 h. It was then diluted with 50 mL of water and acidified with aqueous HCl, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 0.7 g (40%), yellow crystals, mp 248–252°C. IR spectrum, ν, cm^{-1}: 3438 (OH), 3311 (OH), 1671 (C=O), 1605 (C=S). ^1H NMR spectrum, δ, ppm: 12.80 s (1H, COOH), 10.22 s (1H, OH), 7.63–7.84 m (4H, H_{arom}), 3.34 s (1H, =CH). Found, %: C 47.34; H 2.71; N 5.45. $C_{10}H_7NO_3S_2$. Calculated, %: C 47.42; H 2.79; N 5.53.

1-[4-(1*H*-Benzimidazol-2-yl)phenyl]-1*H*-imidazo-[1,2-*a*]benzimidazol-2-ol (16). A mixture of compound **15** (1.0 mmol) and *o*-phenylenediamine (2.0 mmol) in 10 mL of ethanol was refluxed for 6 h. The mixture was cooled and poured into ice-cold water, and the product was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 0.65 g (80%), green crystals, mp 182–184°C. IR spectrum, ν, cm^{-1}: 3441 (NH), 2910 (OH), 1608 (C=N). ^1H NMR spectrum, δ, ppm: 7.00–7.79 m (12H, H_{arom}), 6.98 s (1H, OH, D_2O exchangeable), 6.97 s (1H, NH, D_2O exchangeable), 4.17 s (1H, =CH). Found, %: C 71.23; H 4.06; N 19.11. $C_{22}H_{15}N_5O$. Calculated, %: C 72.32; H 4.14; N 19.17.

4-[6-Methyl-5-oxo-3-sulfanylidene-2,3-dihydro-1,2,4-triazin-4(5*H*)-yl]benzoic acid (18). A mixture of compound **17** (4.0 mmol) and pyruvic acid (4.0 mmol) in 20 mL of pyridine was refluxed for 5 h. The reaction mixture was cooled and poured into ice-cold water. The formed product was filtered off, washed with water, dried and recrystallized from ethylacetate. Yield 0.44 g (40%), yellow powder, mp 260–264°C. IR spectrum, ν, cm^{-1}: 3437 (OH), 3306 (NH), 1673 (C=O), 1600 (C=O), 1292 (C=S). ^1H NMR spectrum, δ, ppm: 12.65 s (1H, COOH), 10.20 s (1H, NH), 7.26–8.30 m (4H, ArH's), 1.95 s (3H, CH_3). Found, %: C 50.12; H 3.37; N 15.89. $C_{11}H_9N_3O_3S$. Calculated, %: C 50.18; H 3.45; N 15.96.

4′-[4-(1*H*-benzoimidazol-2-yl)phenyl]-6′-methyl-1,3-dihydro-2′*H*-spiro[benzoimidazole-2,3′-[1,2,4]-triazin]-5′(4′H)-one (19). A mixture of compound **18** (1.0 mmol) and *o*-phenylenediamine (2.0 mmol) in 10 mL of ethanol was refluxed for 6 h. The mixture was cooled and poured into ice-cold water, and the product was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 0.24 g (30%), green crystals, mp 282–285°C. IR spectrum, ν, cm^{-1}: 3434 (NH), 1692 (C=O), 1610 (C=N). ^1H NMR spectrum, δ, ppm: 8.62 s (1H, NH, D_2O exchangeable), 8.33 s (1H, NH, D_2O exchangeable), 8.03 s (1H, NH, D_2O exchangeable), 6.86–7.81 m (12H, H_{arom}), 6.85 s (1H, NH, D_2O exchangeable), 1.06 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 167.21 (C=O); 165.82, 131.39, 123.92, 118.92 (imidazole); 139.33, 129.19 (triazine); 131.28, 124.64, 122.66, 121.42 (C_6H_4); 126.59, 120.51, 117.84 (spiro imidazole); 14.77 (CH_3). Found, %: C 67.38; H 4.55; N 23.88. $C_{23}H_{19}N_7O$. Calculated, %: C 67.47; H 4.68; N 23.95.

