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Synthesis and antimicrobial evaluation of new derivatives derived from-2-amino-4-(4-nitro-/4-bromo-phenyl thiazole)

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ABSTRACT

Two thiazole parent nucleus, *2-amino-4-(4-nitrophenyl thiazole)* **(4)** and *2-amino-4-(4-bromo phenyl thiazole)* **(5)**, were synthesized by refluxing thiourea **(1)** and 4-nitrophenyl bromide **(2)** or with 4-bromophenyl bromide**(3)** in absolute methanol, respectively .(**4** and **5**) were acetylated by using chloroacetyl chloride in dry benzene to afford **(6** and **7)**, respectively. Then, treatment of **(6** and **7)** with four different heterocyclic 2-thiol compounds (2-mercapto benzimidazole, 5-ethoxy-2-mercapto benzimidazole,5-methoxy-2-mercapto benzimidazole and 2-mercapto pyrimidine), in a basic medium (using anhydrous potassium carbonate), in dry acetone to afford titled compounds **(8a-h).** The new compounds were characterized by means of FTIR spectroscopy, CHNS elemental microanalysis, ^{1}HNMR spectroscopy and by measurements of their physical properties. The titled compounds had been screened for their, *in vitro* preliminary antimicrobial activity against four Gram-positive bacteria (*Staphylococcus aureus, Micrococcus luteus, Bacillus subtilis* and *Bacillus pumilus*), and four Gram-negative bacteria **(***Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis* and *Klebsiella pneumoniae*),and three fungi species: (*Saccharomyces cerevisiae, Candida Tropicalis* and *Candida albicans*),. Among the synthesized derivatives, **(8f)** showed moderate antibacterial activity against two Gram-positive bacteria and slight antifungal activity against *Candida albicans*.

Keywords: Antimicrobial activity, thiazole, synthesis, heterocyclic compounds

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INTRODUCTION

Thiazole is a type of heterocyclic compounds classified under 1,3-azoles class. Amino-1,3- azoles exist as tautomers, where the 2-Amino-1,3 - azoles tend to be more stable than other isomers [1]. 2-amino 1,3-azoles behave as normal aryl amines in their reactions behavior [2]. Thiazole is a worthwhile structural unit in the field of medicinal chemistry and has reported possessing a variety of biological activities [3] such as antimicrobial [4,5], antifungal [6,7], antiulcerogenic [8], anticancer[9], antidiabetic [10] and many others.

Thiazole is an aromatic ring found in the structure of many widely used drugs such as nitazoxanide [11] (broad-spectrum antiparasitic and antiviral drug), ceftazidime [12] (broad spectrum third-generation cephalosporin antibiotic), sudoxicam (anti-inflammatory, NSAID drug) and famotidine (antiulcerogenic) [13]. This work targets to synthesize new thiazole derivatives linked to heterocyclic-2-thiol rings by sulfide bond.

MATERIAL AND METHODS

All chemicals and solvents used during synthesis were of analytical grade and used without further purification. Completion of reactions and the purity of compounds were ascertained by thin-layer chromatography (TLC), using Silica gel GF_{254} (type 60) pre-coated Aluminium sheets, Merck (Germany) exposed to UV-254nm light, and the eluent used is ethyl acetate: *n*-hexane 4:6 (for compounds **(4), (6), (7)** and **(8f);** ethyl acetate: *n*-hexane 5:5 ,for compounds **(5), (8c)** and **(8d)**; Ethyl acetate: *n*-hexane 4.5-5.5 for compounds **(8a),(8b),(8e),(8g)**and **(8h)** to run TLC. Melting points were determined using Stuart SMP3 melting point apparatus in open capillary tubes, and are uncorrected. Fourier-Transform Infrared spectroscopy (FTIR), (KBr disc) (ύ,cm^{-1}) were recorded using (Biotech engineering management FTIR-600, UK) at the University of Baghdad **/**College of Education for Pure Sciences Ibn Al-Haitham /central service laboratory.

Furthermore, The elemental microanalysis of the synthesized compounds was done using (Elementar Vario MICRO cube instrument, Germany) in the University of Mustansiriya-College of Pharmacy. ^{1}HNMR spectra were recorded on BRUKER model Ultra shield 300 MHz spectrophotometer **at Al al-Bayt University, Amman-Jordan**, using tetramethylsilane (TMS) as an internal standard, the chemical shift was expressed as (δ=ppm) and coupling constants in Hz, acetone-d_6 or DMSO-*d6* were used as solvents. The synthetic method is outlined in scheme 1.

