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Synthesis and Antiproliferative Potency within Anticonvulsant of Novel Bichalcone Derivatives

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ABSTRACT. An efficient and facile procedure has been developed for the synthesis of novel bichalcone derivatives (**4a**, **4b**). The key step contains the solvent-free aldol synthesis of bichalcones based on quinones. Bichalcones (**4a**, **4b**) were used as precursors for the synthesis of some interesting heterocyclic compounds like, diazepines (**5a**, **5b**), pyrazolo-pyrimidines (**7a**, **7b**), and pyrazoline derivatives (**8a**, **8b**). Moreover, new thioxopyrimidine derivatives (**9a**, **9b**) were furnished and used as a functionalizing agent to produce the triazole-pyrimidines (**11**, **12**) and the carbonitrile derivative (**14**). All the synthesized compounds were fully characterized using physical and spectral data like, FT-IR, ^{1}H NMR, ^{13}C NMR, and MS. Bichalcones (**4a**, **4b)** and diazepines (**5a**, **5b**) were screened for their anticonvulsant activity, where compounds (**4a**, **5a**, and **5b**) revealed potent anticonvulsant activity compared to diazepam. On the other hand, some of the prepared compounds were screened for their antiproliferative activity and they showed significant cytotoxic effects on most of the cancer cell lines with regard to broad spectrum antitumor activity.

Key words: Diazepines, Pyrimidines, Anticonvulsant activity, Antiproliferative activity

INTRODUCTION

Quinones are the class of natural and synthetic compounds that have several beneficial effects.[1] They represent a class of molecules preventing and treating several anti-oxidant activities, and so improve general health conditions. Many drugs clinically approved or still in clinical trials against cancer are quinone-related compounds. In addition, chalcones and their derivatives were recognized as biologically active compounds.[2–4] Benzodiazepine compounds are widely used as anticonvulsant,[5] anti-cancer,[6-8] and anti-anxiety agents.[9]

The combination of pharmacophores on the same scaffold is a well-established approach to the synthesis of more potent drugs.[10,11] A perusal of literature has shown that chalcones are proved as potential building blocks for the synthesis of various interesting heterocyclic systems.[12,13] We decided to incorporate chalcone system into cyclic products through Michael addition reactions.

In this work, we synthesized new classes of compounds containing seventeen heterocyclic systems quinone moiety bearing chalcone as an important class of heterocyclic or diazepine ring system that may result in enhanced biological activity due to their synergistic effect.

EXPERIMENTAL

General

All reagents and solvents were dried and purified before use by the usual procedures. M.p.: Büchi® melting point apparatus; uncorrected. TLC: Merck TLC aluminum sheets, silica gel 60 F_{254} with detection by UV quenching at 254 nm. IR spectra: FT-IR Nicolet Impact 400D; KBr pellets; ν in cm^{-1}. ^{1}H and ^{13}C NMR spectra: Bruker at 400 and 100 MHz, respectively; in DMSO-d_6; δ in ppm relative to Me_4Si as internal standard, *J* in Hz. DEPT135 NMR spectroscopy: used where appropriate, to aid the assignment of signals in the ^{1}H and ^{13}C NMR spectra. EIMS were recorded on a gas chromatographic GCMS–HP model MS5988. Elemental analyses were carried out at the Technical University of Dortmund.

2,5-Dichloro-3,6-bis-(4-acetylphenylamino)-[1,4]benzoquinone (3). To a solution of chloranil **1** (10 mmol) in 30 mL of acetonitrile, 4-aminoacetophenone **2** (20 mmol) and few drops of piperidine were added. The reaction mixture was heated under reflux for 6 h. The solid that separated after cooling was filtered and recrystallized from acetonitrile to give **3**. Brown crystals (yield 89%) m.p. > 300 ºC. IR (KBr): ν_{max}/cm^{-1} 3207(NH), 1682, 1663(C=O). ^{1}H NMR (DMSO): δ 2.43(s, 6H, 2 Me), 7.31(d, *J*=8.6Hz, 2H, Ar-H), 7.37(d, *J*=8.6Hz, 2H, Ar-H), 7.90–7.95(m, 4H, Ar-H), 8.76(brs, 2H, D_2O Exch., NH's).^{13}C NMR (DMSO): δ 26.5($2CH_3$), 118.3(4CH), 123.2(2C), 127.8(2C), 132.6(4CH), 141.4(2C), 150.7(2C), 177.4(2C), 193.8(2C). MS: m/z(%) 443(M^+, 22.3). Anal. Calcd. for $C_{22}H_{16}Cl_2N_2O_4$(443.28): C, 59.61; H, 3.64; Cl, 16.00; N, 6.32. Found: C, 59.86; H, 3.50; Cl, 15.76; N, 6.58.

Synthesis of Bichalcone Compounds 4a,b

A mixture of **3** (10 mmol), 4-chlorobenzaldehyde and/or 2-furaldehyde (10 mmol), and KOH (6 pellets) was grounded in a porcelain mortar at room temperature. After 10 min, the mixture was treated with water (50 mL) and filtered to give bichalcones **4a**, and **4b**, respectively.

2,5-Dichloro-3,6-bis-{4-[3-(4-chlorophenyl)acryloyl] phenylamino}-[1,4]benzoquinone (4a). Green crystals (yield 95%) m.p. > 300 ºC. IR (KBr): ν_{max}/cm^{-1} 3210(NH), 1660, 1611(C=O). ^{1}H NMR (DMSO): δ 6.54(d, *J*=12.6Hz, 2H, =CHCO), 7.06(d, *J*=8.8Hz, 4H, Ar-H), 7.48–7.70(m, 8H, Ar-H),7.85(d, *J*=12.6Hz, 2 H, =CHAr), 7.90(d, *J*=8.6Hz, 4H, Ar-H), 9.06(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 118.9(4CH), 121.4(2C), 123.2(2C), 128.9(4CH), 129.4(4CH), 131.5(4CH), 135.3(2C), 136.1(2C), 138.9(2C), 142.1(2CH), 143.7(2C), 150.7(2C), 177.4(2C), 191.8(2C). MS: m/z (%) 688 (M^+, 2). Anal. Calcd. for $C_{36}H_{22}Cl_4N_2O_4$ (688.38): C, 62.81; H, 3.22; Cl, 20.60; N, 4.07. Found: C, 62.62; H, 3.04; Cl, 20.25; N, 3.91.

2,5-Dichloro-3,6-bis-[4-(3-furan-2-yl-acryloyl)-phenylamino]-[1,4] benzoquinone (4b). Brown crystals (yield 97%) m.p. > 300 ºC. IR (KBr): ν_{max}/cm^{-1} 3205(NH), 1656, 1609(C=O). ^{1}H NMR (DMSO): δ 6.13(d, *J*=3.7Hz, 2H, furyl-H), 6.41(dd, J_1=1.8Hz, J_2=3.7Hz, 2H, furyl-H), 6.62 (d, *J*=12.7Hz, 2H, =CHCO), 6.98(d, *J*=8.8Hz, 4H, Ar-H), 7.20–7.27(m, 4H, Ar-H), 7. 52(d, *J*=1.8Hz, 2H, furyl-H), 7.85(d, *J*=12.7Hz, 2H, =CHAr), 9.82(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 111.9(2CH), 116.3(2CH), 118.8(4CH), 121.7(2C), 123.2(2C), 131.2(4CH), 136.0(2C), 137.8(2C), 142.3(2C), 145.1(2CH), 148.8(2C), 150.7(2C), 177.4(2C), 189.3(2C). MS: m/z(%) 599(M^+, 4.3), 601 ($[M+2]^+$, 12). Anal. Calcd. for $C_{32}H_{20}Cl_2N_2O_6$(599.42): C, 64.12; H, 3.36; Cl, 11.83; N, 4.67. Found: C, 64.39; H, 3.21; Cl, 11.55; N, 4.82.

