Acta Pharm. **60** (2010) 55–71
10.2478/v10007-010-0004-0

Original research paper

Synthesis and biological activity of some new 1-benzyl and 1-benzoyl-3-heterocyclic indole derivatives

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Accepted January 5, 2010

Starting from 1-benzyl- (**2a**) and 1-benzoyl-3-bromoacetyl indoles (**2b**) new heterocyclic, 2-thioxoimidazolidine (**4a,b**), imidazolidine-2,4-dione (**5a,b**), pyrano(2,3-*d*)imidazole (**8a,b** and **9a,b**), 2-substituted quinoxaline (**11a,b**–**17a,b**) and triazolo(4,3-*a*)quinoxaline derivatives (**18a,b** and **19a,b**) were synthesized and evaluated for their antimicrobial and anticancer activities. Antimicrobial activity screening performed with concentrations of 0.88, 0.44 and 0.22 μg mm^{-2} showed that 3-(1-substituted indol-3--yl)quinoxalin-2(1*H*)ones (**11a,b)** and 2-(4-methyl piperazin-1-yl)-3-(1-substituted indol-3-yl) quinoxalines (**15a,b**) were the most active of all the tested compounds towards *P. aeruginosa*, *B. cereus* and *S. aureus* compared to the reference drugs cefotaxime and piperacillin, while 2-chloro-3-(1-substituted indol-3-yl)quinoxalines (**12a,b**) were the most active against *C. albicans* compared to the reference drug nystatin. On the other hand, 2-chloro-3--(1-benzyl indol-3-yl) quinoxaline **12a** display potent efficacy against ovarian cancer xenografts in nude mice with tumor growth suppression of 100.0 ± 0.3 %.

Keywords: 2-chloro-3-(1-benzyl)quinoxalines, 2-chloro-3-(1--benzoylindol-3-yl)quinoxalines, antimicrobial, ovarian anti-cancer

Indole, a potent basic pharmacodynamic nucleus, has been reported to possess a wide variety of biological properties, *viz.*, anti-inflammatory (1, 2), anticancer (3), antidepressant (4), antibacterial (5) and antifungal (6). Also, imidazole derivatives were found to possess anti-cancer (7) and antimicrobial activities (8), as well as quinoxaline derivatives (9, 10). Encouraged by the above observations, herein we report the synthesis of some new 3-substituted-1-benzyl- and 1-benzoyl-indole derivatives and evaluation of their antimicrobial and anticancer activities.

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EXPERIMENTAL

Melting points were determined in open capillary tubes on an Electrothermal 9100 digital melting point apparatus (Büchi, Switzerland) and are uncorrected. Elemental analyses were on a Perkin-Elmer 2400 analyzer (USA) and were found within ± 0.4 % of the theoretical values (Table I). Physical and analytical data are given in Table I. IR spectra were recorded on a Perkin-Elmer 1600 FTIR in KBr pellets. The ^{1}H NMR spectra were measured with Jeol 270 MHz (Jeol, Japan) in DMSO-d_6 and chemical shifts were recorded in δ ppm relative to TMS. Mass spectra (EI) were run at 70 eV with a Jeol-JMS-AX500 mass spectrometer. Spectral data of the synthesized compounds are listed in Table II. 1-Benzyl- (**1a**) and 1-benzoyl-3-acetyl (**1b**) indoles were prepared as reported (11).

*Synthesis of 1-benzyl-3-bromoacetyl indole (**2a**) and 1-benzoyl-3-bromoacetyl indole (**2b**). General procedure.* – To a stirred and cold suspension of **1a** or **1b** (0.1 mol) in absolute methanol (50 mL), bromine (16 g, 5.3 mL, 0.1 mol) in absolute methanol (10 mL) was added dropwise. After addition, the solvent was evaporated under vacuo. The residue was suspended in water (100 mL) and stirred for 1 h. The solid that precipitated was collected by filtration and recrystallized from methanol.

*Synthesis of 2-(2-(1-benzyl indol-3-yl)-2-oxoethyl amino)acetic acid (**3a**) and 2-(2-(1-benzoyl indol-3-yl)-2-oxoethyl amino)acetic acid (**3b**). General procedure.* – A suspension of **2a** or **2b** (0.001 mol) and glycine (0.07 g, 0.001 mol) in potassium carbonate (5 mL, 1.1 mol L^{-1}) was heated at 50 °C for 10 min and then at 100 °C for 30 min. After cooling, the reaction mixture was neutralized with diluted hydrochloric acid (1:1). The precipitate that was formed was collected by filtration and recrystallized from aqueous dioxane.

*Synthesis of 1-[(1-benzyl indol-3-yl) carbomethyl]-2-thioxoimidazolidine-4-one (**4a**) and 1-[(1--benzoyl indol-3-yl) carbomethyl]-2-thioxoimidazolidine-4-one (**4b**). General procedure.* – A suspension of **3a** or **3b** (0.012 mol), acetic anhydride (6.3 g, 0.067 mol), anhydrous pyridine (15 mL) and ammonium thiocyanate (1.2 g, 0.015 mol) was heated at 110 °C for 1 h. The volatiles were removed in vacuo and the residue was suspended in water (100 mL) and stirred for 1 h. The solid formed was collected by filtration and recrystallized from benzene-petroleum ether (60–80 °C).

*Synthesis of 1-[(1-benzyl indol-3-yl) carbomethyl]imidazolidine-2,4-dione (**5a**) and 1-[(1-benzoyl indol-3-yl) carbomethyl]imidazolidine-2,4-dione (**5b**). General procedure.* – A suspension of **4a** or **4b** (0.0055 mol), chloroacetic acid (10 g, 0.1 mol) and water (3 mL) was heated at 120 °C for 12 h on a sand bath. The reaction mixture was then diluted with water (50 mL) and set aside in refrigerator at 0 °C. The solid formed was collected by filtration and recrystallized from benzene-petroleum ether (60–80 °C).

*Synthesis of 5-(4-fluorobenzylidine)-1-(1-benzyl indol-3-yl)-2-thioxoimidazolidine-4-one (**6a**), 5--(4-fluorobenzylidine)-1-(1-benzoyl indol-3-yl)-2-thioxo-imidazolidine-4-one (**6b**), 5-(4-fluorobenzylidine)-1-(1-benzyl indol-3-yl)imidazolidine-2,4-dione (**7a**) and 5-(4-fluorobenzylidine)-1-(1--benzoyl indol-3-yl)imidazolidine-2,4-dione (**7b**). General procedure.* – To a solution of **4a,b** or **5a,b** (0.001 mol) in absolute ethanol (10 mL) containing 3 drops of triethylamine, *p*-fluoro-benzaldehyde (0.11 g, 0.001 mol) was added. The reaction mixture was refluxed for 3 h.

