J. Indian Chem. Soc.,
Vol. 97, No. 9b, September 2020, pp. 1557-1562

Synthesis, characterization and antimicrobial evaluation of some new substituted 1*H*-indole-2 carboxamide derivatives

Kamal A. Sweidan[a], Ala'a M. Al-Shamaileha[a], Mohammad K. Abu Sini[b] and Rajendra Joshi*[c]

[a]Department of Chemistry, The University of Jordan, Amman, 11942, Jordan

[b]Faculty of Pharmacy, Al-Zaytoonah University of Jordan, Amman, 11733, Jordan

[c]Department of Chemical Science and Engineering, School of Engineering, Kathmandu University, Nepal

E-mail: rajendra.joshi@k.edu.np

Manuscript received online 19 July 2020, accepted 28 August 2020

A new series of 1*H*-indole-2-carboxamide derivatives has been prepared by simple procedures in good yields, followed by complete characterization using nuclear magnetic resonance, infrared spectroscopy, high resolution mass spectrometry and elemental analysis techniques. The prepared compounds have been tested as potential antifungal and anti-bacterial (Gram-positive and Gram-negative) agents. The antifungal and antibacterial results indicated that carboxylic acid compounds exhibited a weak bioactivity; even with replacement of carboxylic acid group with ester, no significant difference in activities was observed relative to standard commercial drugs.

Keywords: Antimicrobial, carboxamide, DEPT-NMR, indole, synthesis.

Introduction

Due to their remarkable medicinal properties, heterocycles are present in a wide variety of drugs, including antibiotic[1], anti-inflammatory[2], and antibacterial[3]. Indole (benzo[*b*]-prrrole), is a fused aromatic heterocyclic ring, in which benzene ring is fused to a pyrrole ring[4]. On the other hand, carboxamide functional group is employed as a significant linker between a specific heterocyclic moiety and other substituents in many systems[5]. This is expected, as carboxamide functional group is neutral, stable and possess the capacity of both hydrogen-bond acceptance and donation.

A novel series of anti-TB (Tuberculosis) agents was synthesized with low aqueous solubility and high mouse liver microsomal clearance. This series was prepared in a straightforward route by coupling of substituted 2-carboxyindole with the corresponding aromatic, alkyl or cycloalkyl amines in the presence of *o*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyl uronium hexafluorophosphate (HATU) and, *N,N*-diisopropylethylamine (DIPEA). All synthesized compounds were analyzed in a whole cell assay for *in vitro* MIC against Mtb[6].

On the other hand, various ester derivatives showed a wide range of biological activities such as antifungal and antimicrobial[7]. Due to the increasing of microbial resistance, the renewal of antimicrobial drugs becomes an important demand. Various indole derivatives have been prepared to show various biological activities like anti-breast cancer[8], anti-inflammatory[9], antibacterial[10] and antimicrobial[11].

Recently, we described the preparation and evaluation of the antimicrobial activity of some heterocyclic compounds[12–15]. In continuation of our further search for new indole derivatives, we report herein the preparation, characterization and antimicrobial screening of new products of the respective nucleus.

Experimental

The following reagents were bought and used as received: indole-2-carboxylic acid (Aldrich), 2-aminobenzoic acid (Aldrich), oxalyl chloride (Aldrich), *N,N*-dimethylformamide (DMF, > 99%) (HPLC grade, Tedia), pyridine (Tedia, 98%), ethyl acetate (AZ Chem.), 1-pentanol (Acros). Chloroform (Labchem) was purified by drying with anhydrous Na_2SO_4 followed by distillation.

IR spectra were obtained by using Thermo Nicolet Impact 400 FT-IR instrument and samples have been prepared as KBr discs. NMR (^1H, ^{13}C and DEPT) data were acquired

by a Bruker 500 MHz-Avance-III equipment working at 500.13 (^{1}H) and 125.03 MHz (^{13}C) from solutions in $CDCl_3$ (**2**) and DMSO-d_6 (**3**, **4**, **5**-**6a**-**e**) using tetramethylsilane as internal standard. Further, chemical shifts (δ) are expressed in ppm and coupling constant (*J*) in hertz (Hz). Mass spectra have been measured by employing an electrospray ion trap (ESI) approach based on collision-induced dissociation on a Bruker APEX-IV equipment; all samples were dissolved in $CHCl_3$. Elemental analyses of the products were performed using the elemental analyzer instrument (EA3000 A, Italy). The monitoring of the reaction progress was tested by thin layer chromatography on ALUGRAM Xtra SIL G/UV254 plates using dichloromethane-methanol (9.5:0.5) (**3**-**4**) and hexane-ethyl acetate (7:3) (**5**-**6a**-**e**) as eluent; spots were visualized under UV light. Melting points were measured using SMP 10 stuart apparatus and are uncorrected.

