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Research Article

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Synthesis and *in vitro* antitumor activity of new benzothiazole and benzoxazole derivatives

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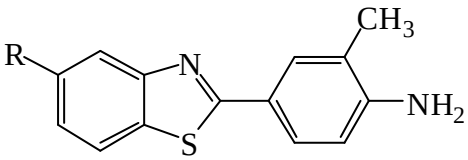
ABSTRACT

*A series of benzothiazole and benzoxazole derivatives were synthesized from their parents whom bearing o-aminocyano groups then functionalized on amino group or cyano group. Some of the newly formed compounds were evaluated, in vitro, for their antitumor activity against MCF-7. Compound **4b** was the most potent, showing activity IC_{50} (0.011 μM).*

Keywords: Antitumor activity, benzothiazoles, benzoxazoles, MCF-7

INTRODUCTION

Formation of a hybride structure between benzene ring and five membered thiazole or oxazole ring resulted in the formation of benzothiazole or benzoxazole, respectively.[1] Benzothiazole and benzoxazole rings were found to possess different pharmacological activities such as anti-viral, [2] anti-bacterial, [3] anti-microbial, [4] fungicidal [5] and antitumor [6-8] activities. Introducing aryl pharmacophore to benzothiazole and benzoxazole at position 2 exhibited a wide range of biological properties specially cytotoxic activity. [9,10] 2-phenylbenzothiazoles showed its antitumor activity by resembling the ATP antagonistic effects of the natural products. Moreover, they have tyrosine kinase inhibitory properties, [11] (Compounds **I-IV**) [12-14]. In this work, we synthesized new compounds containing benzothiazole and benzoxazole derivatives substituted at position 2 with phenyl ring containing substituted amino and/or carbonitrile derivatives aiming at forming compounds having potent antitumor activity against human adenocarcinoma cell line (MCF-7).



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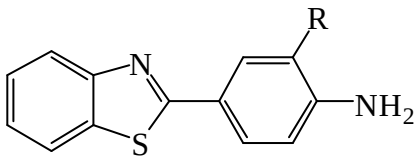
I



R= H, CH_3, Cl, I, Br

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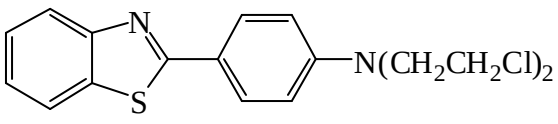

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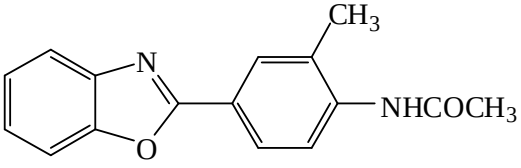


IV

EXPERIMENTAL SECTION

Melting points were determined on a Graffin apparatus and were uncorrected. Element analyses (C, H, N) were carried out on Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA) at the Micro analytical unit of Cairo University, Egypt. All compounds were within ± 0.4% of the theoretical values. IR spectra were determined as KBr discs on Shimadzu IR 435 Spectrophotometer and values were represented in cm^{-1}. ^{1}HNMR was carried out on a Bruker 300 MHz NMR Spectrophotometer in Cairo University, Egypt, using (Bruker, Munich, Germany) in DMSO-d_6 as a solvent, TMS as internal standard and chemical shifts were recorded in ppm on δ scale. Mass spectra were run on Hewlett Packard 5988 Spectrometer, Micro analytical center, Cairo University, Egypt. Progress of the reactions was monitored by TLC using TLC sheets precoated with UV fluorescent silica gel MERCK 60 F 254 that were visualized by UV lamp.

Procedure for synthesis of 2-amino-5-(benzo[*d*]oxazol-2-yl)benzonitrile (2a):
A mixture of **1a** (0.33 g, 0.001 mol) and copper (I) cyanide (0.18 g, 0.002 mol) in dimethylformamide (20 mL) was heated under reflux for 4 h. The solution was evaporated under reduced pressure, extracted with ethyl acetate, filtered, dried and crystallized from dimethylformamide/ethanol (8:2) to afford **2a.**

Isolated as brown solid, Yield: 39%, m.p.: 220-222 ^{0}C; IR (KBr, cm^{-1}), 3436-3354 (NH_2), 2213 (C≡N) and 1632 (C=N); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 6.91-6.95 (m, 3H, Ar-H and NH_2, D_2O exchangeable), 7.34-7.37 (m, 2H, Ar-H), 7.69-7.72 (m, 2H, Ar-H), 8.06 (d, 1H, *J*= 8.7 Hz, Ar-H) and 8.15 (s, 1H, Ar-H); Anal. Calcd for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found: C, 71.17; H, 3.80; N, 18.19.