Chemical synthesis

General method for synthesis of parent nucleus (4and 5) [14]

A mixture of thiourea **(1)** (0.01 mol, 0.76g) and each of: 4-nitrophenyl bromide **(2)** (0.005 mol, 1.22 g) or of 4-bromophenacyl bromide **(3)**, (0.005 mol, 1.38 g) were dissolved in 100 ml of absolute methanol in a round bottom flask and refluxed for 3-4 h. After completion of the reaction, as monitored using TLC, the mixture was cooled to room temperature then poured into cold water. The solid separated was collected by filtration. The residue obtained was dried, recrystallized from absolute EtOH.

2-amino-4-(4-nitrophenyl thiazole) **(4)**

Orange powder; yield 80%; m.p. 288-291°C; **IR** (KBr) ,(υ,cm^{-1}): 3398 and 3305 cm^{-1} *prim*. (<u>NH_2</u>) str, 3153 cm^{-1} Ar-(<u>C-H</u>) str, 1641 cm^{-1} (<u>C=N</u>) str,1593&1325 cm^{-1} *asym*. and *sym*. (<u>N=O</u>) str of NO_2,1539 cm^{-1} (<u>N-H</u>) bend, 1502 cm^{-1} Ar-(<u>C=C</u>)str,1410 cm^{-1} (N=O) bend, 1107 cm^{-1} (<u>C-N</u>) str,1038 & 845cm^{-1} in plane & out of plane Ar-(<u>C-H</u>) bend , 717 cm^{-1} out of plane Ar-(<u>C=C</u>) bend, 663cm^{-1} (<u>C-S</u>) str.

2-amino-4-(4-bromo phenyl thiazole) **(5)**

Off white to pink powder; yield 73%; m.p. 181-184°C; **IR** (KBr), (υ,cm^{-1}): 3429 and 3282 cm^{-1} *prim*. (<u>NH_2</u>) str,3113 cm^{-1} Ar-(<u>C-H</u>) str, 1633 cm^{-1} (<u>C=N</u>) str, 1533 cm^{-1} (<u>N-H</u>) bend,1473 cm^{-1} Ar-(<u>C=C</u>) str,1198 cm^{-1} (<u>C-N</u>) str, 1038 & 906 cm^{-1} in plane& out of plane **Ar-(<u>C-H</u>)** bend, 727 cm^{-1} out of plane **Ar-(<u>C=C</u>)** bend, 669 (<u>C-Br</u>) str, 636 cm^{-1} (<u>C-S</u>) str.

General method for synthesis of compounds (6 and 7) [15**]**

A solution of **(4)** (0.005 mol, 1.10 g) or of **(5)** (0.005 mol, 1.275 g) in dry benzene (30 mL) was cooled to 0-5ºC in an ice bath. Chloroacetyl chloride (0.01 mol, 0.79 ml) dissolved in dry benzene (20 mL) was slowly added to the solution with vigorous stirring. When the addition of chloroacetyl chloride was finished, the reaction mixture was stirred at R.T for 30 minute, then refluxed in a round bottom flask and reflux condenser for 3 h. The reaction was monitored using TLC, and by using litmus paper which turns red indicative of HCl liberation. Then benzene was removed in rotary evaporator. The residue was washed with 5% $NaHCO_3$ to *p*H 7, and subsequently with water. The product was dried and recrystallized from methanol.

2-chloro-N-(4-(4-nitrophenyl)thiazol-2-yl)acetamide **(6)**

Bright yellow powder; yield 82%; m.p. 214-217°C ; **IR** (KBr) υ,cm^{-1}: 3354 cm^{-1} *sec*. amide (N-H) str,3105 cm^{-1} for Ar-(C-H) str, 3001&2947 cm^{-1} for *asym*. & *sym*. aliph (CH_2) str,1701 cm^{-1} (C=O) amide str ,1597&1444 cm^{-1} *asym* & *sym* (N=O) str,1549 cm^{-1} (N-H) amide bend, 1504 cm^{-1} Ar-(C=C) str,1396 cm^{-1} (CH_2) bend,1331 cm^{-1} (N=O) bend;1151 cm^{-1}**, (C-N)** str, 1111&849 cm^{-1} **in plane** & out of plane Ar-(C-H) bend, 849 cm^{-1} (C-Cl) str, 737 cm^{-1} out of plane Ar-(C=C) bend, 634 cm^{-1}(C-S) str, **^{1}HNMR(300 MHz,DMSO-$_{d6}$,δ= ppm):**12.76(1H,s,NHCO); 8.31(2H,d,NO_2-2Ar-H);8.16 (2H,d,NO_2-2Ar-H);8.06(1H,s,H_5-THZ);4.43 (2H,s,$COCH_2$). ;**CHNS** elemental micro analysis Calcd. for ($C_{12}H_{11}N_5O_3S_2$) : found C%44.66, H%2.85, N%14.13, S%10.42; calculated C%44.38,H% 2.71,N%14.11,S%10.77.