Synthesis of Diazepines 5a, and 5b

Bichalcone compounds **4a**, and/or **4b** (10 mmol) were dissolved in acetonitrile and added to a solution of 2,3-diaminomaleonitrile (10 mmol) in acetonitrile. The reaction mixture was catalyzed with 5 drops of acetic acid anhydride and subjected to ultrasound radiation for 2h. The reaction mixture was left at room temperature overnight and the obtained precipitate was recrystallized from absolute ethanol to give the diazepine compounds (**5a** and **5b**), respectively.

7,7'-(((2,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-diylbis(azanediyl))bis(4,1-phenylene))bis(5-(4-chlorophenyl)-4,5-dihydro-1H-1,4-diazepine-2,3-dicarbonitrile) (5a). Brown crystals(yield 64%) m.p.175–176 ºC. IR (KBr): ν_{max}/cm^{-1} 3407, 3318, 3212(NH), 2248, 2210(CN), 1669 (C=O). ^{1}H NMR (DMSO): δ 5.46(d, *J*=8.7 Hz, 2H, diazepine-H), 5.88(d, *J*=8.7Hz, 2H, =CH diazepine), 7.16(d, *J*=8.8Hz, 4H, Ar–H), 7.38(s, 4H, D_2O Exch., NH's diazepine), 7.72–7.91(m, 8H, Ar-H), 8.16(d, *J*=8.6 Hz, 4H, Ar-H), 9.16 (brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 59.7(2CH), 97.0(2C), 97.8(2C), 99.3(2CH), 118.4(4CH), 119.6(4C), 123.2(2C), 128.5(4CH), 129.7(4CH), 131.0(2C), 132.6(2C), 133.2(2C), 133.9(4CH), 136.7(2C), 142.3(2C), 150.7(2C), 177.4(2C). MS: m/z(%) 870 ($[M+2]^+$, 20). Anal. Calcd. for $C_{44}H_{26}Cl_4N_{10}O_2$ (868.55): C, 60.84; H, 3.02; Cl, 16.33; N, 16.13. Found: C, 61.14; H, 3.19; Cl, 16.10; N, 15.95.

7,7'-(((2,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-diyl)bis(azanediyl))bis(4,1-phenylene))bis(5-(furan-2-yl)-4,5-dihydro-1H-1,4-diazepine-2,3-dicarbonitrile) (5b). Yellow crystals(yield 68%) m.p. 150–152 ºC. IR (KBr): ν_{max}/cm^{-1} 3407, 3332, 3213(NH), 2243, 2206(CN), 1671 (C=O). ^{1}H NMR (DMSO): δ 5.48 (d, *J*=8.7Hz, 2H, diazepine-H), 5.83(d, *J*=8.7Hz, 2H, =CH diazepine), 6.38(d, *J*=3.7Hz, 2H, furyl-H), 6.67(dd, J_1=1.8Hz, J_2=3.7Hz, 2H, furyl -H), 7.16(d, *J*=8.8Hz, 4H, Ar-H), 7.54(brs, 4H, D_2O Exch., NH's diazepine), 7.74(d, *J*=1.8Hz, 2H, furyl-H), 7.90–8.06 (m, 4H, Ar-H), 9.19(brs, 2 H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 56.7(2CH), 97.1(4C), 99.4(2CH), 112.1 (2CH), 114.5(2CH), 118.7(4CH), 119.4(4C), 123.2(2C), 129.3 (4CH), 130.7(2C), 131.5(2C), 136.3(2C), 144.1(2CH), 144.8(2C), 150.7(2C), 177.4(2C). MS: m/z(%): 779(M^+, 3). Anal. Calcd. for $C_{40}H_{24}Cl_2N_{10}O_4$ (779.59): C, 61.63; H, 3.10; Cl, 9.16; N, 17.97. Found: C, 61.93; H, 3.25; Cl, 8.85; N, 18.28.

Synthesis of Pyrazolopyrimidines 7a, and 7b

An equimolar mixture of bichalcone **4a** (10 mmol) and 3-aminopyrazoles **6a** and/or **6b** (10 mmol) in DMF (30 mL) and 5mL of 10% KOH was heated under reflux at 110 ºC for 1 h. The reaction mixture was left overnight then poured into ice water. The solid that separated was filtered off, washed with H_2O, and crystallized from the proper solvent to give **7a** and **7b**, respectively.

2,5-Dichloro-3,6-bis-{4-[7-(4-chloro-phenyl)-pyrazolo [1,5-a]pyrimidin-5-yl]-phenylamino}-[1,4]benzoquinone (7a). Brown crystals (yield 58%) (n-BuOH) m.p.178–179 ºC. IR (KBr): ν_{max}/cm^{-1} 3217(NH), 1663(C=O). ^{1}H NMR (DMSO): δ 6.82 (d, *J*=2.4Hz, 2H, pyrazole-H), 7.14(d, *J*=8.8Hz, 4H, Ar-H), 7.33(d, *J*=8.2Hz, 4H, Ar–H), 7.48(s, 2H, pyrimidine-H), 7.69–7.92(m, 4H, Ar-H), 8.14(d, *J*=8.2Hz, 4H, Ar-H), 9.08(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 104.9(2CH), 107.3(2CH), 118.7(4CH), 123.2(2C), 129.5 (4CH), 129.8(4CH), 131.4(2CH), 133.0(4CH), 133.8(2C), 137.1(2C), 138.2(2C), 139.7(2C), 140.6(2C), 149.3(2C), 150.7(2C), 164.2(2C), 177.4(2C). MS: m/z(%) 814 (M$^+$, 4.1), 816 ([M+2]$^+$, 13.2). Anal. Calcd. for $C_{42}H_{24}Cl_4N_8O_2$ (814.50): C, 61.93; H, 2.97; Cl, 17.41; N, 13.76. Found: C, 62.30; H, 3.16; Cl, 17.03; N, 13.98.

2,5-Dichloro-3,6-bis-{4-[7-(4-chloro-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-5-yl]-phenylamino}-[1,4]benzoquinone (7b). Yellow crystals (yield 63%) (EtOH) m.p. 191–193 ºC. IR (KBr): ν_{max}/cm^{-1} 3209(NH), 1668(C=O). ^{1}H NMR (DMSO): δ 2.36(s, 6H, 2Me), 6.67(s, 2H, pyrazole-H), 7.17(d, *J*=8.8Hz, 4H, Ar-H), 7.32(d, *J*=8.2Hz, 4H, Ar-H), 7.51(s, 2H, pyrimidine-H), 7.83(d, *J*=8.8Hz, 4H, Ar-H), 8.22(d, *J*=8.2Hz, 4H, Ar-H), 9.12(brs, 2H, D_2O Exch., NH's).^{13}CNMR(DMSO): δ 13.6(2CH_3), 105.3(2CH), 110.8 (2CH), 118.1(4CH), 123.2(2C), 129.3(4CH), 129.7(4CH), 132.8(4CH), 133.8(2C), 137.1(2C), 137.8(2C), 139.1(2C), 139.4(2C), 139.9(2C), 149.3(2C), 150.7(2C), 164.3(2C), 177.4(2C). MS: m/z (%) 842 (M$^+$, 13). Anal. Calcd. for $C_{44}H_{28}Cl_4N_8O_2$ (842.56): C, 62.72; H, 3.35; Cl, 16.83; N, 13.30. Found: C, 62.36; H, 3.21; Cl, 16.54; N, 13.08.

Synthesis of Pyrazole Derivatives 8a, and 8b

To a solution of bichalcones **4a**, and/or **4b** (10 mmol) in 30 mL of ethanol, hydrazine hydrate (15 mmol) and a catalytic amount of glacial acetic acid (5 drops) were added. The reaction mixture was refluxed for 6 h. The solid that formed after cooling was filtered off, dried, and recrystallized from ethanol to give compounds **(8a**, and **8b)**, respectively.