Table I. Physical and analytical properties of the new compounds

Compd. No.	Formula (M_r)	M.p. (°C)	Yield (%)	Analysis (%) (calcd./found)		
				C	H	N
2a	$C_{17}H_{14}BrNO$ (328.20)	90–92	23	62.21/62.00	4.30/4.08	4.27/4.10
2b	$C_{17}H_{12}BrNO_2$ (342.19)	109–111	30	59.67/59.55	3.53/3.42	4.09/4.00
3a	$C_{19}H_{18}N_2O_3$ (322.36)	366–368	30	70.79/70.60	5.63/5.39	8.69/8.56
3b	$C_{19}H_{16}N_2O_4$ (336.34)	96–98	61	67.85/67.77	4.79/4.57	8.33/8.21
4a	$C_{20}H_{17}N_3O_2S$ (363.43)	280–282	61	66.10/66.00	4.71/4.55	11.56/11.44
4b	$C_{20}H_{15}N_3O_3S$ (377.42)	150–152	81	63.65/63.46	4.01/3.89	11.13/11.00
5a	$C_{20}H_{17}N_3O_3$ (347.37)	210–212	86	69.16/69.00	4.93/4.70	12.10/12.22
5b	$C_{20}H_{15}N_3O_4$ (361.35)	255–257	60	66.48/66.27	4.18/4.00	11.63/11.51
6a	$C_{27}H_{20}FN_3O_2S$ (469.53)	157–159	42	69.07/69.00	4.29/4.06	8.95/8.94
6b	$C_{27}H_{18}FN_3O_3S$ (483.51)	112–114	64	67.07/67.20	3.75/3.53	8.69/8.70
7a	$C_{27}H_{20}FN_3O_3$ (453.46)	252–254	30	71.51/71.40	4.45/4.22	9.27/9.30
7b	$C_{27}H_{18}FN_3O_4$ (467.45)	245–247	58	69.37/69.27	3.88/3.67	8.99/9.01
8a	$C_{30}H_{22}FN_5O_2S$ (535.59)	189–191	67	67.28/67.41	4.14/3.81	13.08/13.01
8b	$C_{30}H_{20}FN_5O_3S$ (549.57)	161–163	74	65.56/65.67	3.67/3.09	12.74/12.66
9a	$C_{30}H_{22}FN_5O_3$ (519.17)	142–144	70	69.36/69.47	4.27/3.67	13.48/13.45
9b	$C_{30}H_{20}FN_5O_4$ (533.51)	282–284	67	67.54/67.66	3.78/3.58	13.13/13.00
11b	$C_{23}H_{15}N_3O_2$ (365.12)	212–214	60	75.60/75.49	4.10/4.24	11.50/11.45
12a	$C_{23}H_{16}ClN_3$ (369.85)	103–105	65	74.69/74.71	4.36/4.13	11.37/11.29
12b	$C_{23}H_{14}ClN_3O$ (383.83)	119–121	61	71.97/72.00	3.68/3.49	10.95/11.01
13a	$C_{28}H_{26}N_4$ (41853)	176–178	53	80.35/80.40	6.26/6.01	13.39/13.25
13b	$C_{28}H_{24}N_4O$ (432.53)	310–312	60	77.75/77.60	5.59/5.45	12.95/13.00
14a	$C_{27}H_{24}N_4O$ (420.51)	187–189	55	77.12/77.00	5.75/5.59	13.32/13.20
14b	$C_{27}H_{22}N_4O_2$ (434.49)	232–234	60	74.64/74.50	5.10/5.20	12.89/12.85
15a	$C_{28}H_{27}N_5$ (433.55)	124–126	50	77.57/77.40	6.28/6.10	16.15/6.10
15b	$C_{28}H_{25}N_5O$ (447.53)	210–212	60	75.51/75.39	5.62/5.45	15.65/15.55
16a	$C_{23}H_{19}N_5$ (365.43)	101–103	50	75.59/75.42	5.24/5.00	19.16/19.20
16b	$C_{23}H_{17}N_5O$ (379.41)	178–180	60	72.82/72.91	4.52/4.31	18.47/18.26
17a	$C_{23}H_{16}N_6$ (376.41)	112–114	48	73.39/73.21	4.28/4.30	22.33/22.15
17b	$C_{23}H_{14}N_6O$ (390.40)	176–178	60	70.76/70.55	3.61/3.48	21.53/21.40
18a	$C_{24}H_{17}N_5$ (375.43)	142–144	47	76.78/76.61	4.56/4.51	18.65/18.30
18b	$C_{24}H_{15}N_5O$ (383.41)	91–93	58	74.02/73.99	3.88/4.01	17.98/18.01
19a	$C_{25}H_{19}N_5$ (389.45)	198–200	55	77.10/76.98	4.92/4.85	17.98/18.00
19b	$C_{25}H_{17}N_5O$ (403.44)	223–225	60	74.43/74.20	4.25/4.20	17.36/17.65

Table II. Spectral characterization of the new compounds

Compd. No.	IR (ν_{max} cm^{-1})	^1H NMR (δ, ppm)	Mass (*m/z*, %)
2a	1720 (C=O), 1601 (C=C), 770 (Br)	8.11 (s, 1H, H-2 indole), 7.01–7.67 (m, 9H, Ar-H), 5.56 (s, 2H, CH_2-N), 5.03 (s, 2H, CH_2-CO)	327 (M^+, 12), 329 (M^++2, 10), 237 (25), 143 (25), 130 (95), 117 (10), 91 (100)
2b	1740 and 1720 (C=O), 1619 (C=C), 753 (Br)	7.13–8.27 (m, 10H, Ar-H), 5.51 (s, 2H, CH_2-CO)	341 (M^+, 7), 343 (M^++2, 5), 313 (83), 262 (10), 236 (40), 158 (100)
3a	4420 (OH), 3320 (NH), 1710 (C=O), 1614 (C=C)	12.51 (s, 1H, OH), 9.92 (s, 1H, NH), 8.21 (s, 1H, H-2 indole), 7.07–7.90 (m, 9H, Ar-H), 5.56 (s, 2H, CH_2-N), 4.01 and 4.25 (2s, 4H, $2CH_2$)	
3b	3360 (OH), 3161 (NH), 1710 and 1702 (C=O), 1614 (C=C)	12.61 (s, 1H, OH), 11.21 (s, 1H, NH), 8.12 (s, 1H, H-2 indole), 7.03–7.67 (m, 9H, Ar-H), 4.11 and 4.20 (2s, 4H, $2CH_2$)	
4a	3160 (NH), 1701 and 1692 (C=O), 1600 (C=C), 1244 (C=S)	11.55 (s, 1H, NH), 8.12 (s, 1H, H-2 indole), 7.03–7.87 (m, 9H, Ar-H), 5.61 (s, 2H, CH_2-N), 4.12 and 4.01 (2s, 4H, $2CH_2$)	363 (M^+, 10), 249 (86), 234 (50), 206 (20), 91 (100)
4b	3250 (NH), 1710 and 1702 (C=O), 1616 (C=C), 1240 (C=S)	11.62 (s, 1H, NH), 8.21 (s, 1H, H-2 indole), 7.01–7.67 (m, 9H, Ar-H), 4.03 and 4.12 (2s, 4H, $2CH_2$)	377 (M^+, 58), 321 (20), 234 (30), 193 (60), 105 (100)
5a	3250 (NH), 1710 and 1702 (C=O), 1635 (C=C)	12.51 (s, 1H, NH), 8.12 (s, 1H, H-2 indole), 7.01–7.87 (m, 9H, Ar-H), 5.56 (s, 2H, CH_2-N), 4.12 and 4.10 (2s, 4H, $2CH_2$)	347 (M^+, 30), 249 (71), 207 (40), 144 (20), 91 (100)
5b	3250 (NH), 1702 and 1699 (C=O), 1616 (C=C)	11.91 (s, 1H, NH), 8.12 (s, 1H, H-2 indole), 7.01–7.64 (m, 9H, Ar-H), 4.16 and 4.01 (2s, 4H, $2CH_2$)	
6a	3220 (NH), 1706 and 1700 (C=O), 1600 (C=C), 1244 (C=S)	11.25 (s, 1H, NH), 8.12 (s, 1H, H-2 indole), 7.01–7.60 (m, 13H, Ar-H), 6.54 (s, 1H, CH=C), 5.65 (s, 2H, CH_2-N), 4.12 (s, 2H, CH_2)	
6b	3220 (NH), 1701 and 1707 (C=O), 1654 and 1601 (C=C), 1244 (C=S)	10.5 (s, 1H, NH), 8.0 (s, 1H, H-2 indole), 7.0–7.68 (m, 13H, Ar-H), 6.56 (s, 1H, CH=C), 4.12 (s, 2H, CH_2)	483 (M^+, 20), 427 (50), 263 (30), 193 (20), 119 (70), 117 (100)
7a	3210 (NH), 1707 and 1701 (C=O), 1601 (C=C)	10.17 (s, 1H, NH), 8.12 (s, 1H, H-2 indole), 7.07–7.68 (m, 13H, Ar-H), 6.65 (s, 1H, CH=C), 5.36 (s, 2H, CH_2-N), 4.11 (s, 2H, CH_2)	
7b	3210 (NH), 1710 and 1735 (C=O), 1635 and 1601 (C=C)	10.17 (s, 1H, NH), 8.21 (s, 1H, H-2 indole), 7.07–7.68 (m, 13H, Ar-H), 6.90 (s, 1H CH=C), 4.20 (s, 2H, CH_2)	467 (M^+, 30), 355 (16), 264 (20), 119 (71), 105 (100)