N-(4-(4-bromophenyl)thiazol-2-yl)-2-chloroacetamide **(7)**

White powder; yield 80%; m.p 167-171ºC; **IR**(KBr) υ,cm^{-1}: 3363 cm^{-1} *sec.* (N-H) amide str, 3103 cm^{-1} **Ar-(C-H)** str, 2993&2862 cm^{-1} *asym* &*sym* aliph. (CH_2) str,1693 cm^{-1} (C=O) amide str,1657 cm^{-1} (C=N) str, 1545 cm^{-1} (N-H) amide bend, 1477 cm^{-1} Ar-(C=C) str,1263&744 cm^{-1} in plane & out of plane Ar-(C-H) bend, 1132 cm^{-1} (C-N) str, 831 cm^{-1} (C-Cl) str, 681 cm^{-1} out of plane Ar-(C=C) bend, 633 cm^{-1} (C-S) str, 517 cm^{-1} (C-Br)str, **^{1}HNMR(300 MHz,DMSO-$_{d6}$,δ= ppm):** 12.65(1H,s,NHCO);

7.85(2H,d,Br-2Ar-H);7.75 (1H,s,H5-THZ);7.61(2H,d,Br-2Ar-H); 4.41(2H,s,$COCH_2$).

CHNS elemental microanalysis Calcd. for ($C_{11}H_8BrClN_2OS$) :found C% 40.36, H%2.47, N%8.22, S%10.002; calculated C%39.84, H% 2.43, N%8.45,S% 9.67.

Synthesis of titled compounds (8a-h) [16, 17**]**

A mixture of 2-chloroacetylamido thiazole **(6)** or **(7)** ;(0.01 mol, 2.97g of (**6**), or 3.31g of **(7),** and 2-mercapto heterocyclic compound: (0.01 mol, (1.5g) of 2-mercapto benzimidazole , (1.94) g of 5-ethoxy-2-mercapto benzimidazole, (1.80g) of 5-methoxy-2-mercapto benzimidazole ,and (1.12g) of 2-mercapto pyrimidine) , and anhyd. K_2CO_3 (0.01 mol,1.38 g) in dry acetone (50 mL) was refluxed for 3-4 h. After cooling, the solvent was evaporated in rotary evaporator, until completely dried. The residue was washed with water, filtered and dried, then recrystallized from EtOH.

Column chromatography was run using silica gel (60-120 mesh) and the mobile phases used ; ethyl acetate: *n*-hexane (4.5:5.5) for (**8a), (8b), (8e), (8g)** and **(8h)** ; ethyl acetate :*n*-hexane (5:5) used for **(8c**) and **(8d)**; ethyl acetate: *n*-hexane (4:6) for **(8f);** to purify the titled compounds.

2-((1H-benzo[d]imidazol-2-yl)thio)-N-(4-(4-nitrophenyl)thiazol-2-yl)acetamide **(8a)**

Yellow powder; yield70%; m.p.211-215ºC; **IR**(KBr)υ,cm^{-1}: 3174 cm^{-1} *sec*. amide and amine(N-H) str., 3103 cm^{-1} Ar-(C-H) str,2924&2854 cm^{-1} *asym* &*sym* aliph (CH_2) str,1666 cm^{-1} (C=O) amide str,**1597, 1338 cm^{-1}** (N=O)***asym*****&***sym* str, 1556 cm^{-1} Ar-(C=C) str, 1508 cm^{-1} (N-H) bend, 1437 cm^{-1} (C=N) str, 1410 cm^{-1} (CH_2) bend, 1223 cm^{-1} (C-N) str, 1107& 850 cm^{-1} in plane& out of plane Ar-(C-H) bend, 658 cm^{-1} out of plane Ar-(C=C) bend, 625 cm^{-1} (C-S) str**; ^{1}HNMR(300 MHz,acetone-$_{d6}$,δ= ppm**): 13.07(1H,br,NHCO);11.87(1H,s,NH-BIM); 8.28(2H,d,NO_2-2Ar-H); 8.24(2H,d,NO_2-2Ar-H);7.86(1H,s,H_5-THZ);7.60-7.27(4H,m,4Ar-BIM);4.33(2H,s,$COCH_2$); **CHNS** elemental micro analysis Calcd. for ($C_{18}H_{13}N_5O_3S_2$): found C% 51.92,H%3.06,N%16.98,S%15.76; calculated C%52.54,H%3.18,N%17.02,S%15.59.

