Synthesis and antimicrobial evaluation of some novel benzoimidazole Schiff's bases and their C-nucleoside derivatives

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Background and objectives
The discovery of C-nucleosides and continuous study of their biological activities led us to construct new compounds containing 4-(5-benzoyl-benzoimidazol-2)-benzoic acid hydrazide Schiff's bases incorporated into different aldoses, thiazolidinones, and/or their C-nucleoside analogues. The aim of this study is to describe the synthesis of some new heterocycles derived from 4-(5-benzoyl-benzoimidazol-2)-benzoic acid hydrazide and to evaluate their antimicrobial activities.

Materials and methods
The starting material 4-(5-benzoyl-1H-benzoimidazol-2-yl)-benzonitrile (**2**) was prepared through the reaction of (3,4-diamino-phenyl)-phenyl-methanone (**1**) with 4-cyanobenzaldehyde in absolute ethanol. Stirring compound **2** with 70% sulfuric acid yielded benzoic acid derivative **3**, followed by esterification and refluxing with hydrazine hydrate to yield the corresponding 4-(5-benzoyl-1H-benzoimidazol-2-yl)-benzoic acid hydrazide (**5**). A series of Schiff's bases derivatives **6a–c** and **8a–e** were prepared by condensation of hydrazide **5** with different monosaccharides and/or with arenaldehydes. Treatment of **6a–c** with thioglycolic acid led to the formation of the C-nucleosides (**7a–c**), whereas treatment of **8a–e** with thioglycolic acid yielded the corresponding 2-arylthiazolidin-4-one (**9a–e**).

Results and conclusion
Compound **6b** showed the highest antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus* (gram-positive bacteria), *Escherichia coli*, and *Pseudomonas aeuroginosa* (gram-negative bacteria), and *Candida albicans* and *Aspergillus niger* (fungi).

Keywords:
antimicrobial activity, 2-aryl-thiazolidinone-4-one, 4-benzoimidazol-2-yl, C-nucleoside, sugar-Schiff's base

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Introduction

Benzoimidazole is an important pharmacophore and privileged bioactive heterocyclic structure in medicinal chemistry. Extensive biochemical and pharmacological studies have confirmed that benzoimidazole molecules are effective against various strains of microorganisms [1–5] and showed antioxidant [6,7], antiparasitic [8], antiproliferative [9], anti-HIV [10], anticonvulsant [11], antidiabetic [11], anti-inflammatory [12,13], antihypertensive [14], and antineoplastic [15,16] activities.

On the basis of all of these findings, it was of interest to construct novel compounds containing benzoimidazole Schiff's bases and their cyclic products and/or their C-nucleoside analogues for evaluation of their antimicrobial activity.

Materials and methods

Chemistry

Melting points (°C) were determined in open capillary tubes using silicon oil on a Gallen Kamp apparatus (Ultraporter Company, Walsall, United Kingdom). ^{1}H-NMR spectra were measured in DMSO-d_6 on a JEOL-270 MHz Spectrometer (JEOL, Canada) with tetramethylsilane as an internal standard. Mass spectra were obtained using a Schimadzu GCS-QP1000EX Spectrometer (Schimadzu Scientific Instruments, Italy) at 70 eV. The IR spectra were recorded using a Philips Infra cord Spectrophotometer Model PU 9712 (PerkinElmer, 940 Winter Street, Waltham, Massachusetts 02451, USA) in KBr discs. Elemental analysis was carried out at the Microanalytical Laboratory of the National Research Center. The antimicrobial activity of the synthesized compounds was assessed at the National Research Centre, Giza, Egypt.

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzonitrile (2)

4-Cyanobenzaldehye (0.6 g, 0.21 mol) and (3,4-diamino-phenyl)-phenyl-methanone (**1**) (1 g, 0.21 mol) were dissolved in ethanol. This mixture was refluxed for 5 h and cooled to room temperature. Then, water was added slowly to the mixture with stirring. The suspension was maintained at -5°C overnight. The product was washed repeatedly with ethanol–water

(1: 1) mixture and then recrystallized from acetone, Scheme 1. Yield = 1.3 g (86%), m.p. = 250–252°C. Analysis for $C_{21}H_{13}N_3O$ (323.4): Calcd.: C, 78.0; H, 4.0; N, 13.0; Fd.: C, 78.0; H, 4.1; N, 13.0. IR (cm^{-1}): 3340 (NH), 2225 (CN), 1705 (CO). MS: *m/z* (%): 323 (M^+, 100). ^{1}H-NMR: δ, ppm (DMSO-d_6); 5.92 (s, 1H, NH); 7.48–8.22 (m, 12H, Ar–H).

