Synthesis and Reactions of Some Novel 5,7-diiodo-8-Hydroxyquinoline Candidates as Antimicrobial Agentes

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Abstract. A series of N- acetamides **2a**,**b**, N-Mannich bases **5a,b**, sugar hydrazone (**6a-e**, **7a-c**), imide and bis-imide derivatives **8-12** have been synthesized by using ethyl-2-(5,7-diiodoquinolin-8-yloxy)acetate **1** as starting material The detailed synthesis, spectroscopic data and microbial evaluation of the synthesized compounds were reported.

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1. Introduction

8-Hydroxyquinolines represent a privileged substructure which is found in bioactive natural products [Balamurugan et al., **2005;** Horton et al., **2003;** Ziegert et al., 2005] and is used as the source for many drugs diversely prescribed among a wide range of pathologies including neurodegenerative diseases [Adlard et al., **2008**], parasitic amoebic dysentery disease [Thompson et al., **1951**], and herpes viral diseases [Oien et al., 2002]. More specifically, 8-hydroxyquinoline moiety has been mostly used for its capacity to strongly chelate metal ions, particularly Cu and Zn [Ji et al., 2005]. In addition to applications in the design of chemosensors and optical devices [Song et al., **2006;** Zhang et al., **2005;** Shavaleev et al., **2008;** Wang et al., **2009**], 8-hydroxyquinoline has been synthesized with a variety of biological activities, such as inhibitors of catechol O-methyltransferase [Borchardt et al., **1976**], inhibitors of HIF-1a prolyl hydroxylase [Saeed et al., **1992**], inhibitors of HIV-1 integrase [Zhuang et al., **2003**], antibacterial [Szabo, **1966;** Gershon et al., **1962**], antimalarial [Negm et al., **2005**], and antitumor agents [Scheibel et al., **1980;** Yamato et al., **1986;** Moret et al., **2009**]. In view of these observations and as continuation of our previous works in heterocyclic and glycoside chemistry with having biological activity [Khalifa et al., **2013;** Khalifa et al., **2008;** Petersen et al., **2002;** Bahgat et al., **2006;** Fahmy et al., **2012;** Abdel Salam et al., **2013**], we have herein report the structural modifications of 8-hydroxyquinoline-derived hydrazide bases with their antimicrobial effect.

2. Experimental

Melting points were measured in open capillary tubes using Griffin apparatus and were uncorrected. Elemental analyses were performed at the Microanalytical Center, Cairo University and the results were within ±0.3 from the theoretical values. The infrared (IR) spectra were recorded using potassium bromide disc technique on Schimadzu 435 IR Spectrophotometer, National Research Center. (^{1}HNMR and ^{13}CNMR) spectra were performed on varian JEOL 270 and 500 MHz (JEOL, Japan) Spectrophotometer using tetramethylsilane (TMS) as internal standard, National Research Center. Mass Spectra were recorded on JEOL-JMS-AX500 70e Spectrometer, National Research Center. Reactions were monitored using thin layer chromatography (TLC), performed on 0.255 mm silica gel plates, with visualization under U.V. light (254 nm). The antimicrobial screening was performed by Professor Abdelhamid A. Hamdy, through the Department of Microbiology, Natural and Microbial Products, National Research Centre, Egypt.

2-(5,7-Diiodoquinolin-8-yloxy)-N- and -N-bis (2-hydroxyethyl) acetamide (2a,b)

A mixture of compound **2** (0.01 mol) and the appropriate ethanolamine (0.08 mol) namely 2-hydroxyethylamine and bis-(2-hydroxyethyl) amine were heated under reflux in ethanol for 6 hrs. The formed precipitate was collected by filtration, washed with petroleum ether then crystallized from ethanol.

