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Design and synthesis of newly substituted 2-(2-Hydroxyethylamino)pyrimidine-5-carbonitrile with potential anticancer and antimicrobial activities

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ABSTRACT

A series of 1,6-dihydro-2-hydroxyethylamino-6-oxo-4-arylpyrimidine-5-carbonitriles **8a-i**, and 4-amino-2-hydroxyethylamino-6-arylpyrimidine-5-carbonitriles **9a-i** were prepared. Multicomponent reaction of araaldehyde **1**a-i , S-methylisothiourea sulfate **2** with ethyl cyanoacetate **3** afforded 1,6-dihydro-2-methylthio-6-oxo-4-arylpyrimidine-5-carbonitriles **4a-i**. Also, multicomponent reaction of **1**, **2** with malononitrile 5 afforded 4-amino-2-methylthio-6-arylpyrimidine-5-carbonitriles **6a-i**. Reaction of compounds **4a-i,** and **6a-i** with ethanolamine **7** under solvent free condition at 130-140 °C afforded **8a-i**, and **9a-i** respectively. The purity of the new compounds was checked by TLC and elucidation of their structures was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectrometry. Compounds were subjected to NCI *in vitro* assessment for their anticancer activity at a single dose of 10 µM of test compounds, Also, all of the tested compounds were *in vitro* assessment for their antibacterial and antifungal activities in a comparison to chloramphenicol and clotrimazole as reference antibacterial and antifungal drugs respectively. All the tested compounds showed varied anticancer activities ranging from weak to moderate activities. In the other hand, most of them showed moderate antibacterial activities without any antifungal activities.

Key words: 2-(2-hydroxyethylamino) pyrimidines, solvent free condition synthesis, anticancer and antimicrobial activities.

INTRODUCTION

The chemistry of 2-aminopyrimidines has been attracting widespread attention over many decades. The popularity of these compounds is due to their a wide range of pharmacological activities such as antibacterial, (Siddiqui et al., 2007; Sreenivas et al.., 2012; Srinivas and Thakur, 2013) antifungal, (Sreenivas et al.., 2012; Srinivas and Thakur, 2013; Kachroo et al., 2014) anti-tuberculosis, (Siddiqui et al., 2007; Kachroo et. al, 2014) antioxidant, (Kachroo et al., 2014; Mondal et al., 2010) antiviral, (Siddiqui et al., 2007; Fujiwara et al., 2008) antiprotozoal, (Scribner et al., 2007; Kumar et al., 2008) anticancer, (Akue-Gedu et al., 2009) analgesic, (Chaudhary et al., 2011; Gupta et al., 2011) and anti-inflammatory activities. (Kachroo et al., 2014; Bahekar and Shinde, 2003) In the same manner, 2-aminopyrimidines have been reported, or included as a part of many clinically active pharmaceutical drugs (Fig. 1). In this manner, pyrimethamine as antiprotozoal, (Russel and Hitchings, 1951) sulfadiazine (Roblin and Winnek, 1940) and trimethoprim (Roth et al., 1987) as antibacterial, glymidine as antidiabetic, (Gutsche et al., 1964) minoxidil as antihypertension, (McCall et al., 1975) temelastine as antihistamine, (Alexander et al., 1956) and imatinib as antineoplastic. (Zimmermann et al., 1997).

On the other hand, the polar functional 2-hydroxyethyamino is included as a part of many active pharmaceutical drugs (Fig. 2) as in metronidazole as antiprotozoal, (Jacob et al., 1960) ethambutol as anti-tuberculosis, (Wilkinson et al., 1962) perphenazine as antipsychotic, (Sherlock and Sperber, 1958) mitoxantrone (Zee-Cheng and Cheng, 1978) and olomoucine (Havlicek et al., 1997) as antineoplastic agents, and miglitol antidiabetic. (Yoshikuni et al., 1988).

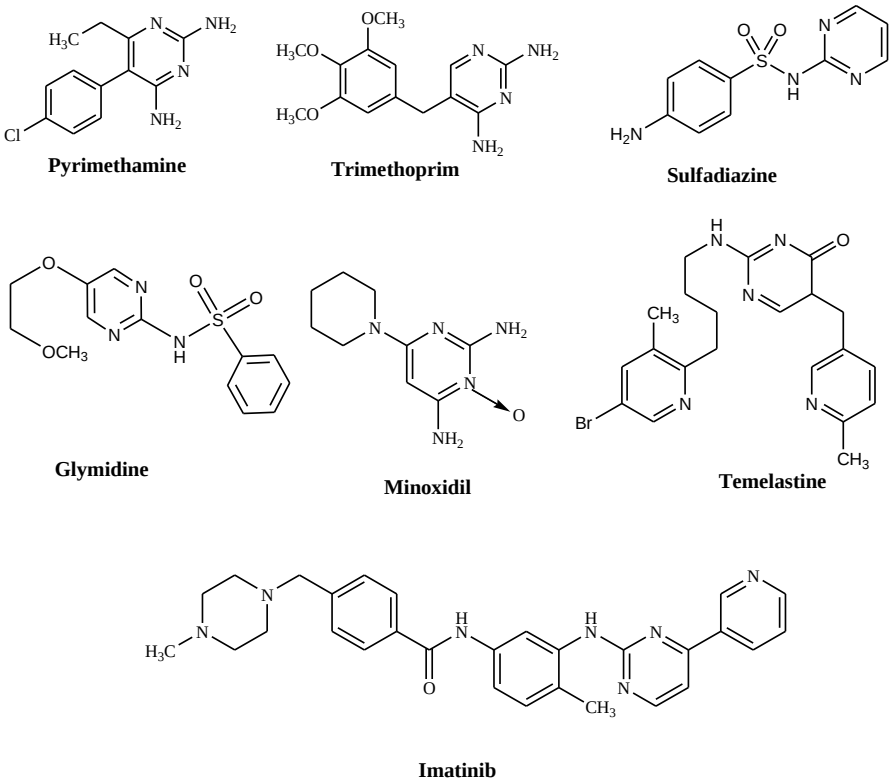


Fig. (1) Chemical structures of pharmacologically or clinically active drugs containing 2-aminopyrimidine moieties

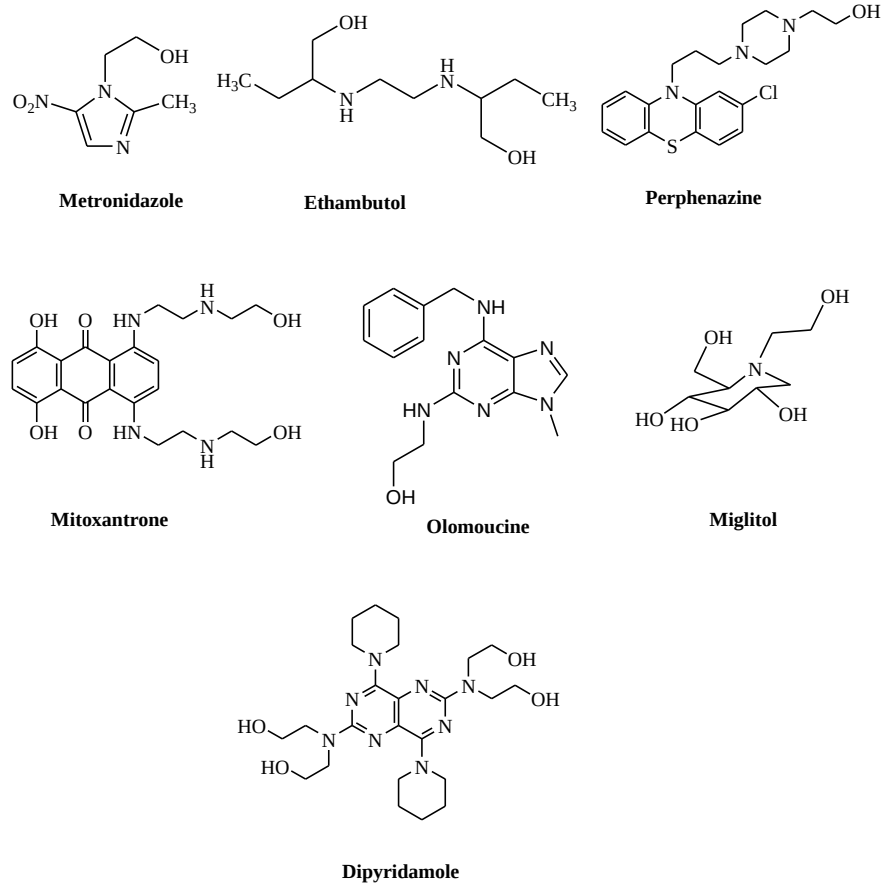


Fig. (2) Chemical structures of pharmacologically or clinically active drugs containing 2-hydroxyethylamino moieties

