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Preparation, characterization, antibacterial, antifungal and antioxidant activities of novel pyrazole-thiazole derivatives

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In the present study, 4-((1*H*-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(2,3-diphenyl-5-aryl-3,3a-dihydro-2*H*-pyrazolo [3,4-d]thiazol-6(5*H*)-yl)benzamide **IVa-h** has been synthesized by reaction between various 4-((1*H*-benzo[d][1,2,3]triazol-1-yl) methylamino)-N-(5-arylidene-4-oxo-2-phenylthiazolidin-3-yl)benzamides **IIa-h** with phenyl hydrazine. The reaction of 4-((1*H*-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(4-oxo-2-aryl thiazolidin -3-yl) benzamide **Ia-h** with benzaldehyde yields **IIa-h**. All the newly prepared compounds have been characterized by various spectroscopic techniques and screened for their *in vitro* antimicrobial and antioxidant activity. The investigation of anti microbial screening data reveals that most of the compounds tested have demonstrated moderate to good activity. Most of the heterocyclic derivatives bearing two hydroxyl groups on the phenyl ring show excellent antioxidant activity in comparison with ascorbic acid.

Keywords: Pyrazole-thiazole, spectral studies, antimicrobial activity, antioxidant activity

Number of organic compounds contains heterocycles as main structural moiety[1]. Heterocyclic moieties are most frequent in naturally occurring compounds and are significant because of their considerable biological efficacies that embrace anticancer[2], cytotoxic[3], anti-malarial[4], anti-microbial[5], anti-inflammatory[6], anti-oxidant[7] and many more[8,9].

Organic compounds bearing thiazoles of different pharmacodynamic moieties have anti-inflammatory[10], antiviral[11], antitumor[12], herbicides[13], and fungicides activities and antimicrobial activity[14-16].

Thiazolo - imidazole fused heterocyclic compounds explain various biological activities such as, antifungal, anthelmintic activity[17], anti-HIV-1 activity[18], as potent cytostatic agents[19], immunomodulatory and anticancer activities[20].

Experimental Section

All chemicals used were of laboratory grade. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ solutions on a BRUKER 400-MHz spectrometer, and chemical shifts were expressed as part per million (ppm; δ values) against tetramethylsilane as internal reference (TMS). The Infrared spectra (ν,cm^{-1}) were obtained with a Perkin−Elmer 1650 FTIR spectrometer in KBr pellets. Mass spectra (MS) were recorded on EI +Q1 MSLMR UPLR. Elemental analyses were performed on an ECS 4010 Elemental Combustion System and the results were within the accepted range (±0.40) of the calculated values. All melting points were determined on an Electro-thermal IA 9100 apparatus and were uncorrected. Progress of reactions was monitored by the of thin-layer chromatography (TLC). All the reagents and solvents were of the commercial quality and purchased from Merck, Fluka and local companies. 4-((1*H*-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(4-oxo-2-arylthiazolidin-3-yl) benzamide **(Ia-h)** was prepared by reported method[21].

General procedure for preparation of 4-((1*H*-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(5-arylidene-4-oxo-2-phenylthiazolidin-3-yl)benzamides, IIa-h

A solution of **(Ia-h)** (1 mmol) and benzaldehyde (1 mmol) in dry benzene (25 mL) was refluxed for about 10-12 h, in the presence of sodium ethoxide (1mmol), cooled, poured into ice cold water and then acidified with glacial acetic acid. The benzene layer was separated, dried over $CaCl_2$ and evaporated in vacuo to give crude product that was purified by recrystallization.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(5-benzylidene-4-oxo-2-phenyl thiazolidin -3-yl)benzamide, IIa

Yield 57%,mp 176–177°C,IR[ν,cm^{-1},KBr]:3445 (NH),3086-3034(C-H aromatic),2965(CH_2), 1690

(CO of thiazolidinone ring), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz,δ,ppm, DMSO-d_6]:9.66 (1H,s, CONH), 8.03-6.82 (18H, m,Ar-H),5.71 (2H,s, CH_2), 5.29(1H,s,SCHN),3.35-5.34(1H,s,C=CH-Ph),3.2(1H,s,NH). ^{13}C NMR[100MHz, δ, ppm, DMSO]: 170.4(CO),152.6-114.3(Ar-C), 168.9(-CO of the ring),129.7(=C-S),125.9(=CH-Ph),75.7 (-CH_2),68.6(-CH of ring). MS (EI^+) calcd for $C_{30}H_{24}N_6O_2S$ M^+ 532.1, found 534.7. Element Anal. Calc. for $C_{30}H_{24}N_6O_2S$ M^+ 532.1: C, 67.65; H, 4.54; N, 15.78; S, 6.02. Found: C, 67.63; H, 4.53; N, 15.76;S, 6.01%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(5-benzylidene-4-oxo-2-p-tolyl thiazolidin-3-yl)benzamide, IIb