Procedure for synthesis of *N*-[4-(benzo[*d*]oxazol-2-yl)-2-cyanophenyl-4-chlorobenzamide (3a):
To a solution of **1a** (2.35 g, 0.01 mol) in dimethylformamide (15 mL), 4-chlorobenzoyl chloride (1.75 g, 0.01 mol) was added. The reaction mixture was stirred at room temperature for 24 h. The solution was poured onto ice-cold water (30 mL), neutralized with sodium carbonate solution (10%). The separated solid was collected by filteration, dried and crystallized from benzene/ethylacetate (8:2) to afford **3a**.

Isolated as brown solid, Yield: 63%, m.p.: 170-172^{0}C; IR (KBr, cm^{-1}), 3420 (NH), 2357 (C≡N), 1716 (C=O) and 1658 (C=N); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 7.54-7.57 (m, 4H, Ar-H), 7.71 (d, 2H, *J*= 8.4 Hz, Ar-H), 7.92-7.95 (m, 3H, Ar-H), 8.15 (d, 2H, *J*= 8.4 Hz, Ar-H) and 13.2 (s, 1H, NH, D_2O exchangeable); EIMS (m/z) (relative abundance %), 375 [$M+2^{\urcorner +\cdot}$, 0.85], 374 [$M+1^{\urcorner +\cdot}$, 1.37], 373 [$M^{\urcorner +\cdot}$, 1.80], 141 [$C_8HN_2O^{\urcorner +}$, 31.17], 139 [$C_7H_4ClO^{\urcorner +}$, 100], 111 [$C_6H_4Cl^{\urcorner +}$, 32.57] and 75 [$C_5H_3^{\urcorner +}$, 20.41]; Anal. Calcd for $C_{21}H_{12}ClN_3O_2$: C, 67.48; H, 3.24; N, 11.24. Found: C, 67.20; H, 3.00; N, 11.19.

General method for preparation of 4a&b:
To a solution of **1a&b** (0.01 mol) in dimethylformamide (15 mL), chloroacetyl chloride (1.13 g, 0.01 mol) was added. The reaction mixture was stirred at room temperature for 48 h. The solution was poured onto ice-cold water (30 mL), neutralized with sodium carbonate solution (10%). The separated solid was collected by filteration, dried and crystallized from dimethylformamide/ethanol (8:2) to afford **4a&b.**

***N*-[4-(Benzo[*d*]oxazol-2-yl)-2-cyanophenyl]-2-chloroacetamide (4a):**
Isolated as white solid, Yield: 75%, m.p.: 175-177^{0}C; IR (KBr, cm^{-1}), 3354 (NH), 2225 (C≡N),1701 (C=O); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 4.45 (s, 2H, CH_2), 7.41-7.45 (m, 2H, Ar-H), 7.79-7.85 (m, 2H, Ar-H), 7.97 (d, 1H, *J*= 8.4 Hz, Ar-H), 8.48 (d, 1H, *J*= 8.4 Hz, Ar-H), 8.55 (s, 1H, Ar-H) and 10.76 (s, 1H, NH, D_2O exchangeable); EIMS (m/z) (relative abundance %), 313 [$M+2^{\urcorner +\cdot}$, 18.54], 312 [$M+1^{\urcorner +\cdot}$, 9.25], 311 [$M^{\urcorner +\cdot}$, 48.69], 235 [$C_{14}H_9N_3O^{\urcorner +\cdot}$, 100] and 64 [$C_4H_2N^{\urcorner +}$, 8.38]; Anal. Calcd for $C_{16}H_{10}ClN_3O_2$: C, 61.65; H, 3.23; N, 11.37. Found: C, 61.86; H, 3.36; N, 11.85.