8a	3220 (NH_2), 2223 (CN), 1707 (C=O), 1676 (C=N), 1601 (C=C), 1244 (C=S), 1011 (C-O-C)	8.12 (s, 1H, H-2 indole), 7.18–7.67 (m, 13H, Ar-H), 5.76 (s, 2H, NH_2), 5.56 (s, 2H, CH_2-N), 4.12 (s, 2H, CH_2)	
8b	3330 (NH_2), 2200 (CN), 1707 and 1712 (C=O), 1679 (C=N), 1601 (C=C), 1242 (C=S), 1101 (C-O-C)	8.21 (s, 1H, H-2 indole), 7.01–7.68 (m, 13H, Ar-H), 5.80 (s, 2H, NH_2), 4.12 (s, 2H, CH_2)	547 (M^+, 61), 502 (30), 264 (50), 248 (78), 105 (100)
9a	3250 (NH_2), 2220 (CN), 1701 and 1699 (C=O), 1670 (C=N), 1597 (C=C), 1111 (C-O-C)	8.12 (s, 1H, H-2 indole), 7.16–7.76 (m, 13H, Ar-H), 5.90 (s, 2H, NH_2), 5.56 (s, 2H, CH_2-N), 4.12 (s, 2H, CH_2)	
9b	3320 (NH_2), 2222 (CN), 1712 and 1722 (C=O), 1676 (C=N), 1601 (C=C), 1100 (C-O-C)	8.12 (s, 1H, H-2 indole), 7.09–7.78 (m, 13H, Ar-H), 6.17 (s, 2H, NH_2), 4.12 (s, 2H, CH_2)	531 (M^+, 30), 503 (50), 396 (61), 193 (78), 65 (100)
11b	3395 (NH), 1738 (C=O), 1653 (C=N), 1618 (C=C)	9.88 (s, 1H, NH), 7.08–7.97 (m, 14H, Ar-H)	365 (M^+, 20), 313 (100), 235 (53), 144 (28), 116 (13)
12a	1643 (C=N), 1530 (C=C), 746 (Cl)	7.09–7.87 (m, 14H, Ar-H), 5.61 (s, 2H, CH_2-N)	369 (M^+, 70), 371 (M^++2, 15), 335 (23), 306 (10), 206 (50), 159 (60), 91 (100)
12b	1719 (C=O), 1618 (C=N), 1544 (C=C), 783 (Cl)	7.99 (s, 1H, H-2 indole), 7.91–7.67 (m, 13H, Ar-H)	383 (M^+, 37), 385 (M^++2, 12), 313 (98), 235 (86), 160 (30), 90 (100)
13a	1643 (C=N), 1562 (C=C)		418 (M^+, 18), 325 (40), 269 (10), 206 (10), 117 (2), 91 (100)
13b	1701 (C=O), 1618 (C=N), 1544 (C=C)	8.12 (s, 1H, H-2 indole), 7.07–7.76 (m, 13H, Ar-H), 2.19–3.22 (m, 8H, CH_2-piperidinyl)	
14a	1623 (C=N), 1601 (C=C), 1024 (C-O-C)		420 (M^+, 18), 404 (2), 350 (40), 203 (30), 108 (80), 91 (100)
14b	1708 (C=O), 1647 (C=N), 1544 (C=C), 1106 (C-O-C)	8.11 (s, H-2 indole), 7.09–7.78 (m, Ar-H), 2.31–3.13 (m, CH_2-morpholine)	
15a	1627 (C=N), 1534 (C=C)		433 (M^+, 28), 348 (50), 232 (60), 205 (50), 91 (100)
15b	1720 (C=O), 1641 (C=N), 1544 (C=C)	8.12 (s, 1H, H-2 indole), 7.01–7.68 (m, 13H, Ar-H), 3.12 (s, 3H, CH_3-N), 1.64–2.66 (m, 8H, CH_2-piperazine)	
16a	3414 (NH_2), 3173 (NH), 1631 (C=N), 1525 (C=C)	8.9 (s, 1H, NH), 7.1–8.1 (m, 14H, Ar-H), 5.5 (s, 2H, CH_2-N), 4.1 (s, 2H, NH_2)	365 (M^+, 3.35), 315 (100), 274 (2), 243 (4), 208 (37), 91 (98)

16b	3409 (NH_2), 3196 (NH), 1701 (C=O), 1619 (C=N), 1547 (C=C)		379 (M^+, 0.1), 335 (60), 323 (33), 217 (20), 164 (10), 65 (10), 91 (100)
17a	1646 (N=N), 1612 (C=N), 1546 (C=C)	7.0–8.1 (m, 14H, Ar-H), 5.6 (s, 2H, CH_2-N)	376 (M^+, 10), 312 (100), 235 (70), 219 (50), 191 (30), 163 (10), 117 (5)
17b	1752 (C=O), 1620 (N=N), 1611 (C=N), 1528 (C=C)		390 (M^+, 3), 335 (81), 244 (1), 115 (10), 91 (100), 65 (10)
18a	1639 (C=N), 1566 (C=C)	8.2 (s, 1H, CH-triazole), 8.01 (s, 1H, H-2 indole), 7.1–7.98 (m, 13H, Ar-H), 5.56 (s, 2H, CH_2-N)	375 (M^+, 3), 298 (100), 245 (48), 207 (47), 206 (30), 142 (10), 91 (30)
18b	1704 (C=O), 1654 (C=N), 1606, 1528 (C=C)		389 (M^+, 1), 335 (40), 325 (38), 308 (20), 148 (30), 91 (100), 65 (30)
19a	1611 (C=N), 1542 (C=C)	8.01 (s, 1H, H-2 indole), 7.1–7.67 (m, 13H, Ar-H), 5.56 (s, 2H, CH_2-N), 2.1 (s, 3H, CH_3)	389 (M^+, 15), 314 (87), 296 (100), 245 (50), 206 (20), 163 (10), 91 (35)
19b	1720 (C=O), 1649 and 1609 (C=N), 1521 (C=C)		403 (M^+, 2), 335 (51), 244 (10), 204 (50), 91 (100), 65 (10)

After evaporation of all solvent under vacuo, the residue was suspended in water (20 mL) and the solid formed was collected by filtration and recrystallized from aqueous ethanol to give **6a,b** and **7a,b**, respectively.