4-[3-(2-Oxo-2*H*-chromen-3-yl)-5-sulfanylidene-1*H*-1,2,4-triazol-4(5*H*)-yl]benzoic acid (21). A mixture of compound **17** (4.0 mmol) and 2-oxo-2*H*-chromene-3-carbonyl chloride (**20**, 4.0 mmol) in 20 mL of pyridine was refluxed for 5 h. The mixture was cooled and poured into ice-cold water, and the product was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 0.23 g (30%), white powder, mp 272–274°C. IR spectrum, ν, cm^{-1}: 3457 (OH), 3309 (NH), 1698 (C=O), 1246 (C=S). ^1H NMR spectrum, δ, ppm: 12.39 s (1H, COOH), 10.86 s (1H, NH), 7.25–8.30 m (8H, H_{arom}), 5.82 s (1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 167.31 (C=S), 163.03 annd 160.55 (C=O), 143.04 (triazole); 142.60, 130.99, 126.04, 125.96 (C_6H_4); 131.68, 131.40, 119.01, 116.85, 113.03 (chromene). Found, %: C 59.08; H 2.91; N 11.39. $C_{18}H_{11}N_3O_4S$. Calculated, %: C 59.17; H 3.03; N 11.50.

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

SUPPLEMENTARY MATERIALS

Supplementary materials are available for this article at https://doi.org/10.1134/S1070428020060159 and are accessible for authorized users.

REFERENCES

1. Maheswari, S.U., Balamurugan, K., Perumal, S., and Yogeeswari, P., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 7278. https://doi.org/10.1016/j.bmcl.2010.10.080
2. Yang, R.Y., Kizer, D., Wu, H., Volckova, E., Miao, X.S., and Ali, S.M., *Bioorg. Med. Chem*., 2008, vol. 16, p. 5635. https://doi.org/10.1016/j.bmc.2008.03.073
3. Shook, B.C., Rassnick, S., Hall, D., Rupert, K.C., Heintzelman, G.R., and Hansen, K., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 2864. https://doi.org/10.1016/j.bmcl.2010.03.042
4. Mal, K., Naskar, B., Mondal, A., Goswami, S., Prodhan, C., Chaudhuri, K., and Mukhopadhyay, C., *Org. Biomol. Chem*., 2018, vol. 16, p. 5920. https://doi.org/10.1039/C8OB01411F
5. Ma, J. and Hecht, S.M., *Chem. Commun*., 2004, vol. 10, p. 1190. https://doi.org/10.1039/B402925A
6. Hassan, A., Abdel-Latif, F.F., Nour El-Din, A.M., Abdel-Aziz, M., Mostafa, S.M., and Bräse, S., *J. Heterocycl. Chem*., 2011, vol. 48, p. 1050. https://doi.org/10.1002/jhet.687
7. Hargrave, K.D., Hess, F.K., and Oliver, J.T., *J. Med. Chem*., 1983, vol. 26, p. 1158. https://doi.org/10.1021/jm00362a014
8. Patt, W.C., Hamilton, H.W., Taylor, M.D., Ryan, M.J., Taylor, D.G., Connolly, C.J.C., Jr., Doherty, A.M., Klutchko, S.R., Sircar, I., Steinbaugh, B.A., Batley, B.L., Painchaud, C.A., Rapundalo, S.T., Michniewicz, B.M., and Olson, S.C.J., *J. Med. Chem*., 1992, vol. 35, p. 2562. https://doi.org/10.1021/jm00092a006
9. Sharma, R.N., Xavier, F.P., Vasu, K.K., Chaturvedi, S.C., and Pancholi, S.S., *J. Enzyme Inhib. Med. Chem*., 2009, vol. 24, p. 890. https://doi.org/10.1080/14756360802519558
10. Jaen, J.C., Wise, L.D., Caprathe, B.W., Tecle, H., Bergmeier, S., Humblet, C.C., Heffner, T.G., Meltzner, L.T., and Pugsley, T.A., *J. Med. Chem*., 1990, vol. 33, p. 311. https://doi.org/10.1021/jm00163a051