*Preparation of the compound **2**:* Oxalyl chloride, 1.3 cm^3 (6.7 mmol), and 0.05 cm^3 DMF were added to a solution of **1**, 0.16 g (0.99 mmol), in 15 cm^3 CH_2Cl_2 at 0°C, the resulting solution was stirred for 30 min, then refluxed for further 45 min. After cooling, CH_2Cl_2 and excess oxalyl chloride were removed by rotavapor equipment, and the remaining was employed for the next step directly.

*1H-Indole-2-carbonyl chloride (**2**)*: Yield 0.15 g (85%). IR wavenumbers (cm^{-1}): 3379 (N-H), 1703 (C=O); ^{1}H NMR data, δ, ppm: 7.15–7.22 m (1H), 7.41–7.43 m (2H), 7.54 m (1H), 7.73 d (1H, *J* 7.5), 8.90 broad s (1H); ^{13}C NMR data: 112.3 (CH), 116.2 (CH), 121.9 (CH), 123.6 (CH), 127.1 (CH), 128.0 (C), 129.6 (C), 138.6 (C), 160.0 C=O.

*General method for the synthesis of **3**-**4**:*

A specific amount of 2- or 4-aminobenzoic acid, 1.36 g (9.9 mmol), in 20 cm^3 $CHCl_3$ was added dropwise to a solution of **2**, 0.89 g (5.0 mmol), in 15 cm^3 $CHCl_3$ and 3 cm^3 pyridine at –5°C. The obtained solution was stirred 12 h to get the desired product which was filtered off and dried.

*2-(1H-Indole-2-carboxamido)benzoic acid (**3**):* Yield 1.11 g (79%), m.p. 250–252°C; R_f 0.75; IR wavenumbers (cm^{-1}): 3287 (N-H amide), 3378 (N-H indole), 1657 (C=O amide), 1741 (C=O carboxylic acid); ^{1}H NMR data: 7.04–7.16 m (2H), 7.17 t (1H, *J* 7.6), 7.21 t (1H, *J* 7.6), 7.49 d (1H, *J* 8.2), 7.68 m (2H), 8.14 d (1H, *J* 7.8), 8.60 d (1H, *J* 8.4), 11.89 s (1H, NH-amide), 12.02 s (1H, NH-indole), 12.20 broad s (1H, OH); ^{13}C NMR data: 103.5 (CH_{arom}), 113.0 (CH_{arom}), 120.1 (CH_{arom}), 120.7 (CH_{arom}), 122.3 (CH_{arom}), 123.2 (CH_{arom}), 124.7 (CH_{arom}), 127.4 (C), 131.8 (CH_{arom}), 132.0 (C), 134.8 (CH_{arom}), 137.5 (C), 137.7 (C), 141.5 (C), 159.8 (C=O amide), 170.5 (C=O carboxylic acid). High-resolution mass spectrum, *m/z*: calculated 303.07388 for $C_{16}H_{12}N_2NaO_3$ $[M+Na]^+$; found 303.07401. Found, %: C, 68.27; H, 4.65; N, 9.92. $C_{16}H_{12}N_2O_3$. Theoretical, %: C, 68.56; H, 4.32; N, 9.99. *M* 281.12.

*4-(1H-Indole-2-carboxamido)benzoic acid (**4**):* Yield 1.21 g (86%); m.p. 256–258°C; R_f 0.60; IR wavenumbers (cm^{-1}): 3291 (N-H amide), 3383 (N-H indole), 1655 (C=O amide), 1776 (C=O carboxylic acid); ^{1}H NMR data: 7.04 t (1H, *J* 7.7), 7.21 t (1H, *J* 7.4), 7.45 d (2H, *J* 7.8), 7.65 d (1H, *J* 7.9), 7.91 s (4H), 10.43 s (1H, NH-amide), 11.74 s (1H, NH-indole), 12.69 broad s (1H, OH); ^{13}C NMR data: 105.5 (CH_{arom}), 112.9 (CH_{arom}), 119.7 (CH_{arom}, CH_{arom}), 120.4 (CH_{arom}), 122.3 (CH_{arom}), 124.4 (CH_{arom}), 127.3 (C), 130.6 (CH_{arom}, CH_{arom}), 131.6 (C), 137.4 (C), 137.4 (C), 143.7 (C), 160.4 (C=O amide), 167.7 (C=O carboxylic acid). High-resolution mass spectrum, *m/z*: calculated 281.17230 for $C_{16}H_{13}N_2O_3$ $[M+H]^+$; found 281.09207. Found, %: C, 78.47; H, 5.65; N, 9.92. $C_{16}H_{12}N_2O_3$. Theoretical, %: C, 78.56; H, 5.84; N, 10.14. *M* 281.12.

