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Original Article

AN EFFICIENT SYNTHESIS AND REACTIONS OF 3-(8-HYDROXYQUINOLIN-5-YL)-7-METYHLTHIO-5-OXO-5H-[1, 3] THIAZOLO [3, 2-a] PYRIMIDINE-6-CARBONITRILE AS ANTIMICROBIAL AGENTS

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ABSTRACT

In the present study, a series of 3-(8-hydroxyquinolin-5-yl)-5-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidines (**4a,b**), (**5a-c**) and (**7a-c**) were synthesized by the reaction of 7-metyhlthio-3-(8-hydroxyquinolin-5-yl)-5-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carbonitrile (**3**) with different N- and O-nucleophiles, such as hetaryl amines, aryl amines, substituted phenols in the presence of anhydrous potassium carbonate (K_2CO_3) and dimethyl formamide (DMF). Also, other fused tetracyclic thiazolo[2′,3′:1,2]pyrimido[5,4-d]thiazolo[3,2-a]pyrimidines (**8a,b**) and (**9**) were synthesized on treatment of **3** with substituted aminothiazoles and 2-aminobenzothiazole. The parent compound (**3**) was reacted with hydrazine hydrate to obtain the corresponding aminopyrazole derivative (**10**) which was conducted to react with various reagents, such as acetic anhydride, acetyl acetone, ethyl acetoacetate and diethyl malonate to yield thiazolo[2,3′:1,2]pyrimido[4,5-c]pyazolo[2,3-a]pyrimidine derivatives (**12-14**). On the other hand, treatment of **10** with appropriate aromatic aldehydes afforded the corresponding arylidene derivatives (**15a-c)**. Finally, reaction of 4-chlorobenzylidine derivative (**15b)** with thioglycolic acid and chloroacetyl chloride furnished the thiazolidinone and azetidenone derivatives (**16)** and (**17)**, respectively. All the new title compounds were characterized by elemental and spectral data. The antimicrobial activity of some novel products was evaluated by agar well-diffusion.

Keywords: Thiazolo [3,2-a] pyrimidines, thiazolpyrimidinothiazolopyrimidines, pyrazolothiazolopyrimidine, thiazolidenone, azetidenone, antimicrobial activity.

INTRODUCTION

Heterocyclic compounds containing thiazole rings represent a very significant group of organic compounds [1-3], which are also found in certain natural products such as vitamin B1 (thiamine) and the penicillin thiazoles. Thiazolopyrimidines have become of interest due to their ability to inhibit 2-methylerythritol-2, 4-cyclodiphosphate synthase [4]. They have been also used as analgesic, antiparkinsonian agents [5], anticancer agents [6–8], phosphate inhibitors [9] and acetyl cholinesterase inhibitors [10].

Various condensed thiazolopyrimidines have been reported as antimicrobial substances [11, 12], anti-inflammatory [13], and antiviral activity and as inhibitors of HIV-1 reverse transcriptase [14]. With all the above facts in mind and as a part of our program directed towards the synthesis of poly functionally substituted 5- heterocyclo-8-quinolinoles of potential biological interest [15-20], we aimed to report herein the preparation of 3-(8-hydroxyquinolin-5-yl)-7- metyhlthio- 5- oxo- 5H [1,3] thiazolo [3,2-a] pyrimidine-6- carbonitrile (**3**) as a conveniently accessible precursor for the synthesis of thiazolo[3,2-a] pyrimidines and other related heterocyclic systems.

MATERIALS AND METHODS

All chemicals used were of analytical grade (Qualigen, Merck). The melting points were determined on a Kofler melting point apparatus. IR spectra were recorded on a Pye Unicam SP3-100 spectrophotometer using the KBr wafer technique.

The 1 H-NMR spectra were recorded on a Joel LA 400 MHz at Assiut University. Mass spectra were taken on a JEOL JMS600 spectrometer at an ionizing potential of 70eV (EI) at Assiut University. Elemental analyses were carried out using a Perkin-Elmer 240 C Micro analyzer at Assiut University and they were found to be within ± 0.4% of the theoretical values. The starting materials of 5-(2-aminothiazol-4-yl)-8-hydroxyquinoline **1** and ethyl 2-cyano-3, 3-bis (methylthio) acrylate **2** were prepared according to reported literatures [19] and [21], respectively.

3-(8-Hydroxyquinolin-5-yl)-7-metyhlthio-5-oxo-5H-[1,3] thiazolo [3, 2-a] pyrimidine-6-Carbonitrile (3)

A mixture of **1** (2.43g, 0.01 mol) and ethyl 2-cyano-3, 3-bis (methylthio) acrylate (**2**) (2.65 g, 0.01 mol) in 20 mL of N, N'-dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 3 hours. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystallized from n-hexane give pure **3** as orange powder, yield 2.96g (81%), mp 209–211℃; IR (KBr, cm^{-1}) υ 2220 (CN),υ 1665 (CO). ^{1}H NMR (DMSO-d_6): δ = 2.75 (s, 3H, CH_3), 6.25 (s, 1H, thiazolyl), 7.20-8.85 (m, 6H, Ar-H). MS (70 eV) m/z = 366.29 (M^+ 53). Anal. Calcd. for $C_{17}H_{10}N_4O_2S_2$ (Mw 366.41): C, 55.72; H, 2.75; N, 15.29; S, 17.50%. Found: C, 55.93; H, 2.88; N, 15.44; S, 17.69%.

General procedure for preparation of 4a, b, 5a-c, 7a-c, 8a, b and 9

A mixture of **3** (0.001 mol) was reacted independently with various heteryl amine, substituted aromatic amines, substituted phenols, 4-substituted 2-aminothiazoles and 2-aminobenzothiazole (0.001 m mol) in dimethyl formamide (20 mL) and anhydrous potassium carbonate (10mg) was refluxed for 4 to 6 hours. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallized from the proper solvent.

3-(8-Hydroxyquinolin-5-yl)-7-piperidino--5-oxo-5H-[1,3] thiazolo [3, 2-a] pyrimidine-6-carbonitrile (4a)

Light brown crystals from ethanol, yield 0.30g (75%) mp 232–234℃; IR (KBr, cm^{-1}) υ 2218 (CN), 1660 (CO). ^{1}H NMR (DMSO-d_6): δ = 1.45 (m, 6H, $3CH_2$), 2.85 (t, *J* = 7.6 Hz, 4H, $2CH_2$), 6.00 (s, 1H, thiazolyl), 7.15-8.80 (m, 6H, Ar-H). Anal. Calcd. for $C_{21}H_{17}N_5O_2S$ (Mw 403.45): C, 62.52; H, 4.25; N, 17.36; S, 7.95%. Found: C, 62.85; H, 4.51; N, 17.63; S, 8.19%.

3-(8-Hydroxyquinolin-5-yl)-7-morpholino-5-oxo-5H-[1,3] thiazolo [3, 2-a] pyrimidine-6-carbonitrile (4b)

Brown crystals from dioxane, yield 0.8g (69%), mp 214–216℃; IR (KBr, cm^{-1}) υ 2225 (CN), 1660 (CO). ^{1}H NMR (DMSO-d_6): δ = 2.85

(t, *J* = 7.5 Hz, 4H, 2N-CH_2), 3.60 (t, *J* = 7.3 Hz, 4H, 2O-CH_2), 6.15 (s, 1H, thiazolyl), 7.00-8.90 (m, 6H, Ar-H). Anal. Calcd. for $C_{20}H_{15}N_5O_3S$ (Mw 405.43): C, 59.25; H, 3.73; N, 17.27; S, 7.91%. Found: C, 59.51; H, 3.93; N, 17.52; S, 8.28%.