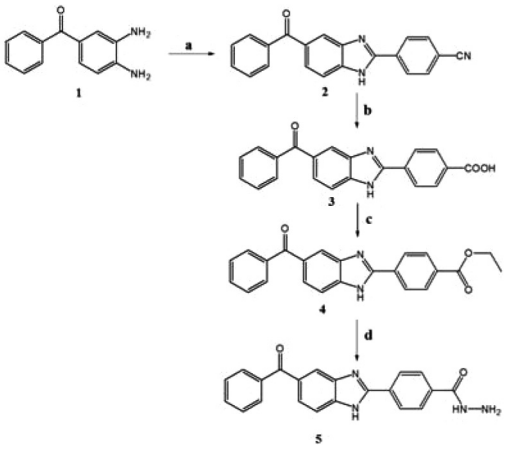
4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid (3)

A mixture of **2** (1 g, 0.01 mol) and 30 ml 70% sulfuric acid was stirred in a 100 ml three-necked flask at 140°C for 5 h, then suspended in 150 ml water, and the resulting precipitate was filtered off. Recrystallization from diluted ethanol yielded yellow crystals Scheme 1. Yield = 0.95 g (90%), m.p. = 280–283°C. Analysis for $C_{21}H_{14}N_2O_3$ (342.4): Calcd.: C, 73.7; H, 4.1; N, 8.2; Fd.: C, 73.7; H, 4.2; N, 8.2. IR (cm^{-1}): 3746 (NH), 3348 (OH), 1701 (COO), 1720 (CO). MS: *m/z* (%): 343 (M^+, 16); 342 (M^+, 60). ^{1}H-NMR: δ, ppm (DMSO-d_6); 5.92 (s, 1H, NH); 7.48–8.22 (m, 12H, Ar–H); 10.92 (s, 1H, OH).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid ethyl ester (4)

To a solution of compound **3** (1 g; 0.073 mol) in absolute ethanol, a few drops of concentrated sulfuric acid were added and the mixture was refluxed for 4 h. The crude product was filtered, air-dried, and crystallized from ethanol Scheme 1. Yield = 0.9 g (83%), m.p. = 107–109°C. Analysis for $C_{23}H_{18}N_2O_3$ (370.4): Calcd.: C, 74.6; H, 4.9; N, 7.6; Fd.: C, 74.5; H, 4.9; N, 7.7. IR (cm^{-1}): 3746 (NH), 3348 (OH), 1717 (COO), 1705 (CO). MS: *m/z* (%): 371 (M^+, 32); 370 (M^+, 72). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.32 (t, 3H, CH_3); 4.32 (q, 2H, CH_2); 5.92 (s, 1H, NH); 7.48–8.22 (m, 12H, Ar–H).

Scheme 1



Reagents: (a) 4-cyanobenzaldehyde, EtOH; (b) 70% H_2SO_4; (c) EtOH,H_2SO_4; (d) $NH_2NH_2.H_2O$, EtOH.

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid hydrazide (5)

To a solution of ester compound **4** (1 g; 0.033 mol) in ethanol, hydrazine hydrate (98%; 2 ml) was added and heated for 5 h on a water bath. The reaction mixture was cooled. The crude product was filtered, washed with water, and dried. It was crystallized from ethanol, Scheme 1. Yield = 0.8 g (83%), m.p. = 73–78°C. Analysis for $C_{21}H_{16}N_4O_2$ (356.4): Calcd.: C, 70.8; H, 4.5; N, 15.7; Fd.: C, 70.7; H, 4.4; N, 15.8. IR (cm^{-1}): 3736 (NH), 3187 (NH_2), 1705 (CO), 1684 (CO). MS: *m/z* (%): 357 (M^+, 33); 356 (M^+, 49). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.96 (s, 2H, NH_2); 5.92 (s, 1H, NH); 7.48–8.22 (m, 12H, Ar–H); 10.45 (s, 1H, NH).

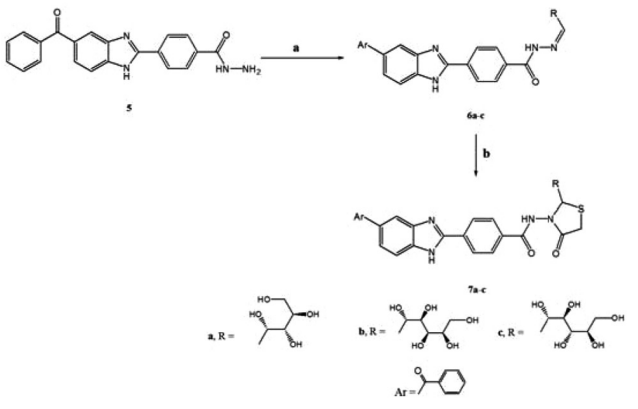
General procedure for the preparation of 4-(5-benzoyl-1H-benzoimidazol-2-yl)-benzoic acid (2,3,4,5-tetrahydroxy-pentylidene)/ (2,3,4,5,6-pentahydroxy-hexylidene)-hydrazide (6a–c)

A mixture of compound **5** (1 g; 0.01 mol) dissolved in ethanol (5 ml) and DMF (5 ml) and the respective monosaccharide, namely, d (+) xylose, d (+) glucose, and/or d (+) galactose (0.01 mol), dissolved in water (1.0 ml) containing a few drops of acetic acid, were heated on a water bath at 60°C for 2 h. The solid that separated after cooling was filtered off, washed with cold ethanol, and dried to yield compounds **6a–c**, respectively, Scheme 2.