2,5-Dichloro-3,6-bis-{4-[5-(4-chlorophenyl)-1H-pyrazol-3-yl]-phenylamino}-[1,4]benzoquinone (8a). Brown crystals (yield 79%) m.p. 167–168 ºC. IR (KBr): ν_{max}/cm^{-1} 3362, 3214(NH), 1660(C=O). ^{1}H NMR (DMSO): δ 6.53(s, 2H, pyrazole-H), 7.28–7.45(m, 8H, Ar-H), 7.64(d, *J*=8.8Hz, 4H, Ar–H), 7.86(d, *J*=8.2Hz, 4H, Ar-H), 8.47(brs, 2H, D_2O Exch., pyrazole NH'), 9.04(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 102.3(2CH), 118.4(4CH), 123.2(2C), 128.1(4CH), 128.8(4CH), 130.7(4CH), 131.9(2C), 134.0(2C), 134.5(2C), 139.8(2C), 146.6(2C), 148.1(2C), 150.7(2C), 177.4(2C). MS: m/z(%) 712 (M$^+$, 27). Anal. Calcd. for $C_{36}H_{22}Cl_4N_6O_2$ (712.41): C, 60.69; H, 3.11; Cl, 19.91; N, 11.80. Found: C, 61.07; H, 3.32; Cl, 20.24; N, 12.05.

2,5-Dichloro-3,6-bis-[4-(5-furan-2-yl-1H-pyrazol-3-yl]-phenylamino}-[1,4] benzoquinone (8b). Yellow crystals (yield 83%) m.p. 201–203 ºC. IR (KBr): ν_{max}/cm^{-1} 3218, 3100(NH), 1684(C=O). ^{1}H NMR (DMSO): δ 6.34(d, *J*= 3.7Hz, 2H, furyl-H), 6.48(s, 2H, pyrazole-H), 6.77(dd, J_1=1.8Hz, J_2=3.7Hz, 2H, furyl-H), 7.08(d, *J*=8.8Hz, 4H, Ar-H), 7.19–7.37(m, 4H, Ar-H), 7.86(d, *J*=1.8Hz, 2H, furyl-H), 8.27(brs, 2H, D_2O Exch., pyraole NH's), 9.13 (brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 102.8(2CH), 110.8(2CH), 115.6(2CH), 118.7(4CH), 123.2(2C), 129.1(4CH), 132.9(2C), 133.4(2C), 141.5(2C), 144.3(2CH), 149.0(2C), 149.2(2C), 150.7(2C), 177.4(2C). MS: m/z(%) 623 (M$^+$, 8), 625 ([M+2]$^+$, 21). Anal. Calcd. for $C_{32}H_{20}Cl_2N_6O_4$ (623.44): C, 61.65; H, 3.23; Cl, 11.37; N, 13.48. Found: C, 61.92; H, 3.06; Cl, 11.09; N, 13.73.

Synthesis of Thioxopyrimidines 9a, and 9b

To a solution of bichalcone **4a** ,and/or **4b** (10 mmol) in 50 mL of ethanol, 1.0 g of sodium hydroxide (25 mmol) and 1.2 g of thiourea (12 mmol) were added. The reaction mixture was refluxed for 6 h, then left to cool overnight and the formed solid product was filtered off, dried, and crystallized from ethanol to give compounds **9a** and **9b**, respectively.

2,5-Dichloro-3,6-bis-{4-[6-(4-chlorophenyl)-2-mercapto-pyrimidin-4-yl]-phenylamino}-[1,4]benzoquinone (9a). Brown crystals (yield 74%) m.p. 184–186 ºC. IR (KBr): ν_{max}/cm^{-1} 3425(SH), 3214(NH), 1659(C=O), 1592(C=N). ^{1}H NMR (DMSO): δ 3.82(s, 2H, D_2O Exch., SH), 7.19(d, *J*=8.8Hz, 4H, Ar-H), 7.53–7.64(m, 10H, pyrimidine-H, 8Ar-H), 7.89 (m, 4H, Ar-H), 9.03(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 108.5(2CH), 117.1(4CH), 123.2(2C), 129.6(4CH), 132.8(2C), 134.9(2C), 135.3(2C), 136.8(2C), 138.7(4CH), 140.5(4CH), 150.7(2C), 155.1(2C), 155.7(2C), 177.4(2C), 179.9(2C). MS: m/z (%) 800 (M$^+$, 7), 802 ([M +2]$^+$, 23). Anal. Calcd. for $C_{38}H_{22}Cl_4N_6O_2S_2$ (800.56): C, 57.01; H, 2.77; Cl, 17.71; N, 10.50; S, 8.01. Found: C, 57.27; H, 2.86; Cl, 17.39; N, 10.34; S, 7.73.

2,5-Dichloro-3,6-bis-[4-(6-(furan-2-yl)-2-mercapto-pyrimidin-4-yl)-phenylamino)-[1,4]bezoquinone (9b). Red crystals (yield 53%) m.p. > 300 ºC. IR (KBr): ν_{max}/cm^{-1} 3349(SH), 3220(NH), 1649(C=O), 1594(C=N). ^{1}H NMR (DMSO): δ 3.87(s, 2H, D_2O Exch., SH), 6.08(d, *J*=3.7Hz, 2H, furyl-H), 6.89(dd, J_1=1.8Hz, J_2=3.7Hz, 2H, furyl-H), 7.19(d, *J*=8.8Hz, 4H, Ar-H), 7.43(d, *J*=8.6Hz, 4H, Ar-H), 7.65(s, 2H, pyrimidine-H), 7.79(d, *J*=1.8Hz, 2H, furyl-H), 8.94(brs, 2 H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 109.8(2CH), 111.3(2CH), 116.5(2CH), 117.9(4CH), 123.2(2C), 135.7(2C), 136.2(2C), 141.1(4CH), 147.4(2C), 148.8(2CH), 150.7(2C), 155.6(2C), 157.3(2C), 177.4(2C), 183.8(2C). MS: m/z(%) 711(M$^+$, 3), 713([M+2]$^+$, 11). Anal. Calcd. for $C_{34}H_{20}Cl_2N_6O_4S_2$ (711.60): C, 57.39; H, 2.83; Cl, 9.96; N, 11.81; S, 9.01. Found: C, 57.06; H, 2.69; Cl, 9.73; N, 12.14; S, 8.77.

Synthesis of Hydrazinopyrimidine 10a, and 10b

A mixture of compounds **9a**, and/or **9b** (10 mmol), hydrazine hydrate (10 mmol), and a catalytic amount of glacial acetic acid (5 drops) in ethanol (30mL) was refluxed for 6 h. Evaporation of excess alcohol and recrystallization from ethanol gave compounds **10a**, and **10b**, respectively.

2,5-Dichloro-3,6-bis-{4-[6-(4-chlorophenyl)-2-hydrazino-pyrimidin-4-yl]-phenylamin}-[1,4] benzoqinone (10a). Yellow crystals (yield 82%) m.p. 221–223 ºC. IR (KBr): ν_{max}/cm^{-1} 3336, 3203(NH), 1658(C=O), 1556(C=N). ^{1}H NMR(DMSO): δ 7.13(d, *J*=8.8Hz, 4H, Ar-H), 7.48(d, *J*= 8.6Hz, 4H, Ar-H), 7.56–7.65(m, 6H, pyrimidine-H, Ar-H), 8.47(brs, 6H, D_2O Exch., NH's), 9.21(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 102.4(2CH), 112.6(4CH), 123.2(2C), 128.9(4CH), 130.5(4CH), 133.1(2C), 134.3(4CH), 134.9(2C), 135.4(2C), 136.7(2C), 150.7(2C), 153.8(2C), 156.2(2C), 157.0(2C), 177.4(2C). MS: m/z (%) 796 (M$^+$, 8). Anal. Calcd. for $C_{38}H_{26}Cl_4N_{10}O_2$ (796.49): C, 57.30; H, 3.29; Cl, 17.80; N, 17.59. Found: C, 57.71; H, 3.15; Cl, 17.98; N, 17.80.