Additionally, 2-hydroxyethylamino residue was chemically connected to variable organic formulations to elicit many desired biological activities as in palmitoyl ethanolamide as anti-inflammatory, (Lambert et al., 2002) 4-(2-hydroxyethylamino) coumarins as antitumor, (Angelova and Momekov, 2014) N-hydroxyethylglycolamides as anti-tuberculosis. (Daryaee et al., 2009) Also the ethanolamine has antimicrobial, (Sandin et al., 1990) and antioxidant properties. (Sergeevna et al., 2013). Supported by the aforementioned biological activities, the present study aimed at gathering the 2-aminopyrimidine derivatives and 2-hydroxyethylamino functional as 2-(2-hyroxyethylamino) pyrimidines and investigate their antimicrobial and anticancer properties aiming to development of a newly active agents.

MATERIALS and METHODS:

Chemistry

Melting points were determined on an electrothermal melting point apparatus (Stuart Scientific Co.) and were uncorrected. Pre-coated silica gel plates (kieselgel 0.25 mm, 60G F254, Merck, Darmstadt, Germany) were used for TLC monitoring of reactions. The developing solvent systems of $CHCl_3/CH_3OH$ (9:1 v/v) were used and the spots were detected at 254 nm wavelength using ultraviolet lamp (Spectroline, model CM-10, Seattle, USA). IR spectra (KBr discs) were recorded for compounds **8a-8e, 9b**, **8d** on a Shimadzu 435 spectrometer at the unit of Microanalysis, Cairo University, and the rest of the compounds were recorded on Thermoscientific, Nicolet-6700 FT-IR spectrometer at the Faculty of Pharmacy, Assiut University. ^{1}H-NMR and ^{13}C-NMR spectra of compounds **8a**, **8c**, **8g**, **9b**, **9c**, and **9g** were recorded using Varian Unity INOVA 400 MHz at university of Aberdeen, United Kingdom, and for the rest of the compounds on a Varian spectrometer or a Varian Mercury machine operating at Research School of Chemistry, Australian National University, Australia. ^{1}H-NMR operating at 400 MHz and ^{13}C-NMR operating at 100 MHz. Chemical shifts are expressed in δ-value (ppm) relative to DMSO-d_6 as internal standard,. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant (s) J (Hz) and relative integral, where multiplicity is defined as: s= singlet; d= doublet; t= triplet; q= quartet; m= multiplet or combinations of the above.

High resolution mass spectrometric data for **8a**, **8c**, **8g**, **9b**, **9c**, and **9g** compounds were obtained using the EPSRC mass spectrometry Centre in Swansea and Thermo Instruments MS system (LTQ XL/LTQ Orbitrap Discovery) coupled to a Thermo Instruments HPLC system (Accela PDA detector, Accela PDA autosampler and Pump) at university of Aberdeen, UK. High resolution MS data for the rest of compounds were obtained using a VG Fisons AutoSpec mass spectrometer (electron impact (EI) mass spectra), high-resolution electrospray (ESI) mass spectra were obtained on a VG Quattro II triple-quadrupole MS instrument operating in positive ionization mode at Research School of Chemistry, Australian National University, Australia. Compounds yields given are those of crude products. Ethyl cyanooacetate was purchased from s.d.fine limited Co., malononitrile was purchased from Acros Co., Compounds **5a-i** (Rong et al., 2013; Hussein et al., 2011; Agarwal et al., 2002) and **6a-i (**Kumar, 2008; Rong et al., 2012; Rostamizadeh and Nojavan, 2014) were prepared according to reported methods. (Rong et al., 2013; Rong et al., 2012) All solvents were obtained from commercial suppliers and used without further purification.

General procedure for synthesis of 2-(2-hydroxyethylamino)-6-oxo(or 4-amino)-pyrimidine-5-carbonitriles (8a-i) and (9a-i)

2-Methylthiopyrimidines **5a-i** or **6a-i** (5.0 mmol) were heated in oil bath under solvent free condition with 2.5 ml of ethanolamine **7** at 130-140 °C for 3 h. The reaction mixture was cooled, diluted with 50 ml isopropyl alcohol and set aside in refrigerator to precipitate. The formed precipitate was filtered, washed with cold isopropyl alcohol, dried and crystallized from isopropyl alcohol.

1,6-dihydro-2-(2-hydroxyethylamino)-6-oxo-4-phenylpyrimidine-5-carbonitrile 8a

Yield, 70%; M.P., 238-40 ºC; IR(KBr) cm^{-1}, 3368(OH), 3272(NH), 3185(CH-Ar), 2198(C≡N), 1575(C=O), 1475(C=N), ^{1}H-NMR (DMSO-d_6) δ: 11.49(s, 1H, NH, D_2O exchanger); 7.86-7.84(d, 2H, Ar-H, J = 6.8); 7.57-7.51(m, 3H, Ar-H,); 7.31(s, 1H, NH, D_2O exchanger); 4.92(bs, 1H, OH, D_2O exchanger); 3.55-3.48(m, 4H, CH_2CH_2OH). ^{13}C-NMR δ, 171.16(PyrC4), 161.84 (PyrC6), 155.13 (PyrC2), 137.07, 131.55, 128.77(Ar. C), 117.66(C≡N), 59.62 (CC≡N), 49.06 (CH_2OH), 43.06 (CH_2NH). HRMS m/z calculated for $C_{13}H_{12}N_4O_2$ $[MH]^+$: 257.1033, found: 257.1032.

4-(4-bromophenyl)-1,6-dihydro-2-(2-hydroxyethylamino)-6-oxopyrimidine-5-carbonitrile 8b

Yield, 75%; M.P., 254-56 ºC; IR(KBr) cm^{-1}, 3368(OH), 3140(NH, CH-Ar), 2206(C≡N), 1579(C=O), 1478(C=N). ^{1}H-NMR(DMSO-d_6) δ: 11.51(s, 1H, NH); 7.81-7.72(m, 4H, Ar-H); 7.31(s, 1H, NH,); 4.91(s, 1H, OH); 3.56-3.34(m, 4H, CH_2CH_2OH). ^{13}C-NMR δ, 169.43 (PyrC4), 161.23(PyrC6), 154.70(PyrC2), 135.70, 131.37, 130.35, 124.76(Ar. C), 117.02 (C≡N), 85.08 (CC≡N), 59.15 (CH_2OH), 43.15 (CH_2NH). HRMS m/z calculated for $C_{13}H_{11}BrN_4O_2$ $[MNa]^+$: 356.9958, found: 356.9966

4-(4-chlorophenyl)-1,6-dihydro-2-(2-hydroxyethylamino)-6-oxopyrimidine-5-carbonitrile 8c

Yield, 78 %; M.P., 251-52 ºC; IR(KBr) cm^{-1}, 3367(OH), 3144(NH, CH-Ar), 2207(C≡N), 1580(CO), 1479(C=N), ^{1}H-NMR(DMSO-d_6) δ: 11.28(s, 1H, NH); 8.49-7.99(bm, 5H, NH, Ar-H); 5.41(bs, 1H, OH); 4.00-3.90(m, 4H, CH_2CH_2OH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 169.09(PyrC4), 164,04(PyrC6), 156.28(PyrC2), 135.68, 130.18, 128.41(Ar. C), 117.69 (C≡N), 84.61 (CC≡N), 59.47(CH_2OH), 43.26 (CH_2NH). HRMS m/z calculated for $C_{13}H_{11}ClN_4O_2$ $[MH]^+$: 291. 0643, found: 291.0645.