3-(8-Hydroxyquinolin-5-yl)-7-(4-methoxyanilino)-5-oxo-5H-[1, 3] thiazolo [3, 2-a] pyrimidine-6-carbonitrile (5a)

Brown powder from dioxane, yield 0.36g (82%), mp 220–222°C; IR (KBr, cm^{-1}) υ 3350 (NH), 2245 (CN), 1645 (CO). ^{1}H NMR (DMSO-d_6): δ = 3.75 (s, 3H, OCH_3), 4.25(s, 1H, NH), 6.30 (s, 1H, thiazolyl), 6.60-8.80 (m, 10H, Ar-H). MS (70 eV) m/z = 441.16 (M^+ 27). Anal. Calcd. for $C_{23}H_{15}N_5O_3S$ (Mw 441.46): C, 62.58; H, 3.42; N, 15.86; S, 7.26%. Found: C, 62.79; H, 3.64; N, 16.10; S, 7.59%.

3-(8-Hydroxyquinolin-5-yl)-7-(4-Chloroanilino)-5-oxo-5H-[1, 3] thiazolo [3, 2-a] pyrimidine-6-carbonitrile (5b)

Brown powder from ethanol, yield 0.35g (79%), mp 250–252°C; IR (KBr, cm^{-1}) υ 3330 (NH), 2220 (CN), 1665 (CO). ^{1}H NMR (DMSO-d_6): δ = 4.15(s, 1H, NH), 6.35 (s, 1H, thiazolyl), 6.70-8.90 (m, 10H, Ar-H). Anal. Calcd. for $C_{22}H_{12}ClN_5O_2S$ (Mw 445.88): C, 59.26; H, 2.71; Cl, 7.95; N, 15.71; S, 7.19%. Found: C, 59.44; H, 3.02; Cl, 8.13; N, 15.86; S, 7.42%.

3-(8-Hydroxyquinolin-5-yl)-7-(4-nitroanilino)-5-oxo-5H-[1,3] thiazolo [3, 2-a] pyrimidine-6-carbonitrile (5c)

Brown crystals from methanol, yield 0.38g (85%), mp 310–312°C; IR (KBr, cm^{-1}) υ 3410 (NH), 2225 (CN), 1660 (CO). ^{1}H NMR (DMSO-d_6): δ = 4.00(s, 1H, NH), 6.20 (s, 1H, thiazolyl), 6.60-8.90 (m, 10H, Ar-H). Anal. Calcd. for $C_{22}H_{12}N_6O_4S$ (Mw 456.43): C, 57.89; H, 2.65; N, 18.41; S, 7.03%. Found: C, 58.13; H, 2.99; N, 18.74; S, 7.31%.

7-Phenoxy- 3-(8-hydroxyquinolin-5-yl)-5-oxo-5H-[1, 3] thiazolo [3, 2-a] pyrimidine-6-carbonitrile (7a*)*

Brown crystals from dimethyl formamide, yield 0.33g (80%), mp 262–264°C; IR (KBr, cm^{-1}) υ 2215 (CN), 1665 (CO). ^{1}H NMR (DMSO-d_6): δ = 6.20 (s, 1H, thiazolyl), 6.65-8.80 (m, 11H, Ar-H). Anal. Calcd. for $C_{22}H_{12}N_4O_3S$ (Mw 412.42): C, 64.07; H, 2.93; N, 13.58; S, 7.77%. Found: C, 64.31; H, 3.24; N, 13.81; S, 8.03%.

7-(4-Methoxyphenoxy)-3-(8-hydroxyquinolin-5-yl)-5-oxo-5H-[1, 3] thiazolo [3, 2-a] pyrimidine-6- carbonitrile (7b)

Brown powder from methanol, yield 0.37g (84%), mp 202–204°C; IR (KBr, cm^{-1}) υ 2230 (CN), 1670 (CO). ^{1}H NMR (DMSO-d_6): δ = 3.75 (s, 3H, OCH_3), 6.15 (s, 1H, thiazolyl), 6.60-8.80 (m, 10H, Ar-H). MS (70eV) m/z = 442.16 (M^+ 15). Anal. Calcd. for $C_{23}H_{14}N_4O_4S$ (Mw 442.45): C, 62.44; H, 3.19; N, 12.66; S, 7.25%. Found: C, 62.81; H, 3.41; N, 13.01; S, 7.58%.

7-(4-Nitrophenoxy)-3-(8-hydroxyquinolin-5-yl)-5-oxo-5H-[1, 3] thiazolo [3, 2-a] pyrimidine-6- carbonitrile (7c)

Brown powder from dimethyl formamide, yield 0.35g (76%), mp 301–303°C; IR (KBr, cm^{-1}) υ 2260 (CN), 1660 (CO). ^{1}H NMR (DMSO-d_6): δ = 6.30 (s, 1H, thiazolyl), 6.70-8.80 (m, 10H, Ar-H). Anal. Calcd. for $C_{22}H_{11}N_5O_5S$ (Mw 457.42): C, 57.77; H, 2.42; N, 15.31; S, 7.01%. Found: C, 58.05; H, 2.74; N, 15.70; S, 7.33%.

3-Methyl-8-(8-hydroxyquinolin-5-yl)-6-oxo-5-imino-thiazolo [3',2':1,2] pyrimido [4, 5-d] thiazolo [3, 2-a] pyrimidine (8a)

Brown crystals from benzene, yield 0.35g (81%), mp 229–231°C; IR (KBr, cm^{-1}) υ 3320 (NH), 1667 (CO). ^{1}H NMR (DMSO-d_6): δ =2.35 (s, 3H, CH_3), 5.95 (s, 1H, thienyl),6.15 (s, 1H, thiazolyl), 6.77-8.70 (m, 6H, Ar-H), 8.95 (br,s, 1H, NH). MS (70 eV) m/z = 432.07 (M^+ 48). Anal. Calcd. for $C_{20}H_{12}N_6O_2S_2$ (Mw 432.48): C, 55.54; H, 2.80; N, 19.43; S, 14.83%. Found: C, 55.86; H, 3.04; N, 19.68; S, 15.10%.

Ethyl-6-amino-9-(p-methoxyphenyl)-3-(8-hydroxyquinolin-5-yl)-5, 8-dioxo-8-9-dihydro-5H-pyrido [2, 3-d] thiazolo [3, 2-a] pyrimidine-7-carboxylate (6)

To a mixture of **5a (**0.55g, 0.001 mol) and diethyl malonate (0.17mL, 0.001 mol) in absolute ethanol (30 ml) was added a few drops of ethanolic sodium ethoxide solution; the mixture was refluxed for 1 hr. The solid product was filtered off and recrystallized from ethanol to give **6** as orange crystals, yield 0.38g (68%), mp 178–180°C; IR (KBr, cm^{-1}) υ 3455, 3330 (NH_2),1735 (CO), 1665, 1654 (CO). ^{1}H NMR (DMSO-d_6): δ = 1.33 (t, *J* = 7.8 Hz,3H,CH_3), 2.85 (s, 3H, OCH_3),4.15 (s, 2H, NH_2), 4.30 (q, *J* = 7.7 Hz, 2H, CH_2), 6.10 (s, 1H, thiazolyl), 6.80-9.05 (m, 10H, Ar-H), . MS (70eV) m/z = 555.51 (M^+ 39). Anal. Calcd. for $C_{28}H_{21}N_5O_6S$ (Mw 555.56): C, 60.53; H, 3.81; N, 12.61; S, 5.77%. Found: C, 60.91; H, 4.12; N, 12.87; S, 6.13%.