*Synthesis of 5-amino-7-(4-fluorophenyl)1,2,3,3a-tetrahydro-1-[1-benzyl indol-3-yl]carbomethyl)--2-thioxopyrano(2,3-*d*)imidazole-6-carbonitrile (**8a**), 5-amino-7-(4-fluorophenyl)1,2,3,3a-tetrahydro-1-[1-benzoyl indol-3-yl] carbomethyl)-2-thioxopyrano(2,3-*d*)imidazole-6-carbonitrile (**8b**), 5-amino-7-(4-fluorophenyl)1,2,3,3a-tetrahydro-2-oxo-1-[1-benzyl indol-3-yl] carbomethyl) pyrano(2,3-*d*)imidazole-6-carbonitrile (**9a**) and 5-amino-7-(4-fluorophenyl)1,2,3,3a-tetrahydro-2-oxo--1-[1-benzoyl indol-3-yl] carbomethyl)pyrano(2,3-*d*)imidazole-6-carbonitrile (**9b**). Method A.* – A mixture of **4a,b** or **5a,b** (0.0005 mol) and *p*-fluorobenzylidene malononitrile (0.086 g, 0.0005 mol) in absolute ethanol (10 mL) containing triethylamine (0.5 mL) was refluxed for 2 h. The solid that formed was collected by filtration and recrystallized from dioxane.

Method B. – A mixture of **6a,b** or **7a,b** (0.001 mol) and malononitrile (0.066 g, 0.001 mol) in absolute ethanol (10 mL) containing triethylamine (0.5 mL) was refluxed for 3 h. The solid that formed was collected by filtration and recrystallized from dioxane.

*Synthesis of 3-(1-benzyl indol-3-yl)quinoxalin-2(1*H*)one (**11a**) and 3-(1-benzoyl indol-3-yl)quinoxalin-2(1*H*)one (**11b**). General procedure.* – To a solution of *o*-phenylenediamine (1.1 g, 0.01 mol) in absolute ethanol (20 mL) **10a** or **10b** (0.01 mol) was added. The reaction mixture was refluxed on a water bath for 1 h. The solvent was then evaporated to dryness under vacuo and the resulting residue was triturated with water (30 mL). The solid formed was collected by filtration, air-dried and recrystallized from chloroform.

*Synthesis of 2-chloro-3-(1-benzyl indol-3-yl)quinoxaline (**12a**) and 2-chloro-3-(1-benzoyl indol--3-yl)quinoxaline (**12b**). General procedure.* – A solution of **11a** or **11b** (0.01 mol) in phosphorus oxychloride (20 mL) was heated on a sand bath at 130 °C for 1 h. After cooling, the reaction mixture was poured onto ice-water under stirring and the solid that formed was collected by filtration, air-dried and recrystallized from chloroform.

*Synthesis of 2-(piperidin-1-yl)-3-(1-benzyl indol-3-yl)quinoxaline (**13a**), 2-(piperidin-1-yl)--3-(1-benzoyl indol-3-yl)quinoxaline (**13b**), 2-morpholino-3-(1-benzyl indol-3-yl)quinoxaline (**14a**), 2-morpholino-3-(1-benzoyl indol-3-yl)quinoxaline (**14b**), 2-(4-methylpiperazin-1-yl)-3-(1--benzyl indol-3-yl)quinoxaline (**15a**) and 2-(4-methylpiperazin-1-yl)-3-(1-benzoyl indol-3-yl)quinoxaline (**15b**). General procedure.* – Compound **12a** or **12b** (0.01 mol) was fused with an appropriate aliphatic cyclic amine (0.01 mol) at 150 °C on a sand bath for 3 h. After cooling and addition of water (20 mL), the solid formed was collected by filtration, air-dried and recrystallized from chloroform.

*Synthesis of 1-(2-(1-benzyl indol-3-yl)quioxalin-3-yl)hydrazine (**16a**) and 1-(2-(1-benzoyl indol-3-yl)quioxalin-3-yl)hydrazine (**16b**). General procedure.* – To a solution of **12a** or **12b** (0.01 mol) in absolute ethanol (50 mL), hydrazine hydrate (2.5 mL, 99 %, 0.05 mol) was added and the reaction mixture was refluxed for 3 h. The solid that formed after cooling in refrigerator was collected by filtration and recrystallized from ethanol.

*Synthesis of 2-azido-3-(1-benzyl indol-3-yl)quinoxaline (**17a**) and 2-azido-3-(1-benzoyl indol-3-yl)quinoxaline (**17b**). General procedure.* – A cold solution (0–5 °C) of sodium nitrite (1 g, 0.144 mol) in water (15 mL) was added gradually within 15 min to a cold solution of **16a** or **16b** (0.01 mol) in concentrated hydrochloric acid (5 mL). After addition, the reaction mixture was set aside at room temperature for 1 h. The solid that formed was collected by filtration, air dried and recrystallized from chloroform.

*Synthesis of 4-(1-benzyl indol-3-yl)-(1,2,4)-triazolo(4,3-*a*)quinoxaline (**18a**), 4-(1-benzoyl indol-3-yl)-(1,2,4)-triazolo(4,3-*a*)quinoxaline (**18b**), 1-methyl-4-(1-benzyl indol-3-yl)-(1,2,4)-triazolo(4,3-*a*)quinoxaline (**19a**) and 1-methyl-4-(1-benzoyl indol-3-yl)-(1,2,4)-triazolo(4,3-*a*)quinoxaline (**19b**). General procedure.* – Compound **16a** or **16b** (0.01 mol) was treated with formic acid (25 mL) or acetic acid (25 mL) and allowed to stand at room temperature for 24 h and then refluxed for 4 h. After cooling, the reaction mixture was poured onto crushed ice and the suspension formed was filtered off, air-dried and recrystallized from chloroform.

Biological assays

Antimicrobial evaluation. – Antimicrobial activity of the synthesized compounds was determined *in vitro* using the disc diffusion method (12) against pathogenic microorganisms: *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative bacteria), *Staphylococcus aureus*, *Bacillus cereus* (Gram-positive bacteria) and one strain of fungi (*Candida albicans*). They were isolated from clinical samples and identified to the species level according to API 20E system (Analytab Products, Inc., USA) (bioMerieux, Australia). Antimicrobial activities of the tested compounds were estimated by placing presterilized filter paper discs (6 mm in diameter) impregnated with 25, 50 and 100 μg per disc in nutrient and MacConky agar media for bacteria and on Sabouraud dextrose agar for fungus. Dimethyl formamide (DMF) which showed no inhibition zone was used as a solvent for impregnation. The inhibition zones (IZ) of the tested compounds were measured after

24–48 h incubation at 37 °C for bacteria and after 5 days incubation at 28 °C for fungi. Cefotaxime (Hoechst-Roussel Pharmaceuticals, Germany, 30 μg per disc) and piperacillin (Bristol-Myers Squibb, Egypt, 100 μg per disc) were used as reference drugs for bacteria, while nystatin (Bristol-Myers Squibb, Egypt, 1.2 μg per disc) was used as reference drug for fungi.