1,6-dihydro-4-(4-fluorophenyl)-2-(2-hydroxyethylamino)-6-oxopyrimidine-5-carbonitrile 8d

Yield, 70%; M.P., 246-48 ºC; IR(KBr) cm^{-1}, 3365(OH), 3145(NH, CH-Ar), 2202(C≡N), 1605(C=O), 1550(C=N), 1483, ^{1}H-NMR(DMSO-d_6) δ: 11.51(s, 1H, NH); 7.95-7.91(d, 2H, Ar-H, J = 16); 7.39-7.31(m, 3H, Ar-H, NH); 4.91(bs, 1H, OH); 3.57-3.33(m, 4H, CH_2CH_2OH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 169.37(PyrC4), 164.90(PyrC6), 162.42(PyrC2), 161.38(Ar.C4-F), 154.65, 133.01, 130.98(Ar. C), 117.21(C≡N), 115.46, 115.25(Ar. C), 84.88(CC≡N), 59.17(CH_2OH), 43.15(CH_2NH). HRMS m/z calculated for $C_{13}H_{11}FN_4O_2$ $[MH]^+$: 275.0939. found: 275.0944.

1,6-dihydro-2-(2-hydroxyethylamino)- 6-oxo-4-*p*-tolylpyrimidine-5-carbonitrile 8e

Yield, 66%; M.P., 252-54 ºC; IR(KBr) cm^{-1}, 3370(OH), 3213(NH, CH-Ar), 2202(C≡N), 1575(C=O), 1479(C=N), ^{1}H-NMR(DMSO-d_6) δ: 11.55(s, 1H, NH); 7.90-7.88(d, 2H, Ar-H, J = 8); 7.45-7.39(m, 3H, Ar-H, NH,); 5.02(bs, 1H, OH); 3.68-3.45(m, 4H, CH_2CH_2OH); 2. 50(s, 3H, CH_3). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 170.89 (PyrC4, PyrC6), 155.03(PyrC2), 141.66, 134.22, 129.29, 128.80(Ar. C), 117.82 (C≡N), 84.66(CC≡N), 59.63(CH_2OH), 43.58(CH_2NH). 21.28 ($PhCH_3$). HRMS m/z calculated for $C_{14}H_{14}N_4O_2$ $[MH]^+$: 271.1189, found: 271.1190

1,6-dihydro-2-(2-hydroxyethylamino)-4-(4-methoxyphenyl)-6-oxopyrimidine-5-carbonitrile 8f

Yield, 72%; M.P., 248-49ºC; IR(KBr) cm^{-1}, 3400(OH), 3228(NH, CH-Ar), 2200(C≡N), 1668(C=O), 1593(C=N), ^{1}H-NMR(DMSO-d_6) δ: 11.38(s, 1H, NH); 7.91-7.89(d, 2H, Ar-H, J = 8); 7.24(s, 1H, NH,); 7.08-7.06(d, 2H, Ar-H, J = 8); 4.92-4.90(bs, 1H, OH); 3.80(s, 3H, OCH_3); 3.55-3.33(m, 4H, CH_2CH_2OH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 169.59(PyrC4), 161.65(PyrC6), 154.38(PyrC2), 130.26, 128.63(Ar. C), 117.63(C≡N), 113.65, 99.51(Ar. C), 83.80 (CC≡N), 59.19(CH_2OH), 55.42(OCH_3),

43.10(CH_2NH). HRMS m/z calculated for $C_{14}H_{14}N_4O_3[MNa]^+$: 309.0958, Found: 309.0965.

1,6-dihydro-2-(2-hydroxyethylamino)-6-oxo-4-(thiophen-2-yl)pyrimidine-5-carbonitrile 8g

Yield, 62%, M..P., 248-50 ºC; IR(KBr) cm^{-1}, 3380(OH), 3289(NH, CH-Ar), 2200(C≡N), 1667(C=O), 1593(C=N), ^{1}H-NMR(DMSO-d_6) δ: 11.40(s, 1H, NH); 8.19-8.16 (d, 1H, Ar-H, J = 12); 7.93-7.90 (d, 1H, Ar-H, J = 12); 7.32-7.24 (m, 2H, NH, Ar-H); 5.06-4.99(s, 1H, OH); 4.04-3.56 (m, 4H, CH_2CH_2OH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 163.33(PyrC4), 161.39(PyrC6), 154.62 (PyrC2), 133.38, 130.50, 128.90(Ar. C), 117.55(C≡N), 88.64(CC≡N), 59.09(CH_2OH), 43.21(CH_2NH). HRMS m/z calculated for $C_{11}H_{10}N_4O_2S$ [M H]$^+$: 263. 0597, found: 263. 0598.

1,6-dihydro-2-(2-hydroxyethylamino)-4-(naphthalen-1-yl)-6-oxopyrimidine-5-carbonitrile 8h

Yield, 68%; M.P., 242-44ºC; IR(KBr) cm^{-1}, 3379(OH), 3220(NH, CH-Ar), 2205(C≡N), 1646(C=O), 1500(C=N), ^{1}H-NMR(DMSO-d_6) δ: 11.61(s, 1H, NH); 8.07-7.93(m, 3H, Ar-H); ; 7.63-7.53(m, 4H, Ar-H), 7.39(s, 1H, NH,); 4.87(bs, 1H, OH); 3.49-3.32 (m, 4H, CH_2CH_2OH). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 172.74 (PyrC4), 161.69(PyrC6), 154.93 (PyrC2), 134.95, 133.07, 129.87, 129.62, 128.27, 126.77, 126,30, 126.14, 125.17, 125.05(Ar. C), 116.41 (C≡N), 88.66 (CC≡N), 59.11(CH_2OH), 43.13(CH_2NH). HRMS m/z calculated for $C_{17}H_{14}N_4O_2[MNa]^+$: 329.1009, found: 329.1014.

1,6-dihydro-4-(furan-2-yl)-2-(2-hydroxyethylamino)-6-oxopyrimidine-5-carbonitrile 8i

Yield, 65%, M..P., 238-40 ºC; IR(KBr) cm^{-1}, 3289(OH), 3136(NH, CH-Ar), 2206(C≡N), 1673(C=O), 1520(C=N), ^{1}H-NMR(DMSO-d_6) δ: 11.33(s, 1H, NH); 8.04-8.03 (d, 1H, Ar-H, j = 4); 7.43-7.42(d, 1H, Ar-H, J = 4); 7.19(s, 1H, NH); 6.77-6.76 (d, 1H, Ar-H); 4.92-4.89(s, 1H, OH); 3.56-3.48 (m, 4H, CH_2CH_2OH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 161.40(PyrC4), 157.64(PyrC6), 154.66 (PyrC2), 149.69, 146.99(Ar. C), 117.07 (C≡N), 116.35, 112.78(Ar. C), 88.14(CC≡N), 59.21(CH_2OH), 43.07(CH_2NH). HRMS m/z calculated for $C_{11}H_{10}N_4O_3S$ [MNa]$^+$: 269.0645, found: 269.0645.

4-amino-2-(2-hydroxyethylamino)-6-phenylpyrimidine-5-carbonitrile 9a

Yield, 73%; M.P., 198-200ºC; IR(KBr) cm^{-1}, 3384(OH), 3267(NH_2), 3130(NH, CH-Ar), 2208(C≡N), 1656, 1609(C=N), ^{1}H-NMR(DMSO-d_6) δ: 7.82-7.73(dd, 2H, Ar-H, J = 16, 4); 7.52-7.49(m, 4H, NH, D_2O exchanger, Ar-H,); 7.29-7.10(bs, 2H, NH_2, D_2O exchanger,); 4.70-4.68(d, 1H, OH, D_2O exchanger); 3.54-3.52(d, 2H, CH_2OH, J = 8); 3.42-3.40(d, 2H, CH_2NH, J = 8). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 168.92(PyrC6), 165.11(PyrC4), 161.77(PyrC2), 137.14, 130,23, 128.26, 128.18(Ar. C), 118.02 (C≡N), 75.22 (CC≡N), 59.64(CH_2OH), 43.28(CH_2NH). HRMS m/z calculated for $C_{13}H_{13}N_5O$ [MH]$^+$: 256.1193, found: 256.1198.