***N*-[4-(Benzo[*d*]thiazol-2-yl)-2-cyanophenyl]-2-chloroacetamide (4b):**
Isolated as white solid, Yield: 69%, m.p.: 380-382^{0}C; IR (KBr, cm^{-1}), 3322 (NH), 2225 (C≡N), 1708 (C=O); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 4.54 (s, 2H, CH_2), 7.49-7.59 (m, 2H, Ar-H), 7.86-7.93 (m, 2H, Ar-H), 8.06 (d, 1H, *J*= 8.7 Hz, Ar-H), 8.55 (d, 1H, *J*= 8.7 Hz, Ar-H), 8.62 (s, 1H, Ar-H) and 10.82 (s, 1H, NH, D_2O exchangeable).; EIMS (m/z) (relative abundance %), 329 [$M+2^{\urcorner +\cdot}$, 9.42], 328 [$M+1^{\urcorner +\cdot}$, 4.74], 327 [$M^{\urcorner +\cdot}$, 25.92], 251 [$C_{14}H_9N_3S^{\urcorner +\cdot}$, 100] and 250 [$C_{14}H_6N_2OS^{\urcorner +\cdot}$, 15.52]; Anal. Calcd for $C_{16}H_{10}ClN_3OS$: C, 58.63; H, 3.07; N, 12.82. Found: C, 58.52; H, 3.51; N, 12.61.

General method for preparation of 5a-d:
A suspension of **4a&b** (0.01 mol), sodium iodide (3 g, 0.02 mol) in absolute ethanol (25 mL) was heated under reflux for 10 h. The reaction mixture was evaporated to dryness, washed with water, filtered, dried and crystallized from dimethylformamide to give **5a-d.**

***N*-[4-(Benzo[*d*]oxazol-2-yl)-2-cyanophenyl]-2-(diethylamino)acetamide (5a):**
Isolated as yellow solid, Yield: 43%, m.p.: 128-130^{0}C; IR (KBr, cm^{-1}), 3423 (NH), 2971-2827 (CH aliph.), 2221 (C≡N),1700 (C=O); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 1.09 (t, 6H, *J*= 6.9 Hz, N($CH_2\underline{CH_3}$)$_2$), 2.65 (q, 4H, *J*= 6.9 Hz, N($\underline{CH_2}CH_3$)$_2$), 3.27 (s, 2H, $\underline{CH_2}$), 7.40-7.48 (m, 2H, Ar-H), 7.78-7.84 (m, 2H, Ar-H), 8.45-8.57 (m, 3H, Ar-H) and 10.56 (s, 1H, NH, D_2O exchangeable); EIMS (m/z) (relative abundance %), 349 [M+1$^{+\cdot}$, 0.30], 348 [M$^{+\cdot}$, 1.21], 86 [$C_5H_{12}N^+$, 100], 80 [$C_4H_2NO^+$, 40.92], 64 [$C_4H_2N^+$, 31.37] and 58 [$C_3H_8N^{+\cdot}$, 23.06].; Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.69; H, 5.96; N, 16.06.

***N*-[4-(Benzo[*d*]oxazol-2-yl)-2-cyanophenyl]-2-(2,6-dimethylphenylamino)acetamide (5b):**
Isolated as green solid, Yield: 54%, m.p.: 200-202^{0}C; IR (KBr, cm^{-1}), 3381, 3274 (2NH), 2967-2914 (CH aliph.), 2217 (C≡N), 1706 (C=O); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 2.30 (s, 6H, 2CH_3), 3.86 (d, 2H, *J*= 6.9 Hz, CH_2), 4.70 (t, 1H, *J*= 6.9 Hz, $CH_2\underline{NH}$, D_2O exchangeable), 6.75-6.80 (m, 1H, Ar-H), 6.97 (d, 2H, *J*= 7.2 Hz, Ar-H), 7.41-7.49 (m, 2H, Ar-H), 7.79-7.85 (m, 2H, Ar-H), 8.30 (d, 1H, *J*= 9 Hz, Ar-H), 8.49 (d, 1H, *J*= 9 Hz, Ar-H), 8.55 (s, 1H, Ar-H) and 10.56 (s, 1H, NH, D_2O exchangeable); EIMS (m/z) (relative abundance %), 397 [M+1$^{+\cdot}$, 1.99], 396 [M$^{+\cdot}$, 0.82], 368 [$C_{22}H_{16}N_4O_2^{+\cdot}$, 15.80], 213 [$C_{12}H_{11}N_3O^{+\cdot}$, 45.66], 111 [$C_5H_7N_2O^+$, 69.75], 84 [$C_4H_8N_2^{+\cdot}$, 78.40] and 69 [$C_3H_5N_2^+$, 100]; Anal. Calcd for $C_{24}H_{20}N_4O_2$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.49; H, 4.89; N, 14.28.