3-Phenyl-8-(8-hydroxyquinolin-5-yl)-6-oxo-5-imino-thiazolo [3',2':1,2] pyrimido [4, 5-d] thiazolo [3, 2-a] pyrimidine (8b)

Brown crystals from dioxane, yield 0.39g (79%), mp >360°C; IR (KBr, cm^{-1}) υ 3315 (NH), 1690 (CO). ^{1}H NMR (DMSO-d_6): δ = 6.35 (s, 1H, thienyl), 6.48 (s, 1H, thiazolyl), 6.75-8.85 (m, 10H, Ar-H), 9.15 (br, s, 1H, NH). Anal. Calcd. for $C_{25}H_{14}N_6O_2S_2$ (494.55): C, 60.72; H, 2.85; N, 16.99; S, 12.97%. Found: C, 60.98; H, 3.13; N, 17.27; S, 13.21%.

3-(8-hydroxyquinolin-5-yl)- 5-oxo-6-imino-thiazolo [3",2':1',2'] pyrimido[4',5':4,5]pyrimido[2,1-b]benzo[d]thiazole (9)

Brown crystals from dioxane, yield 0.36g (77%), mp >360°C; IR (KBr, cm^{-1}) υ 3255 (NH), 1677 (CO). ^{1}H NMR (DMSO-d_6): δ = 6.20 (s, 1H, thiazolyl), 6.60-8.80 (m, 10H, Ar-H), 9.05 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{12}N_6O_2S_2$ (Mw 468.51): C, 58.96; H, 2.58; N, 17.94; S, 13.69%. Found: C, 59.13; H, 3.01; N, 18.09; S, 13.96%.

3-Amino-6-(8-hydroxyquinolin-5-yl)pyrazolo [3,4-d] thiazolo [3, 2-a] pyrimidin-4(1*H*)-one (10)

A mixture of **3** (1.46g, 0.004 mol) and hydrazine hydrate (15 mL) in absolute ethanol (40 mL) was refluxed for 5h. The reaction mixture was poured onto ice. The product was isolated and recrystallized from dioxane to yield **10** as white needles, yield 1.4g (74%), mp 280–282°C; IR (KBr, cm^{-1}) υ 3440, 3335, 3215 (NH, NH_2), 1695 (CO). ^{1}H NMR (DMSO-d_6): δ = 4.85 (s, 2H, NH_2), 6.00 (s, 1H, thiazolyl), 7.10-8.80 (m, 6H, Ar-H), 13.10 (s, 1H, NH). MS (70eV) m/z = 350.12 (M^+ 19). Anal. Calcd. for $C_{16}H_{10}N_6O_2S$ (Mw 350.35): C, 54.85; H, 2.88; N, 23.99; S, 9.15%. Found: C, 55.16; H, 3.10; N, 24.22; S, 9.33%.

3-Acetamido-6-(8-hydroxyquinolin-5-yl)pyrazolo[3,4-d] thiazolo [3, 2-a] pyrimidin-4(1*H*)-one (11)

A solution of **10** (0.35g, 0.001 mol) in acetic anhydride (10 mL) was refluxed for 3h. The reaction mixture was cooled and poured into cold water. The precipitate formed filtered off, washed with water, dried and crystallized from ethanol to give **11**as pale brown crystals, yield 0.25g (65%), mp175–177°C; IR (KBr, cm^{-1}) υ 3340, 3220 (NH), 1675, 1660 (2CO). ^{1}H NMR (DMSO-d_6): δ = 2.30 (s, 3H, CH_3), 6.30 (s, 1H, thiazolyl), 7.15-8.88 (m, 7H, Ar-H and NH)), 12.75 (s, 1H, NH). Anal. Calcd. for $C_{18}H_{12}N_6O_3S$ (Mw 392.39): C, 55.10; H, 3.08; N, 21.42; S, 8.17%. Found: C, 55.29; H, 3.42; N, 21.67; S, 8.57%.

7,9-Dimethyl-3-(8-hydroxyquinolin-5-yl)-5-oxo-pyrimido[3',2':1,5]pyrazolo [3, 4-d] thiazolo [3, 2-a] pyrimidine (12)

A mixture of compound **3** (0.35g, 0.001 mol) and acetyl acetone (0.1mL, 0.001 mol) in absolute ethanol (30mL) was stirred under reflux for 5 h. The reaction mixture was allowed to cool to 0 °C for 3 h. The precipitate was filtered off, dried and recrystallized from ethanol as orange crystals, yield 0.28g (68%), mp 255–257°C; IR (KBr, cm^{-1}) υ 1660 (CO). ^{1}H NMR (DMSO-d_6): δ = 2.25 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.45 (s, 1H, thiazolyl), 7.10-8.85 (m, 7H, Ar-H). Anal. Calcd. for $C_{21}H_{14}N_6O_2S$: (Mw 414.44) C, 60.86; H, 3.40; N, 20.28; S, 7.74%. Found: C, 61.19; H, 3.64; N, 20.61; S, 7.89%.

9-Hydroxy-7-methyl-3-(8-hydroxyquinolin-5-yl)-5-oxo-pyrimido[3',2':1,5]pyrazolo [3, 4-d] thiazolo [3, 2-a] pyrimidine (13)

To a solution of compound **3** (0.35g, 0.001 mol) in acetic acid (15 mL), ethyl acetoacetate (0.13 mL, 0.001 mol) was added. The reaction mixture was kept under reflux for 5h. The solvent was evaporated under reduced pressure.

The solid residue was filtered off, dried and recrystallized from acetic acid as orange crystals, yield 0.3g (74%), mp >360°C; IR (KBr, cm^{-1}) υ 3450 (OH), 1680 (CO). ^{1}H NMR (DMSO-d_6): δ = 2.30 (s, 3H, CH_3), 6.30 (s, 1H, thiazolyl), 7.10-8.85 (m, 7H, Ar-H), 9.45 (s, 1H, OH). Anal. Calcd. for $C_{20}H_{12}N_6O_3S$ (Mw 416.41): C, 57.69; H, 2.90; N, 20.18; S, 7.70%. Found: C, 57.92; H, 3.13; N, 20.33; S, 7.93%.

3-(8-Hydroxyquinolin-5-yl)-5,7,9-trioxo-pyrimido[3',2':1,5] pyrazolo [3, 4-d] thiazolo [3, 2-a] pyrimidine (14)

To a mixture of compound **3** (0.35g, 0.001 mol) and diethyl malonate (0.17mL, 0.001 mol) was heated at 180 ℃ in an oil bath for 1h, the reaction mixture was then cooled and triturated with ethanol. The solid product was filtered off, dried and recrystallized from toluene as orange crystals, yield 0.32g (78%), mp 268-270°C; IR (KBr, cm^{-1}) υ 3325 (NH), 1680, 1665 (CO). ^{1}H NMR (DMSO-d_6): δ = 3.40 (s, 2H, CH_2), 6.50 (s, 1H, thiazolyl), 7.05-8.80 (m, 6H, Ar-H), 11.20 (s, 1H, NH). MS (70eV) m/z = 418.03 (M^+ 11). Anal. Calcd. for $C_{19}H_{10}N_6O_4S$ (Mw 418.39): C, 54.54; H, 2.41; N, 20.09; S, 7.66%. Found: C, 54.81; H, 2.55; N, 20.41; S, 7.91%.

General procedure for preparation of 15a-c

A mixture of compound **10** (0.001 mol) and the appropriate aromatic aldehyde (0.001 mol) was stirred under reflux in ethanol (30 ml) in the presence of a few drops of glacial acetic acid for 5 h. The reaction mixture was allowed to cool to room temperature, poured into water, whereby a solid formed that was filtered off and crystallized from ethanol to produce **15a–c** in good yields.