2,5-Dichloro-3,6-bis-[4-(6-(furan-2-yl)-2-hydrazino-pyrimidin-4-yl)-phenylamino]-[1,4]benzoqinone (10b). Brown crystals (yield 76%) m.p. 218–219 ºC. IR (KBr): ν_{max}/cm^{-1} 3372, 3176(NH), 1648(C=O), 1566(C=N). ^{1}H NMR (DMSO): δ 6.11(d, *J*=3.7Hz, 2H, furyl-H), 6.92(dd, J_1=1.8Hz, J_2=3.7Hz, 2H, furyl-H), 7.22(d, *J*=8.8Hz, 4H, Ar-H), 7.48(d, *J*=8.6Hz, 4H, Ar-H),7.63(s, 2H, pyrimidine-H), 7.78(d, *J*=1.8Hz, 2H, furyl-H), 8.53(brs, 2H, D_2O Exch., NH's), 9.06(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 102.9 (2CH), 106.8(2CH), 113.1(4CH), 114.4(2CH), 123.2(2C), 134.0(4CH), 135.5(2C), 137.1(2C), 144.8(2C), 145.3(2C), 150.4(2CH), 150.7(2C), 158.7(2C), 159.9(2C), 177.4(2C). MS: m/z(%) 707 (M$^+$, 17), 709 ([M+2]$^+$, 39). Anal. Calcd. for $C_{34}H_{24}Cl_2N_{10}O_4$ (707.52): C, 57.72; H, 3.42; Cl, 10.02; N, 19.80. Found: C, 58.02; H, 3.59; Cl, 9.71; N, 19.63.

2,5-Dichloro-3,6-bis-{4-[5-(4-chlorophenyl)-3-methyl-[1,2,4]triazzolo[4,3-a]pyrimidin-7-yl]-phenylamino}-[1,4] benzoqinone (11). A solution of compound **10a** (10 mmol) in 10 mL freshly distilled acetic acid anhydride was heated under reflux for 1 h. The solid that formed after concentration and cooling was filtered off and crystallized from EtOH to give **11**. Reddish brown crystals (yield 79%)m.p. 207–208 ºC. IR (KBr): ν_{max}/cm^{-1} 3213(NH), 1658(C=O). ^{1}H NMR (DMSO): δ 2.37(s, 6H, 2Me), 7.16 (d, *J*=8.8Hz, 4H, Ar-H), 7.43(d, *J*=8.6Hz, 4H, Ar-H), 7.52(s, 2H, pyrimidine-H), 7.61–7.82(m, 8H, Ar-H), 9.17(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 13.7(2CH_3), 104.8(2CH), 118.5(4CH), 123.2(2C), 128.7(4CH), 132.6(4CH), 133.3(4CH), 136.2(2C), 137.5(2C), 139.8(2C), 141.3(2C), 141.9(2C), 149.8(2C), 150.7(2C), 158.6(2C), 165.0(2C), 177.4(2C). MS: m/z (%) 844 (M$^+$, 3). Anal. Calcd. for $C_{42}H_{26}Cl_4N_{10}O_2$ (844.53): C, 59.73; H, 3.10; Cl, 16.79; N, 16.59. Found: C, 59.94; H, 2.91; Cl, 16.46; N, 16.26.

2,5-Dichloro-3,6-bis-{4-[5-(4-chlorophenyl)-3-thioxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl]-phenylamino}-[1,4]benzoqinone (12). To a solution of **10a** (10 mmol) in dry pyridine (30 mL), CS_2 (20 mmol) was added and the reaction mixture was heated under reflux for 10 h. After cooling the reaction mixture was poured into ice/HCl mixture and the solid that separated was washed with cold water, filtered off, and crystallized from EtOH/H_2O to give **12**. Reddish brown crystals (yield 71%) m.p. 248–250 ºC. IR (KBr): ν_{max}/cm^{-1} 3309, 3217(NH), 1658(C=O), 1451(C=S). ^{1}H NMR (DMSO): δ 7.06 (d, *J*=8.8Hz, 4H, Ar-H), 7.48–7.68(m, 10H, pyrimidine-H, Ar-H), 7.92(d, *J*=8.8Hz, 4H, Ar-H), 9.22(brs, 2H, D_2O Exch., NH's), 9.84(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 104.7(2CH), 118.6(4CH), 123.2(2C), 128.5(4CH), 132.8(4CH), 133.2(4CH), 135.9(2C), 137.3(2C), 140.0(2C), 141.2(2C), 150.7(2C), 152.6(2C), 154.9(2C), 164.8(2C), 168.1(2C), 177.4(2C). MS: m/z(%) 880 (M$^+$, 4), 882 ([M+2]$^+$, 17).Anal. Calcd. for $C_{40}H_{22}Cl_4N_{10}O_2S_2$ (880.61): C, 54.56; H, 2.52; Cl, 16.10; N, 15.91; S, 7.28. Found: C, 54.90; H, 2.83; Cl, 15.75; N, 16.17; S, 7.03.

Synthesis of Pyrimidines 13a, and 13b

A mixture of **10a** (10 mmol), piperonal and/or 2-furaldehyde (10 mmol), in 1,4-dioxane (20 mL) was refluxed for 6h. The solid that separated after concentration and cooling was filtered off and crystallized from EtOH/H_2O to give **13a**, and **13b**, respectively.

2,5-Dichloro-3,6-bis-{4-2-(N-benzo[1,3]dioxol-4-yl-methylene-hydrazino)-6-(4-chloro-phenyl-pyrimidin-4-yl]-phenylamino}-[1,4]benzoquinone (13a). Brown crystals (yield 57%) m.p. > 300 ºC. IR (KBr): ν_{max}/cm^{-1} 3366, 3224(NH), 1641(C=O). ^{1}H NMR(DMSO): δ 5.68(s, 4H, $2OCH_2O$), 6.78(d, *J*=8.1Hz, 2H, Ar-H), 7.08–7.17(m, 8H, Ar-H),7.38(s, 2H, pyrimidine-H), 7.43–7.65(m, 8H, Ar-H), 7.84(d, *J*=8.6Hz, 4H, Ar-H), 8.12(s, 2H, =CHN), 9.13(brs, 2H, D_2O Exch., NH's), 9.37(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 99.4($2CH_2$), 104.7(2CH), 107.9(2CH), 110.2(2CH), 115.6(4CH), 123.2(2C), 123.7(2CH), 128.1(2C), 130.4(4CH), 132.0(4CH), 132.3(2C), 132.8(2C), 134.6(4CH), 135.9(2C), 136.3(2C), 137.8(2C), 147.1(2C), 150.7(2C), 150.9(2C), 152.3(2C), 156.8(2C), 157.6(2C), 177.4(2C). MS: m/z (%) 1060 (M^+, 2). Anal. Calcd. for $C_{54}H_{34}Cl_4N_{10}O_6$ (1060.72): C, 61.14; H, 3.23; Cl, 13.37; N, 13.20. Found: C, 61.46; H, 3.39; Cl, 13.08; N, 12.90.

2,5-Dichloro-3,6-bis-{4-[6-(4-chlorophenyl)-2-(N-furn-2-yl-methylene-hydrazino)-pyrimidin-4-yl]phenylamino}-[1,4]benzoquinone (13b). Brown crystals (yield 47%) m.p. > 300 ºC. IR (KBr): ν_{max}/cm^{-1} 3309, 3226(NH), 1654(C=O). ^{1}H NMR (DMSO): δ 6.31(d, *J*=4Hz, 2H, furyl-H), 6.56(dd, J_1=1.8Hz, J_2=4Hz, 2H, furyl-H), 7.12(d, *J*=8.6Hz, 4H, Ar-H), 7.28(d, *J*=8.3Hz, 4H, Ar-H), 7.43(s, 2H, pyrimidine-H), 7.57(s, 2H, =CHN), 7.62(d, *J*=1.8Hz, 2H, furyl-H), 7.81–7.94(m, 8H, Ar-H), 9.17(brs, 2H, D_2O Exch., NH's), 9.48(brs, 2H, D_2O Exch., NH's). ^{13}C NMR (DMSO): δ 105.8(2CH), 114.6(2CH), 115.7(2CH), 123.2(2C), 125.1(2CH), 128.4(4CH), 130.7 (4CH), 131.9 (2C), 133.5 (4CH), 133.8(2C), 134.9(2C), 136.1(2C), 137.7(2C), 140.4(2CH), 144.6(2C), 150.7(2C), 154.9(2C), 158.2(4C), 177.4(C). MS:m/z(%) 878 ($[M^+-1]^+$, 47). Anal. Calcd. for $C_{45}H_{32}Cl_2N_{10}O_6$ (879.70): C, 61.44; H, 3.67; Cl, 8.06; N, 15.92. Found: C, 61.42; H, 3.69; Cl, 8.07; N, 15.94.

