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SYNTHESIS, CHARACTERIZATION, ANTIBACTERIAL, ANTIFUNGAL AND ANTIOXIDANT ACTIVITIES OF NOVEL HETEROCYCLIC DERIVATIVES

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ABSTRACT: The compound 4-((1H-benzo[d] [1,2,3] triazol-1-yl)methyl amino)benzohydrazide **(4)** react with various aromatic aldehyde **(5a-h)** gives 4-((1H-benzo[d][1,2,3]triazol-1-yl) methyl amino)-N'-arylidene benzo hydrazide **(6a-h),** which react with mercapto acetic acid produces 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(4-oxo-2-arylthiazolidin-3-yl)benzamide **(7a-h)**. All the newly prepared compounds were characterized by various spectroscopic techniques and screened for their in-vitro antimicrobial and antioxidant activity. The investigation of anti microbial screening data revealed that most of the compounds tested have demonstrated moderate to good activity. Most of the Schiff's bases and thiazolidine-4-ones derivatives bearing two hydroxyl groups on the phenyl ring showed excellent antioxidant activity in comparison with ascorbic acid.

KEYWORDS: Benzotriazole; Hydrazides; Aromatic Schiff's bases; Spectral Studies; Antimicrobial activity and Antioxidant activity.

1. INTRODUCTION

The major classical division of organic chemistry i.e. heterocycles are of massive significance biologically, industrially and definitely for any developed human society. Nowadays numbers of research works are carried out on heterocyclic synthesis for generating new molecules which are useful for pharmaceutical research, agricultural science and drug discovery[i,ii]. Heterocyclic building blocks also have practical use as components in dyestuffs, antioxidants, copolymers, bases and ligands.

The number of biologically interesting compounds bearing nitrogen and sulphur atom in heterocycles rings in their core structure. One of the most important heterocyclic compound say, thiadiazole derivatives find diverse applications as biological, pharmaceuticals, oxidation inhibitors, cyanine dyes and metal chelating agents. A literature review revealed that compounds with the thiadiazole nucleus possess antimicrobial[i-iii] antiviral, diuretic, anti-HIV, antihistaminic, and analgesic properties[iv-viii].antituberculosis[ix], anti-inflammatory[x], anticonvulsant[xi], antihypertensive[xii], antioxidant[xiii] and anticancer[xiv] activities. Thiazolidin-4-one derivatives exhibit high activity in vitro against mycobacterium tuberculosis (TB) and as drugs to treat HIV and cancer[xv-xvii]. Recently, 2-aryl-4-thiazolidinone has been synthesized and found to exhibit potent selective antiplatelet

activating factors both in vitro and in vivo and anti-inflammatory[xviii], antibacterial, anticancer[xix] and anti-HIV-1 activities[xx]. The fused thiazolidine also show various important activities. Spiroheterocyclic compounds including thiazolidine moiety have antimicrobial activity[xxi]. Both pyrazolothiazole and thiazolo pyrimidine moieties have potent kinase modulators[xxii] and are used in pharmaceutical compositions[xxiii]. The latter compound has analgesic and anti-Parkinson activities[xxiv] and inhibits the growth of parasite Trypanosoma cruzi[xxv].

In continuation to our endeavors on the synthesis of various substituted heterocyclic ring systems of potentially biological activities[xxvi] and the biological significance of this class of compounds impelled us to continue working on the synthesis of new thiazolidine derivatives. In this study we report the synthesis of some new 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(4-oxo-2-arylthiazolidin-3-yl)benzamide**(7a-h)**.