Anti-cancer evaluation. In vitro *studies.* – Human ovarian cancer cell lines (OVCAR3 and BG-1) were obtained from the American Type Culture Collection, Rockville, USA). OVCAR3 cells were propagated in sterile growth medium RPMI-1640* (Sigma-Aldrich, Germany) supplemented with 10 % fetal calf serum (Life Technologies, USA) and 1 % antibiotic mixture penicillin G sodium and streptomycin sulphate, Gibco Germany). BG-1 cells were propagated in DMEM/F-12** medium supplemented with 10 % fetal calf serum. Cells were incubated at 5 % CO_2 and at 37 °C.

Cytotoxicity test (MTT). – Cytotoxicity of the synthesized compounds was determined using the MTT [3-(4,5-dimethylthiazoyl-2-yl)2,5-diphenyltetrazolium bromide] assay according to Mosmann (13). Subconfluent cells (logarithmically growing cells) were trypsinized and collected.

Cells were seeded in 96-well micro-plates (3×10^3 cells per well) in 100 μL RPMI-1640 culture medium and incubated at 37 °C and 5 % CO_2 overnight. After overnight incubation, the cells were treated with the synthesized compounds dissolved in 10 μL DMSO per well and then incubated for further 24 hours. The medium was discarded and the cells were washed with sterile PBS; then 100 μL of the MTT (0.5 mg mL^{-1}) solution were added to each well and cells were incubated for 4 h. The developed purple crystals were dissolved in 100 μL DMSO and absorbance was measured at 570 nm (ELISA reader, Biorad, USA).

Growth suppression of ovarian cancer xenografts in nude mice. In vivo *studies.* – Female Swiss albino mice weighing 25–30 g obtained from Harlan Sprague Dawley, (USA) were housed at a constant temperature (24 ± 2 °C) with alternating 12 h light and dark cycles and fed standard laboratory food and water ad libitum. Statistical analysis was preformed using the SPSS version 11.0. Data were expressed as percent of control of mean ± SD by one-way analysis of variance (ANOVA) followed by the LSD-test. All procedures involving animals were carried out in accordance with the guidelines for the care and use of laboratory animals and were approved by the Ethics Committee of the National Research Centre Cairo, Egypt. For inoculation into nude mice, OVCAR3 cells were washed with PBS, trypsinzed, resuspended in RPMI-1640 containing fetal calf serum, and pooled. After centrifugation, cells were resuspended in matrigel (BD Biosciences Discovery Labware, USA)-RPMI-1640 (1:1) at a concentration of 5×10^6 cells per 0.1 mL of matrigel. The mixture (0.1 mL) was injected subcutaneously into female athymic nude mice on the dorsal surface. Treatment began when the tumor reached a volume of 150 mm^3 on average, which took ~4 weeks. Mice were randomized and treated orally by the tested compounds daily. Tumor volumes and body masses were monitored every 5 days over the course of treatment. Mice were sacrificed after 30 days of treatment (14).

* Roswall Park Memorial Institute
** Dulbecco's Modified Eagle Medium: nutrient mixture F-12

RESULTS AND DISCUSSION

Chemistry

A similar method as that described by Bodendorf and Walk (15) for the preparation of 3-bromoacetyl indole was used to prepare the new starting compounds, 1-benzyl- (**2a**) and 1-benzoyl-3-bromoacetyl (**2b**) indoles. Mass spectra of **2a** and **2b** showed molecular ion peaks at *m/z* % = 327/329 (M^+/M^++2, 12/10) and 341/343 (M^+/M^++2, 7/5), respectively (Table II).

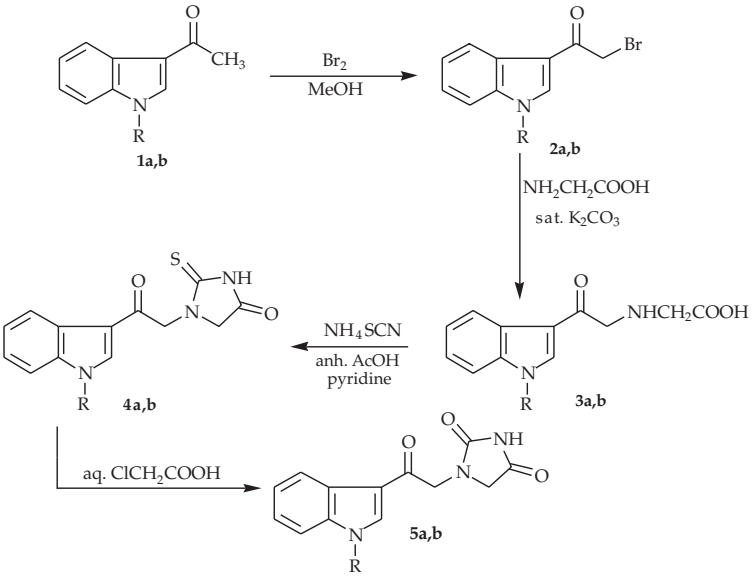
Reaction of **2a,b** with glycine in the presence of saturated potassium carbonate solution led to the formation of 2-(2-(1-benzyl indol-3yl)-2-oxoethyl amino)acetic acid (**3a**) and 2-(2-(1-benzoyl indol-3yl)-2-oxoethyl amino)acetic acid (**3b**) (Scheme 1). Heterocyclization of the latter compounds *via* their reactions with ammonium thiocyanate in acetic anhydride and in the presence of anhydrous pyridine using the method of Okuda *et al*. (16) gave 2-thioxoimidazolidine-4-one derivatives (**4a,b**) (Scheme 1). IR spectra of **4a,b** showed absorption bands at 1240 cm^{-1} for C–S besides the carboxamide group peaks at 1675 and 1686 cm^{-1}. In addition, ^1H NMR spectrum of **4a** revealed singlet signals at 4.01 and 4.12 ppm for CH_2 of the imidazolyl and carbomethyl groups, respectively, besides CH_2 of benzyl at 5.61 ppm (Table II).

Acid hydrolysis of compounds **4a,b** using aqueous monochloroacetic acid yielded the corresponding imidazolidine-2,4-dione derivatives (**5a,b**) (Scheme 1). IR spectra of **5a,b** showed no absorption bands for C=S but showed an absorption band at 1705–1715 cm^{-1} for (C=O) groups.