4-amino-6-*p*-bromophenyl-2-(2-hydroxyethylamino)-pyrimidine-5-carbonitrile 9b

Yield, 70%; M.P., 213-15ºC; IR(KBr) cm^{-1}, 3400(OH), 3344(NH_2), 3128(NH, CH-Ar), 2200(C≡N), 1664, 1544(C=N), ^{1}H-NMR(DMSO-d_6) δ: 7.82-7.68(m, 4H, Ar-H,); 7.56-7.53(s, 1H, NH); 7.32-7.14(bs, 2H, NH_2); 4.70-4.66(s, 1H, OH); 3.53-3.49(m, 2H, CH_2OH); 3-42-3.38(m, 2H, CH_2NH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 168.79(PyrC6), 165.01(PyrC4), 161.72 (PyrC2), 136.26, 131.27, 131.21, 123.85(Ar. C), 117.84(C≡N), 75.13(CC≡N), 59.60(CH_2OH), 43.26(CH_2NH). HRMS m/z calculated for $C_{13}H_{12}BrN_5O$ [MH]$^+$: 334. 0298, found: 333.9988.

4-amino-6-*p*-chlorophenyl-2-(2-hydroxyethylamino)-pyrimidine-5-carbonitrile 9c

Yield, 72%; M.P., 202-04ºC; IR(KBr) cm^{-1}, 3404(OH), 3346(NH_2), 3117(NH, CH-Ar), 2202(C≡N), 1668, 1585(C=N), ^{1}H-NMR(DMSO-d_6) δ: 7.89-7.76(dd, 2H, Ar-H, J = 12, 8); 7.62-7.57(dd, 2H, Ar-H, J = 12,

8); 7.30-7.15(bs, 3H, NH, NH_2); 4.13-4.12 (bs, 1H, OH); 3.53-3.52(d, 2H, CH_2OH, J = 4); 3.44-3.36(dd, 2H, CH_2NH, J = 12, 8). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 167.70(PyrC6), 165.06(PyrC4), 161.75(PyrC2), 135.91, 135.09, 130.11, 128.42(Ar. C), 117.89 (C≡N), 75.20 (CC≡N), 59.64 (CH_2OH), 43.32(CH_2NH). HRMS m/z calculated for $C_{13}H_{12}ClN_5O$ $[MH]^+$: 290.0803, found: 290. 0805.

4-amino-6-*p*-fluorophenyl-2-(2-hydroxyethylamino)- pyrimidine-5-carbonitrile 9d

Yield, 68%; M.P., 182-84ºC; IR(KBr) cm^{-1}, 3377(OH), 3267, 3235(NH_2), 3132(NH, CH-Ar), 2211(C≡N), 1657, 1603(C=N), ^{1}H-NMR(DMSO-d_6) δ: 7.91-7.80(m, 2H, Ar-H); 7.53-7.12(bm, 5H, Ar-H, NH, NH_2); 4.70-4.66(bs, 1H, OH); 3.52-3.48(t, 2H, CH_2OH, J = 8); 3.41-3.34(m, 2H, CH_2NH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 168.18(PyrC6), 166.53(PyrC4), 164.87(PyrC2), 162.16, 134.03, 130.97(Ar. C), 118.42(C≡N), 115.63(Ar. C), 75.54(CC≡N), 60.07(CH_2OH), 43.72(CH_2NH). HRMS m/z calculated for $C_{13}H_{12}FN_5O$ $[M\ H]^+$: 274.1099, found: 274.1104.

4-amino-2-(2-hydroxyethylamino)-6-p-tolylpyrimidine-5-carbonitrile 9e

Yield, 66%; M.P., 212-13 ºC; IR(KBr) cm^{-1}, 3402(OH), 3334(NH_2), 3159(NH, CH-Ar), 2205(C≡N), 1662, 1558(C=N), ^{1}H-NMR(DMSO-d_6) δ: 7.74-7.65(dd, 2H, Ar-H, J = 8 , 8); 7.46(bs, 1H, NH); 7.32-7.06(m, 4H, Ar-H, NH_2); 4.69-4.65(bs, 1H, OH); 3.52-3.49(dd, 2H, CH_2OH, J = 8, 4); 3.36-3.33(m, 2H, CH_2NH); 2.37(s, 3H, CH_3). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 168.68(PyrC6), 166.16(PyrC4), 161.75(PyrC2), 140.05, 134.31, 128.79, 128.17(Ar. C), 118.13(C≡N), 74.95(CC≡N), 59.63(CH_2OH), 43.25(CH_2NH), 20.95($PhCH_3$). HRMS m/z calculated for $C_{14}H_{15}N_5O$ $[M\ H]^+$: 270.1349, found: 270.1365.

4.1.1.15. 4-amino-2-(2-hydroxyethylamino)-6-*p*-methoxyphenylpyrimidine-5-carbonitrile 9f

Yield, 70%; M.P., 189-90 ºC; IR(KBr) cm^{-1}, 3414(OH), 3337(NH_2), 3121(NH, CH-Ar), 2204(C≡N), 1665, 1610(C=N), ^{1}H-NMR(DMSO-d_6) δ: 7.85-7.76(dd, 2H, Ar-H, J = 8, 8); 7.44-7.41(bs, 1H, NH); 7.20-7.03(m, 4H, Ar-H, NH_2); 4.704.66(bs, 1H, OH); 3.82(s, 3H, OCH_3); 3.53-3.49(t, 2H, CH_2OH, J = 8); 3.36-3.33(m, 2H, CH_2NH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 167.68 (PyrC6), 165.27(PyrC4), 161.71(PyrC2), 129.90, 129.78(Ar. C), 118.34(C≡N), 113.62, 113.52(Ar. C), 74.49(CC≡N), 59.66(CH_2OH), 55.32(CH_3O), 43.24(CH_2NH). HRMS m/z calculated for $C_{14}H_{15}N_5O_2$ $[M\ H]^+$: 286.1299, found: 286.1302.

4-amino-2-(2-hydroxyethylamino)-6-thiophen-2-ylpyrimidine-5-carbonitrile 9g

Yield, 60%; M.P., 202-04ºC; IR(KBr) cm^{-1}, 3384(OH), 3267(NH_2), 3130(NH, CH-Ar), 2208(C≡N), 1656, 1608(C=N), ^{1}H-NMR(DMSO-d_6) δ: 8.12 (s, 1H, Ar-H), 7.78 (s, 1H, Ar-H); 7.41-7.14(m, 4H, Ar-H, NH, NH_2); 4.71 (s, 1H, OH), 3.56-3.33(m, 4H, CH_2CH_2OH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 165.33 (PyrC6), 161.50(PyrC4), 160.17(PyrC2), 141.33, 131.17, 129.27, 128.52(Ar. C), 118.46(C≡N), 72.07(CC≡N), 59.74 (CH_2OH), 43.35(CH_2NH). HRMS m/z calculated for $C_{11}H_{11}N_5OS$ $[MH]^+$: 262.0757, found: 262.0754.

4-amino-2-(2-hydroxyethylamino)- 6-naphthalen-1-ylpyrimidine-5-carbonitrile 9h

Yield, 70%; M.P., 179-80 ºC; IR(KBr) cm^{-1}, 3482(OH), 3333(NH_2), 3220(NH, CH-Ar), 2204(C≡N), 1645, 1576(C=N), ^{1}H-NMR(DMSO-d_6) δ: 8.09-8.04(dd, 2H, Ar-H, J = 8 , 8); 7.67-7.56(m, 7H, Ar-H, NH_2); 7.28(s, 1H, NH_2); 4.77(bs, 1H, OH); 3.61-3.57(t, 2H, CH_2OH, J = 8); 3.54-3.51(t, 2H, CH_2NH, J = 4). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.77(PyrC6), 158.96(PyrC4), 158.61 (PyrC2), 133.01, 129.69, 128.48, 127.19, 126.46, 125.41, 124.35(Ar. C), 116.09(C≡N), 82.01(CC≡N), 80.53, 59.26(CH_2OH), 43.28(CH_2NH). HRMS m/z calculated for $C_{17}H_{15}N_5O_2$ $[MH]^+$: 306.1349, found 306.1353.