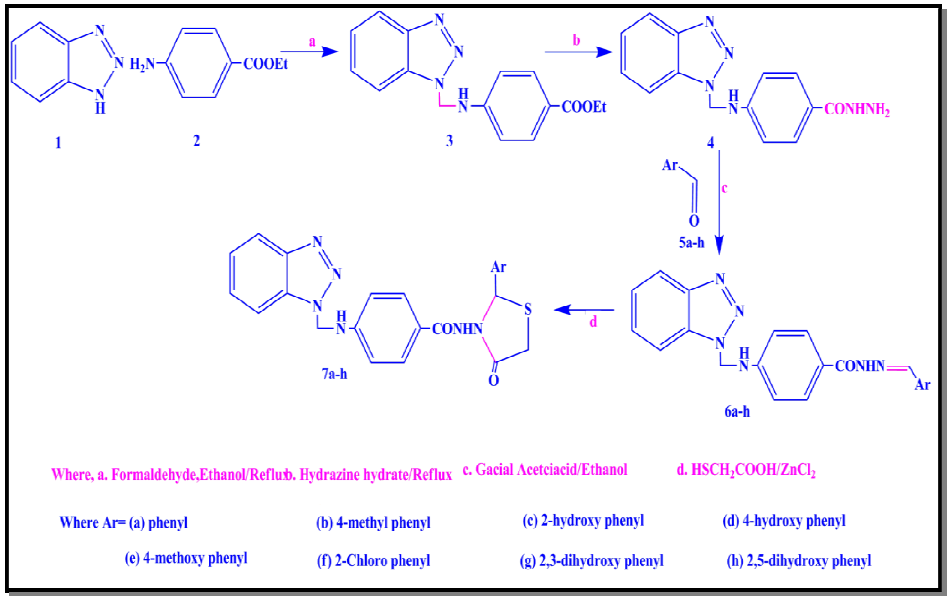

Figure-1. Synthesis of novel heterocyclic derivatives

2. MATERIALS AND METHODS

2.1 Measurements

All chemicals used were of laboratory grade. ^{1}H NMR 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 localize companies. Benzocain and Benzotriazole were prepared by reported method[xxvii].

2.2 Preparation of 4 - (1H) - benzotriazolyl methyl amino benzoate(3)

A mixture of 1H-Benzotriazole **(1)** (0.02 mol), formaldehyde (0.02 mol) and Ethyl-4-amino benzoate **(2)** (0.02 mol) in ethanol (50 ml) was heated under reflux for 4 h. Subsequently, ethanol was distilled off and the pasty mass obtained, which was triturated with petroleum ether (40–60°C). The solid 4-(1H)-benzotriazolyl methyl amino benzoate **(3)** was isolated and dried. Yield 68%, m.p. 146–147°C. IR [ν,cm^{-1},KBr]: 3034–3086 (C–H aromatic), 2965 (CH_2), 2910–2890 (C–H), 1725 (CO of ester), 1456 (C–H), 1255–1197 (C–N). 1H NMR [400 MHz,δ,ppm, DMSO-d_6]: 8.20–6.56 (8H,m,Ar-H,J =8.2, 7.8Hz), 5.71 (2H, s, CH_2), 4.32(2H, q, –O–CH_2),3.20(1H, s, NH), 1.32 (3H,t,CH_3). ^{13}C NMR [100 MHz,δ,ppm, DMSO]: 170.4 (CO), 145.6, 132.9, 127.3, 120.6, 114.3 (benzotriazole Ar-C), 149.1, 130.8, 118.7,114.5 (Ar-C), 75.7 (CH_2),62.1 (CH_2), 13.9 (CH_3). MS (EI^+) calcd for $C_{16}H_{16}N_4O_2$ M^+ 296, found 305. Element Anal. Calc.for $C_{16}H_{16}N_4O_2M^+$ 296: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.83;H, 5.43; N, 18.90%.

2.3 Preparation of 4-(1H) - benzotriazolyl methyl amino benzoyl hydrazide (4)

4-(1H)-benzotriazolyl methyl amino benzoate **(3)** (0.05 mol) was refluxed with hydrazine hydrate (0.05 mol) in absolute ethanol for 8–10 h. It was cooled and kept overnight. The solid so obtained was filtered and recrystallized from ethanol. Yield 63%, m.p.77–78°C.IR [ν,cm^{-1},KBr]:3450,1630(NH_2),3034–3086(C–H aromatic),2965(CH_2), 1725 (CO of ester),1197–1255(C–N).^{1}H NMR [400 MHz,δ,ppm,DMSO-d6]:9.66 (1H,s, CONH), 8.21–6.56 (8H, m, Ar-H,J= 8.2,7.8Hz),5.71(2H,s,CH_2),3.95 (2H,s,NH_2), 3.20(1H,s, NH). ^{13}C NMR [100MHz,δ,ppm,DMSO]:170.4 (CO), 145.6,132.9, 127.3, 120.6, 114.3 (benzotriazole Ar-C), 149.1, 130.8, 118.7, 114.5 (Ar-C), 75.7 (CH_2). MS (EI^+) calcd for $C_{14}H_{14}N_6O$ M^+ 282, found 283.2. Element Anal. Calc. for $C_{14}H_{14}N_6O$ M^+ 282: C, 59.56; H, 5.00; N, 29.77. Found : C, 59.55; H, 4.98; N, 29.75%.

2.4 Preparation of (E)-4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-arylidene benzo hydrazide (6a-h)

A mixture of compound **(4)** (0.01 mole) and a suitable aromatic aldehyde **(5a-h)** (0.01 mole) was refluxed in absolute ethanol (30 mL) in presence of a catalytic amount of glacial acetic acid for 2 to 4 hours. The reaction mixture was cooled and the precipitate was filtered and recrystallized from methanol to give compounds **(6a-h)**.

6a: (E)-4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-benzylidenebenzohydrazide.