2-((5-ethoxy-1H-benzo[d]imidazol-2-yl)thio)-N-(4-(4-nitrophenyl)thiazol-2-yl)acetamide **(8b)**

Brownish orange powder; yield 65%; m.p.181-185ºC; **IR**(KBr)υ,cm^{-1}: 3163cm^{-1} *sec*. amide and amine(N-H) str, 3105 cm^{-1} Ar-(C-H) str,2976&2873 cm^{-1} *asym*. &*sym*. aliph (CH_3) str, 2927& 2698 *asym* &*sym* aliph (CH_2) str, 1657 cm^{-1} (C=O) amide str, 1626 cm^{-1} (N-H) amide bend, 1599 cm^{-1} (C=N) str, 1549 cm^{-1} Ar-(C=C) str,1514&1340 cm^{-1} *asym* &*sym* (N=O) str,1442 cm^{-1} (CH_2) bend, 1392cm^{-1}(N=O)bend**,1200 cm^{-1}** (C-O-C)str, 1163&985 cm^{-1} in plane and out of plane Ar-(C-H) bend, 1068 cm^{-1} (C-N) str ,741 cm^{-1} out of plane Ar-(C=C) bend, 665 cm^{-1} (C-S) str; **^{1}HNMR(300 MHz,acetone-$_{d6}$, δ=ppm**):13.20(1H,br,NHCO);11.40(1H,s,NH-BIM);8.31(2H,d,NO_2-2Ar-H);8.21(2H,d,NO_2-**2Ar-H**);7.86(1H,s,H_5-THZ);7.54(1H,d,H_7-BIM);7.13(1H,s,H_4-BIM);6.92(1H,d,H_6-BIM);4.28(2H,s,$COCH_2$);4.14(2H,q,CH_2);1.41(3H,t,CH_3) **;CHNS** elemental microanalysis Calcd. for ($C_{20}H_{17}N_5O_4S_2$):found C%51.51,H% 3.63,N%14.77,S%13.74; calculated C%52.74,H%3.76,N%15.37,S%14.08.

2-((5-methoxy-1H-benzo[d]imidazol-2-yl)thio)-N-(4-(4-nitrophenyl)thiazol-2-yl)acetamide **(8c)**

Mustard colored powder; yield 79%; m.p.176-179ºC; **IR**(KBr)υ,cm^{-1}: 3336 cm^{-1} *sec.* amide and amine(N-H) str., 3103 cm^{-1} Ar-(C-H) str,2954cm^{-1}aliph (CH_3) str; 2924&2852 cm^{-1} *asym* &*sym* aliphatic (CH_2) str, 1660 cm^{-1} (C=O) amide str, 1630 cm^{-1} (C=N) str, 1601 cm^{-1} Ar-(C=C) str,1564 cm^{-1} amide (N-H) bend,1510&1344 cm^{-1} *asym* & *sym* (N=O) str, 1439 cm^{-1} (CH_2) bend, 1396 cm^{-1} (N=O) bend,1205 cm^{-1} (C-O-C)str, 1111& 978cm^{-1} in plane& out of plane Ar-(C-H) bend,1028 cm^{-1} (C-N) str,741 cm^{-1} out of plane Ar-(C=C) bend, 688 cm^{-1} (C-S) str**.** ; **^{1}HNMR(300 MHz,acetone-$_{d6}$,δ= ppm**): 13.20(1H,br,NHCO);8.31(2H,d,NO_2-2Ar-H);8.21(2H,d,NO_2-2Ar-H);7.86(1H,s,H_5-THZ);7.51(1H,d,H_7-BIM);7.15(1H,s,H_4-BIM);6.92(1H,d,H_6-BIM);4.28(2H,s,$COCH_2$);3.87(3H,s,OCH_3); **CHNS** elemental microanalysis Calcd. for ($C_{19}H_{15}N_5O_4S_2$):found C%50.36,H%3.56 ,N%15.67,S%14.60,calculated C%51.69, H%3.42, N%15.86,S%14.53.