11. Tsuji, K. and Ishikawa, H., *Bioorg. Med. Chem. Lett*., 1994, vol. 4, p. 1601. https://doi.org/10.1016/S0960-894X(01)80574-6
12. Bell, F.W., Cantrell, A.S., Hogberg, M., Jaskunas, S.R., Johansson, N.G., Jordon, C.L., Kinnick, M.D., Lind, P., Morin, J.M., Jr., Noreen, R., Oberg, B., Palkowitz, J.A ., Parrish, C.A., Pranc, P., Sahlberg, C., Ternansky, R.J., Vasileff, R.T., Vrang, L., West, S.J., Zhang, H., and Zhou, X.X., *J. Med. Chem*., 1995, vol. 38, p. 4929. https://doi.org/10.1021/jm00025a010
13. Ergenç, N., Çapan, G., Günay, N.S., Özkirimli, S., Güngör, M., Özbey, S., and Kendi, E., *Arch. Pharm. Pharm. Med. Chem*., 1999, vol. 332, p. 343. https://doi.org/10.1002/(SICI)1521-4184(199910)332:10<343::AID-ARDP343>3.0.CO;2-0
14. Carter, J.S., Kramer, S., Talley, J.J., Penning, T., Collins, P., Graneto, M.J., Seibert, K., Koboldt, C., Masferrer, J., and Zweifel, B., *Bioorg. Med. Chem. Lett*., 1999, vol. 9, p. 1171. https://doi.org/10.1016/s0960-894x(99)00157-2
15. Sangshetti, J.N. and Shinde, D.B., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 742. https://doi.org/10.1016/j.bmcl.2009.11.048
16. Zhan, P., Li, X., Li, Z., Chen, X., Tian, Y., Chen, W., Liu, X., Pannecouque, C., and De Clercq, E., *Bioorg. Med. Chem. Lett*., 2012, vol. 22, p. 7155. https://doi.org/10.1016/j.bmcl.2012.09.062
17. Sztanke, K., Pasternak, K., Rzymowska, J., Sztanke, M., and Kandefer-Szerszen, M.E., *J. Med. Chem*., 2008, vol. 43, p. 1085. https://doi.org/10.1016/j.ejmech.2007.07.009
18. Irannejad, H., Amini, M., Khodagholi, F., Ansari, N., Tusi, S.K., Sharifzadeh, M., and Shafiee, A., *Bioorg. Med. Chem*., 2010, vol. 18, p. 4224. https://doi.org/10.1016/j.bmc.2010.04.097
19. Ban, K., Duffy, S., Khakham, Y., Avery, V.M., Hughes, A., Montagnat, O., Katneni, K., Ryan, E., and Baell, J.B., *Bioorg. Med. Chem*., 2010, vol. 20, p. 6024. https://doi.org/10.1016/j.bmcl.2010.08.065
20. Lv, W., Banerjee, B., Molland, K.L., Seleem, M.N., Ghafoor, A., Hamed, M.I., Wan, B., Franzblau, S.G., Mesecar, A.D., and Cushman, M., *Bioorg. Med. Chem*., 2014, vol. 22, p. 406. https://doi.org/10.1016/j.bmc.2013.11.011
21. Krauth, F., Dahse, H.-M., Rüttinger, H.-H., and Frohberg, P., *Bioorg. Med. Chem*., 2010, vol. 18, p. 1816. https://doi.org/10.1016/j.bmc.2010.01.053
22. Schmitz, W.D., Brenner, A.B., Bronson, J.J., Ditta, J.L., Griffin, C.R., Li, Y.-W., Lodge, N.J., Molski, T.F., Olson, R.E., Zhuo, X., and Macor, J.E., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 3579. https://doi.org/10.1016/j.bmcl.2010.04.121
23. Haggam, R.A., Assy, M.G., Sherif, M.H., and Galahom, M.M., *Res. Chem. Intermed*., 2017, vol. 43, p. 99. https://doi.org/10.5155/eurjchem.9.2.99-106.1701
24. Sherif, M., Assy, M., Yousif, N., and Galahom, M., *J. Iran. Chem. Soc*., 2013, vol. 10, p. 85. https://doi.org/10.1007/s13738-012-0128-x
25. Lobo, G., Zuleta, E., Charris, K., Capparelli, M.V., Briceño, A., Angel, J., and Charris, J., *J. Chem. Res*., 2011, vol. 35, p. 222. https://doi.org/10.3184/174751911X13015834294266
26. Al Osaimi, A.G., Ali, R.S., Saad, H.A., and El Sayed Aly, M.R., *Russ. J. Gen. Chem*., 2017, vol. 87, p. 1246. https://doi.org/10.1134/S1070363217060202
27. Liu, H., Gao, W., Tangadanchu, V.K.R., Zhou, C., and Geng, R., *Eur. J. Med. Chem*., 2018, vol. 143, p. 66. https://doi.org/10.1016/j.ejmech.2017.11.027
28. Gheath, H., El-Abedy, O.O., Alarafi, N.M., and Elzletni, H., *J. Res. Pharm. Sci*., 2016, vol. 3, p. 10. http://www.questjournals.org/jrps/papers/vol3-issue3/C331019.pdf
29. Al-Smaisim, R.F., Al-Bayati, R.E., and Sharba, A.K., *Al-Mustansiriyah J. Pharm. Sci*., 2011, vol. 9, p. 123. https://www.iasj.net/iasj?func=fulltext&aId=34649
30. Bonev, B., Hooper, J., and Parisot, J., *J. Antimicrob. Chemother*., 2008, vol. 61, p. 1295. https://doi.org/10.1093/jac/dkn090