Yield 72%, mp 184–186°C, IR[ν,cm^{-1},KBr]: 3445(NH),3086-3034(C-H aromatic), 2965(CH_2), 1670 (amide C=O), 1630(NH),1596-1548(C=N). ^{1}H NMR[400MHz, δ, ppm, DMSO-d_6]: 9.66(1H,s,CONH), 8.56 (1H,s, HC=N), 8.21-6.56(13H,m,Ar-H),5.71(2H,s, CH_2), 3.20(1H,s,NH). ^{13}C NMR [100 MHz, δ, *ppm*,DMSO]: 170.4 (CO),152.1-114.3 (Ar-C), 143.2 (C=N) ,75.7 (CH_2). MS (EI^+) calcd for $C_{21}H_{18}N_6O$ M^+ 370.1, found 373.4. Element Anal. Calc. for $C_{21}H_{18}N_6O$ M^+ 370.1: C, 68.09; H, 4.90; N, 22.69. Found: C 68.07; H, 4.89; N, 22.67%.

6b: (E)-4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-(4-methylbenzylidene)benzo hydrazide.

Yield 75%, mp 198–199°C, IR[ν,cm^{-1},KBr]: 3445(NH),3086-3034(C-H aromatic), 2965,2925(CH_3,CH_2),1670(amide C=O),1630(NH),1596-1548(C=N).^{1}H NMR[400MHz,δ, ppm,DMSO-d_6]:9.66(1H,s,CONH),8.56(1H,s,HC=N),8.21-6.56(12H,m,Ar-H),5.71(2H,s,

CH_2), 3.20(1H,s,NH), 2.28 (3H, s,CH_3). ^{13}C NMR [100 MHz, δ, *ppm*,DMSO]: 170.4 (CO),152.1-114.3 (Ar-C), 143.2 (C=N) ,75.7 (CH_2), 21.6 (CH_3). MS (EI^+) calcd for $C_{22}H_{20}N_6O$ M^+ 384.1, found 387.6. Element Anal. Calc. for $C_{22}H_{20}N_6O$ M^+ 384.1: C, 68.73; H, 5.24; N, 21.86. Found: C, 68.71; H, 5.23; N, 21.84%.

6c: (E)-4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-(2-hydroxybenzylidene)benzo hydrazide

Yield 73%, mp 191–193°C, IR[ν,cm^{-1},KBr]: 3445(NH),3436(OH),3086-3034(C-H aromatic),2965(CH_2),1670(amideC=O),1630(NH),1596-1548(C=N).^{1}HNMR[400MHz,δ, ppm, DMSO-d_6]:9.66(1H,s,CONH), 8.56 (1H,s, HC=N), 8.21-6.56(12H,m,Ar-H),5.70 (2H, s,CH_2),5.52(1H,s,OH),3.20(1H,s,NH),2.28(3H,s,CH_3). ^{13}C NMR [100 MHz, δ, *ppm*, DMSO]: 170.4 (CO),158.1-114.3 (Ar-C), 143.2 (C=N) ,75.7 (CH_2), 21.6 (CH_3). MS (EI^+) calcd for $C_{21}H_{18}N_6O_2$ M^+ 386.1, found 388.9. Element Anal. Calc. for $C_{21}H_{18}N_6O_2$ M^+ 386.1: C, 65.27; H, 4.70; N, 21.75. Found: C, 65.25; H, 4.68; N, 21.74%.

6d: (E)-4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-(4-hydroxybenzylidene)benzo hydrazide.

Yield 70%, mp 205–207°C, IR[ν,cm^{-1},KBr]: 3445(NH),3436(OH),3086-3034(C-H aromatic), 2965 (CH_2), 1670(amide C=O),1630(NH),1596-1548(C=N).^{1}H NMR[400MHz,δ, ppm,DMSO-d_6]: 9.66(1H,s,CONH),8.56 (1H,s, HC=N), 8.21-6.56(12H, m,Ar-H),5.71 (2H,s, CH_2),5.48(1H,s,OH),3.20(1H,s,NH),2.28 (3H, s,CH_3). ^{13}C NMR [100 MHz, δ, *ppm*, DMSO]: 170.4 (CO),161.1-114.3 (Ar-C), 143.2 (C=N) ,75.7 (CH_2), 21.6 (CH_3). MS (EI^+) calcd for $C_{21}H_{18}N_6O_2$ M^+ 386.1, found 388.9. Element Anal. Calc. for $C_{21}H_{18}N_6O_2$ M^+ 386.1: C, 65.27; H, 4.70; N, 21.75. Found: C, 65.26; H, 4.69; N, 21.73%.

6e: (E)-4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-(4-methoxybenzylidene) benzo hydrazide.