Yield 55%,mp 183–184°C,IR[ν,cm^{-1},KBr]:3445 (NH),3086-3034(C-H aromatic),2965,2935 (CH_3,CH_2), 1690 (CO of thiazolidinone ring), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz,δ,ppm, DMSO-d_6]:9.66 (1H,s, CONH), 8.03-6.82 (17H, m,Ar-H),5.71 (2H,s, CH_2),5.29(1H,s,SCHN),3.35-5.34(1H,s, C=CH-Ph), 3.2(1H,s,NH), 2.28 (3H, s,CH_3).^{13}C NMR[100MHz, δ, ppm, DMSO]: 170.4 (CO),152.6-114.3(Ar-C), 168.9(-CO of the ring),129.7(=C-S),125.9(=CH-Ph),75.7 (-CH_2), 68.6(-CH of ring), 21.6 (CH_3). MS (EI^+) calcd for $C_{31}H_{26}N_6O_2S$ M^+ 546.1, found 549.6. Element Anal. Calc. for $C_{31}H_{26}N_6O_2S$ M^+ 546.1: C, 68.11; H, 4.79; N, 15.37; S, 5.87. Found: C, 68.10; H, 4.77; N, 15.35; S, 5.86%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)(methyl)amino)-N-(5-benzylidene-2-(2-hydroxy phenyl)-4-oxothiazolidin- 3-yl)benzamide, IIc

Yield 58%,mp 186–188°C,IR[ν,cm^{-1},KBr]:3445(NH), 3441(OH),3086-3034(C-H aromatic), 2965 (CH_2), 1690 (CO of thiazolidinone ring), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz,δ,ppm, DMSO-d_6]:9.66 (1H,s, CONH), 8.03-6.82 (17H, m,Ar-H),5.71 (2H,s, CH_2), 5.53(1H,s,OH), 5.29 (1H,s,SCHN),3.35-5.34(1H,s,C=CH-Ph),3.2(1H,s,NH). ^{13}C NMR[100MHz, δ, ppm, DMSO]: 170.4(CO), 154.3-114.3(Ar-C), 168.9(-CO of the ring),129.7(=C-S),125.9(=CH-Ph),75.7 (-CH_2),68.6(-CH of ring). MS (EI^+) calcd for $C_{30}H_{24}N_6O_3S$ M^+ 548.1, found 552.3. Element Anal. Calc. for $C_{30}H_{24}N_6O_3S$ M^+ 548.1: C, 65.68; H, 4.41; N, 15.32; S, 5.84. Found: C, 65.66; H, 4.40; N, 15.30; S, 5.83%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)(methyl)amino)-N-(5-benzylidene-2-(4-hydroxy phenyl)-4-oxothiazolidin-3-yl)benzamide, IId

Yield 61%,mp 142–144°C,IR[ν,cm^{-1},KBr]:3445(NH), 3443(OH),3086-3034(C-H aromatic), 2965 (CH_2), 1690 (CO of thiazolidinone ring), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz,δ,ppm, DMSO-d_6]:9.66 (1H,s, CONH), 8.03-6.82 (17H, m,Ar-H),5.71 (2H,s, CH_2), 5.49(1H,s,OH), 5.29(1H,s,SCHN), 3.35-5.34 (1H,s,C=CH-Ph),3.2(1H,s,NH).^{13}C NMR[100MHz, δ, ppm, DMSO]: 170.4(CO),159.7-114.3(Ar-C), 168.9(-CO of the ring),129.7(=C-S),125.9(=CH-Ph),75.7 (-CH_2),68.6(-CH of ring). MS (EI^+) calcd for $C_{30}H_{24}N_6O_3S$ M^+ 548.1, found 552.3. Element Anal. Calc. for $C_{30}H_{24}N_6O_3S$ M^+ 548.1: C, 65.68; H, 4.41; N, 15.32; S, 5.84. Found: C, 65.67; H, 4.40; N, 15.30; S, 5.82%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)(methyl)amino)-N-(5-benzylidene-2-(4-methoxy phenyl)-4-oxothiazolidin-3-yl)benzamide, IIe