2-(5,7-Diiodoquinolin-8-yloxy)-N-(2-hydroxyethyl)acetamide (2a)

Yield 80%; m.p. 129-131 ^{O}C; IR (KBr, cm^{-1}) ν_{max}: 3397 (OH), 1645 (C=O); ^{1}HNMR (DMSO-d$_6$)

δ: 2.72 (t, 2H, $\underline{CH_2}$-NH), 3.91 (t, 2H, $\underline{CH_2}$-OH), 5.21 (s, 2H, O-CH_2), 5.86 (s, 1H, OH, exchangeable with D_2O), 7.65-8.83 (m, 4H, Ar-H); MS: m/z 497 ($M^{+\cdot}$-1, 8), 78 (100), consistent with the molecular formula ($C_{13}H_{12}I_2N_2O_3$).

2-(5,7-Diiodoquinolin-8-yloxy)-N,N-bis(2-hydroxyethyl)acetamide (2b)

Yield 66%; m.p. 144-146 ^{O}C; IR (KBr, cm^{-1}) ν_{max}: 3372 (OH), 1661 (C=O); ^{1}HNMR (DMSO-d_6) δ: 3.18 (t, 4H, 2 $\underline{CH_2}$-N), 3.70 (t, 4H, 2 $\underline{CH_2}$-OH), 5.27 (s, 2H, O-CH_2), 5.75 (S, 2H, 2OH, exchangeable with D_2O), 7.71-8.86 (m, 4H, Ar-H); MS: m/z 542 ($M^{+\cdot}$, 0.01,), 410 (5.26), 114 (25.53), 56 (100), consistent with the molecular formula ($C_{15}H_{16}I_2N_2O_4$).

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(1-(substitutedmethyl)-2-oxoindolin-3-ylidene)acetohydrazide (5a,b)

A mixture of paraformaldehyde (0.001 mol) and the appropriate secondary amines (0.015 mol), namely, diethylamine or morpholine in absolute ethanol (10 mL) was refluxed for 30 min. till complete solubility of paraformaldehyde. Compound **4** (0.004 mol) was heated in absolute ethanol (10 mL) then added to the reaction mixture which was refluxed for 2 hrs. The reaction mixture was concentrated, cooled, and the separated product was filtered off and crystalized from ethyl alcohol to give the title compounds **5a,b**.

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(1--((Diethylamino)methyl)-2-oxoindolin-3-ylidene)acetohydrazide (5a)

Yield 70%; m.p. 239-241 ^{O}C; ^{1}HNMR (DMSO-d_6) δ: 1.06 (t, 6H, CH_2-$\underline{CH_3}$), 3.74 (s, 2H, N-CH_2-N), 4.06 (q, 4H, $\underline{CH_2}$-CH_3); 4.67 (s, 2H, O-CH_2), 7.60-8.78 (m, 9H, Ar-H and NH); MS: m/z 684 ($M^{+\cdot}$+1, 21.88), 77 (100), consistent with the molecular formula ($C_{24}H_{23}I_2N_5O_3$).

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)acetohydrazide (5b)

Yield 60%; m.p. 209-211 ^{O}C; ^{1}HNMR (DMSO-d_6) δ: 3.14 (s, 1H, NH exchangeable with D_2O), 3.81 (t, 4H, N(CH_2)$_2$ of morpholine ring), 3.84 (S, 2H, N-CH_2-N), 4.1 (t, 4H, O(CH_2)$_2$ of morpholine ring); 4.78 (s ,1H , O-CH_2), 7.68-8.84 (m, 8H, Ar-H and NH); MS: m/z 697($M^{+\cdot}$, 31.61), 61(100), consistent with the molecular formula ($C_{24}H_{21}I_2N_5O_4$).

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(Glycosyl)acetohydrazide (6a-e)

A mixture of **3** (10 mmol), the appropriate monosacchrides (10 mmol) in presence of a catalytic amounts of acetic acid was heated at reflux in ethyl alcohol (50 mL) for 2-4 h, the reaction mixture was allowed to cool to room temperature, the precipitate was filtered off, washed with ethanol, dried and crystallized from ethyl alcohol to afford the title compounds **6a-e**.