Yield 70%, mp 205–207°C, IR[ν,cm^{-1},KBr]: 3445(NH),3086-3034(C-H aromatic), 2965, 2925 (CH_3, CH_2), 1670(amide C=O),1630(NH),1596-1548(C=N),1208,1156(C-O).^{1}H NMR[400MHz,δ, ppm, DMSO-d_6]: 9.66(1H,s,CONH),8.56(1H,s, HC=N), 8.21-6.56(12H, m, Ar-H),5.70(2H,s,CH_2), 3.68(3H, s,OCH_3),3.20(1H,s,NH). ^{13}C NMR [100 MHz, δ, *ppm*, DMSO]:170.4(CO),162.7-114.3(Ar-C),143.2 (C=N) ,75.7 (CH_2),57.4(OCH_3). MS (EI^+) calcd for $C_{22}H_{20}N_6O_2$ M^+ 400.1, found 403.6. Element Anal. Calc. for $C_{22}H_{20}N_6O_2$ M^+ 400.1: C, 65.99; H, 5.03; N, 20.99. Found: C, 65.97; H, 5.01; N, 20.98%.

6f: (E)-4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-(4-chlorobenzylidene) benzo hydrazide.

Yield 67%,mp186–188°C,IR[ν,cm^{-1},KBr]:3445(NH),3086-3034(C-H aromatic),2965 (CH_2),1670(amideC=O),1630(NH),1596-1548(C=N),835(Ar-Cl).^{1}HNMR[400MHz,δ,ppm, DMSO-d_6]:9.66(1H,s,CONH),8.56(1H,s,HC=N),8.21-6.56(12H,m,Ar-H),5.71(2H,s,CH_2), 3.20 (1H,s,NH). ^{13}C NMR [100 MHz, δ, *ppm*,DMSO]: 170.4 (CO),159.7-114.3 (Ar-C), 143.2 (C=N),137.3(Ar-Cl), 75.7 (CH_2). MS (EI^+) calcd for $C_{22}H_{20}N_6O_2$ M^+ 404.1, found 406.9. Element Anal. Calc. for $C_{21}H_{17}N_6OCl$ M^+ 404.1: C, 62.30; H, 4.23; N, 20.76; Cl, 8.76. Found: C, 62.28; H, 4.21; N, 20.75; Cl, 8.74%.

6g: (E)-4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-(2,5-dihydroxybenzylidene) benzohydrazide.

Yield 76%, mp 193–194°C, IR[ν,cm^{-1},KBr]: 3445(NH),3446,3425(OH),3086-3034 (C-H aromatic), 2965(CH_2),1670(amide C=O),1630(NH),1596-1548(C=N).^{1}H NMR [400 MHz, δ, ppm,DMSO-d_6]: 9.66 (1H, s,CONH), 8.56 (1H,s, HC=N), 8.21-6.56(11H, m,Ar-H), 5.71(2H,s,CH_2), 5.40,5.35 (2H,s,OH), 3.20 (1H, s,NH), 2.28 (3H, s,CH_3). ^{13}C NMR [100

MHz, δ,*ppm*,DMSO]:170.4(CO),163.4-114.3(Ar-C),143.2(C=N),75.7 (CH_2), 21.6 (CH_3). MS (EI^+) calcd for $C_{21}H_{18}N_6O_3$ M^+ 402.1, found 405.6. Element Anal. Calc. for $C_{21}H_{18}N_6O_3$ M^+ 402.1: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.66; H, 4.49; N, 20.87%.

6h:(E)-4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-(2,3-dihydroxybenzylidene) benzohydrazide.

Yield 73%, mp 186–188°C, IR[ν,cm^{-1},KBr]: 3445(NH),3448-3425(OH),3086-3034 (C-H aromatic),2965(CH_2),1670(amide C=O),1630(NH),1596-1548(C=N).^{1}HNMR[400 MHz, δ,ppm,DMSO-d_6]: 9.66 (1H, s,CONH), 8.56 (1H,s, HC=N), 8.21-6.56(11H, m,Ar-H), 5.71(2H,s,CH_2),5.38,5.36 (2H,s,OH), 3.20 (1H, s,NH), 2.28 (3H, s,CH_3).^{13}CN-MR[100MHz,δ, *ppm*,DMSO]:170.4(CO),153.4-114.3 (Ar-C), 143.2 (C=N) ,75.7 (CH_2), 21.6 (CH_3). MS (EI^+) calcd for $C_{21}H_{18}N_6O_3$ M^+ 402.1, found 405.6. Element Anal. Calc. for $C_{21}H_{18}N_6O_3$ M^+ 402.1: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.67; H, 4.50; N, 20.86%.