Yield 53%,mp 154–156°C,IR[ν,cm^{-1},KBr]:3445(NH), 3086-3034(C-H aromatic),2965, 2928 (CH_3,CH_2), 1690 (CO of thiazolidinone ring), 1670 (amide C=O), 1630 (NH), 1620(C=CH-Ph), 1208,1156(C-O), 718 (C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz, δ,ppm, DMSO-d_6]: 9.66 (1H,s,CONH), 8.03-6.82 (17H, m,Ar-H),5.71 (2H,s, CH_2),5.29(1H,s,SCHN), 3.68(3H, s,OCH_3),3.35-5.34(1H,s,C=CH-Ph),3.2 (1H,s,NH). ^{13}C NMR[100MHz, δ, ppm, DMSO]: 170.4(CO),164.3-114.3(Ar-C), 168.9(-CO of the ring),129.7(=C-S),125.9(=CH-Ph),75.7 (-CH_2),68.6(-CH of ring),57.4(OCH_3). MS (EI^+) calcd for $C_{31}H_{26}N_6O_3S$ M^+ 562.1, found 565.9. Element Anal. Calc. for $C_{31}H_{26}N_6O_3S$ M^+ 562.1: C, 66.18; H, 4.66; N, 14.94; S, 5.70. Found: C, 66.16; H, 4.64; N, 14.93; S, 5.68%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)(methyl)amino)-N-(5-benzylidene-2-(2-chloro phenyl)-4-oxothiazolidin-3-yl)benzamide, IIf

Yield 58%,mp 171–173°C,IR[ν,cm^{-1},KBr]:3445 (NH),3086-3034(C-H aromatic),2965(CH_2), 1690 (CO of thiazolidinone ring), 1670 (amide C=O), 1630 (NH), 1620(C=CH-Ph),835(Ar-Cl), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz,δ,ppm, DMSO-d_6]: 9.66(1H,s,CONH), 8.03-6.82 (17H, m, Ar-H),5.71 (2H,s, CH_2),5.29(1H,s,SCHN),3.35-5.34 (1H,s,C=CH-Ph),3.2 (1H,s,NH).^{13}C NMR[100MHz, δ, ppm, DMSO]: 170.4(CO),161.6-114.3(Ar-C),

168.9(-CO of the ring), 137.3(Ar-Cl), 129.7(=C-S),125.9(=CH-Ph),75.7 (-CH_2),68.6(-CH of ring). MS (EI^+) calcd for $C_{31}H_{26}N_6O_3S$ M^+ 566.1, found 569.2. Element Anal. Calc. for $C_{30}H_{23}N_6O_2SCl$ M^+ 566.1: C, 63.54; H, 4.09; N, 14.82; S, 5.65;Cl, 6.25. Found: C, 63.52; H, 4.09; N, 14.80; S, 5.64;Cl, 6.23%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)(methyl)amino)-N-(5-benzylidene-2-(2,5-di hydroxy phenyl)-4-oxothiazolidin-3-yl)benzamid, IIg

Yield 56%,mp 163–165°C,IR[ν,cm^{-1},KBr]:3445(NH), 3441,3425(OH),3086-3034(C-H aromatic),2965 (CH_2), 1690 (CO of thiazolidinone ring), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz,δ,ppm, DMSO-d_6]:9.66(1H,s,CONH), 8.03-6.82 (16H, m,Ar-H),5.71 (2H,s, CH_2), 5.49,5.38(2H,s,OH), 5.29 (1H,s,SCHN),3.35-5.34(1H,s,C=CH-Ph),3.2(1H,s,NH). ^{13}C NMR[100MHz, δ, ppm, DMSO]: 170.4(CO), 161.7-114.3(Ar-C), 168.9(-CO of the ring),129.7(=C-S),125.9(=CH-Ph),75.7 (-CH_2),68.6(-CH of ring). MS (EI^+) calcd for $C_{30}H_{24}N_6O_4S$ M^+ 564.1, found 567.3. Element Anal. Calc. for $C_{30}H_{24}N_6O_4S$ M^+ 564.1: C, 63.82; H, 4.28; N, 14.88; S, 5.68. Found: C, 63.81; H, 4.27; N, 14.86; S, 5.66%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)(methyl)amino)-N-(5-benzylidene-2-(2,3-di hydroxy phenyl)-4-oxothiazolidin-3-yl)benzamide, IIg

Yield 59%,mp 158–159°C,IR[ν,cm^{-1},KBr]:3445 (NH),3441,3427(OH),3086-3034(C-H aromatic), 2965 (CH_2), 1690 (CO of thiazolidinone ring), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz,δ,ppm, DMSO-d_6]:9.66(1H,s,CONH), 8.03-6.82 (16H, m,Ar-H),5.71 (2H,s, CH_2), 5.46,5.36(2H,s,OH), 5.29 (1H,s,SCHN),3.35-5.34(1H,s,C=CH-Ph),3.2(1H, s, NH). ^{13}C NMR[100MHz, δ, ppm, DMSO]: 170.4 (CO),155.4-114.3(Ar-C), 168.9(-CO of the ring),129.7(=C-S),125.9(=CH-Ph),75.7 (-CH_2),68.6(-CH of ring). MS (EI^+) calcd for $C_{30}H_{24}N_6O_4S$ M^+ 564.1, found 567.3. Element Anal. Calc. for $C_{30}H_{24}N_6O_4S$ M^+ 564.1: C, 63.82; H, 4.28; N, 14.88; S, 5.68. Found: C, 63.81; H, 4.27; N, 14.86; S, 5.66%.