*General method for the preparation of **5**(**a**-**e**) and **6**(**a**-**e**):* Sulfuric acid, 0.46 cm^3 (8.5 mmol), was added dropwise to a specific solution of **3** or **4**, 0.79 g (2.8 mmol), in 20 cm^3 of different aliphatic alcohol at 0°C, the resulting mixture was stirred for 30 min at room temperature, then refluxed overnight. After cooling, the mixture was neutralized with about 30 cm^3 of 0.5 *M* $NaHCO_3$ solution then the organic layer was extracted with $CH_3COOC_2H_5$ (15 cm^3), dried using Na_2SO_4 then evaporated under reduced pressure to get the desired product.

*Methyl 2-(1H-indole-2-carboxamido)benzoate (**5a**):* Yield 0.68 g (82%); m.p. 219–220°C; R_f 0.65; IR wavenumbers (cm^{-1}): 3285 (N-H amide), 3380 (N-H indole), 1692 (C=O ester); ^{1}H NMR data: 3.94 s (3H), 7.10 t (1H, *J* 7.5), 7.21 s (1H), 7.21–7.28 m (2H), 7.50 d (1H, *J* 8.2), 7.68 t (1H, *J* 7.7), 7.75 d (1H, *J* 7.9), 8.02 d (1H, *J* 6.3), 8.62 d (1H, *J* 8.3), 11.74 s (1H, NH-amide), 11.95 s (1H, NH-indole); ^{13}C NMR data: 53.2 (CH_3), 103.5 (CH_{arom}), 113.0 (CH_{arom}), 120.7 (CH_{arom}), 120.8 (CH_{arom}), 122.4 (CH_{arom}), 123.4 (CH_{arom}), 124.7 (CH_{arom}), 127.4 (C), 131.2 (CH_{arom}), 131.8 (C), 134.9 (CH_{arom}), 137.7 (C), 137.9 (C), 140.1 (C), 159.8 (C=O amide), 168.2 (C=O ester). High-resolution mass spectrum, *m/z*: cal-

culated 317.0896 for $C_{17}H_{14}N_2NaO_3$ $[M+Na]^+$; found 317.0897. Found, %: C, 69.04; H, 4.95; N, 9.26. $C_{17}H_{14}N_2O_3$. Theoretical, %: C, 69.38; H, 4.79; N, 9.52. *M* 295.29.

*Ethyl 2-(1H-indole-2-carboxamido)benzoate (**5b**):* Yield 0.72 g (83%); m.p. 190–192°C; R_f 0.63; IR wavenumbers (cm^{-1}): 3294 (N-H amide), 3370 (N-H indole), 1683 (C=O ester); ^1H NMR data: 1.35 t (3H, *J* 7.1), 4.40 q (2H, *J* 7.1), 7.10 t (1H, *J* 7.5), 7.19 s (1H), 7.20–7.29 m (2H), 7.50 d (1H, *J* 7.9), 7.68–7.71 t (1H, *J* 7.6), 7.74 d (1H, *J* 7.9), 8.03 d (1H, *J* 7.6), 8.60 d (1H, *J* 8.3), 11.73 s (1H, NH-amide), 11.94 s (1H, NH-indole); ^{13}C NMR data: 14.4 (CH_3), 61.9 (CH_2), 103.5 (CH_{arom}), 112.9 (CH_{arom}), 120.7 (CH_{arom}), 120.7 (CH_{arom}), 122.4 (CH_{arom}), 123.5 (CH_{arom}), 124.7 (CH_{arom}), 127.4 (C), 131.2 (CH_{arom}), 131.8 (C), 134.8 (CH_{arom}), 137.7 (C), 137.9 (C), 140.1 (C), 159.8 (C=O amide), 168.2 (C=O ester). High-resolution mass spectrum, *m/z*: calculated 309.12351 for $C_{18}H_{17}N_2O_3$ $[M+H]^+$; found 309.12337. Found, %: C, 69.92; H, 5.63; N, 9.07. $C_{18}H_{16}N_2O_3$. Theoretical, %: C, 70.12; H, 5.23; N, 9.09. *M* 309.46.