2.5 Preparation of 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(4-oxo-2-aryl thiazolidin-3-yl) benzamide (7a-h)

To a solution of 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-arylidene benzo hydrazide **(6a-h)** (0.01 mol) in dry 1,4-dioxane (15 mL), freshly distilled mercapto acetic acid (0.01 mol) and anhydrous $ZnCl_2$ (0.1 g) were added and the mixture was heated under reflux 10 to 12 hours. The solvent was removed (reduced pressure) and residue washed with 5% sodium bicarbonate solution (3 ×20 mL) and water (2 × 20 mL), dried, and recrystallized from an appropriate solvent.

7a: 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(4-oxo-2-phenylthiazolidin-3-yl) benzamide.

Yield73%,mp242–243°C,IR[ν,cm^{-1},KBr]:3445(NH),3095-3075(CH_2 of thiazolidinone ring),3086-3034(C-Haromatic),2965(CH_2),1690cm^{-1}(C=O of thiazolidinone ring),1670 (amide C=O),1630(NH),718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz,δ,ppm, DMSO -d_6]:9.66(s,1H,CONH),8.03-6.82(13H,m,Ar-H),5.71(2H,s,CH_2),5.29(1H,s,SCHN), 3.98, 3.85 (2H,ABsystem, *J*= 9.2 Hz,5-CH_2), 3.20(1H,s,NH).^{13}C NMR [100 MHz, δ, *ppm*,DMSO]: 170.4 (CO), 168.9(CO of the ring),152.6-114.3(Ar-C),75.7(CH_2),68.6(CH of ring),35.9(SCH_2). MS (EI^+) calcd for $C_{23}H_{20}N_6O_2S$ M^+ 444.1, found 446.5. Element Anal. Calc. for $C_{23}H_{20}N_6O_2S$ M^+ 444.1: C, 62.15; H, 4.54; N, 18.91; S, 7.21. Found: 62.13; H, 4.53; N, 18.90; S, 7.19 %.

7b: 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(4-oxo-2-p-tolylthiazolidin-3-yl) benzamide.

Yield70%,mp226–227°C,IR[ν,cm^{-1},KBr]:3445(NH),3095-3075($CH_2$of thiazolidinone ring),3086-3034(C-H aromatic),2965,2930(CH_3,CH_2),1690cm^{-1}(C=O of thiazolidinone ring), 1670 (amide C=O),1630 (NH), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz,δ,ppm, DMSO-d_6]:9.66(s, 1H, CONH), 8.03-6.82(12H,m,Ar-H),5.71(2H,s,CH_2),5.29(1H,s,SCHN), 3.98, 3.85 (2H,AB system, *J*= 9.2 Hz,5-CH_2), 3.20(1H,s,NH), 2.28 (3H, s,CH_3).^{13}C NMR [100 MHz, δ, *ppm*,DMSO]: 170.4 (CO), 168.9(CO of the ring),152.6-114.3(Ar-C),75.7 (CH_2), 68.6 (CH of ring),35.9(SCH_2), 21.6 (CH_3). MS (EI^+) calcd for $C_{24}H_{22}N_6O_2S$ M^+ 458.1, found 460.8. Element Anal. Calc. for $C_{24}H_{22}N_6O_2S$ M^+ 458.1: C, 62.86; H, 4.84; N, 18.33; S, 6.99. Found: C, 62.84; H, 4.83; N, 18.31; S, 6.98%.

7c:4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(2-(2-hydroxyphenyl)-4-oxothiazo lidin-3-yl)benzamide

Yield 76%, mp 233–234°C, IR[ν,cm^{-1},KBr]:3445(NH), 3439(OH),3095-3075(CH_2 of thiazolidinone ring),3086-3034(C-H aromatic),2965(CH_2),1690cm^{-1}(C=O of thiazolidinone ring), 1670 (amide C=O),1630 (NH), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400 MHz, δ,ppm, DMSO-d_6]:9.66(s, 1H, CONH), 8.03-6.82(12H,m,Ar-H),5.71(2H,s,CH_2), 5.52 (1H,s, OH),5.29(1H,s,SCHN), 3.98, 3.85(2H,AB system, *J*= 9.2 Hz,5-CH_2), 3.20(1H,s,NH).^{13}C N-MR [100MHz,δ, *ppm*,DMSO]: 170.4 (CO), 168.9(CO of the ring),157.6-114.3(Ar-C), 75.7 (CH_2), 68.6(CH of ring),35.9(SCH_2). MS (EI^+) calcd for $C_{23}H_{20}N_6O_3S$ M^+ 460.1, found 462.4. Element Anal. Calc. for $C_{23}H_{22}N_6O_3S$ M^+ 460.1: C, 59.99; H, 4.38; N, 18.25; S, 6.96. Found: C, 59.98; H, 4.38; N, 18.24; S, 6.94%.