N-(4-(4-nitrophenyl)thiazol-2-yl)-2-(pyrimidin-2-ylthio)acetamide **(8d)**

Yellowish brown powder; yield 82%; m.p.264-266ºC; **IR**(KBr)υ,cm^{-1} : 3543 cm^{-1} *sec.* amide (N-H) str, 3099 cm^{-1} Ar-(C-H) str ,2981&2935 cm^{-1} a*sym* & *sym* alipha (CH_2) str, 1653 cm^{-1} (C=O)amide str, 1599 cm^{-1} (C=N) str, 1552&**1381** cm^{-1} *asym* &*sym* (N=O) str, 1531 cm^{-1} (N-H) amide bend, 1506 cm^{-1} Ar-(C=C) str,1477 cm^{-1} (CH_2) bend,1194 & 904 cm^{-1} in plane& out of plane Ar-(C-H) bend, 1109 cm^{-1} (C-N) str,744 cm^{-1} out of plane Ar-(C=C) bend, 696cm^{-1} (C-S) str**.**; **^{1}HNMR(300 MHz,acetone-$_{d6}$,δ=ppm**):11.53(1H,s,NHCO);8.65(2H,d,H_4+H_6-pyrimidine); 8.29(2H,d,NO_2-2Ar-H);8.16(2H,d,NO_2-2Ar-H);7.83(1H,s,H_5-THZ);7.25(1H,t,H_5-pyrimidine);4.30(2H,s,$COCH_2$).; **CHNS** elemental microanalysis Calcd. for ($C_{15}H_{11}N_5O_3S_2$) :found C% 47.97, H%2.83, N%17.95, S%17.33, calculated C%48.25, H%2.97,N%18.76 ,S%17.17.

2-((1H-benzo[d]imidazol-2-yl)thio)-N-(4-(4-bromophenyl)thiazol-2-yl)acetamide **(8e)**

White crystals; yield 63%;m.p.191-194ºC; **IR**(KBr)υ,cm^{-1}: 3157 cm^{-1} *sec*. amide and amine(N-H) str, 3107 cm^{-1}Ar-(C-H) str,2927&2848 cm^{-1} *asym* & *sym* aliph (CH_2) str,1685cm^{-1} (C=O) amide str, 1558 cm^{-1} (N-H) amide bend, 1477 cm^{-1} Ar-(C=C)str, 1444 cm^{-1} (C=N) str, 1414 cm^{-1}(CH_2) bend,1140 cm^{-1} (C-N) str, 1068 &906 cm^{-1} in plane& out of plane Ar-(C-H) bend,741cm^{-1}out of plane Ar-(C=C) bend, 677 cm^{-1}(C-S) str, 623cm^{-1} (C-Br) str, **^{1}HNMR(300 MHz,acetone-$_{d6}$,δ=ppm**): 12.90(1H,br,NHCO);7.91(2H,d,Br-2Ar-H);7.89-7.57(4H,m, 4Ar-BIM);7.25(2H,d,Br-2Ar-H);4.32(2H,s,$COCH_2$).**;CHNS** elemental microanalysis Calcd. For ($C_{18}H_{13}BrN_4OS_2$):found:C%48.34,H%3.003,N%12.07,S%14.78; calculatedC%48.54,H%2.94,N%12.58,S%14.40

N-(4-(4-bromophenyl)thiazol-2-yl)-2-((5-ethoxy-1H-benzo[d]imidazol-2-yl)thio)acetamide **(8f)**