General procedure for preparation of 4-((1*H*-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(2,3-diphenyl-5-aryl-3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)benzamide, IVa-h

The respective benzylidene derivative, **IIa-h** (1 mmol) in glacial acetic acid (10 mL), sodium acetate (1 g) and phenyl hydrazine (1 mL) were heated for 7 h. The mixture was filtered hot to remove any insoluble material, cooled, and then water was added and boiled for few minutes, then it was cooled to afford the crude product which was purified by column chromatography from *n*-hexane-ethyl acetate(2:1).

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(2,3,5-triphenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)benzamide, IVa

Yield 49 %,mp 143-144°C,IR[ν,cm^{-1},KBr]: 3445, 3224 (NH),3086-3034(C-H aromatic), 2965(CH_2), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph),1594(C=N),718(C-S-C of thiazolidinone ring). ^{1}HNMR[400MHz,δ,ppm,DMSO-d_6]:9.66(1H,s,CONH), 8.03-6.82 (23H,m,Ar-H),6.09(1H,s,C_5H),5.87(1H,d, J=11.0Hz,C_{3a}H),5.7(2H,s,CH_2),4.61(1H,d,J=11.0 Hz, C_3H), 3.2(s,1H,NH).^{13}CNMR [100 MHz, δ, ppm, DMSO]: 170.4 (CO),157.2,63.5, 47.2 (pyrazole ring C),149.6-114.3 (Ar-C), 75.7 (CH_2), 68.6(CH of ring). MS (EI^+) calcd for $C_{36}H_{30}N_8OS$ M^+ 622.2, found 625.6. Element Anal. Calc. for $C_{36}H_{30}N_8OS$ M^+ 622.2: C, 69.43; H, 4.86; N, 17.99;S, 5.15. Found: C, 69.42; H, 4.84; N, 17.97;S, 5.13%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(2,3-diphenyl-5-p-tolyl-3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)benzamide, IVb

Yield 52 %,mp 139-140°C,IR[ν,cm^{-1},KBr]: 3445,3224 (NH),3086-3034(C-H aromatic), 2965,2938 (CH_3,CH_2), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph), 1594(C=N),718(C-S-C of thiazolidinone ring).^{1}HNMR [400MHz,δ,ppm,DMSO-d_6]:9.66(1H,s,CONH),8.03-6.82 (22H,m,Ar-H),6.09(1H,s,C_5H), 5.87(1H,d, J=11.0Hz,C_{3a}H),5.7(2H,s,CH_2),4.61(1H,d, J=11.0 Hz, C_3H),3.2(s,1H,NH),2.28(3H,s,CH_3). ^{13}C NMR [100 MHz, δ, ppm,DMSO]: 170.4 (CO),157.2,63.5, 47.2 (pyrazole ring C),153.1-114.3 (Ar-C), 75.7 (CH_2), 68.6(CH of ring),21.6 (CH_3). MS (EI^+) calcd for $C_{37}H_{32}N_8OS$ M^+ 636.2, found 639.4. Element Anal. Calc. for $C_{37}H_{32}N_8OS$ M^+ 636.2: C, 69.79; H, 5.07; N, 17.60;S, 5.04. Found: C, 69.77; H, 5.06; N, 17.58;S, 5.02%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(5-(2-hydroxyphenyl)-2,3-diphenyl -3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)benzamide, IVc

Yield 46 %,mp 147-149°C,IR[ν,cm^{-1},KBr]: 3445,3224 (NH), 3443(OH),3086-3034(C-H aromatic), 2965

(CH_2), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph),1594(C=N),718(C-S-C of thiazolidinone ring).[1] HNMR [400MHz,δ,ppm,DMSO-d_6]:9.66(1H,s,CONH), 8.03-6.82 (22H, m, Ar-H), 6.09(1H,s,C_5H), 5.87(1H,d, J=11.0Hz,$C_{3a}H$), 5.7(2H,s,CH_2), 5.56(1H,s,OH), 4.61 (1H,d, J=11.0Hz,C_3H), 3.2(s,1H, NH). ^{13}CNMR [100 MHz, δ, ppm,DMSO]: 170.4 (CO),157.2, 63.5,47.2 (pyrazole ring C),155.3-114.3 (Ar-C), 75.7 (CH_2), 68.6(CH of ring). MS (EI^+) calcd for $C_{36}H_{30}N_8O_2S$ M^+ 638.2, found 642.5. Element Anal. Calc. for $C_{36}H_{30}N_8O_2S$ M^+ 638.2: C, 67.69; H, 4.73; N, 17.54; S, 5.02. Found: C, 67.68; H, 4.72; N, 17.52; S, 5.01%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(5-(4-hydroxyphenyl)-2,3-diphenyl -3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)benzamide, IVd