3-Benzylideneamino-6-(8-hydroxyquinolin-5-yl)pyrazolo[3,4-d][1,3]thiazolo[3,2-a]pyrimidin-4(1*H*)-one (15a)

Orange powder, yield 0.30g (69%), mp 204–206°C; IR (KBr, cm^{-1}) υ 3410 (NH), 1665 (CO). ^{1}H NMR (DMSO-d_6): δ = 6.45 (s, 1H, thiazolyl), 6.95-8.88 (m, 11H, Ar-H), 9.25 (s, 1H, N=CH), 13.15 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{14}N_6O_2S$ (Mw 438.46): C, 63.00; H, 3.22; N, 19.17; S, 7.31%. Found: C, 63.28; H, 3.60; N, 19.41; S, 7.63%.

3-(4-Chlorobenzylideneamino)-6-(8-hydroxyquinolin-5-yl) pyrazolo [3, 4-d] [1, 3] thiazolo [3, 2-a] pyrimidin-4(1*H*)-one (15b)

Orange powder, yield 0.33g (70%), mp 204–206°C; IR (KBr, cm^{-1}) υ 3330 (NH), 1680 (CO). ^{1}H NMR (DMSO-d_6): δ = 6.30 (s, 1H, thiazolyl), 6.90-8.90 (m, 10H, Ar-H), 9.40 (s, 1H, N=CH), 12.85 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{13}ClN_6O_2S$ (Mw 472.91): C, 58.41; H, 2.77; Cl, 7.50; N, 17.77; S, 6.78%. Found: C, 58.77; H, 2.11; Cl, 7.87; N, 17.93; S, 8.06%.

3-(4-Nitrobenzylideneamino)-6-(8-hydroxyquinolin-5-yl)-pyrazolo [3, 4-d] [1, 3] thiazolo [3, 2-a] pyrimidin-4(1H)-one (15c)

Orange powder, yield 0.31g, (64%), mp 259–261°C; IR (KBr, cm^{-1}) υ 3335 (NH), 1685 (CO). ^{1}H NMR (DMSO-d_6): δ = 6.20 (s, 1H, thiazolyl), 6.80-8.99 (m, 10H, Ar-H), 9.75 (s, 1H, N=CH), 13.30 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{13}N_7O_4S$ (Mw 483.46): C, 57.14; H, 2.71; N, 20.28; S, 6.63%. Found: C, 57.43; H, 3.04; N, 20.51; S, 6.81%.

3(4-Cholrophenyl-4-oxo-1,3-thiazolidin-3-yl)-6-(8-hydroxyquinolin-5-yl)pyrazolo[3,4-d][1,3]

thiazolo[3,2-a]pyrimidin-4(1H)-one (16)

A mixture of the Schiff base (**15b**) (0.47g, 0.001mmol) and thioglycolic acid (0.12 mL, 0.001mol) dissolved in 1,4-dioxane (20ml), anhydrous zinc chloride (0.5mg) was added and refluxed for 6 hours. The reaction was subsequently cooled to 30°C and the result solid was washed with sodium bicarbonate solution. Filtered, dried and recrystalized from absolute ethanol as orange crystals, yield 0.36g (66%), mp 180-182°C; IR (KBr, cm^{-1}) υ 3320 (NH), 1715, 1670 (CO). ^{1}H NMR (DMSO-d_6): δ = 3.70 (s, 2H, S-CH_2), 5.50 (s, 1H, N-CH-S), 6.30 (s, 1H, thiazolyl), 6.80-8.90 (m, 10H, Ar-H), 11.90 (s, 1H, NH). MS (70 eV) m/z = 547.04 (M^+ 31). Anal. Calcd. for $C_{25}H_{15}ClN_6O_3S_2$ (Mw 547.01): C, 54.89; H, 2.76; Cl, 6.48; N, 15.36; S, 11.72%. Found: C, 55.08; H, 2.93; Cl, 6.79; N, 15.66; S, 12.10%.

3-(3-Chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-6-(8-hydroxyquinolin-5-yl)pyrazolo [3, 4-d] [1, 3] thiazolo [3, 2-a] pyrimidin-4(1*H*)-one (17)

A mixture of the Schiff base (**15b)** (0.94g, 0.002 mol) and triethyl amine (3 mL) was dissolved in 1, 4-dioxane (30 mL), cooled and stirred. To this well-stirred cooled solution chloroacetyl chloride (0.64 mL, 0.004 mol) was added drop wise within a period of 15 min. The reaction mixture was then stirred for an additional 3 h and left at room temperature for 24 h. The resultant mixture was concentrated, cooled, poured onto ice-cold water, filter and then dried. The product thus obtained was recrystallized from ethanol as orange crystals, yield 0.76 g (70%), mp 180-182℃; IR (KBr, cm^{-1}) υ 3340(NH), 1705, 1670 (CO). ^{1}H NMR (DMSO-d_6): δ = 4.95 (d, *J* = 6.9 Hz, 1H, CH-Cl), 5.35 (m, 1H, N-CH), 6.55 (s, 1H, thiazolyl), 6.90-9.05 (m, 10H, Ar-H), 13.25 (s, 1H, NH). Anal. Calcd. for $C_{25}H_{14}Cl_2N_6O_3S$ (Mw 549.39): C, 54.65; H, 2.57; Cl, 12.91; N, 15.30; S, 5.84%. Found: C, 54.83; H, 2.77; Cl, 13.14; N, 15.49; S, 6.03%.