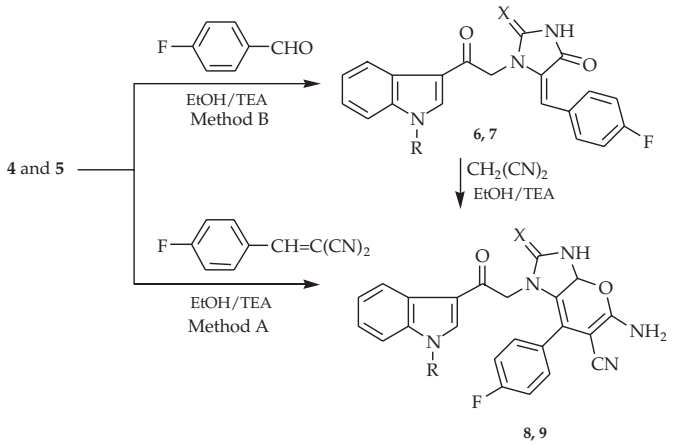
Base catalyzed reaction of **4a,b** and **5a,b** with *p*-fluorobenzaldehyde led to the formation of the corresponding arylidene derivatives **6a,b** and **7a,b,** respectively (Scheme 1). Similarly to Mandour and Kassem's procedure (17), condensation of the latter compounds with malononitrile under reflux and in the presence of a base led to the formation of condensed systems of pyrano(2,3-*d*)imidazole derivatives **8a,b** and **9a,b**, respectively (Scheme 1). The latter compounds could also be obtained by the condensation of **4a,b** and **5a,b** with *p*-fluorobenzylidene malononitrile in the presence of a base (Scheme 1). The products obtained by the two methods are identical in all aspects and were compared by TLC and melting points, which showed no differences. IR spectra of compounds **8a,b** and **9a,b** showed characteristic absorption bands at 2220–2223 cm^{-1} for CN and at 3220–3330 cm^{-1} for NH_2. The ^1H NMR spectra of **8a,b** and **9a,b** showed the absence of CH=C protons of the parent compounds **6a,b** and **7a,b** but revealed singlet signals, 2H, of NH_2 at 5.76, 5.80, 5.90 and 6.1 ppm, respectively, besides other signals which showed similar shifts to that of the protons of the starting compounds (Table II).

Oxidation of compounds **2a,b** with selenium dioxide in absolute methanol under reflux afforded methyl 2-(1-benzyl indol-3-yl)-2-oxoacetate (**10a**) and methyl 2-(1-benzoyl indol-3-yl)-2-oxoacetate (**10b**) (18, 19) (Scheme 2). Heterocyclization of compounds **10a,b** was afforded by their reactions with *o*-phenylenediamine to give quinoxaline-2(1*H*)-one derivatives **11a,b**; compound **11a** was previously reported (20).

Compounds **11a,b**, upon heating with excess of phosphorus oxychloride, afforded the corresponding 2-chloroquinoxaline derivatives **12a,b** (Scheme 2). Reactivity of compounds **12a** and **12b** as chlorocompounds was tested *via* their reactions with different



1-5 a: R = CH_2Ph
b: R = COPh



	R	X		R	X
6a	CH_2Ph	S	**8a**	CH_2Ph	S
6b	COPh	S	**8b**	COPh	S
7a	CH_2Ph	O	**9a**	CH_2Ph	O
7b	COPh	O	**9b**	COPh	O

Scheme 1

secondary amines, namely piperidine, morpholine and *N*-methylpiperazine and gave 2-substituted quinoxaline derivatives **13a,b**-**15a,b**, respectively (Scheme 2).

Reaction of **12a,b** with hydrazine hydrate in refluxed ethanol yielded the corresponding hydrazino derivatives **16a,b** (Scheme 2). Diazotization of **16a**,**b** using sodium nitrite and concentrated hydrochloric acid led to the formation of the azido derivatives **17a** and **17b** (Scheme 2).

On the other hand, the resulting hydrazine compounds **16a,b** were further converted to 1,2,4-triazolo(3,4-*a*)quinoxaline derivatives **18a,b** and **19a,b** upon refluxing in formic acid and acetic acid, respectively (Scheme 2). Structures of the new compounds were confirmed on the basis of elemental analyses (Table I) as well as spectral data, IR, ^{1}H NMR, and MS (Table II).

Antimicrobial activity

All the synthesized compounds were tested for their antimicrobial activity against pathogenic microorganisms *E. coli*, *P. aeruginosa* (Gram-negative bacteria), *S. aureus*, *B. cereus* (Gram-positive bacteria) and one strain of fungi (*C. albicans*) at concentrations of 0.88, 0.44 and 0.22 μg mm^{-2} (Table III). Compounds **15a,b** were the most active of all the tested compounds, with inhibition zones bigger or comparable to that obtained by reference drugs against *P. aeruginosa*, *S. aureus* and *B. cereus*; the same applies to **11a,b** against *E. coli* and *P. aeruginosa*. On the other hand, compounds **12a** and **12b** were found to be most active of all the tested compounds with inhibition zone of 32 mm against *C. albicans* compared to the reference drug nystatin (40 mm) at 1.2 μg per disc. The rest of the tested compounds were non-active against all microorganisms.