7d: 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(2-(4-hydroxyphenyl)-4-oxothiazo lidin-3-yl)benzamide

Yield 71%, mp 210–212°C, IR[ν,cm^{-1},KBr]:3445(NH), 3436(OH),3095-3075(CH_2 of thiazolidinone ring),3086-3034(C-H aromatic),2965(CH_2),1690cm^{-1}(C=O of thiazolidinone ring),1670 (amide C=O),1630 (NH), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz, δ, ppm,DMSO-d_6]:9.66(s,1H,CONH),8.03-6.82(12H,m,Ar-H),5.71(2H,s,CH_2), 5.49 (1H,s, OH), 5.29(1H,s,SCHN), 3.98,3.85(2H,AB system, *J*= 9.2 Hz,5-CH_2), 3.20(1H,s,NH).^{13}C NMR [100 MHz, δ, *ppm*,DMSO]: 170.4 (CO), 168.9(CO of the ring),162.2-114.3(Ar-C),75.7(CH_2),68.6 (CH of ring),35.9(SCH_2). MS (EI^+) calcd for $C_{23}H_{20}N_6O_3S$ M^+ 460.1, found 462.4. Element Anal. Calc. for $C_{23}H_{22}N_6O_3S$ M^+ 460.1: C, 59.99; H, 4.38; N, 18.25; S, 6.96. Found: C, 59.97; H, 4.36; N, 18.24; S, 6.95%.

7e: 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(2-(4-methoxyphenyl)-4-oxothiazo lidin-3-yl)benzamide

Yield71%,mp210–212°C,IR[ν,cm^{-1},KBr]:3445(NH),3095-3075($CH_2$of thiazolidinone ring),3086-3034(C-H aromatic),2965,2932(CH_3,CH_2),1690cm^{-1}(C=O of thiazolidinone ring), 1670(amide C=O),1630 (NH),1208,1156(C-O),718(C-S-C of thiazolidinone ring). ^{1}H NMR [400MHz,δ,ppm,DMSO-d_6]:9.66(s,1H,CONH),8.03-6.82(12H,m,Ar-H),5.71(2H,s,CH_2), 5.29 (1H,s,SCHN),3.98,3.85(2H,AB system, *J*= 9.2 Hz,5-CH_2), 3.68(3H, s,OCH_3), 3.2(1H,s, NH). ^{13}C NMR[100MHz,δ, *ppm*,DMSO]: 170.4 (CO), 168.9(CO of the ring),161.7-114.3(Ar-C), 75.7 (CH_2),68.6(CH of ring), 57.4(OCH_3),35.9(SCH_2). MS (EI^+) calcd for $C_{24}H_{22}N_6O_3S$ M^+ 474.1, found 477.2. Element Anal. Calc. for $C_{24}H_{22}N_6O_3S$ M^+ 474.1: C, 60.75; H, 4.67; N, 17.71; S, 6.76. Found: C, 60.74; H, 4.65; N, 17.70; S, 6.74%.

7f: 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(2-(4-chlorophenyl)-4-oxothiazo lidin-3-yl)benzamide

Yield67%,mp217–219°C,IR[ν,cm^{-1},KBr]:3445(NH),3095-3075($CH_2$of thiazolidinone ring),3086-3034(C-H aromatic),2965,2932(CH_3,CH_2),1690cm^{-1}(C=O of thiazolidinone ring), 1670(amide C=O),1630 (NH),),835(Ar-Cl),718(C-S-C of thiazolidinone ring). ^{1}H NMR [400 MHz,δ,ppm,DMSO-d_6]:9.66(s,1H,CONH),8.03-6.82(12H,m,Ar-H),5.71(2H,s,CH_2),5.29 (1H, s,SCHN), 3.98, 3.85 (2H,AB system, *J*= 9.2 Hz,5-CH_2),3.20(1H,s,NH).^{13}C NMR [100 MHz, δ, *ppm*,DMSO]:170.4 (CO), 168.9(CO of the ring),161.7-114.3(Ar-C),137.3(Ar-Cl), 75.7 (CH_2), 68.6(CH of ring),57.4(OCH_3),35.9(SCH_2). MS (EI^+)calcd for $C_{23}H_{19}N_6O_2SCl$ M^+ 478.5, found 482.2.Element Anal. Calc. for $C_{23}H_{19}N_6O_2SCl$ M^+ 478.5: C,57.68; H, 4.00; N, 17.55; S, 6.69; Cl,7.40. Found: C, 57.67; H, 3.99; N, 17.53; S, 6.67; Cl, 7.39%.