***N*-[4-(Benzo[*d*]thiazol-2-yl)-2-cyanophenyl]-2-(phenylamino)acetamide (5c):**
Isolated as yellow solid, Yield: 43%, m.p.: 245-247^{0}C; IR (KBr, cm^{-1}), 3433-3235 (2NH), 2980 (CH aliph.), 2207 (C≡N), 1708 (C=O); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 3.96 (s, 2H, CH_2), 6.19 (s, 1H, $CH_2\underline{NH}$, D_2O exchangeable), 6.58-6.68 (m, 2H, Ar-H), 7.09-7.12 (m, 3H, Ar-H), 7.41-7.55 (m, 2H, Ar-H), 8.04-8.16 (m, 3H, Ar-H), 8.36-8.44 (m, 2H, Ar-H), and 10.27 (s, 1H, NH, D_2O exchangeable); EIMS (m/z) (relative abundance %), 386 [M+2$^{+\cdot}$, 2.55], 385 [M+1$^{+\cdot}$, 9.69], 384 [M$^{+\cdot}$, 33.83], 251 [$C_{14}H_9N_3S^+$, 83.49], 106 [$C_5H_2N_2O^{+\cdot}$, 100] and 77 [$C_6H_5^+$, 27.65]; Anal. Calcd for $C_{22}H_{16}N_4OS$: C, 68.73; H, 4.19; N, 14.57. Found: C, 69.12; H, 4.60; N, 14.59.

4-{2-[4-(Benzo[*d*]thiazol-2-yl)-2-cyanophenylamino]-2-oxoethylamino}benzoic acid acetamide (5d):
Isolated as yellow solid, Yield: 52%, m.p.: 380-382^{0}C; IR (KBr, cm^{-1}), 3428-2358 (2NH and OH), 2208 (C≡N), 1708-1683 (2C=O); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 4.08 (s, 2H, CH_2), 6.67 (d, 2H, *J*= 8.7 Hz, Ar-H), 6.90 (s, 1H, $CH_2\underline{NH}$, D_2O exchangeable), 7.46-7.57 (m, 2H, Ar-H), 7.71 (d, 2H, *J*= 8.7 Hz, Ar-H), 7.95 (d, 1H, *J*= 8.7 Hz, Ar-H), 8.08 (d, 1H, *J*= 7.8 Hz, Ar-H), 8.18 (d, 1H, *J*= 8.1 Hz, Ar-H), 8.36-8.46 (m, 2H, Ar-H), 10.39 (s, 1H, NH, D_2O exchangeable) and 12.15 (s, 1H, OH, D_2O exchangeable); EIMS (m/z) (relative abundance %), 430 [M+2$^{+\cdot}$, 1.18], 429 [M+1$^{+\cdot}$, 4.26], 428 [M$^{+\cdot}$, 13.73], 251 [$C_{14}H_9N_3S^{+\cdot}$, 100] and 150 [$C_8H_8NO_2^+$, 50.86]; Anal. Calcd for $C_{23}H_{16}N_4O_3S$: C, 64.47; H, 3.76; N, 13.08. Found: C, 64.30; H, 3.80; N, 12.81.