Light brown powder; yield59%;m.p.156-158ºC; **IR**(KBr)υ,cm^{-1}: 3167 cm^{-1} *sec*. amide and amine(N-H) str., 3130 cm^{-1} Ar-(C-H) str, 2974cm^{-1} (CH_3), 2927&2871 cm^{-1} *asym*. &*sym*. aliph (CH_2) str,1685 cm^{-1} (C=O)amide str, 1630 cm^{-1} (C=N) str, 1556 cm^{-1} (N-H) amide bend , 1477 cm^{-1} Ar-(C=C) str, 1433 cm^{-1} (CH_2) bend,1394 cm^{-1} (CH_3) bend ,1200cm^{-1} (C-O-C)str, 1136 cm^{-1} (C-N) str, 1068&978 cm^{-1} in plane & out of plane Ar-(C-H) bend ,741 cm^{-1} out of plane Ar-(C=C) bend, 673 cm^{-1} (C-S) str, 623cm^{-1} (C-Br)str**.** ; **^{1}HNMR(300 MHz,acetone-d$_6$,δ= ppm**): 13.05(1H,br,NHCO);7.92(2H,d,Br-2Ar-H);7.54(2H,d,Br-2Ar-H);7.51(1H,d,H_7-BIM);7.12(1H,s,H_4-BIM);6.88(1H,d,H_6-BIM); 4.25(2H,s,$COCH_2$); 4.12(2H,q,OCH_2); 1.41(3H,t,CH_3)**;** **CHNS** elemental microanalysis Calcd. for ($C_{20}H_9BrN_4O_2S_2$): found C% 48.07,H%3.62,N%11.65, S%12.53;calculated C%49.08, H%3.50, N% 11.45,S%13.10.

N-(4-(4-bromophenyl)thiazol-2-yl)-2-((5-methoxy-1H-benzo[d]imidazol-2-yl)thio)acetamide **(8g)**

Off white powder; yield 75%;m.p.178-181ºC; **IR**(KBr)υ,cm^{-1}: 3165 cm^{-1} *sec*. amide and amine (N-H) str, 3109 cm^{-1} Ar-(C-H) str,2925&2852 cm^{-1} *asym* & *sym* aliph (CH_2) str,1685 cm^{-1} (C=O) amide str, 1631 cm^{-1} (C=N) str, 1558 cm^{-1} (N-H) amide bend , 1454 cm^{-1} Ar-(C=C)str,1483 cm^{-1}(CH_2) bend,1454cm^{-1}(CH_3) bend; 1201cm^{-1} (C-O-C)str, 1153&978 cm^{-1} in plane &out of plane Ar-(C-H) bend, 1070 cm^{-1} (C-N) str,741 cm^{-1} out of plane Ar-(C=C) bend, 675 cm^{-1} (C-S) str.;648 cm^{-1} (C-Br)str, **^{1}HNMR(300 MHz,acetone-d_6,δ= ppm)**: 13.05(1H,br,NHCO);11.71(1H,s,NH-BIM);

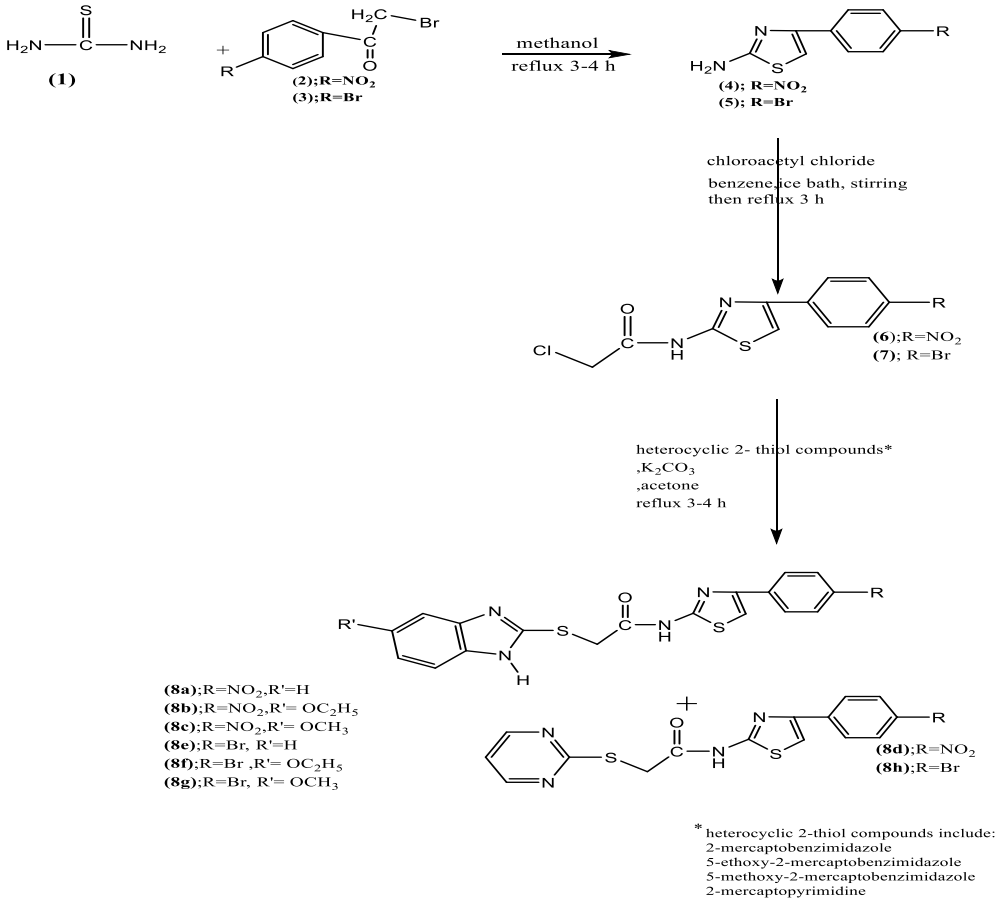
7.92(2H,d,Br-2Ar-H);7.74(2H,d,Br-2Ar-H);7.57(1H,d,H_7-BIM);7.04(1H,s,H_4-BIM); 6.90(1H,d,H_6-BIM);4.26(2H,s,$COCH_2$);3.87(3H,s,OCH_3);**CHNS** elemental microanalysis Calcd.for ($C_{19}H_{15}BrN_4O_2S_2$): found C%47.78,H%3.098,N%12.13,S%13.16; calculated C%48.00, H%3.18, N%11.79, S%13.49.