Antimicrobial activity

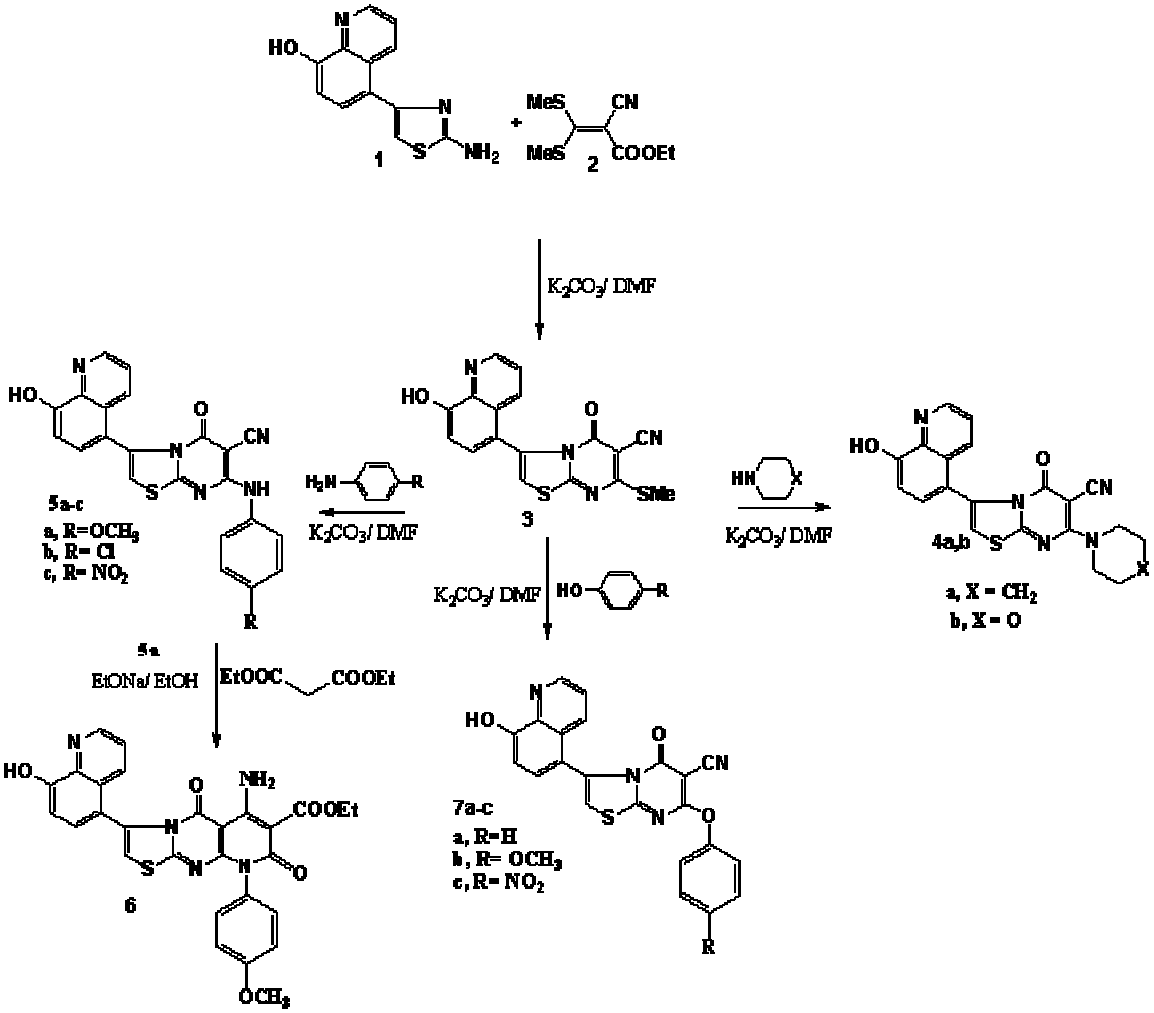
Using the agar well-diffusion method [22], the antimicrobial activity of 15 new chemical compounds was tested in *vitro* against six fungal species which are involved in human and animal diseases (*Geotrichum candidum* [AUMC No. 226], *Candida albicans* [AUMC No. 418], *Aspergillus flavus* [AUMC No. 3214], *Scopulariopsis brevicaulis* [AUMC No. 729], *Trichophyton rubrum* [AUMC No. 1804] and or plant diseases (*Fusarium oxysporum* [AUMC No. 5119]. They were also tested against five bacterial species obtained from contaminated soil, water and food substances (*Bacillus cereus* [AUMC No. B-52], *Staphylococcus aureus* [AUMC No. B-54] as Gram positive bacteria [AUMC NoB-112] and *Serratia marcescens* [AUMC No. B-55], *Escherichia coli* [AUMC No. B-53], *Pseudomonas aeruginosa* [AUMC No. B-73] as Gram negative bacteria. These strains are common contaminants of the environment in Egypt and some of all microbial strains were kindly provided by the Assiut University Mycological Centre (AUMC). To prepare inocula for bioassay, bacterial strains were individually cultured for 48 h in 100 mL conical flasks containing 30 mL nutrient broth medium. Fungi were grown for 7 days in 100 mL conicals containing 30 mL Sabouraud's dextrose broth. Bioassay was done in 10 cm sterile plastic Petri plates in which microbial suspension (1 mL/plate) and 15 mL appropriate agar medium (15 mL/plate) were poured. Nutrient agar and Sabouraud's dextrose agar were respectively used for bacteria and fungi. After solidification of the media, 5 mm diameter cavities were cut in the solidified agar (4 cavities/plate) using sterile cork borer. Chemical compounds dissolved in DMSO at 2%w/v (=20 mg/mL) were pipetted in the cavities. The screening tests were carried out in triplicate and the results were expressed as a mean of three determinations.

RESULTS AND DISCUSSION

According to the previously reported method [23], the parent compound3-(8-hydroxyquinolin-5-yl)-7-metyhlthio-5-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-Carbonitrile **3** was obtained on refluxing 5-(2-Aminothiazol-4-yl)-8-hydroxyquinoline (**1)** and ethyl 2-cyano-3,3-bis(methylthio) acrylate (**2)** in the presence of dimethyl formamide and a catalytic amount of anhydrous potassium carbonate. The structure of **3** was confirmed according to its elemental analyses and spectral data. The IR spectra revealed the presence of characteristic absorption bands at ν 2221 and at 1665 cm^{-1} assignable to cyano and carbonyl groups, respectively. The ^{1}H NMR spectra showed the presence of singlet signals at δ 2.75 and 6.25 ppm attributable to the methyl and thiazole proton H-2, respectively. Its mass spectrum showed a peak analogous to the molecular ion at *m/z* 366.29. Compound **3** possesses a replaceable active methylthio group at the 7-position that is activated by the ring 1-nitrogen atom and the electron withdrawing 6-cyano group. Literature [24] showed that thiazolopyrimidine type **3** is typically used as synthon for preparing of some novel substituted thiazolopyrimidines. In view of these, compound **3** was reacted with selected nitrogen and oxygen nucleophiles like hetaryl amines, aryl amines and substituted phenols, respectively. These reactions resulted in the formation of 6, 7-disubstituted derivatives of 5-oxo-3-(8-hydroxyquinolin-5-yl)-5*H*-[1,3] thiazolo [3,2-a] pyrimidine. According to this method, compound **3** independently, on reaction with piperidine and morpholine in dimethyl formamide and a catalytic amount of anhydrous potassium carbonate afforded 7-piperidino/morpholino-3-(8-hydroxyquinolin-5-yl)-5-oxo-5*H*-[1,3]thiazolo[3,2-a]pyrimidine-6-arbonitrile (**4a,b**), respectively. Under similar experimental conditions, compound **3** reacted independently with, 4-methoxyaniline, 4-chloroaniline and 4-

nitroaniline to yield 7-(p-methoxyanilino/ p-chloroanilino/ p-nitroanilino)-3-(8-hydroxyquinolin-5-yl)-5-oxo-5H-[1,3] thiazolo [3, 2-a] pyrimidine-6-carbonitrile (**5a-c**),respectively.7-(phenoxy/p-methoxyphenoxy/p-nitrophenoxy)-3-(8-hydroxy quinolin -5-yl) -5-oxo-5H-[1,3] thiazolo [3,2-a] pyrimidine-6-carbonitrile (**7a-c**) derivatives were obtained by the condensation of compound **3** independently with phenol, 4-methoxyphenol and 4-nitrophenol in N, N'- dimethyl formamide and a catalytic amount of anhydrous potassium carbonate **(Scheme 1)**. The structures of the compounds **4a, b, 5a-c** and **7a-c** were elucidated on the basis of their spectral data and elemental analyses. For example, the IR spectra of **5a-c** revealed absorption bands at ν 3330-3410 and at 2220 - 2245 cm^{-1} assignable to NH and CN groups, respectively. The ^1H NMR spectrum of **7b** exhibited two singlets at δ 3.75 and 6.15 ppm representing the protons of the methoxy (OCH_3) and thiazole H-2, respectively. Its mass spectrum showed a peak corresponding to the molecular ion at *m/z* 442.16 (M^+ 15) reinforcing the structure of **7b.** The 4-methoxyanilino derivative **5a** was allowed to react with diethyl malonate in ethanolic sodium ethoxide solution to yield pyrido [2, 3-d] thiazolo [3, 2-a] pyrimidine derivative **6**. The IR spectrum of compound **6** revealed the disappearance of an absorption band at 2245cm^{-1} due to the cyano group and the appearance of absorption bands at ν 3455, 3330 and 1735 cm^{-1} attributed to the NH_2 and the CO ester groups, respectively.