General method for preparation of 6a&b:
A mixture of compound **1a&b** (0.01 mol) and potassium hydroxide (8.4 g, 0.15 mol) was dissolved in ethanol 50% (20 mL). The reaction mixture was heated under reflux for 24 h. After cooling, the solution was acidified by hydrochloric acid till neutral to litmus paper. The separated solid was filtered, dried and crystallized from dimethylformamide to give **6a&b.**

2-Amino-5-(benzo[*d*]oxazol-2-yl)benzoic acid (6a):
Isolated as brown solid, Yield: 43%, m.p.: 370-372^{0}C; IR (KBr, cm^{-1}), 3416-2500 (NH_2 and OH), 1667 (C=O), 1622 (C=N); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 3.30 (s, 2H, NH_2, D_2O exchangeable), 6.68-6.97 (m, 3H, Ar-H), 7.30-7.49 (m, 1H, Ar-H), 7.70-7.87 (m, 3H, Ar-H) and 9.22 (s, 1H, OH, D_2O exchangeable); EIMS (m/z) (relative abundance %), 255 [M+1$^{+\cdot}$, 13.67], 254 [M$^{+\cdot}$, 2.41], 253 [M-1$^{+\cdot}$, 11.45], 224 [$C_{13}H_8N_2O_2^{+\cdot}$, 15.50], 172 [$C_{10}H_6NO_2^{+\cdot}$, 18.96], 158 [$C_8H_2N_2O_2^{+\cdot}$, 28.01], 149 [$C_8H_5O_3^+$, 58.52] and 69 [$C_3H_3NO^{+\cdot}$, 100]; Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 66.49; H, 3.94; N, 10.76.

2-Amino-5-(benzo[*d*]thiazol-2-yl)benzoic acid (6b):
Isolated as brown solid, Yield: 39%, m.p.: 210-212^{0}C; IR (KBr, cm^{-1}), 3445-2500 (NH_2 and OH), 1677(C=O), 1616 (C=N); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 3.35 (s, 2H, NH_2, D_2O exchangeable), 6.83 (d, 1H, *J*= 8.4 Hz, Ar-

H), 7.35-7.49 (m, 2H, Ar-H and OH, D_2O exchangeable), 7.86-7.94 (m, 2H, Ar-H), 8.04 (d, 1H, *J*= 8.4 Hz, Ar-H) and 8.44 (s, 1 H, Ar-H); EIMS (m/z) (relative abundance %), 272 [M+2 ⌉$^{+\cdot}$, 6.45], 271 [M+1 ⌉$^{+\cdot}$, 18.65], 270 [M ⌉$^{+\cdot}$, 100], 252 [$C_{14}H_8N_2OS$ ⌉$^{+\cdot}$, 82.61], 226 [$C_{13}H_{10}N_2S$ ⌉$^{+\cdot}$, 32.24] and 224 [$C_{13}H_8N_2S$ ⌉$^{+\cdot}$, 65.54]; Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36. Found: C, 62.46; H, 3.96; N, 10.26.

General method for preparation of 7a&b:
A solution of **1a&b** (0.01 mol) in concentrated sulfuric acid (10 mL) was stirred at room temperature for 24 h. The solution was poured onto ice-cold water (30 mL), neutralized with ammonia till neutral to litmus paper. The separated solid was filtered, dried and crystallized from dimethylformamide to yield **7a&b.**

2-Amino-5-(benzo[*d*]oxazol-2-yl)benzamide (7a):
Isolated as yellow solid, Yield: 65%, m.p.: 185-187^{0}C; IR (KBr, cm^{-1}), 3462-3184 ($2NH_2$), 1622 (C=O), 1543 (C=N); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 6.86 (d, 1H, *J*= 8.7 Hz, Ar-H), 7.28 (s, 2H, NH_2, D_2O exchangeable), 7.32-7.40 (m, 2H, Ar-H), 7.67-7.83 (m, 3H, Ar-H and $CONH_2$, D_2O exchangeable), 7.94 (d, 1H, *J*= 8.7 Hz, Ar-H), 8.15-8.18 (m, 1H, Ar-H) and 8.38 (s, 1H, Ar-H); EIMS (m/z) (relative abundance %), 254 [M+1 ⌉$^{+\cdot}$, 11.23], 253 [M ⌉$^{+\cdot}$, 63.85], 238 [$C_{13}H_8N_3O_2$ ⌉$^{+}$, 100], 236 [$C_{14}H_8N_2O_2$ ⌉$^{+\cdot}$, 65.21], 210 [$C_{13}H_{10}N_2O$ ⌉$^{+\cdot}$, 78.33] and 64 [C_5H_4 ⌉$^{+\cdot}$, 39.99]; Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.59; H, 4.34; N, 16.38.