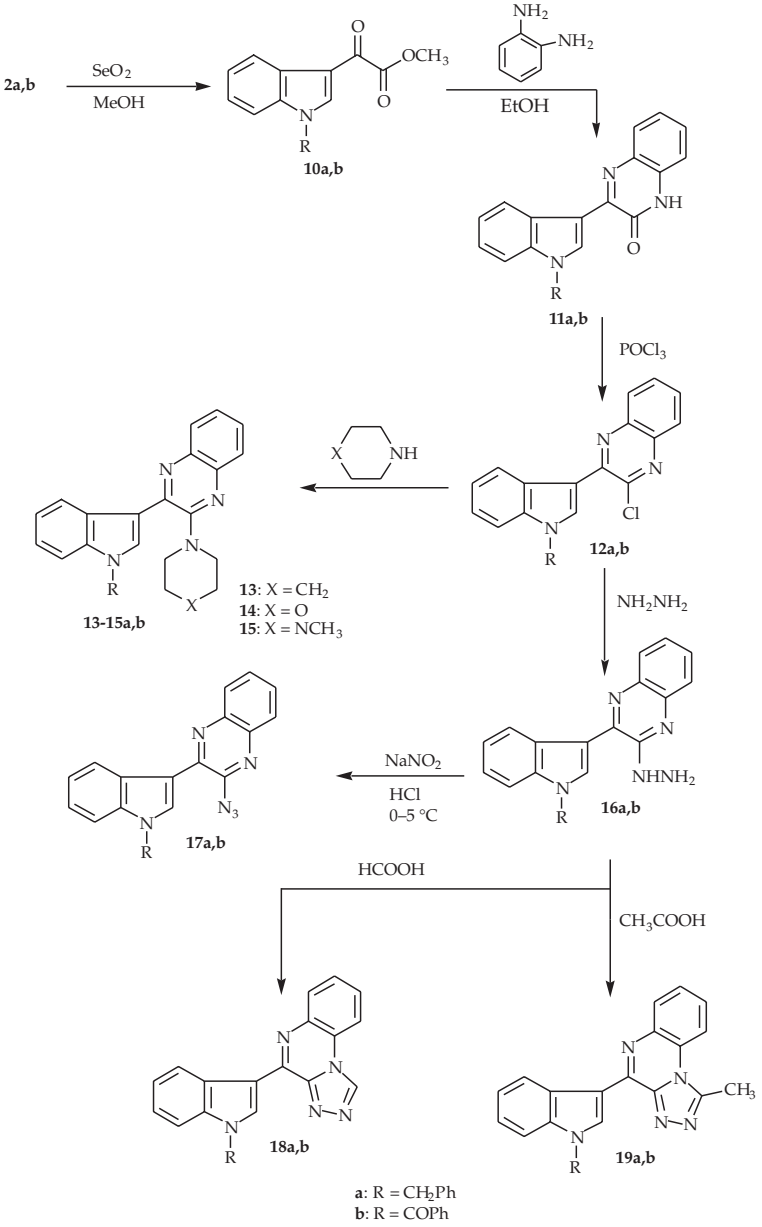
Anticancer activity

All the synthesized compounds were initially screened for *in vitro* anticancer activity at a concentration of 10^{-7} mol L^{-1} against two human cancer cell lines, OVCAR3 and BG-1, compared to vitamin D [1,25$(OH)_2D_3$] (10^{-7} mol L^{-1}) using the MTT assay (13). The growth inhibition action of the tested compounds was reported after 24 and 48 h for each cell line (Table IV). Compounds **18a**, **12a** and **12b** were found to be the most cytotoxic, with growth inhibition of 98.5 ± 1.2, 97 ± 0.6 and 96.14 ± 0.5 %, respectively, after treatment for 24 h and 99.9 ± 1.5, 98.6 ± 0.6 and 97.6 ± 0.6, respectively, after treatment for 48 h compared to vitamin D (43.9 ± 7.8 and 59.8 ± 5.3 %) against OVCAR3. Also, compounds **18a**, **12a** and **12b** were most cytotoxic against BG-1, with inhibition growth of 98.9 ± 1.1, 98.0 ± 0.8 and 97.7 ± 0.7 %, respectively, after treatment for 24 h and 99.8 ± 1.3, 98.9 ± 0.8 and 98.0 ± 0.5 %, respectively, after treatment for 48 h compared to vitamin D (62.4 ± 17.7 and 71.1 ± 14.2 %), respectively.

The most cytotoxic of all the tested compounds (**4a,b**, **5a,b**, **12a,b**, **13a,b**, **14a**, **15a**, **17a**, **18a,b** and **19a,b**) were next evaluated for *in vivo* growth suppression of ovarian cancer xenografts in nude mice. OVCAR3 cell was injected subcutaneously to a size of about 150 mm^3. Subsequently, daily drug administration of 1 μmol per day per gram body mass was conducted for five days and mice were scarificed after 30 days of treatment (Table V). Data expressed as percent of tumor growth suppression compared to control were calculated. 2-Chloro-3-(1-benzyl indol-3-yl) quinoxaline (**12a**) showed potent efficacy, with tu-

Table III. Antimicrobial activity of the synthesized compounds

Compd. No.	Inhibition zone (mm)														
	E. coli			*P. aeruginosa*			*S. aureus*			*B. cereus*			*C. albicans*		
	Concentration (μg mm^{-2})														
	0.88	0.44	0.22	0.88	0.44	0.22	0.88	0.44	0.22	0.88	0.44	0.22	0.88	0.44	0.22
4a	18	14	10	17	12	8	14	9	5	14	9	–	26	16	10
4b	16	12	10	17	12	8	14	9	5	14	9	–	24	16	10
5a	14	9	–	14	10	7	14	9	5	14	9	–	20	14	10
5b	14	9	–	14	10	7	14	9	5	14	9	–	20	14	10
6a	15	10	8	14	10	7	14	9	5	14	9	–	28	16	10
6b	15	10	8	14	10	7	14	9	5	14	9	–	28	16	10
7a	14	9	–	14	10	7	12	8	5	12	8	–	26	16	10
7b	14	9	5	14	10	7	12	8	5	12	8	–	26	16	10
8a	12	8	5	12	8	–	11	7	–	11	8	–	26	16	10
8b	12	8	5	12	8	–	11	7	–	11	8	–	26	16	10
9a	11	8	5	11	8	–	11	7	–	11	8	–	26	16	10
9b	11	8	5	11	8	–	11	7	–	11	8	–	26	16	10
11a	22	19	17	21	20	15	21	14	14	21	19	15	–	–	–
11b	26	22	20	21	20	15	21	14	14	12	19	15	–	–	–
12a	17	14	10	18	14	10	18	14	10	17	14	10	32	25	12
12b	17	14	10	18	14	10	17	14	10	17	14	10	32	25	12
13a	11	7	–	11	7	–	11	7	–	11	7	–	22	15	10
13b	11	7	–	11	7	–	11	7	–	11	7	–	22	15	10
14a	11	7	–	11	7	–	11	7	–	11	7	–	22	15	10
14b	11	7	–	11	7	–	11	7	–	11	7	–	22	15	10
15a	24	20	15	25	20	17	24	20	17	28	20	17	–	–	–
15b	24	20	15	25	20	17	24	20	17	28	20	17	–	–	–
16a	11	7	–	11	7	–	11	7	–	11	7	–	11	7	–
16b	11	7	–	11	7	–	11	7	–	11	7	–	11	7	–
17a	11	7	–	11	7	–	11	7	–	11	7	–	11	7	–
17b	11	7	–	11	7	–	11	7	–	11	7	–	11	7	–
18a	11	7	–	11	7	–	11	7	–	11	7	–	11	7	–
18b	11	7	–	11	7	–	11	7	–	11	7	–	11	7	–
19a	11	7	–	11	7	–	11	7	–	11	7	–	11	7	–
19b	11	7	–	11	7	–	11	7	–	11	7	–	11	7	–
Cefotaxime (0.27 μg mm^{-2})	32	22	17	22	18	12	31	26	17	26	20	14	–	–	–
Piperacillin	–	–	–	20	15	10	27	18	10	20	15	10	–	–	–
Nystatin (0.01 μg mm^{-2})	–	–	–	–	–	–	–	–	–	–	–	–	40		


2a,b
SeO2
MeOH
10a,b
NH2
NH2
EtOH
11a,b
POCl3
12a,b
X
NH
13-15a,b
13: X = CH2
14: X = O
15: X = NCH3
NH2NH2
16a,b
NaNO2
HCl
0–5 °C
17a,b
HCOOH
CH3COOH
18a,b
19a,b
a: R = CH2Ph
b: R = COPh

Scheme 2

Table IV. In vitro *cytotoxic activity of synthesized compounds*[a]

Compd. No.	OVCAR3 cell		BG-1 cell	
	Growth inhibition (%) after treatment for			
	24 h[b]	48 h[b]	24 h[b]	48 h[b]
Vitamin D	43.9	59.8	62.4	71.1
4a	91.3	93.3	91.3	94.2
4b	80.1	82.1	85.4	86.6
5a	90.2	92.7	90.3	92.5
5b	87.9	90.4	88.5	90.8
6a	28.6	35.6	48.6	56.5
6b	19.6	24.8	29.7	35.7
7a	40.9	58.9	60.8	68.7
7b	38.7	49.5	54.8	59.4
8a	45.7	59.8	62.6	63.6
8b	22.7	28.7	40.9	44.8
9a	21.0	27.6	38.7	41.7
9b	39.1	53.3	58.6	65.9
11a	29.6	38.9	50.0	57.3
11b	42.8	59.1	61.3	71.2
12a	97.5	98.6	98.0	98.9
12b	96.1	97.6	97.7	98.0
13a	55.4	65.7	67.4	70.3
13b	48.6	59.9	62.7	64.5
14a	49.2	61.6	65.4	68.8
14b	23.7	30.9	41.6	48.7
15a	65.5	69.1	70.6	72.3
15b	26.5	34.5	46.5	53.6
16a	20.6	26.7	31.6	38.2
16b	25.6	32.7	44.4	51.9
17a	70.9	72.1	74.1	77.8
17b	68.7	70.6	72.1	75.6
18a	98.5	99.9	98.9	99.8
18b	75.1	77.1	80.3	82.6
19a	94.4	96.6	94.5	96.1
19b	74.6	76.2	77.8	79.6

Negative control: 10 μL DMSO per well added to control cells.
[a] $c = 10^{-7}$ mol L^{-1}.
[b] Mean value of duplicate analyses.