1,1'-(6,6'-(((2,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-diyl)bis(azanediyl))bis(4,1-phenylene))bis(4-(4-chloro-phenyl)pyrimidine-6,2-diyl))bis(5-amino-1H-pyrazole-4-carbonitrile) (14a). To a solution of compound **10a** (10 mmol) in absolute ethanol (30 mL), methoxy methylene malononitrile (10 mmol) was added. The reaction mixture was heated under reflux for 8h. The formed precipitate was filtered off and recrystallized from ethanol to give compound **14a**. Yellowish brown crystals (yield 64%) m.p. > 300 ºC. IR (KBr): ν_{max}/cm^{-1} 3346, 3916(NH), 2221(C=N), 1633(C=O), 1593(C=N). ^{1}H NMR (DMSO): δ 7.12(d, *J*=8.8Hz, 4H, Ar-H), 7.30(s, 2H, pyrazole-H), 7.34–7.46(m, 10H, pyrimidine-H, Ar-H), 7.78(d, *J*=8.8Hz, 4H, Ar-H), 8.89(brs, 4H, D_2O Exch., NH's), 9.21(brs, 2H, D_2OExch., NH's). ^{13}CNMR (DMSO): δ 97.8(2C), 108.3(2CH), 109.5(2C), 116.6(4CH), 123.2(2C), 129.1(4CH), 131.0(4CH), 132.7(4CH), 134.8(2C), 135.2(2CH), 135.8(2C), 136.4(2C), 137.9(2C), 150.7(2C), 151.5(2C), 156.8(4C), 160.3(2C), 177.4(2C). MS: m/z(%) 948 (M^+, 17). Anal. Calcd. for $C_{46}H_{26}Cl_4N_{14}O_2$ (948.60): C, 58.24; H, 2.76; Cl, 14.95; N, 20.67.Found: C, 58.03; H, 3.05; Cl, 15.18; N, 20.45.

Biological

Anticonvulsant Activity

Bichalcone compounds (**4a**, **4b**) and diazepines (**5a**, and **5b**) were screened for their anticonvulsant activity via pentylenetetrazole metrazole induced convulsions test. The results were compared with diazepam as a standard anticonvulsant.

Swiss albino adult male mice, weighing 20–25g were used. They were obtained from an animal facility (Animal House, Department of pharmacology and Toxicology, Faculty of Pharmacy, Al-Azhar University). Mice were housed in stainless steel wire-floored cages without any stressful stimuli and kept under well-ventilated conditions at room temperature (25–30 ºC). They were fed on an adequate standard laboratory chow (El-Nasr Co., Abou Zabal, Egypt) and allowed to acclimatize with free access to food and water for 24 h before testing.

The study was approved by the Institutional Animal Ethical Committee (IAEC) and was in accordance with the guideline of the Committee for the purpose of control and Supervision of Experimental Animal (PCSEA). Pentylenetetrazole was used to induce convulsions, the tested compounds were solubilized in DMSO and orally administered in dose ranging from 500–200 mg/kg animal weight using the same dosing volume of a 2 mL per 20g pentylenetetrazole (PTZ, Sigma) was dissolved in normal saline at 2% concentration and was given intraperitoneally in a dose of 60 mg/kg body weight (dose that could induce convulsions in at least 80% of the animals without death during the following 24 h.) Diazepam (sigma, USA) was dissolved in normal saline at 2% concentration and was given in doses of 62.50, 125, 250 mg/kg using the same dosing volume. All drugs were freshly prepared according to the desired concentration just before use.

Mice were administered as the graded doses of the test compounds and diazepam orally. Control animals received an equal volume of saline (10 mL/kg). After one hour the animals were subcutaneously injected with the convulsive dose of (PTZ) (60 mg/kg). The criterion of anticonvulsant activity is complete protection against convulsions of any kind. Observations were made at least 60 minutes after the administration of (PTZ).

Anti-proliferative Activity

The newly synthesized compounds **4a**, **4b**, **5a**, **5b**, **8a**, **8b**, **9a**, and **9b** were tested for their *in vitro* anti-proliferative activities in the National Cancer Institute (NCI), where a single dose (10 μM) of the test compounds was used against 60 cell lines panel assay.[29–33] All cells were cultured using Dulbecco's modified Eagle's medium (DMEM) and Roswell Park Memorial Institute (RPMI-1640) medium. All media were supplemented with 4.5 g/L Glucose with L-Glutamine and 10% fetal bovine serum (FBS). The cells were incubated in 5% CO_2 humidified at 37 °C for growth maintenance. All compounds were evaluated by MTT assay. Briefly, the cells were cultured in 96-well plates at a density of 1×10^4 cells/well. Culture media without compound administration was used as a negative control and doxorubicin (a standard anticancer drug) administration was used as a positive control. After 24 h incubation, MTT dissolved in PBS was added to each well at a final concentration of 5 mg/mL, and the samples were incubated at 37 °C for 4 h. Water-insoluble dark blue formazan crystals that formed during MTT cleavage in actively metabolizing cells were then dissolved in dimethyl sulfoxide (DMSO). Absorbance was measured at 540 nm, using a microplate reader (BMG Labtech, Germany). The cell viability (%) was calculated and compared with the controls.

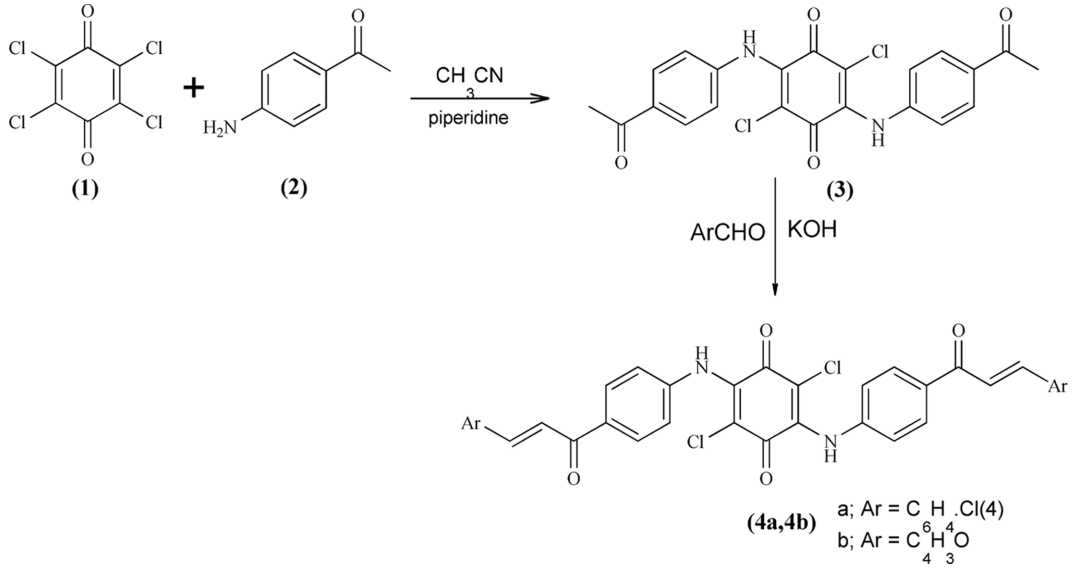
The data reported as mean-graph of the percent of the growth of the treated cells, as percentage growth of the treated cells and as a percentage of growth inhibition (GI%) caused by the tested compounds.