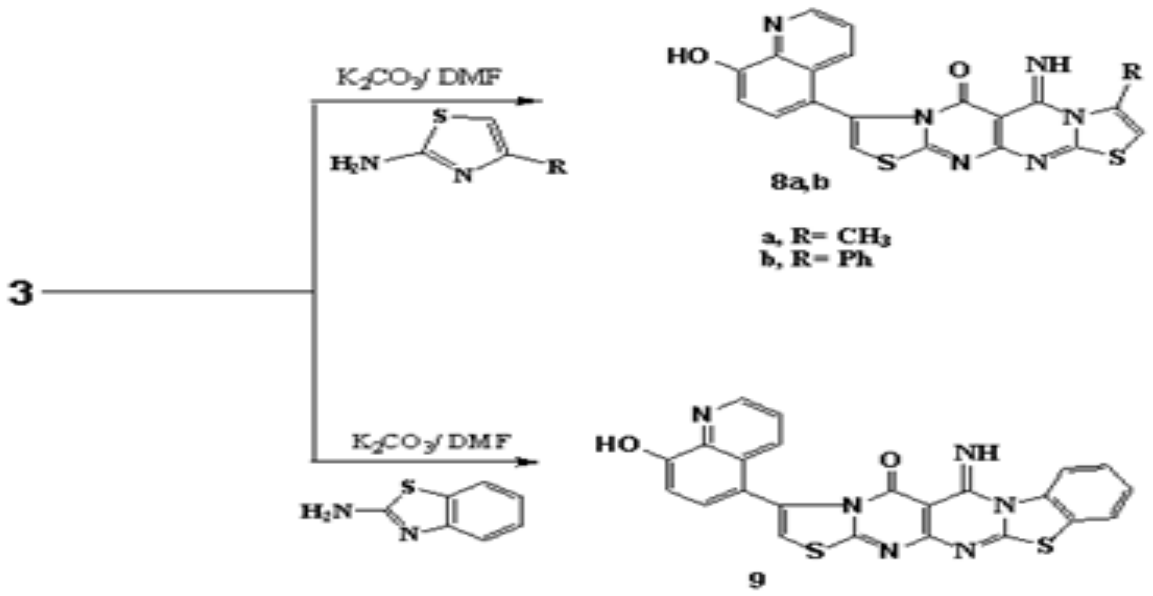
The ^1H NMR spectrum of compound **6** revealed a triplet at δ 1.33 ppm (*J* = 7.8 Hz) assigned to the CH_3 protons and a quartet at δ 4.40 ppm (*J* = 7.7 Hz) for the CH_2 protons besides other signal at δ 4.15 ppm assigned to the NH_2 group, which ensure the possibility of closure of the pyridine ring *via* an intra-molecular cyclization, resulting in the formation of compound **6** (**Scheme 1).**



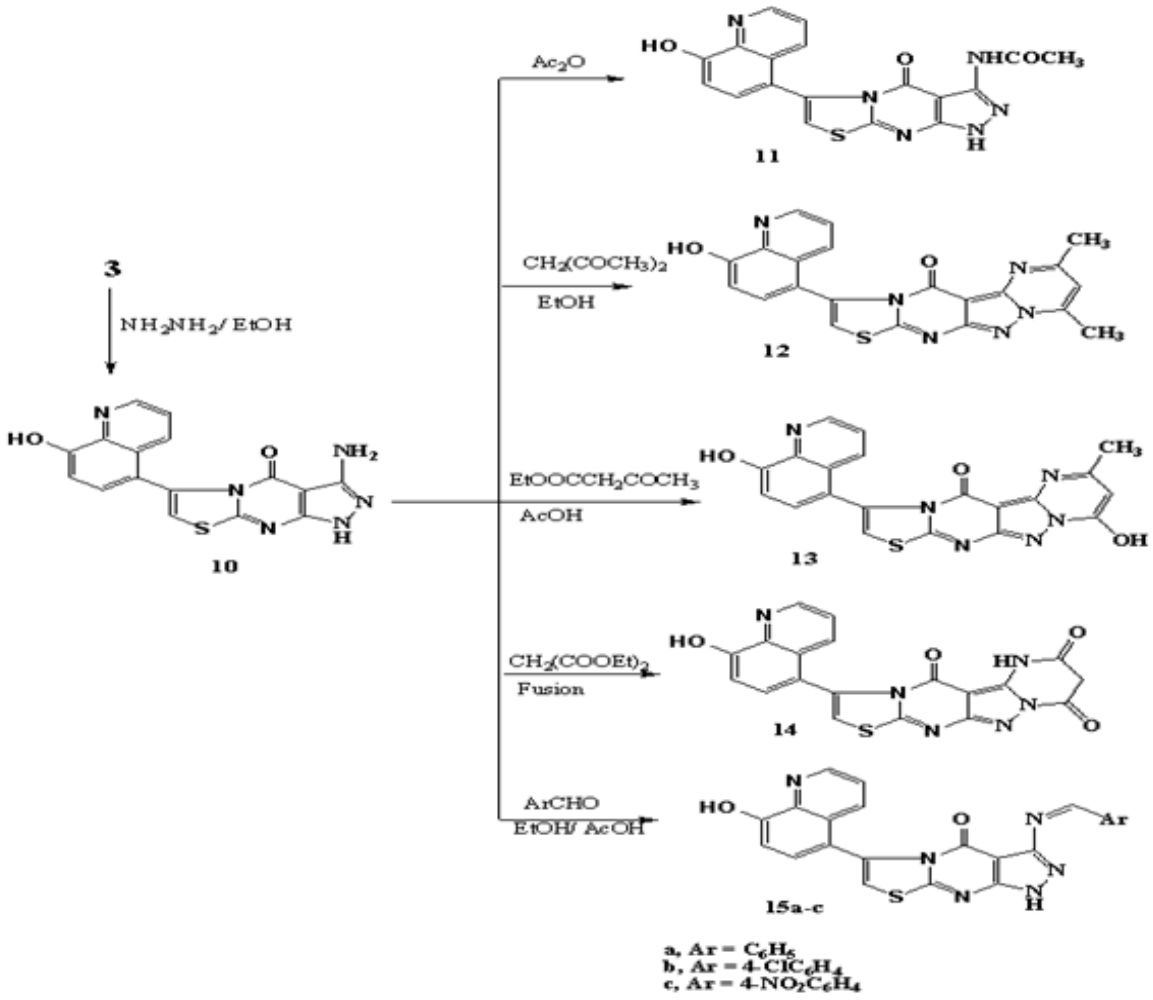
Scheme 1: Synthesis of compounds 3- 7a-c

New tetracyclic thiazolo[2′,3′:1,2] pyrimido [5,4-d] thiazolo [3,2-a] pyrimidines **8a,b** and **9** were obtained *via* the reaction of **3** with 4-methyl(phenyl)-2-aminothiazoles and 2-aminobenzothiazole independently in the presence of dimethyl formamide and a catalytic amount of anhydrous potassium carbonate, respectively.