Yield 49 %,mp 143-145°C,IR[ν,cm^{-1},KBr]: 3445, 3224 (NH), 3447(OH),3086-3034(C-H aromatic), 2965(CH_2), 1670 (amide C=O),1630 (NH), 1620 (C=CH-Ph),1594(C=N),718(C-S-C of thiazolidinone ring).[1]HNMR[400MHz,δ,ppm,DMSO-d_6]:9.66(1H,s,CONH),8.03-6.82 (22H, m,Ar-H),6.09 (1H,s,C_5H), 5.87(1H,d,J=11.0Hz,$C_{3a}H$), 5.7(2H,s,CH_2), 5.53(1H,s,OH), 4.61 (1H,d, J=11.0Hz,C_3H), 3.2(s,1H, NH). ^{13}CNMR [100 MHz, δ, ppm,DMSO]: 170.4 (CO),157.2,63.5,47.2(pyrazole ring C),159.9-114.3 (Ar-C), 75.7 (CH_2), 68.6(CH of ring). MS (EI^+) calcd for $C_{36}H_{30}N_8O_2S$ M^+ 638.2, found 642.7. Element Anal. Calc. for $C_{36}H_{30}N_8O_2S$ M^+ 638.2: C, 67.69; H, 4.73; N, 17.54; S, 5.02. Found: C, 67.67; H, 4.73; N, 17.53; S, 5.00%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(5-(4-methoxyphenyl)-2,3-diphenyl -3,3a-dihydro -2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)benzamide, IVe

Yield 45 %,mp 136-138°C,IR[ν,cm^{-1},KBr]: 3445,3224 (NH),3086-3034(C-H aromatic), 2965,2928 (CH_3,CH_2), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph), 1594(C=N), 1208, 1158(C-O), 718(C-S-C of thiazolidinone ring).[1]HNMR[400MHz,δ,ppm,DMSO-d_6]:9.66 (1H,s,CONH),8.03-6.82(22H,m,Ar-H),6.09 (1H,s,C_5H), 5.87(1H,d,J=11.0Hz,$C_{3a}H$), 5.7(2H,s, CH_2), 4.61(1H,d, J=11.0Hz,C_3H), 3.69(3H, s,OCH_3), 3.2(s,1H, NH). ^{13}CNMR [100 MHz, δ, ppm,DMSO]: 170.4 (CO),157.2,63.5,47.2(pyrazole ring C),165.1-114.3 (Ar-C), 75.7 (CH_2), 68.6(CH of ring),57.3 (OCH_3). MS (EI^+) calcd for $C_{37}H_{32}N_8O_2S$ M^+ 652.2, found 655.8. Element Anal. Calc. for $C_{37}H_{32}N_8O_2S$ M^+ 652.2: C, 68.08; H, 4.94; N, 17.17; S, 4.91. Found: C, 68.06; H, 4.92; N, 17.17; S, 4.90%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(5-(4-chlorophenyl)-2,3-diphenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)benzamide, IVf

Yield 47 %,mp 144-145°C,IR[ν,cm^{-1},KBr]: 3445,3224 (NH),3086-3034(C-H aromatic), 2965(CH_2), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph),1594 (C=N), 837(Ar-Cl),718(C-S-C of thiazolidinone ring).[1]HNMR [400MHz,δ,ppm,DMSO-d_6]:9.66(1H,s,CONH),8.03-6.82(22H,m,Ar-H),6.09(1H,s,C_5H), 5.87(1H,d,J=11.0Hz, $C_{3a}H$), 5.7(2H,s,CH_2), 4.61(1H,d, J=11.0Hz,C_3H), 3.2(s,1H, NH). ^{13}CNMR [100 MHz, δ, ppm,DMSO]: 170.4 (CO),157.2,63.5,47.2(pyrazole ring C),165.1-114.3 (Ar-C), 137.4(Ar-Cl), 75.7 (CH_2), 68.6(CH of ring). MS (EI^+) calcd for $C_{36}H_{29}N_8OSCl$ M^+ 656.1, found 659.7. Element Anal. Calc. for $C_{36}H_{29}N_8OSCl$ M^+ 656.1: C, 65.79; H, 4.45; N, 17.05;S, 4.88; Cl, 5.39. Found: C, 65.78; H, 4.43; N, 17.03;S, 4.87; Cl, 5.38%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(5-(2,5-dihydroxyphenyl)-2,3-diphenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)benzamide, IVg