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(Glucosyl)acetohydrazide (6a)

Yield 66%; m.p. 179-181 ^{O}C; IR (KBr, cm^{-1}) ν_{max}: 3353 (OH), 3200 (NH), 1671 (C=O); ^{1}HNMR (DMSO-d_6) δ: 3.15-3.59 (m, 4H, 6'H, 6"H, 5'H, 4'H), 3.88 (t, 1H, 6'OH), 4.42 (m, 2H, 5'OH, 4'OH), 4.79 (s, 2H, O-CH_2),5.36 (m, 3H, 2'H, 3'H, 3'OH), 5.59 (d, 1H, 2'OH), 7.34 (d, 1H, 1'H), 7.34 (d, 1H, 1'H), 7.74-8.99 (m, 4H, Ar-H); 10.41 (s, 1H, NH exchangeable with D_2O).

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(xylosyl)acetohydrazide (6b)

Yield 71%; m.p. 174-176 ^{O}C; IR (KBr, cm^{-1}) ν_{max}: 3374 (OH), 3211 (NH), 1652 (C=O); MS: m/z 601 ($M^{+\cdot}$, 56,72 (100), consistent with the molecular formula ($C_{16}H_{17}I_2N_3O_6$).

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(arabinosyl)acetohydrazide (6c)

Yield 69%; m.p. 179-181 ^{O}C; IR (KBr, cm^{-1}) ν_{max}: 3303 (OH), 3200 (NH), 1661 (C=O); ^{1}HNMR (DMSO-d_6) δ: 3.36-3.86 (m, 4H, 5'H, 5"H, 4'H, 5'OH), 4.30 (m, 1H, 2'H), 4.55-4.92 (m, 4H, 3'H, 3'OH, 4'OH, 2'OH), 5.35 (s, 2H, O-CH_2), 7.10 (d, 1H, 1'H), 7.74-8.94 (m, 4H, Ar-H), 10.43 (s, 1H, NH exchangeable with D_2O).

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(mannosyl)acetohydrazide (6d)

Yield 61%; m.p. 179-181 ^{O}C; IR (KBr, cm^{-1}) ν_{max}: 3397 (OH), 3253 (NH), 1662 (C=O); MS: m/z 631 ($M^{+\cdot}$, 40.1), 254 (100), consistent with the molecular formula ($C_{17}H_{19}I_2N_3O_7$).

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(mannosyl)acetohydrazide (6e)

Yield 74%; m.p. 174-176 ^{O}C; IR (KBr, cm^{-1}) ν_{max}: 3487 (OH), 3264 (NH), 1692 (C=O); MS: m/z 631 ($M^{+\cdot}$, 9.36), 410 (100), 254 (100), consistent with the molecular formula ($C_{17}H_{19}I_2N_3O_7$).

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(O-acetyl Glycosyl)acetohydrazide (7a-c)

Asolution from each of **6a**, **6d** and **6e** (10 mmol) in amixture of acetic anhydride / pyridine (40 mL, 1:1) was stirred at room temperature for 24 h, poured onto water (100 mL). The mixture was then extracted with chloroform several times (150 mL), after the removal of chloroform under reduced pressure; the precipitate was filtered off, dried, and crystallized from ethyl alcohol to obtain **7a–c**.

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(1′2′,3′,4′,5′-Penta-O-acetylglucosyl)- acetohydrazide (7a)

Yield 73%; m.p. 103-106 ^{O}C; IR (KBr, cm^{-1}) ν_{max}: 3177 (NH), 1747 (C=O), 1702 (C=O, amide); ^{1}HNMR (DMSO-d_6) δ: 1.80-2.10 (m, 15H, 5 $COCH_3$), 3.80-4.30 (m, 3H, 6"H, 6'H, 5H), 4.50-4.90 (m, 3H, 4'H, 3'H, 2'H), 5.04 (s, 2H, OCH_2), 7.56 (d,

1H, 1'H), 7.68-8.90 (m, 4H, Ar-H), 10.35 (s, 1H, NH exchangeable with D_2O); MS: m/z 841 ($M^{+.}$, 32), 410 (100), consistent with the molecular formula ($C_{27}H_{29}I_2N_3O_{12}$).