*Isopropyl 2-(1H-indole-2-carboxamido)benzoate (**5c**):* Yield 0.75 g (83%); m.p. 210–211°C; R_f 0.82; IR wave numbers (cm^{-1}): 3286 (N-H amide), 3389 (N-H indole), 1683 (C=O ester); ^1H NMR data: 1.35 d (6H, *J* 6.1), 5.24 m (1H), 7.10 t (1H, *J* 7.6), 7.19 s (1H), 7.21–7.27 m (2H), 7.50 d (1H, *J* 8.2), 7.68 t (1H, *J* 7.7), 7.73 d (1H, *J* 7.9), 8.02 d (1H, *J* 7.8), 8.52 d (1H, *J* 8.3), 11.75 s (1H, NH-amide), 11.92 s (1H, NH-indole); ^{13}C NMR data: 22.0 ($2CH_3$), 69.6 (CH), 103.5 (CH_{arom}), 112.9 (CH_{arom}), 117.4 (C), 120.7 (CH_{arom}), 120.9 (CH_{arom}), 122.4 (CH_{arom}), 123.5 (CH_{arom}), 124.7 (CH_{arom}), 127.4 (C), 131.2 (CH_{arom}), 131.8 (C), 134.8 (CH_{arom}), 137.7 (C), 140.7 (C), 159.9 (C=O amide), 167.7 (C=O ester). High-resolution mass spectrum, *m/z*: calculated 345.12106 for $C_{19}H_{18}N_2NaO_3$ $[M+Na]^+$; found 345.12096. Found, %: C, 70.88; H, 5.43; N, 8.57. $C_{19}H_{18}N_2O_3$. Theoretical, %: C, 70.79; H, 5.63; N, 8.69. *M* 323.63.

*Butyl 2-(1H-indole-2-carboxamido)benzoate (**5d**):* Yield 0.81 g (86%); m.p. 183–184°C; R_f 0.75; IR wavenumbers (cm^{-1}): 3269 (N-H amide), 3375 (N-H indole), 1739 (C=O ester); ^1H NMR data: 0.92 t (3H, *J* 7.4), 1.39–1.47 m (2H), 1.69–1.74 m (2H), 4.36 t (2H, *J* 6.5), 7.11 t (1H, *J* 7.6), 7.20 s (1H), 7.20–7.29 m (2H), 7.50 d (1H, *J* 8.2), 7.7 m (2H), 8.01–8.10 d (1H, *J* 7.6), 8.60 d (1H, *J* 8.3), 11.72 s (1H, NH-amide), 11.93 s (1H, NH-indole); ^{13}C NMR data: 13.8 (CH_3), 18.9 (CH_2), 30.2 (CH_2), 65.3 (CH_2), 103.5 (CH_{arom}), 117.1 (CH_{arom}), 120.7 (CH_{arom}), 121.0 (CH_{arom}), 121.7 (CH_{arom}), 122.4 (CH_{arom}), 124.6 (CH_{arom}), 127.4 (C), 131.2 (CH_{arom}), 131.8 (C), 134.8 (CH_{arom}), 137.7 (C), 137.7 (C), 140.1 (C), 159.8 (C=O amide), 168.2 (C=O ester). High resolution mass spectrum, *m/z*: calculated 335.13904 for $C_{20}H_{19}N_2O_3$ $[M-H]^-$; found 335.1401. Found, %: C, 71.19; H, 6.33; N, 7.97. $C_{20}H_{20}N_2O_3$. Theoretical, %: C, 71.41; H, 5.99; N, 8.33. *M* 337.80.

*Pentyl 2-(1H-indole-2-carboxamido)benzoate (**5e**):* Yield 0.79 g (80%); m.p. 183–184°C; R_f 0.85; IR wavenumbers (cm^{-1}): 3284 (N-H amide), 3391 (N-H indole), 1681 (C=O ester); ^1H NMR data: 0.86 t (3H, *J* 7.2), 1.30–1.38 m (4H), 1.73 m (2H), 4.34 t (2H, *J* 6.5), 7.10 t (1H, *J* 7.4), 7.22 s (1H), 7.25 t (2H, *J* 7.6), 7.49 d (1H, *J* 8.2), 7.68–7.74 m (2H), 8.04 d (1H, *J* 7.9), 8.55 d (1H, *J* 8.3), 11.67 s (1H, NH-amide), 11.92 s (1H, NH-indole); ^{13}C NMR data: 14.0 (CH_3), 21.9 (CH_2), 27.8 (CH_2), 27.9 (CH_2), 65.6 (CH_2), 103.5 (CH_{arom}), 117.2 (CH_{arom}), 120.7 (CH_{arom}), 121.0 (CH_{arom}), 122.4 (CH_{arom}), 122.4 (CH_{arom}), 124.7 (CH_{arom}), 127.5 (C), 131.2 (CH_{arom}), 131.8 (C), 134.9 (CH_{arom}), 137.7 (C), 137.8 (C), 140.7 (C), 159.8 (C=O amide), 168.2 (C=O ester). High-resolution mass spectrum, *m/z*: 349.15537 calculated for $C_{21}H_{21}N_2O_3$ $[M-H]^-$; found 349.15577. Found, %: C, 71.64; H, 6.70; N, 7.63. $C_{21}H_{22}N_2O_3$. Theoretical, %: C, 71.98; H, 6.33; N, 7.99. *M* 351.97.