N-(4-(4-bromophenyl)thiazol-2-yl)-2-(pyrimidin-2-ylthio)acetamide **(8h)**

Light orange crystals;yield 81%;m.p.147-151ºC; **IR**(KBr)υ,cm^{-1}: 3186 cm^{-1} *sec*. amide (N-H) str, 3111 cm^{-1} Ar-(C-H) str ,2983&2931 cm^{-1} *asym* &*sym* alipha (CH_2) str,1684 cm^{-1} (C=O) amide str, 1556 cm^{-1} (N-H)amide bend,1475 cm^{-1} (C=N) str , 1446 cm^{-1} **Ar-(C=C)** str, 1377 cm^{-1} (CH_2) bend, 1273&904 cm^{-1} in plane& out of plane Ar-(C-H) bend, 1196 cm^{-1} (C-N) str ,741 cm^{-1} out of plane Ar-(C=C) bend, 673 cm^{-1} (C-S) str,636 cm^{-1} (C-Br)str,**^{1}HNMR(300 MHz,acetone-d_6,δ= ppm**): 11.40(1H,s,NHCO);

8.66(2H,d,H4+H6-pyrimidine);7.87(2H,d,Br-2Ar-H);7.57(2H,d,Br-2Ar-H);7.56(1H,s,H5-THZ);7.25(1H,t,H5-pyrimidine);4.28(2H,s,COCH2); **CHNS** elemental microanalysis Calcd. for ($C_{15}H_{11}BrN_4OS_2$): found C%44.09,H%2.60,N%13.41,S%16.24; calculated C%44.23,H%2.72,N%13.76,S%15.74.

Note: THZ= thiazole; BIM= benzimidazole



Scheme 1: Synthesis of titled thiazole derivatives 4-8h

Antimicrobial screening

The antimicrobial activities of the synthesized compounds **(8a-h)** were measured using well diffusion technique **[**18**]**, against G (+ve) and G(-ve) bacteria, with a comparison to cefotaxime sodium(cefot.) and sulfamethoxazole (sulf.) as standard antibacterial agents ,and miconazole as standard antifungal agent, using dimethylsulfoxide(DMSO) as solvent and as a control**.** All the synthesized compounds had been screened for their preliminary antimicrobial activity against four Gram-positive bacteria (*Staph. aureus, Micrococcus luteus, Bacillus subtilis* and *Bacillus pumilus*), and four Gram-negative bacteria (*Pseud. aeruginosa, E. coli, Proteus mirabilis* and *Klebsiella pneumoniae*)and three fungi species (*Saccharomyces cerevisiae, Candida tropicalis,* and *Candida albicans*), were clinically activated and maintained on nutrient agar medium for testing antibacterial activity and potato dextrose agar medium for antifungal activity **[**19**]**, using a minimum inhibitory concentration (MIC) of 100µg/ml of synthesized derivative in DMSO.

RESULTS AND DISCUSSION

Chemistry

The new thiazole derivatives were **synthesized** according to Hantzsch's method for the preparation of parent nucleus (**4** and **5**), by refluxing 4-substituted(4-Bromo or 4-nitro) phenacyl bromide, and thiourea in absolute methanol. They are characterized by FTIR, due to the appearance primary amine (NH_2) stretching at 3398 &3305 cm^{-1} and 3429&3282 cm^{-1} for **(4)** and **(5**), respectively.