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(1′,2′,3′,4′-tetra-O-acetylxylosyl) acetohydrazide (7b)

Yield 69%; m.p. 114-116 ^{O}C; IR (KBr, cm^{-1}) ν_{max}: 3175 (NH), 1750 (C=O), 1703 (C=O, amide); ^{1}HNMR (DMSO-d_6) δ: 1.84-2.07 (m, 12H, 4 $COCH_3$), 3.92-5.1 (m, 2H, 5''H, 5'H), 5.15-6.13 (m, 5H, OCH_2, 4'H, 3'H, 2'H), 6.85 (d, 1H, 1'H), 7.70-8.88 (m, 4H, Ar-H); 11.94(s, 1H, NH exchangeable with D_2O); MS: m/z 438 (8.36), 482 (3.03), 410 (100), 397 (18.09); 85 (43.02).

2-(5,7-Diiodoquinolin-8-yloxy)-N'-(1′,2′,3′,4′-tetra-O-acetylarabinosyl) acetohydrazide (7c)

Yield 71%; m.p. 109-111 ^{O}C; IR (KBr, cm^{-1}) ν_{max}: 3178 (NH), 1750 (C=O), 1704 (C=O, amide); ^{1}HNMR (DMSO-d_6) δ: 1.61-2.35 (m, 12H, 4 $COCH_3$), 3.90-4.20 (m, 2H, 5''H, 5'H), 4.85-5.33 (m, 5H, OCH_2, 4'H, 3'H, 2'H), 7.38 (d, 1H, 1'H), 7.75-8.92 (m, 4H, Ar-H), 11.2 (s, 1H, NH exchangeable with D_2O).

Synthesis of imide derivatives (8a,b, 9 and 10)

A stirred glacial acetic acid suspension (50 mL) of hydrazide **3** (1 mmol) and acid anhydride derivatives, namely phthalic anhydride, 1,2,4,5-tetrachlorophethalic anhydride, 1,8-naphthalene anhydride or quinolinic anhydride (1 mmol), was heated at 80 ^{o}C for 6-8 h. The reaction mixture was concentrated under reduced pressure, cooled, and the separated solid was collected by filtration, dried, and crystallized to yield the corresponding imide derivatives **8a,b**, **9**, **10** respectively.

2-(5,7-diiodoquinolin-8-yloxy)-N-(1,3-dioxoisoindolin-2-yl)acetamide (8a)

Yield 82%; m.p. 211-213 ^{O}C (AcOH/H_2O); IR (KBr, cm^{-1}) ν_{max}: 3219 (NH), 1735, 1739, 1685 (3 C=O); ^{1}HNMR (DMSO-d_6) d: 5.34 (s, 2H, CH_2), 7.14-8.23 (m, 8H, Ar-H), 8.95 (s, 1H, NH exchangeable with D_2O); ^{13}CNMR: δ 68.12, 78.37, 89.56, 126.19, 128.29, 129.75, 132.94, 133.62, 141.23, 143.80, 147.59, 153.47, 165.01, 167.84, 169.43; MS: m/z 599 (M^{+}), consistent with the molecular formula ($C_{19}H_{11}I_2N_3O_4$).

2-(5,7-diiodoquinolin-8-yloxy)-N-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)acetamide (8b)

Yield 85%; m.p. 285-287 ^{O}C (AcOH/H_2O); IR (KBr, cm^{-1}) ν_{max}: 3231 (NH), 1739, 1736, 1674 (3 C=O); ^{1}HNMR (DMSO-d_6) d: 5.46 (s, 2H, CH_2), 7.21-8.15 (m, 4H, Ar-H), 9.34 (s, 1H, NH exchangeable with D_2O); ^{13}CNMR: δ 69.62, 77.86, 86.94, 125.83, 128.52, 129.73, 134.51, 139.15, 141.08, 143.59, 148.25, 153.41, 165.38, 167.47, 168.55; MS: m/z 736 (M^{+}), consistent with the molecular formula ($C_{19}H_7Cl_4I_2N_3O_4$).