*Methyl 4-(1H-indole-2-carboxamido)benzoate (**6a**):* Yield 0.61 g (74%); m.p. 260–262°C; R_f 0.57; IR wavenumbers (cm^{-1}): 3377 (N-H amide), 3369 (N-H indole), 1700 (C=O ester); ^1H NMR data: 3.85 s (3H), 7.01 t (1H, *J* 7.5), 7.25 t (1H, *J* 7.7), 7.48–7.51 m (2H), 7.70 d (1H, *J* 8.0), 8.01 s (4H), 10.52 s (1H, NH-amide), 11.81 s (1H, NH-indole); ^{13}C NMR data: 52.3 (CH_3), 105.1 (CH_{arom}), 112.9 (CH_{arom}), 119.7 (CH_{arom}, CH_{arom}), 120.3 (CH_{arom}), 121.7 (CH_{arom}), 122.3 (CH_{arom}), 127.4 (C), 130.7 (CH_{arom}, CH_{arom}), 131.3 (C), 137.2 (C), 137.5 (C), 143.9 (C), 160.5 (C=O amide), 166.3 (C=O ester). High-resolution mass spectrum, *m/z*: calculated 317.08949 for $C_{17}H_{14}N_2NaO_3$ $[M+Na]^+$; found 317.08966. Found, %: C, 69.22; H, 4.91; N, 9.31. $C_{17}H_{14}N_2O_3$. Theoretical, %: C, 69.38; H, 4.79; N, 9.52. *M* 295.29.

*Ethyl 4-(1H-indole-2-carboxamido)benzoate (**6b**):* Yield 0.71 g (82%); m.p. 218–220°C; R_f 0.75; IR wavenumbers (cm^{-1}): 3378 (N-H amide), 3371 (N-H indole), 1690 (C=O ester); ^1H NMR data: 1.23 t (3H, *J* 7.1), 4.26 q (2H, *J* 7.1), 7.05 t (1H, *J* 7.5), 7.21 d (1H, *J* 7.7), 7.46–7.49 m (2H), 7.72

d (1H, *J* 8.0), 7.95 s (4H), 10.46 s (1H, NH-amide), 11.76 s (1H, NH-indole); ^{13}C NMR data: 14.6 (CH_3), 60.9 (CH_2), 105.1 (CH_{arom}), 112.9 (CH_{arom}), 119.7 (CH_{arom}, CH_{arom}), 120.3 (CH_{arom}), 122.3 (CH_{arom}), 124.5 (CH_{arom}), 130.6 (CH_{arom}, CH_{arom}), 131.3 (C), 137.5 (C), 137.8 (C), 143.9 (C), 160.5 (C=O amide), 165.8 (C=O ester). High-resolution mass spectrum, *m/z*: calculated 309.12337 for $C_{18}H_{17}N_2O_3$ $[M+H]^+$; found 309.23994. Found, %: C, 69.76; H, 5.58; N, 8.79. $C_{18}H_{16}N_2O_3$. Theoretical, %: C, 70.12; H, 5.23; N, 9.09. *M* 309.46.

*Isopropyl 4-(1H-indole-2-carboxamido)benzoate (**6c**):* Yield 0.79 g (88%); m.p. 190–193°C; R_f 0.81; IR wave numbers (cm^{-1}): 3366 (N-H amide), 3384 (N-H indole), 1693 (C=O ester); ^{1}H NMR data: 1.35 d (6H, *J* 6.4), 5.18 m (1H), 7.07 s (1H), 7.22 t (1H, *J* 7.1), 7.39 t (1H, *J* 7.7), 7.60 d (1H, *J* 8.3), 7.80 d (2H, *J* 8.5), 7.84 d (1H, *J* 8.1), 8.05 d (1H, *J* 8.4), 10.42 s (1H, NH-amide), 11.92 s (1H, NH-indole); ^{13}C NMR data: 22.2 ($2CH_3$), 68.6 (CH_2), 99.1 (CH_{arom}), 112.3 (CH_{arom}), 121.5 (C), 123.7 (CH_{arom}), 123.9 (CH_{arom}), 125.0 (CH_{arom}, CH_{arom}), 130.3 (CH_{arom}, CH_{arom}), 131.5 (C), 133.7 (CH_{arom}), 137.6 (C), 137.6 (C), 141.1 (C), 158.7 (C=O amide), 165.1 (C=O ester). High-resolution mass spectrum, *m/z*: calculated 345.12154 for $C_{19}H_{18}N_2NaO_3$ $[M+Na]^+$; found 345.12910. Found, %: C, 72.66; H, 5.01; N, 7.59. $C_{19}H_{18}N_2O_3$. Theoretical, %: C, 72.98; H, 5.29; N, 7.74. *M* 323.63.