7g:4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(2-(2,5-dihydroxyphenyl)-4-oxo thiazolidin-3-yl)benzamide

Yield77%,mp238–240°C,IR[ν,cm^{-1},KBr]:3445(NH),3448-3429(OH),3095-3075(CH_2 ofthiazolidinonering),3086-3034(C-Haromatic),2965(CH_2),1690cm^{-1}(C=Oof thiazolidinone ring), 1670 (amide C=O),1630 (NH), 718(C-S-C of thiazolidinone ring). ^{1}H NMR[400MHz,δ, ppm,DMSO-d_6]:9.66(s,1H,CONH),8.03-6.82(11H,m,Ar-H),5.71(2H,s,CH_2), 5.42, 5.37 (2H,s, OH),5.29(1H,s,SCHN),3.98,3.85(2H,AB system, *J*= 9.2 Hz,5-CH_2),3.20(1H,s, NH).^{13}C NMR [100 MHz, δ, *ppm*,DMSO]: 170.4 (CO), 168.9(CO of the ring),153.4-114.3(Ar-C), 75.7 (CH_2),68.6(CH of ring),35.9(SCH_2). MS (EI^+) calcd for $C_{23}H_{20}N_6O_4S$ M^+ 476.1, found 479.2. Element Anal. Calc. for $C_{23}H_{20}N_6O_4S$ M^+ 476.1: C, 57.97; H, 4.23; N, 17.64; S, 6.73. Found: C, 57.95; H, 4.22; N, 17.63; S, 6.71%.

7h: 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(2-(2,3-dihydroxyphenyl)-4-oxo thiazolidin-3-yl)benzamide

Yield 72%, mp 215–216°C, IR[ν,cm^{-1},KBr]:3445(NH), 3448-3426(OH),3095-3075 (CH_2 of thiazolidinone ring),3086-3034(C-H aromatic),2965(CH_2),1690cm^{-1}(C=O of thiazolidinone ring),1670(amide C=O),1630(NH),718(C-S-C of thiazolidinone ring).^{1}H NMR [400MHz,δ,ppm, DMSO-d_6]:9.66(s, 1H, CONH), 8.03-6.82(11H,m,Ar-H),5.71 (2H,s, CH_2), 5.41, 5.35(2H,s,OH),5.29(1H,s,SCHN), 3.98, 3.85 (2H,AB system, *J*= 9.2 Hz,5-CH_2), 3.20 (1H,s,NH). ^{13}C NMR [100 MHz, δ, *ppm*,DMSO]:170.4(CO), 168.9(CO of the ring), 150.4 - 114.3(Ar-C), 75.7 (CH_2),68.6(CH of ring),35.9(SCH_2). MS (EI^+) calcd for $C_{23}H_{20}N_6O_4S$ M^+ 476.1, found 479.2. Element Anal. Calc. for $C_{23}H_{20}N_6O_4S$ M^+ 476.1: C, 57.97; H, 4.23; N, 17.64; S, 6.73. Found: C, 57.95; H, 4.21; N, 17.62; S, 6.72%.

2.7 Evaluation of antimicrobial activity

The *in vitro* antimicrobial activity was carried out by agar cup plate method[xxviii]. 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 1.

Table 1. Antimicrobial activity of the compounds

Compd.	Antibacterial activity Zone of Inhibition in mm				Antifungal activity Zone of Compound Inhibition in mm		
	K.promioe	***B.subtilis***	***E.coli***	***S.aureus***	***A.niger***	***B.thiobromine***	***R.nigricum***
6a	+	++	+	++	+	+	+
6b	++	++	++	++	+	+	+
6c	+++	++	+++	+++	+	+	+
6d	++	+++	++	++	+	+	+
6e	+++	+++	++++	+++	+	+	+
6f	+++	+++	+++	++++	+	+	+
6g	++++	+++	+++	++++	+	+	+
6h	+++	+++	++++	+++	+	+	+

7a	++	++	++	++	+	+	+
7b	+++	++	++	+++	+	+	+
7c	+++	+++	++++	++++	+	+	+
7d	+++	+++	+++	+++	+	+	+
7e	++++	++++	++++	++++	+	+	+
7f	++++	++++	+++	++++	+	+	+
7g	++++	++++	++++	++++	+	+	+
7h	+++	+++	++++	++++	+	+	+
Standard	++++	++++	++++	++++	++	++	++
DMF	+	+	+	+	+	+	+

Zone of inhibition: '+' indicates growth of microbes. (+) 6-15 mm; (+ +) 16-20mm; (+ + +) 21-25 mm; (+ + + +) 26-40 mm.

Control: DMF (0.01% solution in distilled water).

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

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

2.8 Evaluation of antioxidant activity

The antioxidant activity of tested 4-thiazolidinone derivatives was evaluated by the phosphomolybdenum method according to the procedure in[xxix]. 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.