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid (2,3,4,5-tetrahydroxy-pentylidene)-hydrazide (6a)

Yield = 1.2 g (88%), m.p. = 144–148°C. Analysis for $C_{26}H_{24}N_4O_6$ (488.5): Calcd.: C, 63.9; H, 5.0; N, 11.5; Fd.: C, 63.9; H, 5.1; N, 11.5. IR (cm^{-1}): 3755(NH), 3220 (OH), 1705 (CO). MS: *m/z* (%): 489 (M^+, 16); 488 (M^+, 32). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.49–2.53 (s, 4H,

Scheme 2



Reagents: (a) d (+) xylose, d (+) glucose, and/or d (+) galactose, DMF, CH_3COOH (b) $HSCH_2COOH$, dioxane. DMF, dimethylformamide.

OH); 3.29 (m, 1H, ″H_5); 4.10 (m, 1H, ″H_5); 4.20 (t, 1H, $^1H_2$); 4.31 (t, 1H, $^1H_4$); 5.16 (t, 1H, $^1H_3$); 5.45 (s, 1H, NH); 6.52 (d, 1H, CH); 7.25 (s, 1H, NH); 7.48–8.22 (m, 12H, Ar–H). ^{13}C-NMR δ, ppm (DMSO-d_6): showed the presence of 26 signals corresponding to the 26 different carbon groups and signals appeared at δ 64.5 (CH_2OH), 66.5–72.5 (3CHOH), 115.4–130.7 (Ar–12CH), 131.3 (C–CO), 134.1 (C–C = N), 134.7 (C–CO), 138.3 (C–N), 139.7 (C–CO), 142.3 (C–NH), 152.7 (C = N), 163.0 (CO), 167.2 (CH = N), and 196.5 (CO).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid (2,3,4,5,6-pentahydroxy-hexylidene)-hydrazide (6b)

Yield = 1.3 g (89%), m.p. = 150–154°C. Analysis for $C_{27}H_{26}N_4O_7$ (518.5): Calcd.: C, 62.5; H, 5.1; N, 10.8; Fd.: C, 62.5; H, 5.0; N, 10.8. IR (cm^{-1}): 3755(NH), 3220 (OH), 1705 (CO). MS: *m/z* (%): 519 (M^+, 13); 518 (M^+, 18). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.30 (s, 5H, OH); 3.13 (m, 1H, ″H_6); 3.29 (m, 1H, ″H_6); 4.20 (t, 1H, $^1H_2$); 4.31 (t, 1H, $^1H_4$); 4.89 (m, 1H, $^1H_5$); 5.16 (t, 1H, $^1H_3$); 5.45 (s, 1H, NH); 6.52 (d, 1H, CH); 7.25 (s, 1H, NH); 7.48–8.22 (m, 12H, Ar–H). ^{13}C-NMR δ, ppm (DMSO-d_6): showed the presence of 27 signals corresponding to the 27 different carbon groups, and signals appeared at δ 64.5 (CH_2OH), 66.5–72.5 (4CHOH), 115.4–130.7 (Ar–12CH), 131.3 (C–CO), 134.1 (C–C = N), 134.7 (C–CO), 138.3 (C–N), 139.7 (C–CO), 142.3 (C–NH), 152.7 (C = N), 163.0 (CO), 167.2 (CH = N), and 196.5 (CO).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid (2,3,4,5,6-pentahydroxy-hexylidene)-hydrazide (6c)

Yield = 1.2 g (82%), m.p. = 157–159°C. Analysis for $C_{27}H_{26}N_4O_7$ (518.5): Calcd.: C, 62.5; H, 5.1; N, 10.8; Fd.: C, 62.5; H, 5.0; N, 10.8. IR (cm^{-1}): 3652 (NH), 3265 (OH), 1705 (CO), 1678 (CO). MS: *m/z* (%): 519 (M^+, 23); 518 (M^+, 31). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.30 (s, 5H, OH); 3.13 (m, 1H, ″H_6); 3.29 (m, 1H, ″H_6); 4.20 (t, 1H, $^1H_2$); 4.31 (t, 1H, $^1H_4$); 4.89 (m, 1H, $^1H_5$); 5.16 (t, 1H, $^1H_3$); 5.45 (s, 1H, NH); 6.52 (d, 1H, CH); 7.25 (s, 1H, NH); 7.48–8.22 (m, 12H, Ar–H).