*Butyl 4-(1H-indole-2-carboxamido)benzoate (**6d**):* Yield 0.79 g (84%); m.p. 182–183°C; R_f 0.82; IR wavenumbers (cm^{-1}): 3295 (N-H amide), 3367 (N-H indole), 1685 (C=O ester); ^{1}H NMR data: 0.94 t (3H, *J* 7.4), 1.43 m (2H), 1.69 (2H), 4.27 t (2H, *J* 6.5), 7.09 t (1H, *J* 7.5), 7.25 t (1H, *J* 7.4), 7.46–7.50 m (2H), 7.70 d (1H, *J* 8.0), 7.99 t (4H), 10.50 s (1H, NH-amide), 11.80 s (1H, NH-indole); ^{13}C NMR data: 13.8 (CH_3), 18.9 (CH_2), 30.5 (CH_2), 64.3 (CH_2), 105.0 (CH_{arom}), 112.9 (CH_{arom}), 119.8 (CH_{arom}, CH_{arom}), 120.5 (CH_{arom}), 122.3 (CH_{arom}), 124.5 (CH_{arom}), 127.8 (C), 130.6 (CH_{arom}, CH_{arom}), 131.5 (C), 137.6 (C), 137.5 (C), 143.9 (C), 160.5 (C=O amide), 165.8 (C=O ester). High-resolution mass spectrum, *m/z*: calculated 335.14012 for $C_{20}H_{19}N_2O_3$ $[M-H]^-$; found 335.1401. Found, %: C, 71.26; H, 6.12; N, 7.99. $C_{20}H_{20}N_2O_3$. Theoretical, %: C, 71.42; H, 5.99; N, 8.33. *M* 337.80.

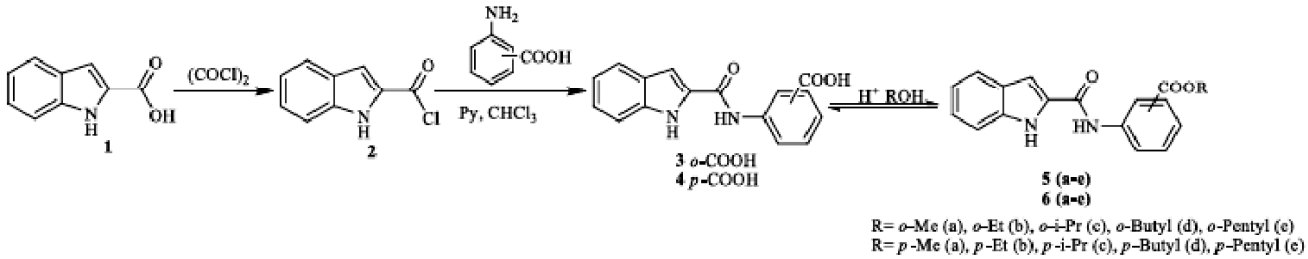
*Pentyl 4-(1H-indole-2-carboxamido)benzoate (**6e**):* Yield 0.83 g (84%); m.p. 210–212°C; R_f 0.84; IR wavenumbers (cm^{-1}): 3292 (N-H amide), 3374 (N-H indole), 1688 (C=O ester); ^{1}H NMR data: 0.89 t (3H, *J* 6.8), 1.30 m (4H), 1.71 t (2H, *J* 6.3), 4.25 t (2H, *J* 6.3), 7.07 t (1H, *J* 7.2), 7.25 t (1H, *J* 7.5), 7.48–7.51 m (2H), 7.70 d (1H, *J* 7.9), 7.99 s (4H), 10.50 s (1H, NH-amide), 11.80 s (1H, NH-indole); ^{13}C NMR data: 14.1 (CH_3), 22.0 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 64.6 (CH_2), 105.1 (CH_{arom}), 112.9 (CH_{arom}), 119.8 (CH_{arom}, CH_{arom}), 120.5 (CH_{arom}), 122.3 (CH_{arom}), 124.5 (CH_{arom}), 127.4 (C), 130.6 (CH_{arom}, CH_{arom}), 131.5 (C), 137.3 (C), 137.5 (C), 143.9 (C), 160.5 (C=O amide), 165.8 (C=O ester). High-resolution mass spectrum, *m/z*: calculated 349.1565 for $C_{22}H_{21}N_2O_3$ $[M-H]^-$; found 349.1558. Found, %: C, 71.74; H, 6.68; N, 7.73. $C_{20}H_{22}N_2O_3$. Theoretical, %: C, 71.98; H, 6.33; N, 7.99. *M* 351.97.