2-Amino-5-(benzo[*d*]thiazol-2-yl)benzamide (7b):
Isolated as yellow solid, Yield: 61%, m.p.: 210-212^{0}C; IR (KBr, cm^{-1}), 3475-3193 ($2NH_2$), 1628 (C=O), 1577 (C=N); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 6.84 (d, 1H, *J*= 8.7 Hz, Ar-H), 7.16 (s, 2H, NH_2, D_2O exchangeable), 7.38 (t, 1H, *J*= 7.5 Hz, Ar-H), 7.47 (t, 1H, *J*= 7.5 Hz, Ar-H), 7.86 (d, 1H, J= 8.7 Hz, Ar-H), 7.91 (d, 1H, *J*= 8.1 Hz, Ar-H), 8.04-8.06 (m, 3H, Ar-H and $CONH_2$, D_2O exchangeable) and 8.21 (s, 1H, Ar-H); EIMS (m/z) (relative abundance %), 271 [M+2 ⌉$^{+\cdot}$, 6.07], 270 [M+1 ⌉$^{+\cdot}$, 18.40], 269 [M ⌉$^{+\cdot}$, 100], 252 [$C_{14}H_8N_2OS$ ⌉$^{+\cdot}$, 87.16], 226 [$C_{12}H_8N_3S$ ⌉$^{+}$, 40.20], 224 [$C_{13}H_8N_2S$ ⌉$^{+\cdot}$, 58.50] and 69 [C_4H_7N ⌉$^{+\cdot}$, 29.85]; Anal. Calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.38; H, 4.40; N, 15.30.

General method for preparation of 8a&b:
A solution of **1a&b** (0.01 mol) in acetic anhydride (20 mL) was heated under reflux for 24 h. After cooling, the separated solid was filtered, dried and crystallized from dioxane to yield **2a&b**.

***N*-[4-(Benzo[*d*]oxazol-2-yl)-2-cyanophenyl)acetamide (8a)**:
Isolated as creamy solid, Yield: 62%, m.p.: 265-267^{0}C; IR (KBr, cm^{-1}), 3439 (NH), 2930 (CH aliph.), 2199 (C≡N), 1656 (C=O); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 2.18 (s, 3H, CH_3), 7.39-7.45 (m, 3H, Ar-H and NH, D_2O exchangeable), 7.75-7.80 (m, 2H, Ar-H), 8.34 (d, 1H, *J*= 8.7 Hz, Ar-H), 8.68 (d, 1H, *J*= 8.7 Hz, Ar-H) and 8.76 (s, 1H, Ar-H); EIMS (m/z) (relative abundance %), 278 [M ⌉+1$^{+\cdot}$, 23.20], 277 [M ⌉$^{+\cdot}$, 25.98], 236 [$C_{14}H_8N_2O_2$ ⌉$^{+\cdot}$, 100], 235 [$C_{14}H_7N_2O_2$ ⌉$^{+}$, 32.26], 208 [$C_{13}H_8N_2O$ ⌉$^{+\cdot}$, 34.90] and 64 [C_5H_4 ⌉$^{+\cdot}$, 40.08]; Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.09; H, 4.09; N, 14.87.

***N*-[4-(Benzo[*d*]thiazol-2-yl)-2-cyanophenyl)acetamide (8b)**:
Isolated as creamy solid, Yield: 58%, m.p.: 235-237^{0}C; IR (KBr, cm^{-1}), 3336 (NH), 2930 (CH aliph.), 2356 (C≡N),1640 (C=O); ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 2.50 (s, 3H, CH_3), 7.51-7.63 (m,3H, 2 Ar-H, NH, D_2O exchangeable), 7.88 (d, 1H, *J*= 8.4 Hz, Ar-H), 8.13 (d, 1H, *J*= 7.8 Hz, Ar-H), 7.23 (d, 1H, *J*= 7.5 Hz, Ar-H), 8.53 (d, 1H, 1H, *J*= 8.4 Hz, Ar-H) and 8.69 (s, 1H, Ar-H); EIMS (m/z) (relative abundance %), 295 [M+2 ⌉$^{+\cdot}$, 40.51], 293 [M ⌉$^{+\cdot}$, 100], 274 [$C_{15}H_4N_3OS$ ⌉$^{+}$, 67.09], 240 [$C_{13}H_8N_2OS$ ⌉$^{+\cdot}$, 83.54], 215 [$C_{11}H_7N_2OS$ ⌉$^{+}$, 71.52], 173 [$C_9H_5N_2S$ ⌉$^{+}$, 73.42], 172 [$C_9H_4N_2S$ ⌉$^{+\cdot}$, 69.62] and 162 [$C_9H_{10}N_2O$ ⌉$^{+\cdot}$, 69.84]; Anal. Calcd for $C_{16}H_{11}N_3OS$: C, 65.51; H, 3.78; N, 14.32. Found: C, 65.31; H, 3.52; N, 14.19.