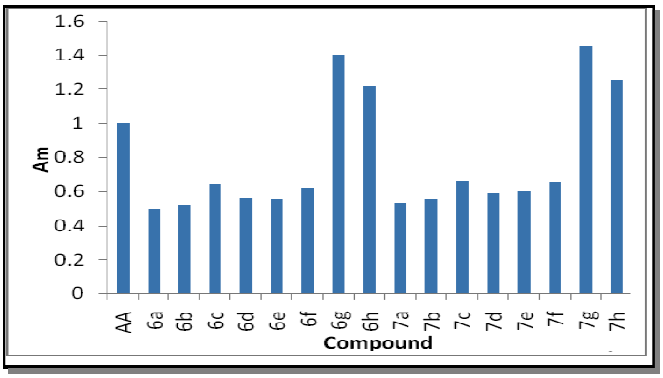

Figure-2. Antioxidant activities of novel heterocyclic derivatives relative to ascorbic acid (*Am*– activity relative to ascorbic acid (AA) on a molar basis)

3. RESULTS AND DISCUSSION

3.1 Chemistry

The Novel heterocyclic compounds were prepared starting from 4-((1H-benzo[d] [1,2,3] triazol-1-yl)methylamino)benzohydrazide **(4)** derivative. In the first step, the hydrazide **(4)** derivative was synthesized by the Mannich reaction of Benzotriazole, formaldehyde and ethyl-4-amino benzoate(22-26).Then compound **(4)** was condensed with

various aromatic aldehyde **(5a-h)** gives 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-arylidene benzo hydrazide **(6a-h),** which were then reacted with thioglycolic acid in the presence of anhydrous $ZnCl_2$ to afford the new 4-thiazolidinone derivatives **(7a-h)**.

The structures of the new compounds were assigned on the basis of their analytical and spectral data. Compounds **(7a-h)** display in their 1H-NMR spectra, in addition to other signals, doublets at δ 3.85,3.98 of $COCH_2S$ ppm due to the HA and HB system.

Characteristic C=O bands appeared in the 1690 cm^{-1} region in the FT-IR spectra of the thiazolidinones **(7a-h)**. Although the new compounds have stereogenic centers, we were not able to separate the diastereomers due to their similar Rf values.

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.

3.2 Antimicrobial activity

Compounds (**6a-h and 7a-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 **7g,7e, 7c,6g,6e and 6c** were found to display considerable activity against all the bacteria, whereas compounds **7g and 6g** were found to exhibit promising activity against ***B.subtilis*** and **7h and 6h** shows good activity against ***E.coli***. The compounds **7f and 6f** were found to exhibit promising activity against *K.promioe* and *S.aureus*. The compounds 7a-h and 6a-h exhibited almost moderate to less antifungal activity.

3.3 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: $2,5(OH)_2$ (**7g)**> $2,5(OH)_2$ (**6g)**> $2,3(OH)_2$ (**7h)**> $2,3(OH)_2$ (**6h)**> 2-OH (**7c)**> 2-Cl (**7f)**> 2-OH (**6c)**> 2-Cl (**6f)**> $4\text{-}OCH_3$ (**7e)**>4-OH (**7d)**> 4-OH (**6d)**> $2\text{-}CH_3$ (**7b)**> $4\text{-}OCH_3$ (**6e)**>H(**7a)**> $2\text{-}CH_3$(**6b)**>H(**6a).**Among the all the synthesized compounds 7g,6g,7h and 6h 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 7d,6d, 7c and 6c 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 7**g** shows the greatest antioxidant activity of all investigated compounds, followed by the **6g,** both having $2,5\text{-}(OH)_2$ substituents on phenyl ring**,** which is in accordance with the results of Lin et al. (Lin *et al*.,2008) who reported correlation of radical-scavenging effects of thiazolidine with the number of hydroxyl groups.

4. CONCLUSIONS

In this study a series of Novel heterocyclic compounds, 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(4-oxo-2-aryl thiazolidin-3-yl) benzamide **(7a-h)** were synthesized and evaluated for their in-vitro antimicrobial and antioxidant activity. Which contains 1,3-thiazolidine-4-one derivatives with the benzotriazole moiety were synthesized by cyclocondensation of the Schiff's bases 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N'-

arylidene benzo hydrazide **(6a-h)** and mercapto acetic acid. 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 promioe*. 4-((1H-benzo[d][1,2,3]triazol-1-yl)methylamino)-N-(4-oxo-2-aryl thiazolidin-3-yl) benzamide **(7a-h)** showed good antibacterial activities.

1,3-thiazolidine-4-ones (7**g,7h**) and Schiff's bases (**6g,6h**) 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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