Antimicrobial evaluation: All synthesized compounds were dissolved in DMSO (1:20) and prepared at concentration 0.5 mg/cm^3, then screened for their antifungal activity against *C. albicans* DSMZ 11949 by the agar diffusion method[16]. Further, all above compounds were screened against different types of Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538), and Gram-negative bacteria (*Escherichia coli* ATCC 8739) according to the procedure described elsewhere[17]. Incubation of microtiter plates was performed at temperature of 37°C and the growth of bacterial cells was assessed after 24 h.

Results and discussion

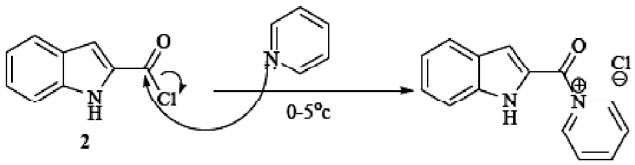
Compound **1** was converted into its corresponding acyl chloride **2** since the latter one is more reactive than the acid itself towards the nucleophilic acyl substitution reaction. Compound **2** was synthesized in a simple method and excellent yield; it involves the reaction of **1** with excess oxalyl chloride in dry DCM as solvent and drops of DMF as catalyst. The ^{1}H NMR spectrum of **2** shows two different regions of signals, the first one resonates at 8.90 ppm which belongs to the NH, while the second one at 7.15–7.73 ppm that belong to aromatic protons. The ^{13}C NMR spectrum indicates the presence of signal of carbon in COCl which resonates at 160.0 ppm while that carbon in COOH (163.3 ppm) was not detected.

The reaction of **2** with 2- and 4-aminobenzoic acids produced the target products **3**-**4** in high yield, respectively (Scheme 1). Dry pyridine was used as a catalyst and as an organic base in the reaction mixture. Compound **2** was con-



Scheme 1. Synthesis of the target products.

verted into more reactive species by reaction with pyridine (Scheme 2). This step enhanced the progress of the nucleophilic substitution reaction to form the desired amide group, since 2- and 4-aminobenzoic acids are considered weak nucleophiles due to the delocalization of the lone pair of electrons at nitrogen atom.



Scheme 2. Conversion of **2** into more reactive species [(indole-2-carbonyl)pyridinium chloride].

Chemical structures of **3**-**4** were confirmed by different spectroscopic techniques such as, ^{1}H NMR, ^{13}C NMR, DEPT, FT-IR, HRMS and elemental analysis. ^{1}H NMR spectra of **3**-**4** showed new signals at 11.89 and 10.43 ppm for the NH amide, respectively.

The ^{13}C NMR spectra of **3**-**4** indicated that a new signal of carbon in the amide group is formed and the corresponding one in **2** was absent. The signal of carbon atom of the amide group resonates at 159.8; 160.4 ppm in **3** and **4**, respectively. FT-IR spectra of **3**-**4** showed new bands at 3287 and 3314 cm^{-1}, respectively; which belong to N-H bond of the amide group. In addition, the IR band of N-H bond of indole system in **3**-**4** was detected at 3378 and 3399 cm^{-1}, respectively.

As expected; the IR band of the carbonyl group of COCl (1703 cm^{-1}) was disappeared and a new band of the corresponding carbonyl group, which belong to an amide group in **3**-**4**, was observed at 1657 and 1655 cm^{-1}, respectively. Fischer esterification reaction of **3** and **4** afforded the target products **5**-**6**(**a**-**e**) in moderate yields. The carbonyl group of carboxylic acid in **3**-**4** was activated toward nucleophilic attack of alcohol by using H_2SO_4. In ^{1}H NMR spectra of **5**-**6**(**a**-**e**), new peaks of aliphatic protons have been detected in the aliphatic region from about 0.8 to 5 ppm. Regarding ^{13}C NMR data, the signal of carbon of carbonyl group in carboxylic acid disappeared in **3**-**4**. On the other hand, DEPT, ^{13}C NMR analysis assures the proposed chemical structure of all target products; in which CH and CH_3 atoms showed up peaks, CH_2 atoms showed down peak and quaternary carbon showed no peak.