RESULTS and DISCUSSIONS

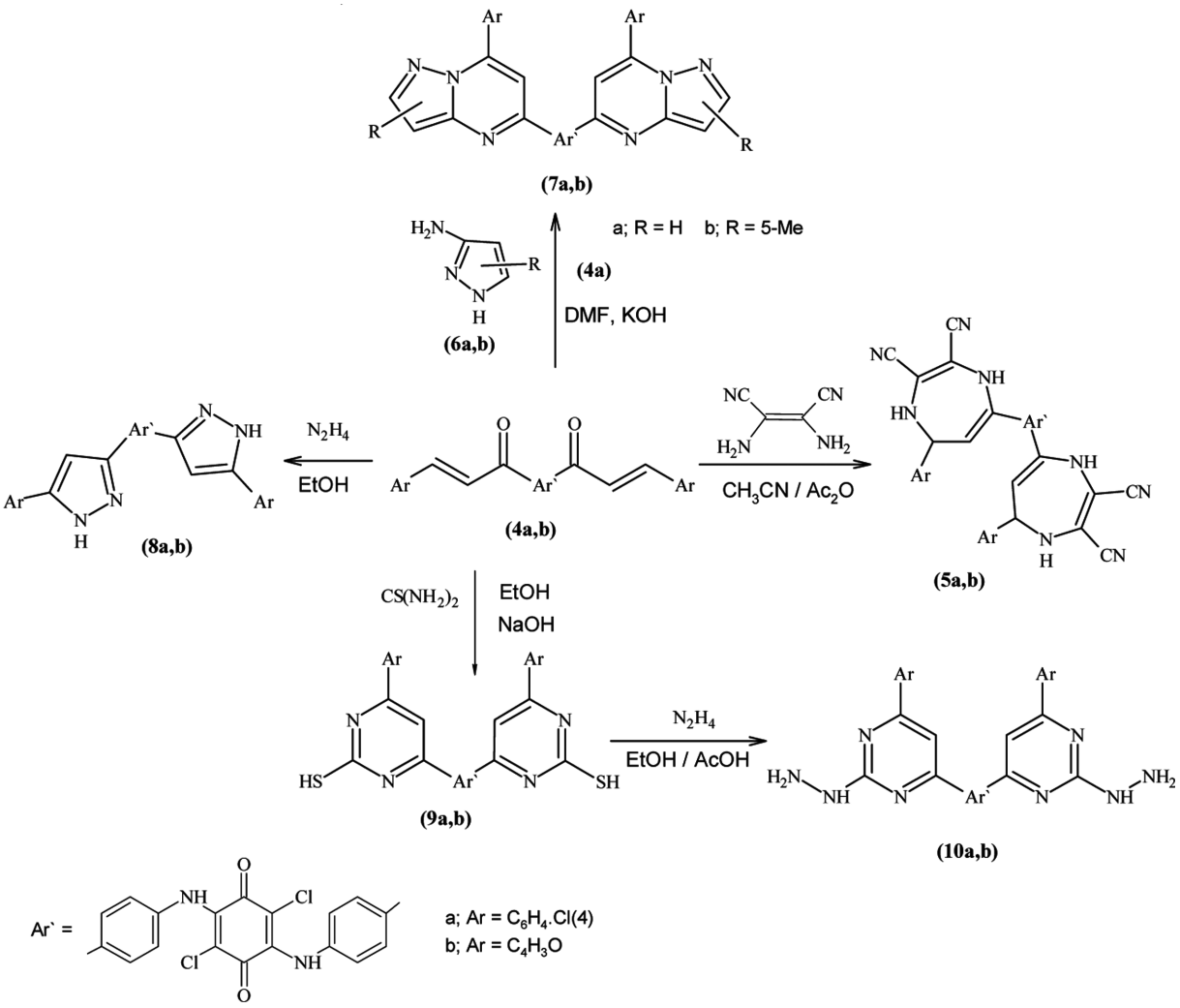
Chemistry

Preparation of bichalcone derivatives was initiated by reaction of 2,3,5,6-tetrachloro-[1,4]benzoquinone (**1**) and a solution of 4-aminoacetophenone (**2**) in acetonitrile with a few drops of piperidine, according to the recently published procedure.[14] This rection afforded 2,5-bis(4-acetylphenylamino)-3,6-dichloro-[1,4]benzoquinone (**3**) in 89% yield (*Scheme* 1).

The synthesis of bichalcone derivatives **4a**, and **4b** was shown in *Scheme* 1. Chalcone formation is usually accomplished using Claisen-Schmidt reaction under basic medium in a polar solvent.[15] The condensation was carried out with equimolar quantities of 2,5-bis(4-acetylphenylamino)-3,6-dichloro-[1,4]benzoquinone (**3**), and 4-chlorobenzaldehyde, (or 2-furaldehyde) in methanolic KOH solution, according to the reported procedure,[16] furnishing **4a**, and **4b** in 68% and 73% yield, respectively. Remarkable improvement in yields (95–97%) was obtained by carrying out the Aldol condensation under solvent-free conditions.[17,18] In this respect, solvent-free aldol condensation, by grinding a mixture of equimolar quantities of compound **3** and 4-chlorobenzaldehyde (or 2-furaldehyde) with KOH, in a porcelain mortar, furnished bichalcone derivatives **4a** (95%) and **4b** (97%), respectively (*Scheme* 1). The IR spectra of the new compounds displayed the characteristic absorption bands for conjugated carbonyl group at ν_{max}: 1660-1656 cm^{-1}. The ^1H NMR spectra revealed the olefinic H in the aro-



***Scheme* 1.** Synthesis of bichalcones **4a**, and **4b**.



***Scheme* 2.** Reactions of bichalcone derivatives **4a**, and **4b**.

matic region beside the other signals at their expected positions. The MS spectra showed their exact molecular ion peak.

We began our investigation of utilities of the prepared bichalcone derivatives **4a**, and **4b** by considering 1,4-cycloaddition reactions to α,β-unsaturated carbonyl compounds (chalcones). They are versatile tools for building heterocycles, so we aimed to synthesize new diazepine derivatives **5a**, and **5b** by reacting the bichalcone derivatives **4a**, and **4b** with 2,3-diaminomaleonitrile in acetonitrile under ultrasonic conditions. The structures of the new diazepines **5a**, and **5b** were deduced from their analytical and spectral data, where IR spectra showed two absorption bands at ν_{max} ranging from 3407 to 3212 cm^{-1}, assignable for two NH groups; and two bands ranging from 2248 to 2206 cm^{-1}, assignable for two C≡N groups. The ^{1}H NMR spectra showed two NH singlets (D_2O exchangeable) in the region 9.17–9.21 ppm. MS data of the diazepines **5a**, and **5b** were found to be in full agreement with the proposed structures.