4-amino-6-furan-2-yl-2-(2-hydroxyethylamino)-pyrimidine-5-carbonitrile 9i

Yield, 60%; M.P., 198-200ºC; IR(KBr) cm^{-1}, 3383(OH), 3269(NH_2), 3148(NH, CH-Ar), 2216(C≡N), 1605, 1559(C=N), ^{1}H-NMR(DMSO-d_6) δ: 7.97-7.95(d, 1H, Ar-H, J = 8), 7.47-7.44 (t, 1H, Ar-H, J = 12); 7.35-7.07(m, 3H, NH, NH_2); 6.73-6.71(d, 1H, Ar-H, J = 8); 4.71-4.65(bs, 1H, OH), 3.54-3.49(m, 2H, CH_2OH), 3.42-3.33 (m , 2H, CH_2NH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 165.10(PyrC6), 161.70(PyrC4), 156.74(PyrC2), 150.12 145.54(Ar. C), 117.51(C≡N), 114.06, 112.27(Ar. C), 71.83(CC≡N), 59.65(CH_2OH), 4326(CH_2NH). HRMS m/z calculated for $C_{11}H_{11}N_5O_2$ $[MH]^+$: 246.0986, found 246.0987.

Biology

Anticancer screening

The methodology of the NCI anticancer screening has been described previously. (http://www.dtp.nci.nih.gov) Briefly, the primary anticancer assay was performed at approximately 60 human tumor cell lines panel derived from nine neoplastic diseases, in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda. They include nine tumor subpanels namely; leukaemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancer cells. The data reported as mean graph of the percent growth of the treated cells, and presented as percentage growth inhibition (GI %).

Tested compounds were added to the culture at a single concentration (10 µM) and the cultures were incubated for 48 h. End point determinations were made with a protein binding dye, SRB. Results for each tested compound were reported as the percent of growth of the treated cells when compared to the untreated control cells. The percentage growth was evaluated spectrophotometrically versus controls not treated with test agents.

Antibacterial activity

Eighteen compounds **8a–g**, and **9a–g** were tested for their antibacterial activity in *vitro*, in comparison with chloramphenicol as a reference drug using the standard agar cup diffusion method (Hussein *et al.*, 2016) at the Assiut University Mycological Center (AUMC), Faculty of Science, Assiut University, Assiut, Egypt. The study included 5 bacterial species representing both Gram-positive and Gram-negative bacteria which are common contaminants of the environments in Egypt and some of which are involved in human and animal diseases.

The used bacterial strains are *Staphylococcus aureus* (AUMC No. B-54) and *Bacillus* cereus (AUMC No. B-5) as Gram-positive bacteria, and *Escherichia colli* (AUMC No. B-53), *Pseudomonas* aeruginosa (AUMC No. B-73), as well as *Serratia marcescens* (AUMC No. B-55) as Gram-negative bacteria. To prepare inocula, bacterial strains were individually cultured for 24 h in 100 ml conical flasks containing 30 ml nutrient broth medium. Bioassay was done in 10 cm sterile plastic about 1m of bacterial suspension was mixed with 15 ml Nutrient agar medium and poured in Petri plates. After solidification of the media, cups were cut in the solidified agar (4 cups/plate) using sterile cork borer. Tested compounds dissolved in dimethylsulfoxide (DMSO) at 100 µmol/ML were pipetted in the cups (20 ul/ cavity). Cultures were then incubated at 28 ± 2 °C for 48 h. The diameter (in mm) of inhibition zone was recorded.

The test compounds giving positive results were diluted with DMSO to prepare a series of descending concentrations and were similarly assayed as mentioned before and the least concentration which inhibited bacterial growth was recorded as the MIC.

Antifungal activity

All the newly synthesized compounds **8a–g**, and **9a–g** were tested for their antifungal activity *in vitro*, in comparison with cloterimazole as a reference drug using the standard agar cup diffusion method (Hussein et al., 2016) at the Assiut University Mycological Center (AUMC), Faculty of Science, Assiut University, Assiut, Egypt.

Six pathogenic, phytogenic, or food poisoning fungal species were used in the

present study: *Candida albicans* (AUMC No. 418), *Geotrichum candidum* (AUMC No. 226), *Aspergillus flavus* (AUMC No. 1276), *Trichophyton rubrum* (AUMC No. 1804), *Scopulariopsis brevicaulis* (AUMC No. 729), *Fusarium oxysporum* (AUMC No. 5119). To prepare inocula, Fungi were grown for 7 days in 100 ml conical flasks containing 30 ml sabouraud`s dextrose broth. Bioassay was done in 10 cm sterile Petri plates in which 1 ml of fungal suspension and 15 ml sabouraud`s dextrose agar medium were mixed and poured. After solidification of the media, cups were cut in the solidified agar (4 cups/plate) using sterile cork borer. Tested compounds dissolved in dimethylsulfoxide (DMSO) at 100 µmol/ml were pipetted in the cups (20 µl/cavity). Cultures were then incubated at 28°C up to 7 days. Results were read as the diameter (in mm) of inhibition zone.

RESULTS and DISCUSSION:

Chemistry

1,6-dihydro-2-(2-hydroxyethylamino)-6-oxo-4-arylpyrimidine-5-carbonitriles **8a-i** were prepared according to Scheme 1.

The synthones 1,6-dihydro-2-methylthio-6-oxo-4-arylpyrimidine-5-carbonitriles **4a-i** were prepared by multicomponent reaction of araldehydes **1a-i**, S-methylisothiourea sulfate **2** and ethyl cyanoacetate **3** by reflux in ethanol containing sodium hydroxide. (Rong et al., 2013)

Heating of compounds **4a-i** with ethanolamine **7** under solvent free condition at 130-140 °C for 3 hour afforded 1,6-dihydro-2-(2-hydroxyethylamino)-6-oxo-4-arylpyrimidine-5-carbonitriles **8a-i**. This is a simple green with high yield and easily purified condition method.

IR spectra of compounds **8a-i** showed broad bands at 3400-3200 cm^{-1} (OH, 2NH) and a characteristic bands at 2200 cm^{-1} (C≡N), 1667 cm^{-1} (C=O), 1575 cm^{-1}(C=N).^{1}H-NMR spectra of these compounds showed the appearance of a broad signal for the amidic NH protons at δ 11.60-11.3, and the other amino signal appeared incorporated with aromatic proton at about δ 7.2. A characteristic broad signal appeared at δ 5.0 assigned for OH proton. Also, appearance of the aliphatic side chain proton signals at δ 3.55-3.33 as triplet or incorporate together as a multiplet.

^{13}C NMR spectra for this series showed characteristic two peaks in about δ 43 and δ 59 corresponding to aliphatic side chain carbon atoms, peaks appeared at *δ* 75 - 90 assigned for pyrimidine C5C≡N carbon atom. Also, a characteristic peak at δ 117 assigned for C≡N, peaks between δ 145-112 assigned for aromatic carbons. Additionally, peaks at δ 155-160, 160-164, and 169-171 assigned for Pyrimidine C2, Pyrimidine C6(CO) and pyrimidine C4 respectively.