Synthesis of (**6**, **7**) was carried out by adding chloroacetyl chloride to a stirring solution of (**4**and **5**) respectively, in dry benzene, at temperature 0-5^{o}C. Compound **(6)**, characterized by the appearance of (C=O) amide stretching at 1701 cm^{-1} and a characteristic ^{1}HNMR peak, as a *singlet* due to (NHCO) at δ=12.76ppm, in addition to the aromatic protons displayed at their expected region. While compound **(7)** characterized by the appearance of (C=O) amide stretching at 1693 cm^{-1} and a characteristic ^{1}HNMR peak recorded as *singlet* at δ=12.65 attributed to (NHCO).

Furthermore, compounds **(8a-h)** involved S-alkylation of side chain of (**6** and **7**). They were produced by refluxing one of the four different heterocyclic 2-thiol rings, with either **(6**) or **(7)** (acetylated derivatives), in dry acetone using a basic medium. These derivatives displayed a peak of *sec*. amide and of sec. amine, due to (N-H) stretching at (3543-3157) cm^{-1}, in addition to the appearance of (C=O) amide stretching at (1685-1653) cm^{-1}. The signals of **^{1}HNMR** for **(8a-h)** are consented with the **proposed** structure (see exp.section).

The elemental microanalysis **(CHNS)** was accomplished for synthesized compounds to confirm their basic chemical structures and, revealed acceptable agreement with the calculated percentages.

Antimicrobial evaluation

From the data shown in tables **1** and **2**, the synthesized thiazole derivatives did not exhibit any antibacterial activity towards tested Gram-negative bacteria species.

Compound **(8f)** showed moderate antibacterial activity against the four tested species of Gram-positive bacteria (***Micrococcus luteus, and Bacillus subtilis***).while **(8d)** and **(8g)** displayed moderate antibacterial activity against only two of Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus pumilus*).

On the other hand, compounds **(8d)** and **(8f)** showed slight antifungal activity, towards *Candida albicans*.

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Table 1: The antibacterial activity of the tested compounds.

Cpd. No.	Conc. µg/ml	*Staph. aureus*	*Micrococcus luteus*	*Bacillus pumilus*	*Bacillus subtilis*	*Pseud. aeruginosa*	*E.coli*	*Proteus mirabilis*	*Klebsiella pneumoniae*
		Inhibition zone (mm)							
(8a)	100	–	–	–	–	–	–	–	–
(8b)	100	–	–	–	–	–	–	–	–
(8c)	100	–	–	–	–	–	–	–	–
(8d)	100	11.8	–	11.7	–	–	–	–	–
(8e)	100	–	–	–	–	–	–	–	–
(8f)	100	9.7	10.8	8.9	11	–	–	–	–
(8g)	100	10.3	–	9.9	–	–	–	–	–
(8h)	100	–	–	–	–	–	–	–	–
Cefot.	100	50.11	59	41.5	45	32.5	53.2	27	28
Sulf.	100	24	29	32.4	20	25	27.8	27	23
DMSO	–	–	–	–	–	–	–	–	–

Table 2: The antifungal activity of the tested compounds

Compound No.	Conc. µg/ml	*Saccharomyces cerevisiae*	*Candida tropicalis*	*Candida albicans*
		Zone of inhibition(mm)		
(8a)	100	–	–	–
(8b)	100	–	–	–
(8c)	100	–	–	–
(8d)	100	–	–	7.6
(8e)	100	–	–	–
(8f)	100	–	–	9.3
(8g)	100	–	–	–
(8h)	100	–	–	–
Miconazole	100	36.5	16	23.8
DMSO	–	–	–	–

(-)= No activity, slightly active (Inhibition Zone in between 5-10 mm), moderately active (Inhibition Zone in between 10-15 mm), highly active (Inhibition Zone More Than 15 mm).

CONCLUSION

The titled thiazole derivatives were synthesized and characterized successfully and evaluated *in vitro* for their preliminary antimicrobial activity.All titled compounds fail to exhibit any antibacterial activity against tested Gram-negative bacteria.

Compound **(8f)** showed moderate antibacterial activity against the **two** tested species of Gram-positive bacteria and a slight antifungal activity, towards *Candida albicans*.

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