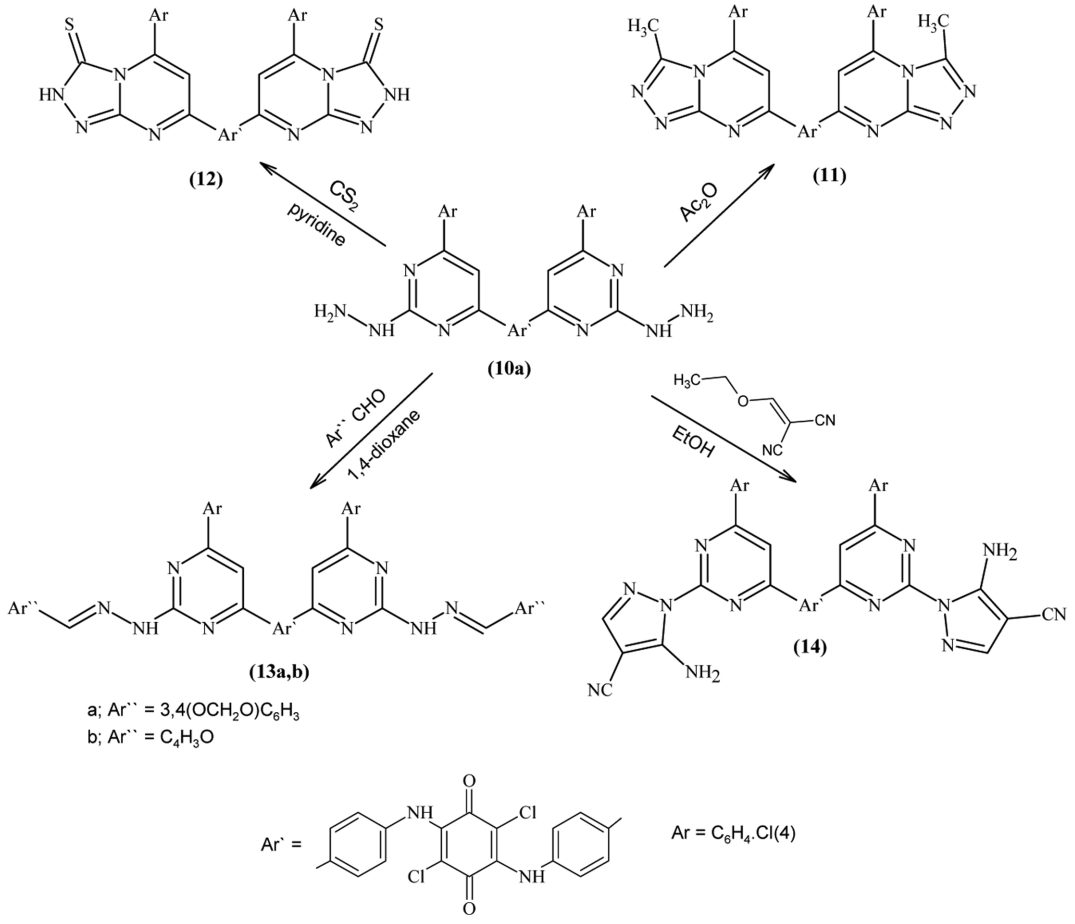
There are a few reports with bichalcones or even chalcones as precursors for the synthesis of pyrazolo[1,5-a]pyrimidines. For example, Elnagdi and Erian synthesized analogs of tetrasubstituted pyrazolo[1,5-a]pyrimidines with chalcones as precursors in moderate yields.[19–22] We achieved the synthesis of pyrazolo[1,5-a]pyrimidines (**7a**, and **7b**) through the tandem reaction of 3-amino pyrazoles (**6a**, and **6b**) and bichalcone derivative **4a** in the presence of catalytic amounts of KOH.[23] The ^{1}H NMR spectra of **7a**, and **7b** displayed two doublets of pyrazole protons at δ = 6.82 and 6.67 ppm. Cyclocondensation of **4a**, and **4b** with hydrazine hydrate in refluxing ethanol gave the corresponding pyrazoline derivatives **8a**, and **8b**. The structures of these products were ascertained by their elemental and spectral data, where their IR spectra of **8a** showed absorption bands at 3362 and

3214 cm^{-1} characteristic for (NH groups).

Furthermore, the new pyrimidine-2-thiol derivatives **9a**, and **9b** were prepared via the condensation reactions of the bichalcone derivatives **4a**, and **4b** with thiourea in the presence of a catalytic amount of sodium ethoxide. The reaction possibly takes place via Aza-Michael addition to the unsaturated carbonyl moiety of the chalcone followed by cyclo-condensation reaction with the loss of water to give thioxopyrimidines **9a**, and **9b**. The structures of the obtained new pyrimidines were substantiated by their spectral and analytical data.

The behavior of the thioxopyrimidines **9a**, and **9b** towards nitrogen nucleophiles have been studied; its reaction with hydrazine hydrate was chosen as a model reaction. The reaction of compounds **9a**, and **9b** with hydrazine hydrate in ethanol afforded the hydrazino-pyrimidine derivatives **10a**, and **10b**. The disappearance of the absorption bands characteristic of the SH group, which are present in the starting compounds **9a**, and **9b**, are confirmatory from their IR and ^{1}H NMR spectra of compounds **10a**, and **10b**, in addition to their exact molecular weights given by the mass spectra for their structures.

The chemistry of pyrimidines has become a subject of great interest in the last few years because they display some interesting properties in functionalization of other heterocycles.[24–26] Considering the importance of pyrimidines, and the uses of bichalcones as key precursors we have successfully attempted to use hydrazino-pyrimidine based on bichalcones as a key starting material for the synthesis of some interesting nitrogen bridgehead compounds. Indeed, the hydrazino-pyrimidine derivative **10a** was allowed to react with Ac_2O, and the bis 3-methyl-1,2,4-triazolo[4,3-a]pyrimidine derivative **11** was afforded. When compound **10a** was reacted with CS_2 in pyridine, the bis 3-thioxo-1,2,4-triazolo[4,3-a]pyrimidine derivative **12** was obtained. Moreover, compound **10a** was condensed with piperonal or 2-furaldehyde in 1,4-dioxane to afford the corresponding hydrazone derivatives **13a**, and **13b**, respectively (*Scheme* 3). The structures of compounds **11**, **12**, **13a**, and **13b** were deduced from their analytical and spectral data, which were



***Scheme* 3.** Reactions of hydrazinopyrimidines **10a**.

***Table* 1.** Anticonvulsant activity of compounds **4a**, **4b**, **5a**, **5b**, and diazepam

Compd.	Dose mg/kg	No. of protected animal	% protection	ED_{50} mcg/kg	MWt	ED_{50} mol/kg	Relative potincy
	82.5	1	16.66				
Diazepam	125	3	50	125	284	0.44	1
	250	6	100				
	500	4	66.66				
4a	1000	5	83.33	250	688	0.36	0.73
	2000	6	100				
	500	3	50				
4b	1000	4	66.66	500	599	0.83	0.34
	2000	6	100				
	500	6	100				
5a	1000	4	66.66	250	868	0.29	0.67
	2000	5	83.33				
	500	4	66.66				
5b	1000	5	83.33	250	764	0.33	0.63
	2000	6	100				

ED_{50} (Median effective dose = the effective that protects 50% of the animal against PTZ induced convulsion.
RP = Relative potencies.
The tested compounds revealed good anticonvulsant activity compared to that of Diazepam, but the bichalcone **4b** was the less reactive one.

in full agreement with the proposed structure.

Finally, the hydrazino-pyrimidine derivative **10a** was used as an assorted precursor for the synthesis of some biologically active heterocycles, where the amino pyrazole carbonitrile compound **14** was synthesized by refluxing an equimolar mixture of compounds **10a** and methoxy methylene malononitrile in boiling absolute ethanol. The structure of compound **14** was confirmed by spectral and elemental analysis, where its IR spectrum gave the absorption bands at ν_{max} = 3346 and 2221 cm^{-1} for NH_2 and CN groups, respectively. Its ^1H NMR substantiated the signal for NH_2 as a broad singlet (D_2O exchangeable) at δ = 8.89 ppm.

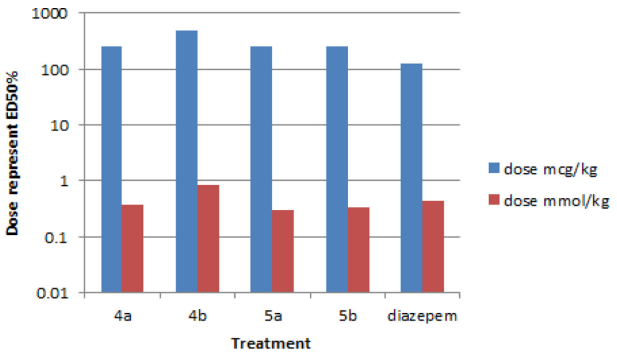


***Figure* 1.** Anticonvulsant activity of compounds **4a**, **4b**, **5a**, **5b**, and diazepam.

Biological

Anticonvulsant Activity

Doses that gave full protection against the induced convulsions and that which exhibited 50% protection in addition to the relative potencies of the test compounds to diazepam were recorded. The ED_{50} of each compound (mg/kg and mmol.) and the relative potencies of the test compounds to Diazepam were calculated and presented in *Table* 1.