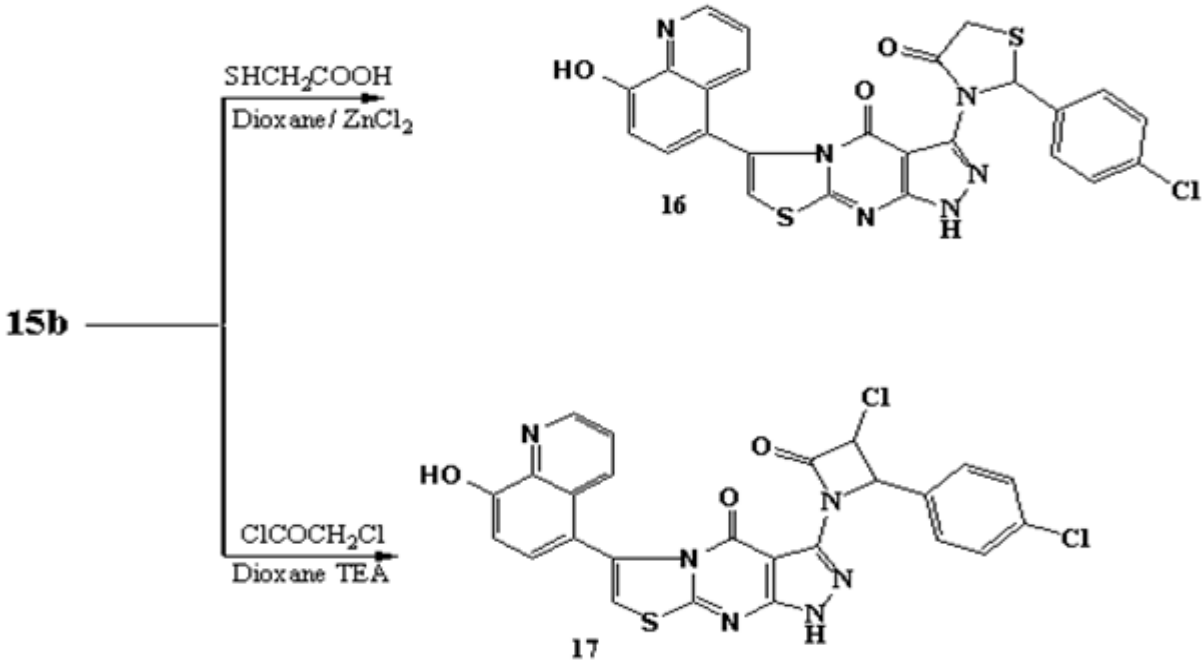
It is clear that nucleophilic substitution with subsequent *in situ* cyclization took place (**Scheme 2**). The structures of compounds **8a, 8b** and **9** were deduced on the basis of their spectral data and elemental analyses. The IR spectrum of compound **8a** revealed the disappearance of an absorption band at ν 2220 cm^{-1} due to CN function, and the appearance of an absorption band at ν 3320 for C=NH. ^1H NMR spectra exhibited singlet signal at *δ* 2.35 ppm for CH_3 protons. Two singlets at *δ* 5.95 and 6.15 ppm attributable to both thiazoles H-2 and H-9 protons. Its mass spectrum showed a peak analogous to the molecular ion at *m/z* 432.07 (M^+ 48) (**Scheme 2**).



Scheme 2: Synthesis Of Compounds 8s,b and 9.



Scheme 3: Synthesis Of Compounds 10-15 a-c.



Scheme 4: synthesis of compounds 16 and 17

On the other hand, heating of compound **3** with hydrazine hydrate in ethanol afforded the corresponding 3-amino-6-(8-hydroxyquinolin-5-yl)pyrazolo[3,4-d]thiazolo[3,2-a]pyrimidin-4(1H)-one(**10**).
Refluxing of **10** with acetic anhydride afforded the expected 3-acetylamino derivative (**11).** The IR spectrum of compound **11**displayed absorption bands at ν 3340, 3220 and 1660 cm^{-1} corresponding to the amide NH and amide carbonyl groups, respectively. In accord to the well known cyclocondensation of aminopyrazole with β-bifunctional reagents to yield pyrazolopyrimidines [25], compound (**10**) reacted with acetyl acetone, ethyl acetoacetate and diethyl malonate to yield **pyrimido[3',2':1,5]pyrazolo[3,4-d]thiazolo[3,2-a] pyrimidine** derivatives (**12-14**). The structure of compounds **12-14** was assigned on the basis of analytical and spectral data. ^{1}H NMR spectra of compound **12** showed characteristic two singlets at δ 2.25 and 2.37 ppm attributable to both CH_3 protons. The disappearance of the NH and NH_2 signals in the ^{1}H NMR spectra of compounds **12** was in favor of an intramolecular cyclization. Condensation of **3** with aromatic aldehydes, such as benzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde in in refluxing ethanol and a few drops of acetic acid afforded the corresponding Schiff's bases (**15a-c**) (**Scheme 3**). The structure of compounds **15a-c** was characterized by the analytical and spectral data. The ^{1}HNMR spectra of all synthesized Schiff bases are consistent with their structures. The 1 H NMR spectra of these compounds are simple and consist of the two singlet signals related to the resonance of the C-H and N-H proton, which appeared at δ 9.25-9.75 and δ 12.85-13.30 ppm, respectively. The preparation of 4-thiazolidinone and 4-azetidenone **16** and **17** has been undertaken by the heterocyclisation of Schiff's bases with thioglycolic acid and chloroacetyl chloride, respectively. Thus, 4-chloro arylidene derivative **15b** when heated with 2-marcapto acetic acid in the presence of anhydrous zinc chloride underwent cyclisation to give thiazolidin-4-one derivative (**16)**. Also, compound **15b** reacted with chloroacetyl chloride in the presence of triethylamine undergo cyclisation to give azetidin-2-one derivative **17.** The structure **16** and **17** was supported by IR and ^{1}H NMR spectral studies. The IR spectra of compound **16** exhibited an absorption band at ν 1715 cm^{-1} this can be attributed to the cyclic C=O. The N-H is observed at ν 3320 cm^{-1}. The ^{1}H NMR spectra displayed two significant singlets signals at δ 3.70 and 5.50 ppm attributed to the CH_2 (cyclic) and N-CH, respectively. Its mass spectrum showed a peak corresponding to the molecular ion at m/z 547.24 (M^+ 31). Finally, the ^{1} H NMR of the azetidinone derivative **17** exhibited CHCl proton of β-lactam ring as doublet at δ 4.95 ppm (J = 6.9 Hz) and N-CH proton as multiplet at δ 5.35 ppm reinforcing the structure of **17.** (**Scheme 4**).

Antimicrobial Evaluation

Fifteen selected derivatives (compounds **3, 4b, 5a, 5c, 6, 7b, 8a, 8b, 10, 12, 14, 15b, 15c, 16** and **17**) were evaluated for their antifungal and antibacterial activities. Thus, these compounds were screened were screened for their antifungal activities against six fungal strains: *Geotrichum candidum, Candida albicans, Aspergillus flavus, Scopulairopsis brevicaulis,* Trichophyton *rubrum and Fusarium oxysporum* using clotrimazole as control (**Table 1**). Also, for their antibacterial activity against *Bacillus cereus, Staphylococcus aureus* as a Gram positive bacteria and *Serratia marcescens, Escherichia coli*, *Pseudomonas aeruginosa* as Gram negative bacteria using chloramphenicol as control (**Table 2**). All experiments were carried out three times. The mean and standard deviation values were recorded using standard deviation calculator. The inhibition zones produced by the various synthesized compounds on the microbial growth were measured (diameter in mm)

Antifungal activity.