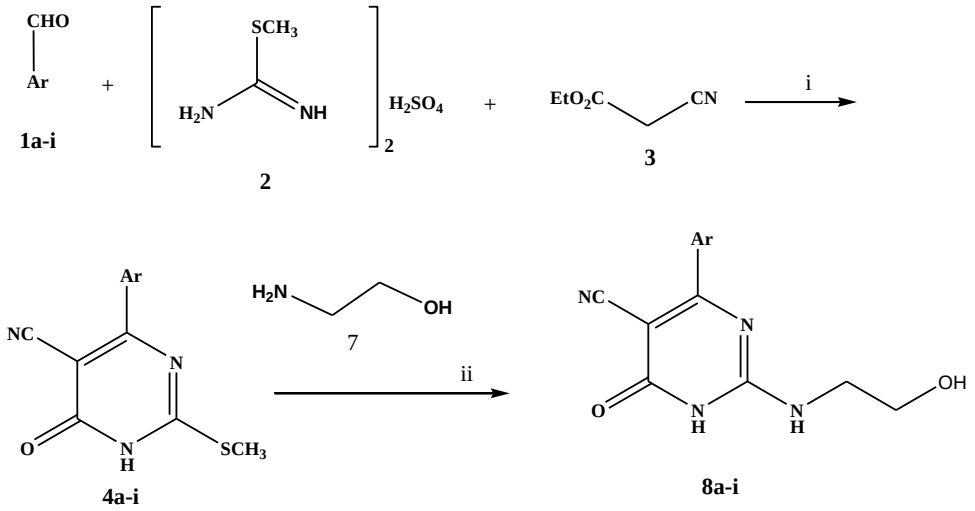
4-amino-2-(2-hydroxyethylamino)-6-arylpyrimidine-5-carbonitriles **9a-i** were prepared according to Schemes 2.

Again, the other synthones 4-amino-2-methylthio-6-arylpyrimidine-5-carbonitriles **6a-i** were prepared by multicomponent reaction of **1**, **2** with malononitrile **5** by refluxing in ethanol containing sodium hydroxide. (Rong et al., 2012)

In the same way, heating of compounds **6a-i** with ethanolamine **7** under solvent free condition at 130-140 °C for 3 hour afforded 4-amino-2-(2-hydroxyethylamino)-6-arylpyrimidine-5-carbonitriles **9a-i**

IR spectra of compounds **9a-i** showed broad bands at 3400, 3200, 3120 cm^{-1} (OH, NH_2, NH) and a characteristic bands at 2200 cm^{-1} C≡N, and 1660-1600 cm^{-1} which assigned for C=N.^{1}H-NMR spectra of these compounds showed the appearance of a broad signal at δ 7.50 assigned for the NH proton. Other NH_2 signals appeared as a broad single band or incorporated with aromatic proton signals at δ 7.3-7.0. Also, appearance of characteristic broad signal at δ 5.0 assigned for OH proton. Again, the presence of aliphatic side chain proton signals at δ 3.55-3.33 as triplet or incorporate together as a multiplet.

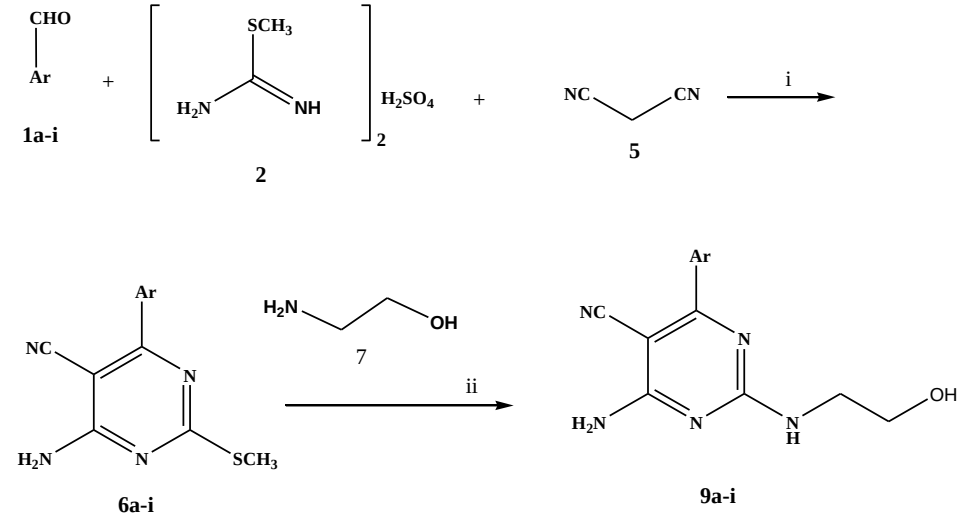
^{13}C NMR spectra for this series showed characteristic two peaks in the region δ 43 and δ 60 corresponding to aliphatic side chain carbon atoms, peaks at *δ* 72 - 80 for pyrimidine C5C≡N carbon atom. Also, a



1a, 4a 8a, Ar = C_6H_5;
1b, 4b, 8b, Ar = 4-Br-C_6H_4;
1c, 4c, 8c, Ar = 4-Cl-C_6H_4;
1d, 4d, 8d, Ar = 4-F-C_6H_4;
1e, 4e, 8e, Ar = 4-CH_3-C_6H_4;
1f, 4f, 8f, Ar = 4-$CH_3OC_6H_4$;
1g, 4g, 8g, Ar = thiophen-2-yl;
1h, 4h, 8h, Ar = 1-naphthyl;
1i, 4i, 8i, Ar = 2-furyl.

i, ethanol, sodium hydroxide, reflux; ii, heat at 130-140 °C.

Scheme 1. General synthetic procedure for synthesis of target compounds **8a-i**



1a, 6a, 9a, Ar = C_6H_5;
1b, 6b, 9b, Ar = 4-Br-C_6H_4;
1c, 6c, 9c, Ar = 4-Cl-C_6H_4;
1d, 6d, 9d, Ar = 4-F-C_6H_4;
1e, 6e, 9e, Ar = 4-CH_3-C_6H_4;
1f, 6f, 9f, Ar = 4-$CH_3OC_6H_4$;
1g, 6g, 9g, Ar = thiophen-2-yl;
1h, 6h, 9h, Ar = 1-naphthyl;
1i, 6i, 9i, Ar = 2-furyl.

i, ethanol, sodium hydroxide, reflux; ii, heat at 130-140 °C

Scheme 2. General synthetic procedure for synthesis of target compounds **9a-i**

characteristic peak appeared at δ 117 assigned for C≡N, peaks between δ 112-155 assigned for aromatic carbons. Additionally, peaks at δ 155-160, 160-164, and 169-171 assigned for Pyrimidine C2, Pyrimidine C4($C4NH_2$), and Pyrimidine C6 respectively.

Biology

Anticancer activity

Eleven newly synthesized compounds **8a, 8c**, **8d**, **8f**, **8g**, **8h**, **8i**, **9a**, **9d**, **9e**, and **9f** were selected by the National Cancer Institute (NCI) according to the protocol of the Drug Evaluation Branch of the National Cancer Institute, Bethesda, USA for *in vitro* anticancer screening. (NCI methodology, http://www.dtp.nci.nih.gov) A single dose (10 μM) of the test compounds was used in the full NCI 60 cell lines panel assay which includes nine tumor subpanels namely; leukaemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancer cells. The data reported as mean graph of the percent growth of the treated cells, and presented as percentage growth inhibition (GI %). The obtained results of the tested 2-(2-hyroxyethylamino)pyrimidine derivatives are shown in **Table 1.**

The obtained results of tested compounds, 2-(2-hyroxyethylamino)-6-oxopyrimidines series **8** showed variable sensitivity profiles against most of the tested compounds (**Table 1**). Regarding the activity towards individual cell lines, the most sensitive cancer cell line to series **8a-i** were CNS cancer (SNB-75) with moderate activity of compounds **8a** (4-phenyl derivatives), **8c** (4-*p*-chlorophenyl derivatives), and **8g** (4-(thiophen-2-yl derivative) with GI % 23.03, 19.02, and 19.39 respectively; renal cancer (UO-31) with moderate activity of compounds **8a** (4-phenyl derivatives), and **8c** (4-*p*-chlorophenyl derivatives) with GI % 23.65, and 25.61 respectively. Also, compound **8g**(4-thiophen-2-yl derivative) showed moderate activity against leukemia (MOLT-4) with GI % 21.37; and compound **8h** (4-(1-naphthyl) derivative) showed moderate activity against non-small cell lung cancer (NCI-H522) GI % 22.59. The most active compounds for this series were **8a**, **8c**.