General procedure for the preparation of 4-(5-benzoyl-1H-benzoimidazol-2-yl)-*N*-[4-oxo-2-(1,2,3,4-tetrahydroxy-butyl)/(1,2,3,4,5-pentahydroxy-pentyl)-thiazolidin-3-yl]-benzamide (7a–c)

A solution of compounds **6a–c** (1 g; 0.01 mol) and mercaptoacetic acid (2 ml, 0.02 mol) in dioxane (20 ml) was stirred at room temperature for 48 h. The solvent was evaporated under vacuum and the residue was washed with a 4N Na_2CO_3 solution and then with water. The separated solid was filtered off, washed with water till carbonate free was obtained, then with cold ethanol and ether, and dried under vacuum at room temperature Scheme 2.

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-*N*-[4-oxo-2-(1,2,3,4-tetrahydroxy-butyl)-thiazolidin-3-yl]-benzamide (7a)

Yield = 0.9 g (78%), m.p. = 114–117°C. Analysis for $C_{28}H_{26}N_4O_7S$ (562.6): Calcd.: C, 59.8; H, 4.7; N, 10.0; S, 5.7; Fd.: C, 59.8; H, 4.8; N, 10.0; S, 5.7. IR (cm^{-1}): 3786 (NH), 3208 (OH), 1718 (CO), 1705 (CO), 1679 (CO). MS: *m/z* (%): 562 (M^+, 34). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.30 (s, 4H, OH); 3.76 (s, 2H, CH_2); 4.20 (t, 1H, $^1H_2$); 4.31 (t, 1H, $^1H_4$); 4.89 (m, 1H, $^1H_5$); 5.16 (t, 1H, $^1H_3$); 5.36 (d, 1H, CH); 5.45 (s, 1H, NH); 7.19 (s, 1H, NH); 7.48–8.22 (m, 12H, Ar–H).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-*N*-[4-oxo-2-(1,2,3,4,5-pentahydroxy-pentyl)-thiazolidin-3-yl]-benzamide (7b)

Yield = 0.85 g (75%), m.p. = 92–95°C. Analysis for $C_{29}H_{28}N_4O_8S$ (592.6): Calcd.: C, 58.8; H, 4.8; N, 9.5; S, 5.4; Fd.: C, 58.9; H, 4.8; N, 9.4; S, 5.4. IR (cm^{-1}): 3755 (NH), 3220 (OH), 1718 (CO), 1705 (CO), 1669 (CO). MS: *m/z* (%): 592 (M^+, 34). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.30 (s, 5H, OH); 3.13 (m, 1H, ″H_6); 3.29 (m, 1H, ″H_6); 3.76 (s, 2H, CH_2); 4.20 (t, 1H, $^1H_2$); 4.31 (t, 1H, $^1H_4$); 4.89 (m, 1H, $^1H_5$); 5.16 (t, 1H, $^1H_3$); 5.36 (d, 1H, CH); 5.45 (s, 1H, NH); 7.19 (s, 1H, NH); 7.48–8.22 (m, 12H, Ar–H).

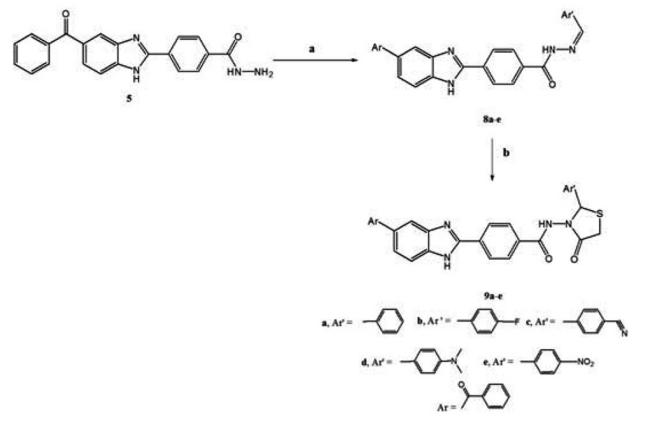
4-(5-Benzoyl-1H-benzoimidazol-2-yl)-*N*-[4-oxo-2-(1,2,3,4,5-pentahydroxy-pentyl)-thiazolidin-3-yl]-benzamide (7c)

Yield = 0.8 g (70%), m.p. = 85–88°C. Analysis for $C_{29}H_{28}N_4O_8S$ (592.6): Calcd.: C, 58.8; H, 4.8; N, 9.5; S, 5.4; Fd.: C, 58.9; H, 4.8; N, 9.4; S, 5.4. IR (cm^{-1}): 3755 (NH), 3220 (OH), 1718 (CO), 1705 (CO), 1669 (CO). MS: *m/z* (%): 592 (M^+, 34). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.30 (s, 5H, OH); 3.13 (m, 1H, ″H_6); 3.29 (m, 1H, ″H_6); 3.76 (s, 2H, CH_2); 4.20 (t, 1H, $^1H_2$); 4.31 (t, 1H, $^1H_4$); 4.89 (m, 1H, $^1H_5$); 5.16 (t, 1H, $^1H_3$); 5.36 (d, 1H, CH); 5.45 (s, 1H, NH); 7.19 (s, 1H, NH); 7.48–8.22 (m, 12H, Ar–H).