Yield 51 %,mp 155-156°C,IR[ν,cm^{-1},KBr]: 3445,3224 (NH), 3443,3427(OH),3086-3034(C-H aromatic), 2965(CH_2), 1670 (amide C=O),1630 (NH), 1620(C=CH-Ph), 1594(C=N),718(C-S-C of thiazolidinone ring).[1]HNMR[400MHz,δ,ppm,DMSO-d_6]:9.66(1H,s, CONH),8.03-6.82 (21H, m,Ar-H), 6.09(1H,s,C_5H), 5.87(1H,d,J=11.0Hz,$C_{3a}H$),5.7(2H,s,CH_2), 5.52,5.42 (2H,s, OH), 4.61(1H,d, J=11.0Hz, C_3H), 3.2(s,1H, NH). ^{13}CNMR [100 MHz, δ, ppm,DMSO]: 170.4 (CO),157.2,63.5,47.2(pyrazole ring C),161.6-114.3 (Ar-C), 75.7 (CH_2), 68.6(CH of ring). MS (EI^+) calcd for $C_{36}H_{30}N_8O_3S$ M^+ 654.2, found 657.8. Element Anal. Calc. for $C_{36}H_{30}N_8O_3S$ M^+ 654.2: C, 66.04; H, 4.62; N, 17.11; S, 4.90. Found: C, 66.03; H, 4.60; N, 17.09; S, 4.88%.

4-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(5-(2,3-dihydroxyphenyl)-2,3-diphenyl-3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)benzamide, IVh

Yield 48 %,mp 148-149°C,IR[ν,cm^{-1},KBr]: 3445,3224 (NH), 3443,3428(OH),3086-3034(C-H aromatic), 2965 (CH_2), 1670 (amide C=O),1630 (NH), 1620 (C=CH-Ph),1594(C=N),718(C-S-C of thiazolidinone ring). [1]HNMR[400MHz,δ,ppm,DMSO-d_6]:9.66(1H,s,CONH), 8.03-6.82(21H,m,Ar-H), 6.09(1H,s,C_5H),5.87(1H,d, J=11.0Hz,$C_{3a}H$),5.7(2H,s,CH_2), 5.50,5.43 (2H, s,OH),

4.61(1H,d, J=11.0Hz, C_3H), 3.2(s,1H, NH). ^{13}CNMR [100 MHz, δ, ppm,DMSO]: 170.4 (CO),157.2, 63.5, 47.2(pyrazole ring C),159.3-114.3 (Ar-C), 75.7 (CH_2), 68.6(CH of ring). MS (EI^+) calcd for $C_{36}H_{30}N_8O_3S$ M^+ 654.2, found 657.8. Element Anal. Calc. for $C_{36}H_{30}N_8O_3S$ M^+ 654.2: C, 66.04; H, 4.62; N, 17.11; S, 4.90. Found: C, 66.03; H, 4.60; N, 17.09; S, 4.88%.

Evaluation of antimicrobial activity

The *in vitro* antimicrobial activity was carried out by agar cup plate method[22]. All the synthesized compounds were screened for antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *E.coli* and *Klebsiella promioe* at a concentration of 50µg/ML using Chloramphenicol (0.001 mole/ml) as standard. The antifungal activity was investigated against *Aspergillus niger*, *Botrydepladia thiobromine* and *Rhizopus nigricum* using Flucanazole (0.001 mole/ml) as standard. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 hr for bacteria and 48 hr for fungi. Each experiment was repeated thrice and the average of the three independent determinations was recorded. The results are summarized in Table I.

Evaluation of antioxidant activity

The antioxidant activity of tested 4-thiazolidinone derivatives was evaluated by the phosphomolybdenum method[23]. This method is based on the reduction of Mo(VI) to Mo(V) by the tested compounds followed by formation of a green phosphate/Mo(V) complex at acid pH. An aliquot of sample solution (100 µL, 2 mM in DMSO) is mixed with the reagent solution (1 mL, 0.6 M sulphuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate). The samples are incubated in a water bath at 95 °C for 90 minutes. Samples are cooled to room temperature and the absorbance was measured at 695 nm. The antioxidant activity was expressed relative to the antioxidant activity of same concentration of ascorbic acid.