2-[(5,7-diiodoquinolin-8-yl)oxy]-*N*-(1,3-dioxo-2,3-dihydro-1*H*-phenalen-2 yl)acetamide (9)

Yield 68%; m.p. 246-248 ^{O}C (AcOH/H_2O); IR (KBr, cm^{-1}) ν_{max}: 3228 (NH), 1731, 1725, 1665 (3 C=O); ^{1}HNMR (DMSO-d_6) d: 5.51 (s, 2H, CH_2), 7.12-8.26 (m, 10H, Ar-H), 9.12 (s, 1H, NH exchangeable with D_2O); ^{13}CNMR: δ 68.24, 76.91, 87.19, 123.85, 125.87, 126.43, 128.67, 129.13, 131.34, 137.69, 138.42, 141.16, 143.28, 148.20, 153.17, 159.48, 167.39, 167.89; MS: m/z 649 (M^{+}), consistent with the molecular formula ($C_{23}H_{13}I_2N_3O_4$).

2-(5,7-diiodoquinolin-8-yloxy)-N-(5,7-dioxo-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)acetamide (10)

Yield 76%; m.p. 249-251 ^{O}C (AcOH/H_2O); IR (KBr, cm^{-1}) ν_{max}: 3311 (NH), 1745, 1732, 1680 (3 C=O); ^{1}HNMR (DMSO-d_6) d: 5.41 (s, 2H, OCH_2), 7.18-8.22 (m, 7H, Ar-H), 9.85 (s, 1H, NH exchangeable with D_2O); ^{13}CNMR: δ 68.65, 76.95, 87.32, 125.84, 128.21, 128.68, 129.21, 139.14, 141.18, 142.74, 146.86, 148.42, 152.71, 153.12, 165.22, 166.32, 167.30, 168.71; MS: m/z 600 (M^{+}), consistent with the molecular formula ($C_{18}H_{10}I_2N_4O_4$).

Synthesis of bis-imide derivatives (11 and 12)

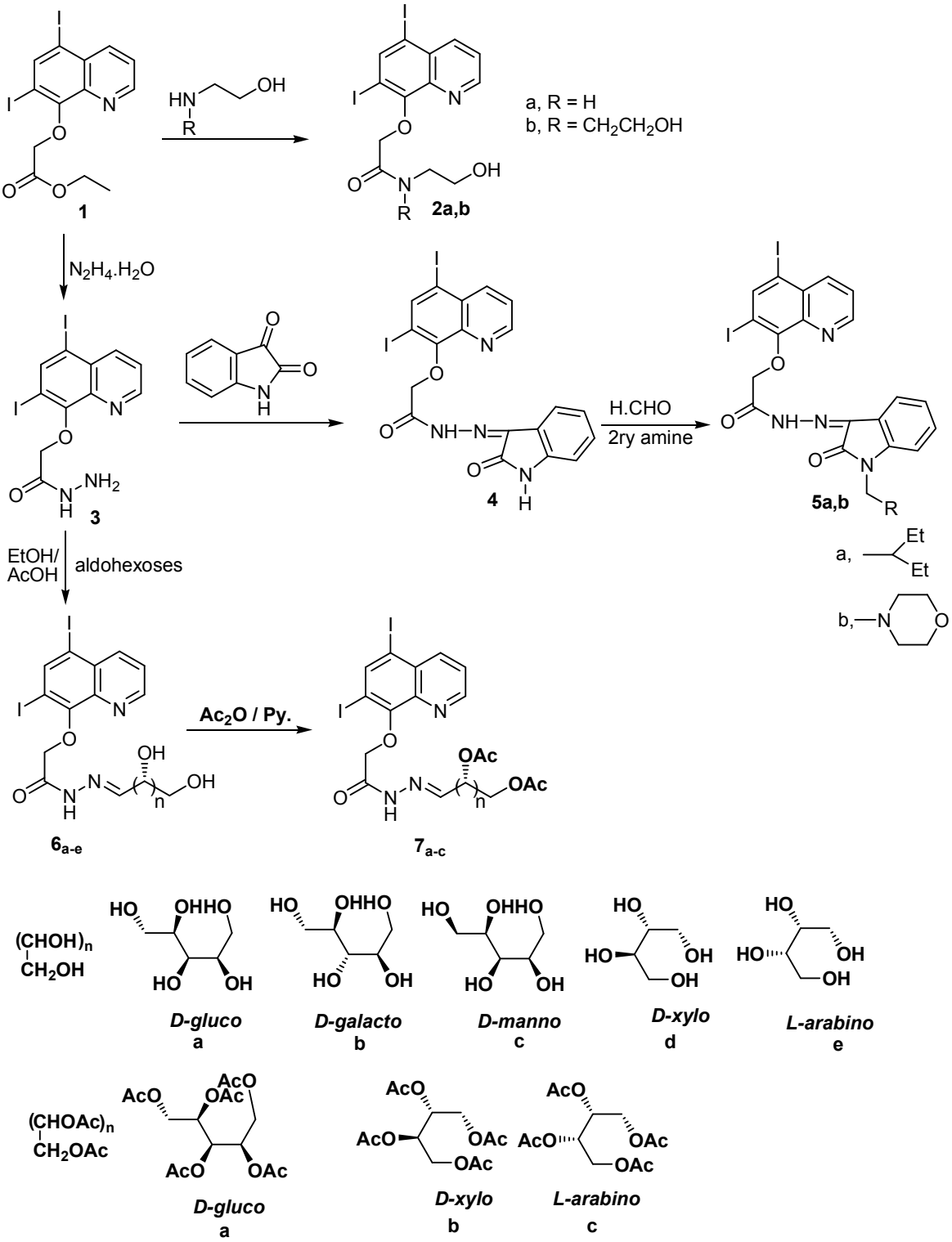
The same procedure except using 1,2,4,5-benzenetetracarboxylic di-anhydride or 1,4,5,8-naphthylenetracarboxylic di-anhydride (20 mmol) in refluxing glacial acetic acid.