On the other hand, 4-amino-2-(2-hyroxyethylamino)-pyrimidine analogues series **9** also showed variable sensitivity profiles against most of the tested compounds (**Table 1**). The most sensitive cancer cell line by this series **9** were non-small cell lung cancer (A549/ATCC) with moderate activity of compound **9d** (6-*p*-fluorophenyl derivatives) with GI % 28.21; (Hop-920 with moderate activity of compounds **9d** (6-(p-fluorophenyl derivatives), and **9f** (6-*p*-methoxyphenyl derivatives) with GI % 24.09, and 28.91 respectively; NCI-H226 with moderate activity to compounds **9d** (6-(p-fluorophenyl derivatives), and **9f** (6-(p-methoxyphenyl derivatives) with GI % 22.94, and 19.63 respectively; (NCI-H522) with moderate activity of compound **9e** (6-*p*-tolyl derivatives) with GI % 20.62; and CNS cancer (SNB-75) with moderate activity of compound **9a** (6-phenyl derivatives), and **9d** (6-*p*-fluorophenyl derivatives) with GI % 19.23, and 21.79 respectively; renal cancer (A498) with moderate activity of compound **9e** (6-*p*-tolyl derivatives) with GI % 22.23; and breast cancer (T-47D) with moderate activity of compound **9d** (6-*p*-fluorophenyl derivatives) with GI % 20.28; the most active compounds for this series were compounds **9d**, and **9f**.

Antibacterial activity

Results of the antibacterial activity for 6-oxo-2-hydroxyethylpyrimidines **8a-i**, revealed that at concentration of 100 μmol/mL, most of the test compounds show moderate activity against most of the used bacterial strains (**Table 2**). The most sensitive strain for the compounds **8a-i** were *Staph. aureus* and *E. coli* and the least sensitive strain was *Ps. aeruginosa*. The activities of tested compounds ranging 43-55% to the activities of the reference drug.

Table 1. Percentage growth inhibition (GI %) of i*n vitro* subpanel tumor cell lines of compounds **8a-i** and **9a-i** at 10 µM concentration.

Panel/Cell Line	% Growth Inhibition (GI %)[a]										
	8a	8c	8d	8f	8g	8h	8i	9a	9d	9e	9f
Leukemia											
CCRF-CEM	-	-	-	-	-	-	-	-	-	-	-
HL-60(TB)	-	-	-	-	-	-	-	-	-	-	-
K-562	-	-	-	-	-	-	-	-	-	-	12.13
MOLT-4	-	-	-	-	21.37	-	-	-	-	-	-
SR	-	-	-	-	-	10.16	-	-	-	-	-
Non-Small Cell Lung Cancer											
A549/ATCC	-	-	-	-	-	10.91	-	15.65	28.21	-	10.18
EKVX	-	-	-	-	-	-	-	-	10.10	-	-
HOP-62	15.78	11.45	10.16	13.67	15.66	-	10.84	17.33	-	10.48	-
HOP-92	13.67	-	-	-	10.52	-	-	10.21	24,09	17.77	28.91
NCI-H226	-	-	-	-	-	12.35	-	-	22.94	16.57	19.63
NCI-H23	11.66	-	-	-	-	-	-	-	-	-	-
NCI-H322M	-	-	-	-	-	-	-	-	-	-	-
NCI-H460	-	-	-	-	-	-	-	-	-	-	-
NCI-H522	-	-	10.01	11.49	-	22.59	-	15.13	13.40	20.62	-
Colon Cancer											
COLO 205	-	-	-	-		-	-	-	-	-	-
HCC-2998	-	-	-	-	-	-	-	-	-	-	-
HCT-116	-	-	-	-	-	-	-	-	-	-	-
HCT-15	-	-	-	-	-	-	-	-	-	-	-
HT29	-	-	-	-	-	-	-	-	-	-	-
KM12	-	-	-	-	-	-	-	-	-	-	-
SW-620	-	-	-	-	-	-	-	-	-	-	-
CNS Cancer											
SF-268	-	10.37	-	-	-	-	-	-	-	-	-
SF-295	-	-	-	-	-	-	-	-	-	-	-
SF-539	-	-	-	-	-	-	-	-	-	-	-
SNB-19	-	-	-	-	-	-	-	-	-	-	-
SNB-75	23.03	19.02	13.47	-	19.39	-	-	19.23	21.79	13.55	17.69
U251	-	-	-	-	-	-	-	-	-	-	11.73
Melanoma											
LOX IMVI	-	-	-	-	-	-	-	-	-	-	-
MALME-3M	-	-	-	-	-	-	-	-	-	-	-
M14	-	-	-	-	-	-	-	-	-	-	-
MDA-MB-435	-	-	-	-	-	-	-	-	-	-	-
SK-MEL-2	-	-	-	-	-	-	-	-	-	-	-
SK-MEL-28	-	-	-	-	-	-	-	-	-	-	-
SK-MEL-5	-	-	-	-	-	-	-	-	-	-	-
UACC-257	-	-	-	-	-	15.55	-	13.16	-	-	-
UACC-62	-	15.66	-	-	-	-	-	-	-	11.21	-

Table 1 (continued)

Panel/Cell Line	% Growth Inhibition (GI %)[a]										
	8a	8c	8d	8f	8g	8h	8i	9a	9d	9e	9f
Ovarian Cancer											
OVCAR-3	-	-	-	-	-	-	-	-	-	-	-
OVCAR-4	-	-	-	-	-	-	-	-	-	-	-
OVCAR-5	-	-	-	-	-	-	-	-	-	-	-
OVCAR-8	-	-	-	-	-	-	-	-	-	-	-
NCI/ADR-RES	-	-	-	-	-	-	-	-	-	-	-
SK-OV-3	-	-	-	-	-	-	11.76	11.41	15.10	11.41	14.99
Renal Cancer											
786-0	-	-	-	-	-	-	-	-	-	-	-
A498	-	-	-	-	-	-	14.26	-	10.94	-	22.23
ACHN	-	-	-	-	-	-	-	-	-	-	-
CAKI-1	-	-	-	-	-	-	-	-	-	-	-
RXF 393	-	-	-	-	-	-	-	-	-	-	-
SN12C	-	-	-	-	-	-	-	-	-	-	-
TK-10	-	-	-	-	-	17.55	-	-	-	-	-
UO-31	23.65	25.51	14.42	-	10.94	-	-	-	-	-	-
Prostate Cancer											
PC-3	10.57	-	-	-	10.29	-	-	-	-	11.25	11.26
DU-145	-	-	-	-	-	-	-	-	-	-	
Breast Cancer											
MCF7	-	-	-	-	11.50	-	-	-	-	-	-
HS 578T	-	-	-	-	-	-	-	-	-	-	-
BT-549	-	-	-	-	-	-	-	-	-	-	-
T-47D	10.98	10.66	-	17.16	10.82	-	-	-	20.28	-	15.47
MDA-MB-468	-	-	-	-	-	-	-	-	-	-	-

[a] (-), GI < 10%.

The most active compounds for these series were compounds **8d** (4-*p*-fluorophenyl derivatives) which is active against all used organisms and it has 50, 50, 43, 55, and 45% activity of the reference drug on *Staph. aureus*, *B.* cereus, *E. Coli*, *Ps aeruginosa*, and *S. marcescens*, respectively. Compounds having 4-hetero or 4-bulky aryl moieties **8g** (thiophen-2-yl), **8h** (1-naphthyl), or **8i** (2-furyl) were completely inactive against all used organisms. Additionally, the MICs for the tested compounds of this series ranging between 50 and 100 µmol/mL which is weakly active in comparison to reference drug chloramphenicol ranging between 3 and 6.5 µmol/mL, and the most effective tested compounds of these series, were compounds **8c** (4-*p*-chlororophenyl derivatives), and **8d** (4-*p*-fluorophenyl derivatives) that have MICs 50 µmol/mL against *Staph. aureus*.