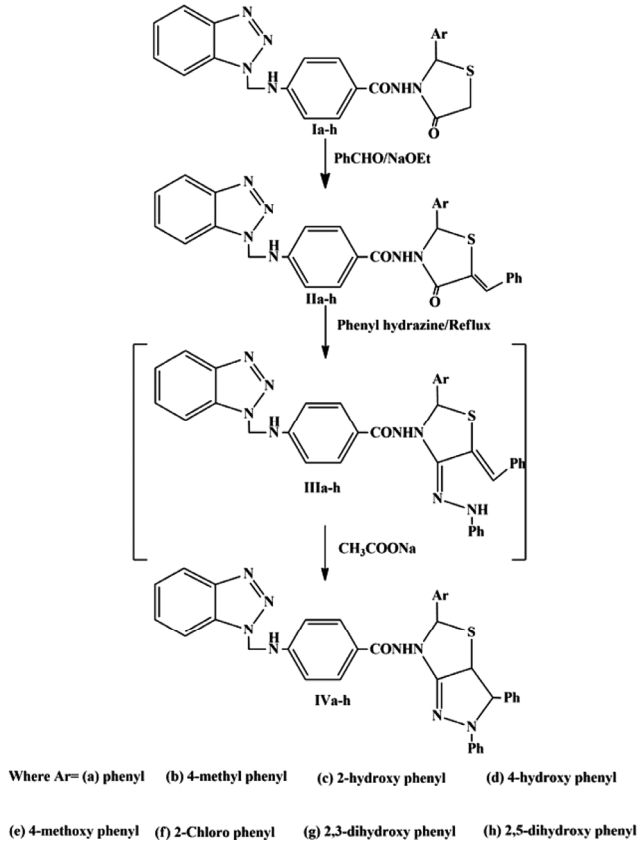
Results and Discussion

The compounds **(Ia-h)** were reacted with benzaldehyde in the presence of sodium ethoxide to afford the new 5-benzylidene derivatives **(IIa-h)**.Next, compounds **(IIa-h)** condensed with phenyl hydrazine in glacial acetic acid in the presence of sodium acetate to give products **(IVa-h)** (Scheme I). In a typical reaction, 5-benzylidene derivatives, sodium acetate and phenyl hydrazine were refluxed for 7 h in glacial acetic acid. The crude reaction mixture was filtered hot to remove any insoluble material, and cooled. Water was added to the resulting mixture which was boiled for a few minutes. Finally, the mixture was cooled to afford the crude product which was then purified by column chromatography using the appropriate solvent system. Compounds **(IVa-h)** are presumably formed by way of the phenyl hydrazones **(IIIa-h)**, followed by cyclization and proton transfer (Scheme I).

Table I — Antimicrobial activity of the compounds

Compd	Antibacterial activity Zone of Inhibition in mm				Antifungal activity Zone of Inhibition in mm		
	K.promioe	*B.subtilis*	*E.coli*	*S.aureus*	*A.niger*	*B.thiobromine*	*R.nigricum*
IIa	22	21	20	24	09	08	07
IIb	24	23	22	26	11	10	09
IIc	28	24	29	30	11	10	10
IId	26	25	24	27	12	11	10
IIe	28	28	30	30	15	14	13
IIf	29	27	25	29	16	15	14
IIg	31	29	27	34	16	14	13
IIh	26	26	31	28	15	14	12
IVa	24	23	22	26	10	09	10
IVb	26	26	24	28	12	11	10
IVc	30	27	30	32	13	12	12
IVd	28	28	26	31	14	12	13
IVe	31	30	33	32	17	16	14
IVf	30	29	27	31	20	19	17
IVg	32	31	29	34	16	14	14
IVh	29	29	32	31	19	18	16
Standard*	37	35	38	44	19	17	16

*Standard for antibacterial: Chloramphenicol (0.001 mole/ml).
Standard for antifungal: Flucanazole (0.001mole/ml).



Scheme I

In the benzylidene derivatives **(IIa-h),** this AB system was absent, confirming that condensation had been taken place. Regarding compounds **(IVa-h),** their 1H-NMR spectra showed two doublets at δ 5.87 ppm due to a proton on 3a-CH and at 4.61ppm, due to a proton on 3-CH, respectively. These signals reveal that the cyclization step had happened.

Characteristic C=O bands appeared in the 1690 cm-1 region in the FT-IR spectra of the thiazolidinones **(Ia-h)** and benzylidene derivatives **(IIa-h)**. In the FT-IR spectra of compounds **(IVa-h)**, the amide carbonyl band was absent, which clearly confirmed that a cyclocondensation with phenyl hydrazine had been taken place. Besides, the C=N bands of **(IVa-h)** were observed in the 1594cm^{-1} region. Although the new compounds have stereogenic centers, we were not able to separate the diastereomers due to their similar Rf values.

Our results have shown that the sequential condensation of phenyl hydrazine and compounds **(IIa-h)** containing carbonyl functionalities is a useful reaction for the construction of novel heterocycles of possible pharmacological interest.