Table V. In vivo *growth inhibition of xenografts in nude mice treated with tested compounds*[a]

Compd. No.	Tumor growth suppression (mean ± SD) (%)					
	5 days	10 days	15 days	20 days	25 days	30 days
Vitamin D	23.5 ± 1.2	55.5 ± 5.4	77.7 ± 4.4	80.1 ± 4.2	98.6 ± 5.4	100.0 ± 1.2
4a	30.8 ± 0.7	58.7 ± 0.6	65.9 ± 0.8[c]	77.8 ± 0.7[c]	89.0 ± 0.8[c]	90.6 ± 0.7[c]
4b	22.0 ± 0.2	41.9 ± 0.8	57.0 ± 1.2	64.9 ± 0.8[c]	67.1 ± 1.5[c]	79.0 ± 1.5[c]
5a	24.0 ± 0.8	46.5 ± 0.8	59.0 ± 0.9	67.1 ± 0.7[c]	73.2 ± 0.7[c]	81.2 ± 0.6[c]
5b	22.3 ± 0.5	43.1 ± 0.8	58.2 ± 0.8	66.2 ± 0.7[c]	70.2 ± 0.7[c]	80.0 ± 1.2[c]
12a	41.5 ± 0.6	70.8 ± 0.7[c]	88.2 ± 0.8[c]	98.6 ± 1.5[c]	100.0 ± 0.3[c]	–
12b	40.0 ± 0.8	69.8 ± 0.8[c]	88.2 ± 0.6[c]	90.5 ± 0.3[c]	99.5 ± 1.3[c]	100.0 ± 0.1[c]
13a	12.0 ± 0.2	30.7 ± 0.7	46.0 ± 0.8	51.3 ± 0.7	59.5 ± 0.7	69.7 ± 0.7[c]
14a	10.0 ± 0.9	25.3 ± 0.7	39.7 ± 0.8	51.3 ± 0.7	59.5 ± 0.7[c]	69.7 ± 0.7[c]
15a	15.0 ± 0.8	33.1 ± 0.8	46.3 ± 0.9	51.9 ± 0.9	60.7 ± 0.8[c]	73.1 ± 0.7[c]
17a	20.8 ± 0.6	34.2 ± 0.6	47.1 ± 0.8	55.3 ± 0.7	60.9 ± 0.8[c]	75.0 ± 0.7[c]
17b	20.0 ± 0.8	35.1 ± 0.8	51.5 ± 0.8	55.6 ± 0.8	60.1 ± 0.8[c]	75.8 ± 0.6[c]
18a	39.7 ± 0.9	66.8 ± 0.8[c]	71.8 ± 0.2[c]	81.0 ± 0.7[c]	95.7 ± 0.1[c]	96.9 ± 0.6[c]
18b	21.8 ± 0.7	39.5 ± 0.6	54.8 ± 0.5	60.1 ± 0.7	65.2 ± 0.7[c]	78.0 ± 0.8[c]
19a	33.8 ± 0.6	55.7 ± 0.6	67.9 ± 0.8[c]	79.8 ± 0.7[c]	91.9 ± 0.8[c]	95.0 ± 1.5[c]
19b	21.1 ± 0.1	39.2 ± 0.6	56.1 ± 1.2	59.1 ± 0.9	61.9 ± 0.1[c]	77.1 ± 0.8[c]

Negative controls: mice injected with 0.1 mL saline.
[a] 1 μmol of the tested compounds per day per gram body mass.
[b] Mean ± SD, $n = 10$.
[c] Significantly different from control, $p < 0.05$.

mor growth suppression 100.0 ± 0.3 % after 25 days, whereas vitamin D showed tumor growth suppression of 98.6 ± 5.4 % after 25 days.

CONCLUSIONS

Described herein are the synthesis, antimicrobial and anticancer activities of some new 1-benzyl- and 1-benzoyl-3-heterocyclic indole derivatives. The results show that compounds 3-(1-substituted indol-3-yl)quinoxalin-2(1*H*)ones (**11a,b**) and 2-(4-methyl piperazin-1-yl)-3-(1-substituted indol-3-yl) quinoxalines (**15a,b**) were most active against *P. aeruginosa*, *B. cereus* and *S. aureus*, while 2-chloro-3-(1-substituted indol-3-yl)quinoxalines (**12a,b**) were most active against *C. albicans*. On the other hand, 2-chloro-3-(1-benzyl indol-3-yl) quinoxaline (**12a**) displays potent efficacy of ovarain cancer xenografts in nude mice with complete tumor growth suppression. Finally, this SAR study has indicated that the conjugated indole-quinoxaline is vital for the antimicrobial activity and potential anti-cancer efficacy.

Acknowledgments. – The authors express their thanks to Adel Shehab El-Din, Pharmaceutical Microbiological Lab., National Centre for Radiation Research and Technology, Atomic Energy Authority, Cairo, Egypt, for carrying out the antimicrobial activity screening. Also, the author are grateful to the Micro Analytical Unit, National Research Center, Cairo, Egypt, for carrying out elemental analyses, ^{1}H-NMR and mass spectra and Micro Analytical Center, Cairo University, Egypt, for recording the IR spectra.

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S A Ž E T A K

Sinteza i biološko djelovanje novih 1-benzil i 1-benzoil 3-heterocikličkih derivata indola

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U radu je opisana sinteza, antimikrobno i antitumorsko djelovanje heterocikličkih derivata indola. Polazeći iz 1-benzil- i 1-benzoil-3-bromacetil indola (**2a** i **2b**) sintetizirani su novi heterociklički spojevi 2-tioksoimidazolidini (**4a,b**), imidazolidin-2,4-dioni (**5a,b**), pirano(2,3-*d*)imidazoli (**8a,b** i **9a,b**), 2-supstituirani kinoksalini (**11a,b**-**17a,b**) i triazolo(4,3-*a*)kinoksalini (**18a,b** i **19a,b**). Sintetizirani spojevi testirani su na antimikrobno i antitumorsko djelovanje. Ispitivanje antimikrobnog djelovanja provedeno je s koncentracijama otopina 0,88, 0,44 i 0,22 μg mm^{-2} i uspoređeno s referentnim lijekovima cefotaksimom i piperacilinom. Rezultati pokazuju da su 3-(1-supstituirani indol-3-il)kinoksalin-2(1*H*)oni (**11a,b**) i 2-(4-metil piperazin-1-il)-3-(1-supstituirani indol-3-il) kinoksalini (**15a,b**) najaktivniji spojevi na sojeve *P. aeruginosa*, *B. cereus* i *S. aureus*, dok su 2-klor-3-(1--supstituirani indol-3-il)kinoksalini (**12a,b**) najaktivniji na *C. albicans* (usporedba s nistatinom). Osim toga, 2-klor-3-(1-benzil indol-3-il) kinoksalin (**12a**) pokazuje veliku učinkovitost na tumore ovarija miševa (supresija rast a tumora 100 ± 0,3 %).

Ključne riječi: 2-klor-3-(1-benzil)kinoksalini, 2-klor-3-(1-benzoilindol-3-il)kinoksalini, antimikrobno djelovanje, antitumorsko djelovanje

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