RESULTS AND DISCUSSION

Chemistry
In the present work, compounds **2b** was prepared according to the method described in the literature [15].

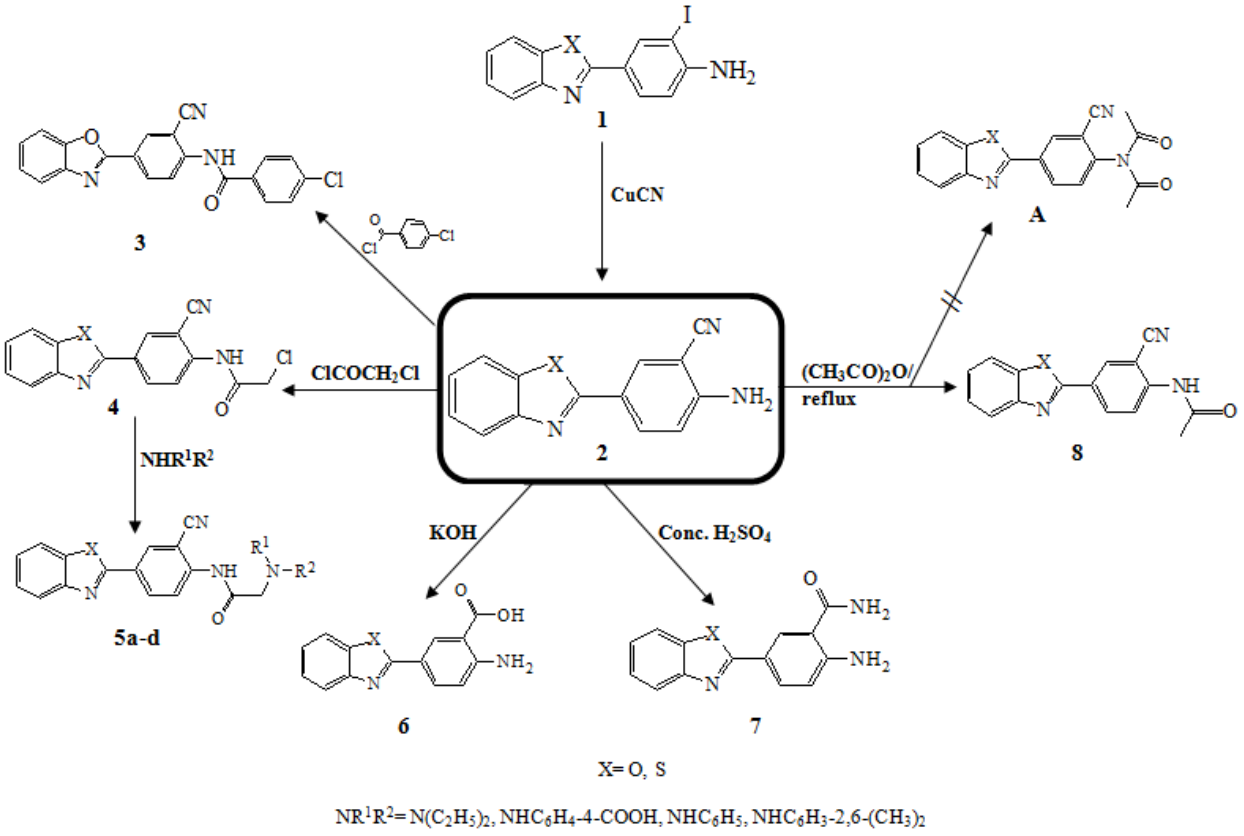
Alkylation of amino group in benzoxazole derivative **2a** using 4-chlorobenzoyl chloride yielded compound **3a**. The structure of compound **3a** was confirmed by element analysis and spectral data. IR spectrum showed C=O group at 1716 cm^{-1}. Moreover, Mass spectrum of **3a** reveled its molecular ion peak at m/z 373.