Benzene tetracarboxamido bis-[2-(5,7-diiodoquinolin-8-yloxy)-N-acetamide] (11)

Yield 53%; m.p. 201-203 ^{O}C (AcOH/ether); IR (KBr, cm^{-1}) ν_{max}: 3324, 3316 (2NH), 1730 (4 C=O), 1668 (2 C=O); ^{1}HNMR (DMSO-d_6) d: 5.48 (s, 4H, $2CH_2$), 7.11-8.89 (m, 10H, Ar-H), 9.82 (s, 2H, NH exchangeable with D_2O); ^{13}CNMR: δ 67.96, 76.15, 87.62, 125.58, 126.23, 129.45, 136.20, 141.17, 143.54, 147.83, 153.41, 165.36, 167.25, 169.01; MS: m/z 1120 (M^{+}.), consistent with the molecular formula ($C_{32}H_{16}I_4N_6O_8$).

Naphthalene tetracarboxamido bis-[2-(5,7-diiodoquinolin-8-yloxy)-N-acetamide] (12)

Yield 62%; m.p. 229-281 ^{O}C (AcOH/ether); IR (KBr, cm^{-1}) ν_{max}: 3309, 3295 (2NH), 1721 (4 C=O), 1687 (2 C=O); ^{1}HNMR (DMSO-d_6) d: 5.40 (s, 4H, $2CH_2$), 7.25-8.32 (m, 12H, Ar-H), 9.96 (s, 2H, NH exchangeable with D_2O); ^{13}CNMR: δ 68.34, 77.21, 86.46, 121.52, 126.32, 129.62, 135.70, 140.68, 141.21, 143.12, 147.63, 153.06, 159.33, 166.92, 169.17; MS: m/z 1170 (M^{+}.), consistent with the molecular formula ($C_{36}H_{18}I_4N_6O_8$).