It is clear that all tested compounds exhibit a weak activity (the inhibition zone diameter 9–14 mm) relative to the reference drug, flucanazole (the inhibition zone diameter 45 mm at 0.5 mg/cm^3). On the other hand, the variation of alkyl group C1-C5 has no significant effect on the activity, at both positions 2 and 4. Finally, replacement of carboxylic acid in **3** and **4** with ester group **5**-**6**(**a**-**e**) showed no effect in terms of the activity. In addition, all tested compounds exhibit a weak activity (the inhibition zone diameter 7–14 mm) relative to the reference drug, ciprofloxacin (the inhibition zone diameter 53 mm towards *E. coli* and 42 mm against *S. aureus*, at 0.5 mg/mL). On the other hand, the variation of alkyl group C1-C5 has no significant effect on the activity at both positions 2 and 4. Each experiment was conducted in duplicate.

Conclusions

New ester derivatives of 1*H*-indole-2-carboxamide have been synthesized by reacting of 1*H*-indole-2-carbonyl chloride with different anilines, containing carboxylic group. All prepared compounds were fully characterized using various spectroscopic approaches. All target products have been preliminary tested towards antifungal and antibacterial activities. Results indicate that further modification should be done on the chemical structure followed by retesting against different antimicrobial targets.

Acknowledgements

The authors are grateful to Kathmandu University for supporting the present research and also would like to thank University of Jordan, Deanship of Scientific Research for the financial support of this research.

References

1. P. Martins, J. Jesus, S. Santos, L. R. Raposo, C. Roma-Rodrigues, P. V. Baptista and A. R. Fernandes, *Molecules,* 2015, **20**, 16852.
2. A. S. H. S. Guerra, D. J. N. Malta, L. P. M. Laranjeira, M. B. S. Maia, N. C. Colaço, M. C. A. Lima, S. L. Galdino, I. R. Pitta and T. Gonçalves-Silva, *Int. Immunopharmacol*., 2011, **11**, 1816.
3. H. Tashtoush, Y. Al-Soud, A. Maslat, M. Shkoor and M. Al-Talib, *Jordan J. Chem*., 2007, **2**, 11.
4. L. G. N. Raju, K. B. Sai, M. S. Meghana, K. Chandana, P. V. Suresh and R. R. Nadendla, *Int. J. Pharm. Chem*., 2015, **5**, 201.
5. M. Szostak, L. Yao and J. Aube, *J. Org. Chem*., 2009, **74**, 1869.
6. R. R. Kondreddi, J. Jiricek, S. P. S. Rao, B. S. Lakshminarayana, R. L. Camacho, R. Rao, M. Herve, P. Bifani, L. N. Ma, K. Kuhen, A. Goh, K. A. Chatterjee, T. Dick, T. T. Diagana, H. U. Manjunatha and W. P. Smith, *J. Med. Chem*., 2013, **56**, 8849.
7. P. D. Darbre and P. W. Harvey, *J. Appl. Toxicol*., 2008, **28**, 561.
8. S. B. Dongare, B. P. Bandgar, P. S. Bhale, S. N. Shringare and H. V. Chavan, *Croat. Chem. Acta,* 2019, **92**, DOI: 10.5562/cca3418.
9. R. M. Phillips, H. R. Hendriks and G. J. Peters, *Br. J. Pharmacol*., 2012, **168**, 11.
10. D. Kumar, N. Kumar, S. Kumar, T. Singh and C. P. Singh, *Int. J. Eng. Sci. Technol.*, 2010, **2**, 2553.
11. F. Du, X. Lia, C. Li, Z. Shang and B. Wang, *Bioorganic. Med. Chem. Lett*., 2012, **22**, 4650.
12. K. Sweidan, J. Engelmann, W. Abu Rayyan, D. Sabbah, M. Abu Zarga, T. Al-Qirim, Y. Yusuf Al-Hiari, G. Abu Sheikha and G. Shattat, *Lett. Drug Des. Discov*., 2015, **12**.
13. K. Sweidan, W. Abu Rayyan, M. Abu Zarga, M. M. El-Abadelah and H. A. Y. Mohammad, *Lett. Org. Chem*., 2014, **11**, 422.
14. G. Shattat, T. Al-Qirim, G. Abu Sheikha, Y. Al-Hiari, K. Sweidan, R. Al-Qirim, S. Hikmat, L. Hamadneh and S. Al-kouz, *J. Enzym. Inhib. Med. Chem*., 2013, **28**, 863.
15. K. Sweidan, M. Khanfar, A. Al-Shamaileh, M. Sunjuk and R. Joshi, *Current Chem. Lett*., 2019, **8**, 63.
16. E. J. Threlfall, I. S. T. Fisher, L. R. Ward, H. Tschape and P. Gerner-Smidt, *Microb. Drug Resist*., 1999, **5**, 195.
17. G. N. Pershin, "Metody eksperimental'noi khimioterapii (Methods of Experimental Chemotherapy)", Moscow, Meditsina, 1971.