Anti-proliferative Activity

The tested compounds displayed significant in vitro screening on the tested cell lines and showed cytotoxic effects on most of the cancer cell lines with regard to broad spectrum antitumor activity. Close examination of the data presented in *Table* 2 revealed that compounds **5a**, **5b**, and **8a** were the most active members of this study showing effectiveness towards numerous cell lines within different tumor subpanels.

Consequently, compounds **5a**, **5b**, and **8a** were tested against a panel of 32 different tumor cell lines at a 5-log dose range. Three response parameters GI_{50}, TGI, and LC_{50} were calculated for each cell line using the known drug 5-fluorouracil (5-FU) as a positive control (*Table* 3). Compounds **5a**, **5b**, and **8a** exhibited remarkable growth inhibitory activity pattern against renal cancer (GI_{50} = 4.26, 3.47 and 12.30 μM), breast cancer (GI_{50} = 4.16, 4.16 and 6.16 μM), ovarian cancer (GI_{50} = 9.54, 6.30 and 10.23 μM), melanoma cancer (GI_{50} = 6.58, 4.24 and 3.70 μM), and prostate cancer (GI_{50} = 27.22, 4.89 and 18.8 μM), respectively.[29–33]

Comparing with the antitumor activities of Gefitinib

***Table* 2.** Percentage growth inhibitor (GI %) of in vitro subpanel tumor cell lines at 10 μM concentration

Subpanel tumor cell lines	% Growth inhibition (GI%)							
	4a	**4b**	**5a**	**5b**	**6a**	**6b**	**7a**	**7b**
Melanoma								
LOX IMVI	-	-	26	18	39	-	32	29
MALME-3M	-	17	39	19	51	16	55	67
M14	-	22	27	-	35	25	61	13
MDA-MB-435	-	-	22	11	33	12	24	-
SK-MEL-2	-	-	23	16	43	27	55	48
SK-MEL-28	-	-	22	-	25	30	40	27
SK-MEL-5	-	-	55	13	61	26	33	10
UACC-257	-	-	31	11	39	39	80	43
UACC-62	-	-	57	34	47	47	24	15
Ovarian Cancer								
IGROVI	-	-	16	-	26	-	25	-
OVCAR-3	-	-	23	12	57	-	31	33
OVCAR-4	11	-	19	37	77	39	52	L
OVCAR-5	-	-	15	-	-	12	-	-
OVCAR-8	-	55	32	21	59	27	L	71
NCI/ADR-RES	-	-	33	18	34	16	nt	17
SK-OV-3	-	28	28	-	61	19	53	70
Renal Cancer								
786-o	-	-	42	17	57	-	L	28
A498	-	17	89	36	86	65	L	33
ACHN	-	-	43	22	63	55	34	47
CAKI-1	-	12	24	28	18	37	16	35
RXF 393	-	29	70	-	76	43	64	64
SN12C	-	-	12	18	17	21	31	11
TK-10	-	-	28	-	45	-	L	-
UO-31	-	23	38	55	29	26	52	29
Prostate Cancer								
PC-3	10	-	29	34	26	57	65	17
DU-145	-	-	28	-	20	-	46	17
*B*reast Cancer								
MCF7	21	-	30	16	30	30	18	23
MDA-MB-231/TCC	-	15	56	36	65	49	59	48
HS 578T	-	45	53	23	56	60	76	94
BT-549	-	28	69	12	47	27	87	-
T-47D	-	-	45	22	88	36	27	65
MDA-MB-468	-	nt	nt	-	nt	-	nt	32

and Erlotinib, compounds **5a**, **5b**, and **8b** (*Table* 4) possess activities almost equal to or higher than those of Gefitinib and Erlotinib against most cell lines except melanoma (SK-MEL-28), ovarian (IGROVI and SK-OV-3), renal (ACHN and TK-10), and breast cancer (MDA-MB-435).

The 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide is based on the conversion of MTT into formazan crystals by living cells,which reflects cytotoxicity based on mitochondrial activity. Thus, the pathway of cancerous cell death may be through mitoptosis, a de novo mitochondrial death mechanism. The detailed mechanism of action may be further investigated in an *in vivo* study that we are proposing to approach.

CONCLUSION

We successfully endeavor to design, synthesize, and evaluated new anticonvulsant bichalcone derivatives **4a**, and

***Table* 3.** Compounds **5a**, **5b**, and **6a** medium growth inhibitory (GI_{50}, μM), total Growth inhibitory (TGI, μM), and medium lethal concentration (LC_{50}, μM) of in vitro subpanel cell lines

Activity	Melanoma	Ovarian cancer	Renal cancer	Prostate cancer	Breast cancer	MG-MID[a]
GI_{50}	6.56	9.54	4.26	27.22	4.16	10.5
TGI	19.85	60.25	39.8	b	67.1	58.8
LC_{50}	b	b	b	b	b	b
GI_{50}	4.24	6.3	3.47	4.89	4.16	7.24
TGI	45.47	26.0	26.7	b	27.3	36.3
LC_{50}	b	93.11	98.0	b	70.8	87.9
GI_{50}	3.7	10.23	12.3	18.8	6.16	14.1
TGI	79.03	87.09	45.5	b	57.3	60.3
LC0	b	b	97.72	B	b	95.5
GI_{50}	70.6	61.4	45.6	22.7	76.4	22.6
TGI	b	b	b	B	b	b
LC_{50}	b	b	b	B	b	b

***Table* 4.** GI_{50} values (μM) of compounds **5a**, **5b**, **6a**, gefitinib and erlotinib over the most cell lines of non-small lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, and breast cancer

Subpanel tumor cell lines	GI_{50} (μM)				
	5a	**5b**	**6a**	Erlotinib	Gefitinib
Melanoma					
LOX IMVI	55.0	4.71	6.4	5.01	7.94
MALME-3M	4.07	3.3	4.73	5.01	3.16
M14	8.38	16.1	24.4	6.30	5.01
MDA-MB-435	9.55	4.91	>100	15.84	3.16
SK-MEL-2	3.38	3.41	4.40	12.58	12.58
SK-MEL-28	7.04	3.02	6.30	31.62	0.31
SK-MEL-5	3.67	-	32.4	15.84	3.98
UACC-257	4.86	3.55	4.96	100.00	6.30
UACC-62	2.93	2.35	15.7	1.25	5.01
Ovarian Cancer					
IGROVI	32.5	7.34	27.7	0.25	0.20
OVCAR-3	9.36	7.68	5.05	3.16	5.01
OVCAR-4	3.41	2.11	3.95	19.95	7.94
OVCAR-5	58.0	>100	>100	19.95	10.00
OVCAR-8	4.42	3.46	5.01	7.94	10.00
NCI/ADR-RES	8.97	3.30	9.25	6.30	12.58
SK-OV-3	3.06	2.91	4.75	0.39	0.63
Renal Cancer					
786-O	3.2	3.51	4.17	5.01	7.94
A498	1.01	1.75	15.8	1.58	0.4
ACHN	3.49	4.63	3.72	0.15	0.2
CAKI-1	5.08	3.05	>100	0.10	0.16
RXF 393	2.24	2.55	3.48	6.3	5.01
SN12C	5.24	4.70	78.0	6.3	6.3
TK-10	5.58	4.06	7.43	0.10	0.10
UO-31	5.97	1.95	11.6	1.99	1.25
Breast Cancer					
MCF7	9.98	7.93	32.0	10.0	10.0
MDA-MB-231/ATCC	3.42	3.73	4.2	1.99	12.58
HS 578T	3.23	2.46	2.18	6.3	10.0
BT-549	2.98	2.02	5.02	39.81	7.94
T-47D	4.01	6.57	7.04	3. 16	6.3
MDA-MB-468	4.11	5.72	5.39	0.2	0.01

4b and their utilization for producing more interesting functionalized heterocycles like pyrazoles, diazepines, and pyrimidine-based compounds. We hereby highlighted the potential of such new heterocycles as anti-proliferative agents.

Conflict of Interest. The authors declare no conflict of interest.

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