General procedure for the preparation of 4-(5-benzoyl-1H-benzoimidazol-2-yl)-benzoic acid-[(un)substituted-benzylidene]-hydrazide (8a–e)

A mixture of the arenaldehydes, namely, benzaldehyde, 4-fluoro benzaldehyde, 4-cyanobenzaldehyde, 4-dimethylaminobenzaldehyde, and/or 4-nitro benzaldehyde (0.01 mol) and compound **5** (1 g; 0.01 mol) in ethanol (30 ml) containing a few drops of glacial acetic acid was refluxed for 3 h. Then, the hot mixture was filtered off. After cooling, the filtrate was diluted with 50 ml of water and the resulting precipitate was filtered off and recrystallized from methanol to yield **8a–e**, respectively Scheme 3.

Scheme 3



Reagents: (a) benzaldehyde, 4-fluorobenzaldehyde, 4-cyanobenzaldehyde, 4-dimethylaminobenzaldehyde, and/or 4-nitrobenzaldehyde, EtOH, CH_3COOH; (b) $HSCH_2COOH$, dioxane.

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid benzylidene-hydrazide (8a)

Yield = 1.1 g (88%), m.p. = 292–295°C. Analysis for $C_{28}H_{20}N_4O_2$ (444.5): Calcd.: C, 75.6; H, 4.5; N, 12.6; Fd.: C, 75.6; H, 4.6; N, 12.6. IR (cm^{-1}): 3322 (NH), 3286 (NH), 1705 (CO), 1683 (CO). MS: *m/z* (%): 445 (M^+, 36); 444 (M^+, 59). ^{1}H-NMR: δ, ppm (DMSO-d_6); 4.99 (s, 1H, NH); 6.48 (s, 1H, CH); 7.43–8.46 (m, 17H, Ar–H); 7.99 (s, 1H, NH). ^{13}C-NMR δ, ppm (DMSO-d_6): showed the presence of 28 signals corresponding to the 28 different carbon groups, and signals appeared at δ 118.4–130.7 (Ar–17CH), 131.3 (C–CO), 134.1 (C–C = N), 134.7 (C–CO), 138.3 (C–N), 139.7 (C–CO), 142.3 (C–NH), 152.7 (C = N), 163.0 (CO), 167.2 (CH = N), and 196.5 (CO).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid (4-fluoro-benzylidene)-hydrazide (8b)

Yield = 1.2 g (92%), m.p. = 277–279°C. Analysis for $C_{28}H_{19}FN_4O_2$ (462.5): Calcd.: C, 72.7; H, 4.1; N, 12.1; Fd.: C, 72.7; H, 4.0; N, 12.1. IR (cm^{-1}): 3422 (NH), 3286 (NH), 1705 (CO), 1683 (CO). MS: *m/z* (%): 462 (M^+, 59). ^{1}H-NMR: δ, ppm (DMSO-d_6); 4.99 (s, 1H, NH); 6.48 (s, 1H, CH); 7.43–8.46 (m, 16H, Ar–H); 7.99 (s, 1H, NH).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid (4-cyanobenzylidene)-hydrazide (8c)

Yield = 1.2 g (91%), m.p. = 250–253°C. Analysis for $C_{29}H_{19}N_5O_2$ (469.5): Calcd.: C, 74.2; H, 4.1; N, 14.9; Fd.: C, 74.3; H, 4.1; N, 14.8. IR (cm^{-1}): 3421 (NH), 3216 (NH), 2219 (CN), 1705 (CO), 1683 (CO). MS: *m/z* (%): 469 (M^+, 27). ^{1}H-NMR: δ, ppm (DMSO-d_6); 4.99 (s, 1H, NH); 6.48 (s, 1H, CH); 7.43–8.46 (m, 16H, Ar–H); 7.99 (s, 1H, NH). ^{13}C-NMR δ, ppm (DMSO-d_6): showed the presence of 29 signals corresponding to the 29 different carbon groups, and signals appeared at δ 114.9 (C–CN), 115.8 (C≡N), 118.4–130.7 (Ar–16CH), 131.3 (C–CO), 134.1 (C–C = N), 134.7 (C–CO), 138.3 (C–N), 139.7 (C–CO), 142.3 (C–NH), 152.7 (C = N), 163.0 (CO), 167.2 (CH = N), and 196.5 (CO).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid (4-dimethylamino-benzylidene)-hydrazide (8d)