Scheme 1: Synthesis route of compounds **2-7**

3. Results and Discussion

The synthetic scheme which has been developed in order to elaborate this library of 19 analogues is outlined in Schemes [1 and 2]. Synthesis of analogues **1**, **3** and **4** have already been reported [Soliman and Hammouda, **1979;** Fahmy and Hamdy, **2003;** Fahmy, **1997**]. The new analogues **2**–**12**, have been synthesized starting by ethyl 2-(5,7-diiodoquinolin-8-yloxy)acetate **1** which on reaction with appropriate substituted hydroxyethylamine gav 2-(5,7-diiodoquinolin-8-yloxy) -N- or -N-bis (2-hydroxyethyl) acetamides **(2a,b)** (Scheme 1) [Soliman and Hammouda, **1979**]. The N-Mannich bases **5a,b** were synthesized by condensing the acidic imino group of isatin derivative **4** with formaldehyde and secondary amines in ethanol [Sridhara et al., **2001**]. By reacting the acetohydrazide derivative **3** with appropriate aldohexoses sugar, namely D-glucose, D-galactose, D-mannose, D-xylose or L-arabinose in a mixture of ethanol and a catalytic amount of acetic acid gave the corresponding β-glycoside analogues **6a-e** which on stirring in a mixture of acetic anhydride / pyridine (1:1) [El-Ashry et al., **1998**]. afforded the respective O-acetyl derivatives **7a-c** (Scheme 1). Condensation of **3** with selected acid anhydrides, namely phthalic anhydride, 1,2,4,5-tetrachlorophethalicn anhydride, 1,8-naphthalene anhydride, quinolinic anhydride, 1,2,4,5-benzenetetracarboxylic di-anhydride or 1,4,5,8-naphthylenetracarboxylic di-anhydride afforded the corresponding imide and bis-imide derivatives **8-12**, respectively (Scheme 2).

Microbiological Evaluation:

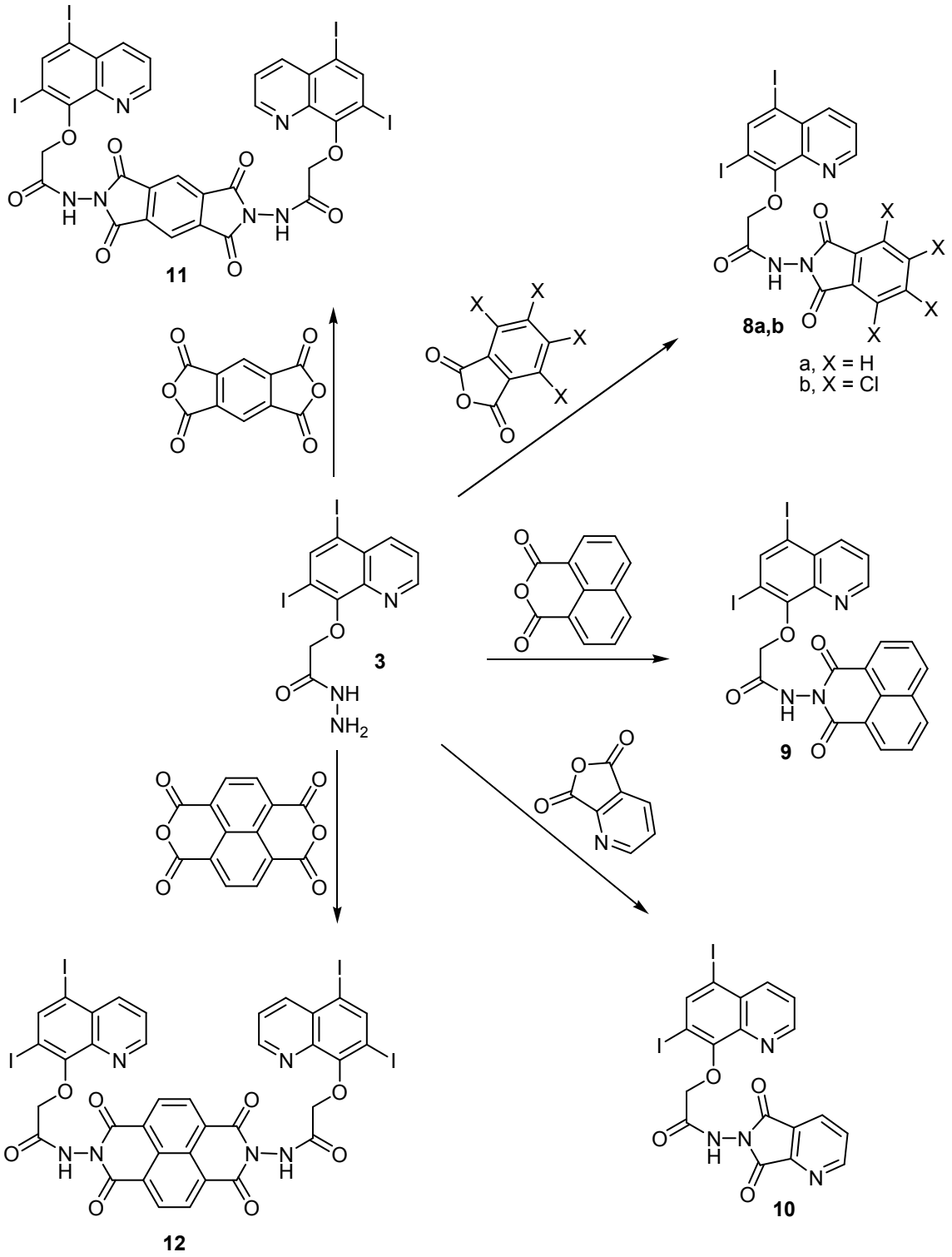
Eight of the newly synthesized compounds were screened for their antibacterial and antifungal activities. All microbial strains used were local isolates and obtained from National Research Center, Cairo, Egypt. Antibacterial activity was tested against *Escherichia coli* (Gram negative short rods) and *Bacillus subtilis* (Gram positive spore forming bacilli). Antifungal activity was tested against *Aspergillus niger* (mould) and *Candida albicans* (yeast). Inocula of 24 hrs age from each strain (except in case of Aspergillus niger, 27 hrs age inoculum has been used) were prepared and used in seeding bioassay media. Antimicrobial activity was assayed in agar plates of medium 1 (for testing antibacterial activity) or medium 2 (for testing antifungal activity). Molten sterile 80 mL of medium were allowed to cool to 45 ºC before seeding with the test strain and poured in Petri dish of 20 cm diameter. One mg of each studied compound was loaded on a filter paper disc (Whatman No.3) of 6.5 mm diameter and allowed to dry in air. Discs loaded with tested compounds were gently overlaid on the surface of the agar media under sterile conditions. Then, the agar plates with discs were maintained in refrigerator at 4 ºC for 30 min before incubation.

Medium 1: peptone 5g, glucose 5g, beef extract 3g, Yeast extract 1g, Agar 11g and PH 7. Medium 2: peptone 2g, glucose 5g, Agar 11g, distilled water 1 L and PH 7.

The results have been represented by inhibition zone (mm), <6.5 mm indicates no activity. The results are summarized in (Table 1). Only one compound **5a** exerted slight antibacterial activities against *Escherichia coli* (Gram negative bacteria) when compared with Ciprofloxacin as standard drug.

Table 1: Results of antimicrobial activities for compounds (**2a**, **2b**, **5a**, **5b**, **6a**, **6b**, **6d** and **7**).

Test organism Inhibition zone (mm)				Compound No.
A. niger	*C. albicans*	*B. subtilis*	*E. coli*	
<6.5	<6.5	<6.5	<6.5	2a
<6.5	<6.5	<6.5	<6.5	2b
<6.5	<6.5	<6.5	7	5a
<6.5	<6.5	<6.5	<6.5	5b
<6.5	<6.5	<6.5	<6.5	6a
<6.5	<6.5	<6.5	<6.5	6b
<6.5	<6.5	<6.5	<6.5	6d
<6.5	<6.5	<6.5	<6.5	7a
-	-	30	22	Ciprofloxacin
7.6	10	-	-	Nystatin



Scheme 2: Synthesis route of compounds **8** -**12**

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