Reaction of **2a&b** and chloroacetyl chloride afforded **4a&b**. Compounds **4a&b** were subjected to nucleophilic substitution reaction with different primary and secondary amines to give **5a-d**. The ^{1}H NMR spectrum of **5a** showed triplet and quartet groups of ethyl moiety at δ 1.09 and 2.65 ppm, sequentially.

Changing cyano group in compounds **2a&b** to carboxylic acid or carboxamide derivatives was occurred either in basic conditions or in acidic medium giving compounds **6a&b** or **7a&b**, respectively.

IR spectrum of compounds **6a&b** showed the presence of carboxylic acid group as dragged peak at the range of 3445-2500 cm^{-1}, while Mass spectrum of **7a&b** appeared at m/z 253 and 269, sequentially.

Acetylation of amino group in compound **2a&b** using acetic anhydride under reflux condition afforded **8a&b** rather than double acetylation in compound **A**. ^{1}H NMR spectrum of compounds **8a&b** shown the presence of one set for CH_3 protons at δ 2.18 and 2.50, respectively.



Scheme 1. Synthesis of some new benzothiazole and benzoxazole derivatives

BIOLOGICAL TESTING

The human breast tumor cell line (MCF-7) was obtained from NCI, Cairo, Egypt.

Measurement of potential cytotoxicity

The effects of compounds on the growth of tumor cell lines (MCF-7), were evaluated according to the procedure adopted by the National Cancer Institute, Cairo, Egypt for the *in vitro* anticancer drug screening that use the protein-binding dye sulforhodamine B (SRB) to assess growth inhibition. [16] Cell were routinely maintained as adherent cell cultures in RPMI- 1640 medium supplemented with 10% heat-inactived fetal bovine serum (FBS) and 1% penicillin/ streptomycin at 37^{o}C in humidified atmosphere containing 5% CO_2. The cell line was regularly subcultured to be maintained in the expotential growth phase. Cells were exposed for 48 h to five concentrations of compounds (0, 5, 12.5, 25 and 50 ug/ml). Compounds were prepared in dimethylsulphoxide (DMSO), were freshly diluted with cell culture medium just prior the assays. For each test compound and the cell line a dose-response curve was generated and the growth inhibition of 50% (IC_{50}), corresponding to the concentration of compound that inhibits 50% of the net cell growth was determined. The results of *in vitro* cytotoxic activity experiments are presented in **(Table 1)**.

Table 1: Results of *in vitro* cytotoxic activity of some of the synthesized compounds on human breast adenocarcinoma cell line (MCF-7)

Compound no.	IC_{50} in μM[a]
3a	0.033
4a	0.012
4b	**0.011**
5a	0.044
5b	0.028
5c	0.044
6a	0.065

[a] *The values given are means of three experiments.*

RESULTS AND DISCUSSION

Seven of the newly test compounds exhibited antitumor activity against MCF-7 with IC_{50} between 0.011 to 0.065 μM. On the other hand, compound **4b** gave the highst result than all the other compounds. Furthermore, the result obtained from compounds **3a, 4a, 5a-c** and **6a** showed good antitumor activity (IC_{50} between 0.012 to 0.065 μM).

CONCLUSION

New heterocycles were obtained from the reaction between compounds **1a&b** and different commercially available reagents. All compounds obtained retain the benzoxazole and benzothiazole core. Some of the newly synthesized compounds were tested *in vitro* on human breast cancer cell line (MCF-7). Some of the test compounds showed potent antitumor activity, especially compound **4b** with IC_{50} equal to 0.011 μM. The other test compounds showed also good antitumor activity with IC_{50} between 0.012 and 0.065 μM. Thus, introducing substituted amino group with chloroacetyl chloride resulted in higher cytotoxic activity.

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