Yield = 1.3 g (95%), m.p. = 287–289°C. Analysis for $C_{30}H_{25}N_5O_2$ (487.5): Calcd.: C, 73.9; H, 5.2; N, 14.4; Fd.: C, 73.9; H, 5.2; N, 14.4. IR (cm^{-1}): 3421 (NH), 3216 (NH), 2219 (CN), 1705 (CO), 1683 (CO). MS: *m/z* (%): 487 (M^+, 24). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.37 (s, 6H, CH_3); 4.99 (s, 1H, NH); 6.48 (s, 1H, CH); 7.43–8.46 (m, 16H, Ar–H); 7.99 (s, 1H, NH).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-benzoic acid (4-nitro-benzylidene)-hydrazide (8e)

Yield = 1.3 g (95%), m.p. = 180–184°C. Analysis for $C_{28}H_{19}N_5O_4$ (489.5): Calcd.: C, 68.7; H, 3.9; N, 14.3; Fd.: C, 68.6; H, 3.9; N, 14.4. IR (cm^{-1}): 3421 (NH), 3216 (NH), 2219 (CN), 1705 (CO), 1683 (CO). MS: *m/z* (%): 489 (M^+, 47). ^{1}H-NMR: δ, ppm (DMSO-d_6); 4.99 (s, 1H, NH); 6.48 (s, 1H, CH); 7.43–8.46 (m, 16H, Ar–H); 7.99 (s, 1H, NH).

General procedure for the preparation of 4-(5-benzoyl-1H-benzoimidazol-2-yl)-*N*-[4-oxo-2-(un)substituted-phenyl)-thiazolidin-3-yl]-benzamide (9a–e)

The foregoing method is the same as described for the preparation of C-nucleosides **7a–c**, but with the use of the Schiff's bases **8a–e** instead of **6a–c** derivatives, Scheme 3.

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-*N*-(4-oxo-2-phenyl-thiazolidin-3-yl)-benzamide (9a)

Yield = 0.9 g (77%), m.p. = 145–148°C. Analysis for $C_{30}H_{22}N_4O_3S$ (518.6): Calcd.: C, 69.5; H, 4.3; N, 10.8; S, 6.2; Fd.: C, 69.5; H, 4.4; N, 10.8; S, 6.2. IR (cm^{-1}): 3322 (NH), 3188 (NH), 1720 (CO), 1706 (CO), 1689 (CO). MS: *m/z* (%): 518 (M^+, 24). ^{1}H-NMR: δ, ppm (DMSO-d_6); 3.45 (s, 2H, CH_2); 4.32 (s, 1H, NH); 5.97 (s, 1H, CH); 7.43–8.46 (m, 17H, Ar–H); 10.42 (s, 1H, NH).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-*N*-[2-(4-fluoro-phenyl)-4-oxo-thiazolidin-3-yl]-benzamide (9b)

Yield = 0.85 g (73%), m.p. = 112–115°C. Analysis for $C_{30}H_{21}FN_4O_3S$ (536.6): Calcd.: C, 67.2; H, 3.9; N, 10.4; S, 6.0; Fd.: C, 67.2; H, 3.9; N, 10.4; S, 6.0. IR (cm^{-1}): 3322 (NH), 3188 (NH), 1720 (CO), 1706 (CO), 1689 (CO). MS: *m/z* (%): 536 (M^+, 29). ^{1}H-NMR: δ, ppm (DMSO-d_6); 3.45 (s, 2H, CH_2); 4.32 (s, 1H, NH); 5.97 (s, 1H, CH); 7.43–8.46 (m, 16H, Ar–H); 10.42 (s, 1H, NH).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-*N*-[2-(4-cyano-phenyl)-4-oxo-thiazolidin-3-yl]-benzamide (9c)

Yield = 0.95 g (82%), m.p. = 92–95°C. Analysis for $C_{31}H_{21}N_5O_3S$ (543.6): Calcd.: C, 68.5; H, 3.9; N, 12.9; S, 5.9; Fd.: C, 68.5; H, 4.0; N, 13.1; S, 5.8. IR (cm^{-1}): 3329 (NH), 3183 (NH), 2219 (CN), 1720 (CO), 1706 (CO), 1689 (CO). MS: *m/z* (%): 543 (M^+, 32). ^{1}H-NMR: δ, ppm (DMSO-d_6); 3.45 (s, 2H, CH_2); 4.32 (s, 1H, NH); 5.97 (s, 1H, CH); 7.43–8.46 (m, 16H, Ar–H); 10.42 (s, 1H, NH).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-*N*-[2-(4-dimethylamino-phenyl)-4-oxo-thiazolidin-3-yl]-benzamide (9d)

Yield = 0.85 g (74%), m.p. = 134–137°C. Analysis for $C_{32}H_{27}N_5O_3S$ (561.6): Calcd.: C, 68.4; H, 4.9; N, 12.5; S, 5.7; Fd.: C, 68.4; H, 4.9; N, 12.5; S, 5.7. IR (cm^{-1}): 3322 (NH), 3188 (NH), 1720 (CO), 1706 (CO), 1689 (CO). MS: *m/z* (%): 561 (M^+, 29). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.37 (s, 6H, CH_3); 3.45 (s, 2H, CH_2); 4.32 (s, 1H, NH); 5.97 (s, 1H, CH); 7.43–8.46 (m, 16H, Ar–H); 10.42 (s, 1H, NH).