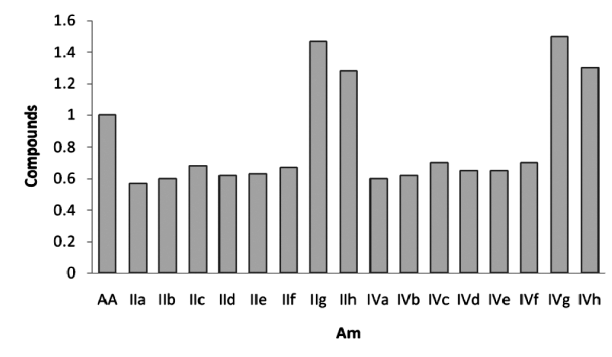


Figure 1 — Antioxidant activities of novel heterocyclic derivatives relative to ascorbic acid (*Am*– activity relative to ascorbic acid (AA) on a molar basis)

The structure of all the synthesized compounds was further confirmed by mass spectral analysis. It exhibited a molecular ion peak of compound is concurred with its molecular weight.

Antimicrobial activity

Compounds (**IIa-h and IVa-h**) were tested for antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *E.coli and klebsiella promioe*. Amongst the compounds tested for antibacterial activity, the compound **IVg,IVe,IVc,IIg,IIe and IIc** were found to display considerable activity against all the bacteria, whereas compounds **IVg** was found to exhibit promising activity against *B. subtilis* and 10h,8h,7h and 6h shows good activity against *E. coli*. The compounds **IVf and IIf** were found to exhibit promising activity against *K.promioe* and *S.aureus*. The compound **IVf** showed more antifungal activity than the standard flucanazole and the compound **IVh** exhibited almost equipotent activity against A. niger and *R. nigricum* and was found to be more active than the standard against *B. thiobromine*.

Antioxidant activity

Data in Figure 1 show that substituents on the phenyl ring have a great influence on antioxidant activity. In descending order the effects of the various substituents on the phenyl ring of the all the synthesized compounds were found to be: 2,5(OH)$_2$**(IVg)**> 2,5(OH)$_2$ **(IIg)**> 2,3(OH)$_2$ **(IVh)**> 2,3(OH)$_2$ **(IIh)** > 2-Cl **(IVf)**> 2-OH **(IVc)**> 2-OH **(IIc)**> 2-Cl **(IIf)**> 4-OCH$_3$ **(IVe)**> 4-OH**(IVd)**> 4-OCH$_3$ **(IIe)**> 4-OH **(IId)**> 2-CH$_3$ **(IVb)**> 2-CH$_3$ **(IIb)**> H**(IVa)**> H**(IIa).**Among the all the synthesized compounds IVg,IIg,IVh and IIh have better antioxidant activities than ascorbic acid. These compounds have two electron donating OH groups on

phenyl ring, one of them being in *ortho* position in both cases. They also posses another electron donating group, the presence of which obviously contributes to increased antioxidant activity, as the compounds IVd,IId,IVc and IIc with only one OH group in the *ortho* and *para* position did not show relevant antioxidant activity.

Observing the overall data for antioxidant activity, it is clear that the presence of two hydroxyl groups has a great influence on radical scavenging activity. The compound **IVg** shows the greatest antioxidant activity of all investigated compounds, followed by the 5-arylidene-1,3-thiazolidine-4-one **IIg,** both having 2,5-$(OH)_2$ substituents on phenyl ring, due to correlation of radical-scavenging effects of thiazolidine with the number of hydroxyl groups[24].

Conclusion

In this study a series of Novel fused heterocyclic compounds,4-((1H-benzo[d][1,2,3]triazol-1-yl) methyl amino)-N-(2,3-diphenyl-5-aryl-3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*) yl) benzamide **(IVa-h)** and novel 4-((1H-benzo[d][1,2,3]triazol-1-yl) methylamino)-N-(5-arylidene-4-oxo-2-phenylthiazolidin- 3-yl)benzamides **(IIa-h)** were synthesized and evaluated for their in-vitro antimicrobial and antioxidant activity. For all the novel compounds structures were elucidated by the means of various spectral methods.

All synthesized compounds are active against *Staphylococcus aureus*, *Bacillus subtilis*, *E. coli* and *Klebsiella pneumoniae*. 4-((1*H*-Benzo[d][1,2,3] triazol-1-yl)methylamino)-N-(2,3-diphenyl-5-aryl-3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)benzamide**(IVa-h)** derived from 4-((1*H*-benzo[d][1,2,3] triazol-1-yl) methylamino)-N-(5-arylidene-4-oxo-2-phenylthiazolidin-3-yl)benzamides **(IIa-h)** showed good antibacterial activities.

Two of the fused pyrazolo-thiazol compounds (**IVg,IVh**), 5-arylidene-1,3-thiazolidine-4-one (**IIg,IIh**) proved to have better antioxidant activity in comparison with ascorbic acid. In conclusion, it is evident that the substituents on the phenyl ring have a great influence on antioxidant activity.

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