The results obtained from Table 1 revealed that the starting compound **3** has no effect against all tested fungi species except against *C. albicans* (72.6% inhibition) and Aspergillus *flavus* (89.6 % inhibition).When the methylthio (SMe) group in compound **3** is substituted with a morphlino one (**4b**), it exhibit activity only with *T.rubrum* (67.5% inhibition) and *F. oxysporum* (73.7% inhibition). Also, by the replacement of SMe group with the 4-methoxy and 4-nitrophenylamino compounds **5a** and **5c**, respectively we noticed that **5c** is more potent against all of the tested fungi especially with *A. flavus* (99.4% inhibition) and *S.brevicaulis* (90.8% inhibition) than **5a.** On heterocyclization of **5a** to obtain pyridothiazolopyrimidine compound (**6**), the activity diminished to zero against most of the fungi species. A comparison of the antifungal activity of the thiazolopyrimidinothiazolopyrimidine derivatives **8a (R=CH_3)** and **8b (R=ph),** indicated that the methyl derivative (**8a**) induces more fungitoxicity against all fungi tested except against *A.flavus* than the

other substituent **8b**. It was noted that amongst pyrimidine derivatives **10**, **12** and **14,** only the pyrimidinedione (**14**) exhibit a moderate activity against *C.albicans* (91.4.6% inhibition) *and A. flavus* (83.6% inhibition). A comparison of the antifungal activity data of compounds **15b (R = 4-Cl)** and **15c (R =4-NO_2)** clearly indicates that the 4-chloro derivative **15b** is more active against all of the tested fungi except against *T.rubrum* than the other substituent **15c**. Also the thiazolidenone derivative (**16**) is more active than the azetidenone one (**17**) against all of the tested fungi species.

Table 1: Antifungal activity of some synthesized 3-(8-hydroxyquinolin-5-yl)-[1, 3] thiazolo [3, 2-a] pyrimidine derivatives

Compound No.	Inhibition zone (mm)[a] mean ± SD (n=3)[b]					
	G.candidum	***C.albicans***	***A.flavus***	***S.brevicaulis***	***T.rubrum***	***F.oxysporum***
3	--	19.32± 0.28	35.90± 0.4	--	--	--
4b	--	--	--	--	37.35± 0.55	21.25± 0.82
5a	12.48± 0.42	8.06± 0.40	-	18.16± 0.61	26.50± 1.13	15.47± 0.45
5c	22.60± 0.55	25.80± 0.61	39.83± 0.72	38.63± 0.31	29.90± 0.82	24.30± 0.30
6	--	8.50± 0.50	12.76± 0.80	--	--	--
7b	11.90± 0.79	8.36± 0.40	--	--	18.23± 0.73	10.16± 0.45
8a	23.93± 0.90	25.80± 0.46	--	40.10± 1.01	43.50± 0.40	26.13± 0.70
8b	18.96± 1.00	11.50± 0.20	33.83± 0.35	--	--	6.43± 0.45
10	--	--	--	17.16± 0.47	--	--
12	--	--	--	8.40± 0.36	6.40± 0.40	8.30± 0.38
14	--	24.23± 0.25	33.53± 0.40	--	--	--
15b	18.76± 0.71	22.16± 0.21	34.70± 0.66	30.26± 0.25	--	19.93± 0.81
15c	--	--	--	38.36± 0.40	17.80± 0.26	21.50± 0.50
16	23.56± 0.60	21.16± 0.15	30.66± 0.31	36.26± 0.31	41.06± 0.31	20.80± 0.92
17	--	--	--	20.10± 0.17	11.26± 0.37	8.26± 0.31
Clotrimazole	25.60± 0.60	26.50± 0.46	40.06± 0.12	42.50± 0.44	55.30± 0.36	28.83± 0.76

[a] All the test and the standard drug were tested at the concentration of 20 mg/ml [b] Each result represents the average of triplicate readings.
-- No inhibition observed.

Table 2: Antibacterial activity of some synthesized 3-(8-hydroxyquinolin-5-yl)-[1, 3] thiazolo [3, 2-a] pyrimidine derivatives

Compound No.	Inhibition zone (mm)[a] mean ± SD (n=3)[b]				
***B. cereus* (+*ve*)**		***S. aureus* (+*ve*)**	***S. marcescens* (-*ve*)**	***E. coli* (-*ve*)**	***P. aeruginosa* (-*ve*)**
3	16.43± 0.40	28.76±0.80	18.76± 0.68	34.53± 0.47	21.60± 0.53
4b	--	--	--	--	--
5a	19.93± 0.90	20.86±0.81	23.06± 0.12	18.30± 0.30	23.23± 1.08
5c	28.40± 0.36	31.53± 0.47	29.08± 0.72	22.33± 0.53	26.36± 0.40
6	10.07± 0.12	10.33± 0.30	12.86± 0.76	16.53± 0.50	8.09± 0.17
7b	16.16± 0.29	12.36± 0.35	10.63± 0.65	8.13± 0.23	14.33± 0.35
8a	19.83± 0.76	25.56± 0.51	19.10± 1.15	22.36± 0.40	25.27± 0.23
8b	15.23± 0.32	20.16± 0.29	15.77± 0.68	17.50± 0.50	14.47± 0.45
10	12.13± 0.23	17.16± 0.38	13.30± 0.26	20.60± 0.53	22.10± 0.17
12	16.40± 0.35	20.33± 0.58	16.60± 0.53	23.37± 0.35	19.07± 1.10
14	15.47± 0.45	24.73± 0.64	10.20± 0.20	19.10± 0.17	20.33± 0.58
15b	18.33± 0.29	21.13± 0.23	23.87± 0.81	20.23± 0.40	20.73± 0.75
15c	8.33± 0.29	15.60± 0.56	20.60± 0.53	18.13± 0.23	10.66± 0.58
16	14.30± 0.36	13.86± 0.81	22.03± 1.05	20.40± 0.36	9.09± 0.17
17	21.23± 0.40	11.53± 0.50	17.13± 0.15	18.17± 0.29	20.13± 0.23
Chloramphenicol	38.33± 0.29	44.50± 0.46	34.77± 0.68	36.23± 0.40	32.87± 0.81

[a]All the test and the standard drug were tested at the concentration of 20 mg/ml [b]Each result represents the average of triplicate readings. -
- No inhibition observed.

Antibacterial activity.

The results of antibacterial activity of some synthesized compounds against different bacterial species were tabulated in table-2 The study revealed that all compounds exerted moderate to significant antibacterial activity against the Gram positive as well as the Gram-negative bacteria, except 3-(8-Hydroxyquinolin-5-yl)-7-morpholino-5-oxo-5H-[1,3] thiazolo [3, 2-a] pyrimidine-6-carbonitrile (**4b**) failed to exhibit inhibition against all the organisms. Compounds **3, 5a**, **5c**, **8a** and **15b** were found to possess appreciable antibacterial activity. The3-(8-Hydroxyquinolin-5-yl)-7-metyhlthio-5-oxo-5H-[1,3] thiazolo [3, 2-a] pyrimidine-6-Carbonitrile (**3**) showed an excellent inhibition zone against *E. coli* **(**95.30% inhibition). The 4-nitrophenylamino derivative (**5c)** showed good activity (83.63% inhibition against *S. marcescens*) comparable to the 4-methoxy one (**5a**) (66.32% inhibition against *S. marcescens*). Also, the methylthiazole derivative (**8a**) (76.87% inhibition against *P. aeruginosa*) is potent than the phenylthiazole derivative (**8b**). 4-Chlorobenzylideneamino derivative (**15b**) was found to be better than that of the 4-nitro derivative (**15c).** No definite trend was discernable that could lead to draw a correlation of the activities between these compounds.

CONCLUSION

It is concluded that the present work provides a convenient and efficient route for the preparation of new thiazolo [3,2-a] pyrimidine derivatives and their fused thiazolo, pyrazolo, and pyrimidopyrazolo ring systems. Fifteen of the newly synthesized compounds have been screened for their antimicrobial activities. Most of the tested compounds showed activities against the strains used. The results of the present study may serve as a ready reference for the researchers

to take advantage of proficient procedure applied for the synthesis of novel series of derivatives and further plausible modifications which will augment the therapeutic potential of thiazolo [3,2-a] pyrimidine derivatives.

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