4-(5-Benzoyl-1H-benzoimidazol-2-yl)-*N*-[2-(4-nitro-phenyl)-4-oxo-thiazolidin-3-yl]-benzamide (9e)

Yield = 0.9 g (78%), m.p. = 92–95°C. Analysis for $C_{30}H_{21}N_5O_5S$ (563.6): Calcd.: C, 63.9; H, 3.8; N, 12.4; S, 5.7; Fd.: C, 63.9; H, 3.8; N, 12.4; S, 5.7. IR (cm^{-1}): 3322 (NH), 3188 (NH), 1720 (CO), 1706 (CO), 1689 (CO). MS: *m/z* (%): 563 (M^+, 19). ^{1}H-NMR: δ, ppm (DMSO-d_6); 3.45 (s, 2H, CH_2); 4.32 (s, 1H, NH); 5.97 (s, 1H, CH); 7.43–8.46 (m, 16H, Ar–H); 10.42 (s, 1H, NH).

Antimicrobial activity test

The *in-vitro* antimicrobial activity was assessed against *Bacillus subtilis* NRRL 543, *Staphylococcus aureus* NRRL B-313 (gram-positive bacteria), *Escherichia coli* NRRL B-210 and *Pseudomonas aeuroginosa* NRRL B-23 (gram-negative bacteria), *Candida albicans* NRRL Y-477, and *Aspergillus niger* NRRL 599 (fungi) using the agar diffusion method [17]. A suspension of the organisms was added to sterile nutrient agar media at 45°C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 10 mm in diameter were made using a cork borer; 0.1 ml of the synthesized compounds was poured into the holes. A hole filled with DMSO was also used as a control. The plates were left for 1 h at room temperature for a period of preincubation diffusion to minimize the effects to variation in time between the applications of the different solutions. The plates were then incubated at 37°C for 24 h and observed for antibacterial activity. The diameters of zone of inhibition were measured and compared with that of the standard, and the values were tabulated. Ciprofloxacin and fluconazole were used as standards for antibacterial and antifungal activity, respectively.

To evaluate the activity of synthesized compounds against bacteria and fungi, minimum inhibitory concentration (MIC) was determined using the agar streak dilution method; 100 mg/ml stock solution of the synthesized compounds was prepared using DMSO as the solvent. From this stock solution, a range of concentrations from 5 to 0.05 mg/ml of the tested compounds' solutions were mixed with known quantities of molten sterile agar media aseptically. About 20 ml of nutrient agar medium for bacteria and Sabouraud dextrose agar medium for fungi containing the tested compound under study were dispensed into each sterile Petri dish. Then, the media were allowed to solidify. Microorganisms were then streaked one by one on the agar plates aseptically. After streaking, all the plates were incubated at 30°C for 24 h/48 h for bacteria and fungi, respectively. Then, the plates were observed for the growth of microorganisms. The lowest concentration of the synthesized compounds inhibiting the growth of the given bacteria/fungus was considered the MIC of the test compounds against that bacteria or fungi on the plate.

Results and discussion

Chemistry

The starting material 4-(5-benzoyl-1H-benzoimidazol-2-yl)-benzonitrile (**2**) was prepared through the reaction of (3,4-diamino-phenyl)-phenyl-methanone (**1**) with 4-cyanobenzaldehyde in absolute ethanol. Stirring of compound **2** with 70% sulfuric acid yielded benzoic acid derivative **3**, followed by esterification and refluxing with hydrazine hydrate to form the corresponding 4-(5-benzoyl-1H-benzoimidazol-2-yl)-benzoic acid hydrazide (**5**) (Scheme 1).

Thus, the reaction of 4-(5-benzoyl-1H-benzoimidazol-2-yl)-benzoic acid hydrazide (**5**) dissolved in DMF containing a few drops of acetic acid with various monosaccharide (aldoses) namely, d (+) xylose, d (+) glucose, and/or d (+) galactose dissolved in water yielded the corresponding Schiff's bases **6a–c**. Cyclocondensation of Schiff's bases **6a–c** with thioglycolic acid in dry dioxane yielded the corresponding C-nucleosides **7a–c** as shown in Scheme 2.