On other hand, the antibacterial activity for 4-amino-2-hydroxyethylpyrimidines **9a-i**, revealed that at concentration of 100 µmol/mL most of test compounds show moderate activity against most of the used organisms (**Table 2**). The

most sensitive strains for these compounds **9a-i** were *Staph. aureus*, *E. coli*, and *Ps aeruginosa*, and least sensitive strains was *S. marcescens*. The activities of the tested compounds ranging 43-55% to the activities of the reference drug. The most active compound for these series was compound **9a** (6-phenyl derivatives) which is active against all used organisms and it has 40, 50, 43, 55, and 36% activity of the reference drug on *Staph. aureus*, *B.* cereus, *E. Coli*, *Ps aeruginosa*, and *S. marcescens*, respectivly. Again, compounds having 6-hetero or 6-bulky aryl moieties **9g** (thiophen-2-yl), **9h** (1-naphthyl), or **9i** (2-furyl) were completely inactive against all used organisms. In addition, the MICs for the tested compounds of this series ranging between 50 and 100 µmol/mL which is weakly active in comparison to reference drug ranging between 3 and 6.5 µmol/mL, and the most effective tested compounds of these series, were compounds **9a** (6-phenyl derivatives)**, 9c** (6-*p*-chlororophenyl derivatives) that have MICs 50 µmol/mL against the *Staph. aureus*, and *B. cereus* respectively. Also, compound **9e** (6-*p*-tolyl derivatives) that have MICs 50 µmol/mL against the *B. cereus, E. colli*, and *Ps aeruginosa*.

Table 2. Antibacterial activity of compounds **8a–i**, **9a–i** and chloramphenicol (inhibition zone in mm at100 µmol/ml) and MICs given in brackets (µmol/ml).

No.	*Staphylococcus aureus*	*Bacillus cereus*	*Escherichia colli*	*Pseudomonas aeruginosa*	*Serratia marcescens*
8a	10(100)	8(100)	10(100)	-	8(100)
8b	8(100)	-	8(100)	-	8(100)
8c	8(50)	-	8(100)	-	8(100)
8d	10(50)	10(100)	10(100)	10(100)	10(100)
8e	10(100)	8(100)	10(100)	-	10(100)
8f	8(100)	-	8(100)	-	8(100)
8g	-	-	-	-	-
8h	-	-	-	-	-
8i	-	-	-	-	-
9a	8(50)	10(100)	10(100)	10(100)	8(100)
9b	10(100)	8(100)	8(100)	10(100)	-
9c	8(100)	8(50)	8(100)	8(100)	-
9d	8(100)	8(100)	8(100)	-	-
9e	8(100)	8(50)	8(50)	10(50)	-
9f	8(100)	-	8(100)	-	-
9g	-	-	-	-	-
9h	-	-	-	-	-
9i	-	-	-	-	-
CHL	20(3)	20(3)	23(3)	18(6.25)	22(3)

Antifungal activity

The results showed that none of the tested compounds showed any activity against all of the used fungi strains.

CONCLUSION:

New two series of 1,6-dihydro-2-(2-hydroxyethylamino)-6-oxo-4-arylpyrimidine-5-carbonitriles **8a-i**, and 4-amino-2-(2-hydroxyethylamino)-6-arylpyrimidine-5-carbonitriles **9a-i** were synthesized for evaluation as anticancer and antimicrobial activities. Structure-activity data acquired and biological studies showed that, regarding anticancer screening i) all compounds of the two series showed varied anticancer activities ranging from weak to moderate activities; ii) in series **8**, compounds having 4-phenyl (**8a**), and 4-*p*-chlorophenyl (**8c)** were the most active compounds against CNS cancer (SNB-75) with moderate GI % 23.03, 19.02

respectively; and renal cancer (UO-31) with moderate GI % 23.65, and 25.61 respectively, iii) regarding series **9**, compounds having 6-*p*-fluorophenyl (**9d**), and 6-*p*-methoxyphenyl (**9f**) were the most active compounds of this series, **9d** showed moderate activity against non-small cell lung cancer (A549/ATCC, Hop-92, NCI-H226), CNS cancer (SNB-75), and breast cancer (T-47D) with GI % 28.21, 24.09, 22.94, 21.79, and 20.28 respectively**; 9f** showed moderate activity against non-small cell lung cancer (Hop-92, NCI-H226), and renal cancer (A498) with GI % 28.91, 19.63, and 22.23 respectively; iv) the sensitivity of cancer cell lines toward the synthesized two new series was pounced in 4-amino-2-(2-hydroxyethylamino)-6-arylpyrimidines **9a-i** more than 4-2-(2-hydroxyethylamino)-6-oxo-arylpyrimidines **8a-i**.

Regarding antimicrobial screening: i) Most of the tested compounds of the two series showed moderate activity against most of the used organisms at concentration of 100 µmol/mL**.** ii) The most sensitive strain for the two tested series were *Staph. aureus*, and *E. colli*. iii) The sensitivity of *Ps aeruginosa* was increased to series **9** (4-aminopyrimidines) more than series **8** (6-oxopyrimidines) but in case of *S. marcescens* the sensitivity was increased to series **8** more than series **9**. iv) The most active compound of series **8** was **8d** (4-*p*-fluorophenyl derivatives) which was active against all used organism and has MIC 50 µmol/mL against the *Staph aureus,* and the most active compound of series **9** was **9a** (6-phenyl derivatives) which was active against all used organism and has MIC 50 µmol/mL against *Staph aureus.* v) Compounds having hetero or bulky aryl moieties in both series (**8g**, **9g**, **8h**, **9h**, **8i**, or **9i)** were completely inactive against all used organisms. vi) Non of the test compounds showed any activity against all of the used fungi strains at a concentration of 100 µmol/mL.

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تصميم و تشييد بعض المشتقات الجديدة من 2-هيدروكسي إيثيل أمينو-بيريميدين-5-كاربونيتريل ذات الفاعلية البيولوجية كمضادات للسرطان والميكروبات

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تم في هذا البحث تشييد وتصميم بعض المشتقات الجديدة من 1و6-ثنائي الهيدرو-2-هيدروكسي إيثيل أمينو-6-أوكسو-4-(مستبدل أريل)--بيريميدين-5-كاربونيتريل **(8a-i)** و4-أمينو-2-هيدروكسي إيثيل أمينو-6-(مستبدل أريل)--بيريميدين-5-كاربونيتريل **(9a-i)** من خلال تفاعل العديدات من الألديهدات الأروماتيه **(1a-i)** وسلفات الميتيل أيزو ثيويوريا **(2)** مع ثيانو أسيتات الإيثيل **(3)** معطيا 1و6-ثنائي الهيدرو-2-ميثيل ثيو-6-أوكسو-4-(مستبدل أريل)- بيريميدين-5-كاربونيتريل **(4a-i)** و تفاعل العديدات من **(1a-i)** و **(2)** مع المالنونيتريل (5) معطيا 4-أمينو-2-ميثيل ثيو-6-(مستبدل أريل)- بيريميدين-5-كاربونيتريل **(6a-i)**. تفاعل المركب **(4a-i)** مع إيتانول أمين **(7)** بالتسخين بدون مذيب في درجة 130-140 درجة مئوية معطيا المركبات **(8a-i)** وعلي الجانب الآخر تفاعل المركب **(6a-i)** مع إيتانول أمين **(7)** بالتسخين بدون مذيب في درجة 130-140 درجة مئوية معطيا المركبات **(9a-i)**. تم إثبات التراكيب البنائية للمركبات الجديدة المحضرة باستخدام تحاليل كلا من تحاليل الأشعة تحت الحمراء والرنين المغناطيسي للهيدروجين والكربون وكذلك طيف الكتلة العالي الكفاءة. وقد تم اختبار تأثير المركبات الجديدة كمضادات للسرطان والبكتيريا والفطريات. وقد أظهرت الدراسة نتائج متوسطة لبعض المركبات كمضادات للسرطان والبكتيريا. أما الفطريات فلم تظهر أي استجابة لأي من المركبات المستخدمة.