Also, the reaction of 4-(5-benzoyl-1H-benzoimidazol-2-yl)-benzoic acid hydrazide (**5**) with different arenaldehydes, namely, benzaldehyde, 4-fluorobenzaldehyde, 4-cyanobenzaldehyde,

4-dimethylaminobenzaldehyde, and/or 4-nitrobenzaldehyde in the presence of a few drops of acetic acid yielded Schiff's bases **8a–e**. Cyclocondensation of Schiff's bases **8a–e** with thioglycolic acid in dry dioxane yielded the corresponding thiazolidinones **9a–e** as shown in Scheme 3.

Antimicrobial activity test

The results indicated that compounds **4**, **5**, **6b**, **8a**, **8b**, and **8d** showed the best antimicrobial activity against the tested microorganisms. Compounds **2**, **7b**, **9a**, **9b**, and **9d** showed less activity against all the tested microorganisms. Compounds **3**, **6a**, and **7a** showed moderate activity. The antifungal activities shown in (Table 1) indicates that compounds **4** and **6b** showed good activity against *C. albicans* and *A. niger*, followed by compounds **5**, **8a**, **8b**, and **8d**, which were moderately active, whereas compounds **6a**, **7a**, **7b**, **9a**, **9b**, and **9d** showed the lowest antifungal activities.

Structure–activity relationship

The MIC of synthesized compounds, which are shown in (Table 2), was in accordance with the results obtained in the primary screening. The structure–activity relationship indicated that the attachment of 4-(5-benzoyl-1H-benzoimidazol-2-yl)-benzoic acid hydrazide (**5**) with different monosaccharides and/or with aromatic aldehydes moieties through Schiff's linkage resulted in a marked increase in antimicrobial activity. The ethyl ester **4** and compound **6b** showed high activity against gram-positive bacteria (*B. subtilis* and *S. aureus*), gram-negative bacteria (*E. coli* and *P. aeuroginosa*), and the yeast-like pathogenic fungus (*C. albicans* and *A. niger*). Furthermore, compound **6b** showed higher activity than ciprofloxacin and fluconazole, which were used as the standard for antibacterial and antifungal activity, respectively. In addition, the antimicrobial activity observed for the thiazolidinones **7a**, **7b**, **9a**, **9b**, and **9d** indicated the importance of the free Schiff's linkage as the activity was reduced when this group was cyclized to yield the corresponding thiazolidinone. Moreover, the

Table 1 Inhibition zone (mm) as a criterion of antibacterial and antifungal activities of the newly synthesized compounds

Compounds	Microorganism inhibition zone diameter (mm)					
	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeuroginosa*	*Candida albicans*	*Aspergillus niger*
2	–	–	11	–	13	–
3	20	19	15	17	18	–
4	16	17	23	20	22	17
5	17	16	17	15	19	14
6a	12	12	16	14	11	–
6b	27	26	24	25	27	20
7a	15	14	–	13	11	–
7b	–	–	–	–	–	–
8a	21	19	20	18	20	15
8b	20	19	24	23	20	14
8d	21	20	20	20	17	11
9a	–	–	–	–	–	–
9b	–	–	–	–	–	–
9d	–	–	–	–	–	–
Ciprofloxacin	22	24	24	23	–	–
Fluconazole	–	–	–	–	22	24

Highly active,inhibition zone>20 mm; moderately active,inhibition zone 15–20 mm; slightly active,inhibition zone 11–14 mm; inactive, inhibition zone <11 mm.

Table 2 MIC (mg/ml) of the newly synthesized compounds against microorganisms

Compounds	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeuroginosa*	*Candida albicans*	*Aspergillus niger*
4	0.53	0.56	0.4	0.57	0.48	0.6
5	0.55	0.6	0.6	0.6	0.55	0.7
6b	0.05	0.05	0.05	0.05	0.05	0.06
8a	0.5	0.53	0.55	0.55	0.55	0.7
8b	0.49	0.5	0.4	0.57	0.54	0.7
8d	0.1	0.4	0.6	0.15	0.6	0.8
Ciprofloxacin	0.05	0.05	0.05	0.05	–	–
Fluconazole	–	–	–	–	0.05	0.05

MIC, minimum inhibitory concentration.

antibacterial activity observed for the thiazolidinone derivative **7a** was relatively higher than that of the corresponding thiazolidinone **7b**, 9a, **9b**, and **9d**. In addition, benzylidene **8d** showed high activity against tested gram-positive bacteria and gram-negative bacteria and showed moderate activity against the yeast-like pathogenic fungus (*C. albicans* and *A. niger*).

Conclusion

The preliminary *in-vitro* antibacterial and antifungal screening results of novel benzoimidazole derivatives reported here have indicated the antimicrobial activity of the synthesized compounds. SAR observation has shown the importance of free Schiff's linkage. The presence of substituents on the aromatic ring has increased the activity of the compounds compared with that of unsubstituted benzylidene. Findings from SAR have encouraged us to make some modifications on the basic structure of the compounds obtained to obtain selective and more active derivatives in ongoing studies.

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Conflicts of interest

There are no conflicts of interest.

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