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Synthesis, spectral investigation and biological evaluation of novel hydrazones derivative of substituted 1,2-dihydropyrimidine ring

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ABSTRACT

In this study, 6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carbohydrazide (2) was synthesized by facile and fast procedure using ethyl 6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (1) with hydrazine, which further underwent condensation with various aromatic aldehydes to afford N'-benzylidene-6-methyl-2-oxo-4-phenyl-1,2-dihydro pyrimidine-5-carbohydrazide (3a-h). Compounds (3a-h) were used as precursor for the preparation of various 6-methyl-2-oxo-N-(4-oxo-2-phenylthiazolidin-3-yl)-4-phenyl-1,2-dihydro pyrimidine-5-carboxamide (4a-h). All synthesized compounds were characterized by various spectroscopic techniques and screened for their in-vitro antimicrobial activity. Also MIC (Minimum inhibitory concentration) values of these compounds were determined. The investigation of antimicrobial screening data revealed that most of the compounds tested have demonstrated congruent activity. In summary, preliminary results indicate that, the compounds 3g, 3f, 4g and 4f found to possess better antibacterial activity than Tetracycline (Reference standard) in MIC also compounds 3g ,4e.4f and 4g found to possess better antifungal activity against Trichphyton longifusus and Candida glabrata than Miconazole (Reference standard).

Keywords: Antimicrobial activity; Substituted acetohydrazides; Spectral studies.

INTRODUCTION

Small heterocyclic ring containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal properties. In recent scenario heterocyclic compounds play an important role in various drug synthesis. Pyrimidine moiety is an important class of nitrogen containing heterocycles and is widely used as a key building block for pharmaceutical agents [1]. Literature survey reviewed that, 3,4-dihydropyrimidin-2(1H)-ones have attracted considerable interest in recent years because of their therapeutic and pharmacological properties. Several of them have been found to exhibit a wide spectrum of biological effects including antimicrobial [2], antitumor activity [3] , antiviral, anti-HIV [4,5], anti-inflammatory [6], antihypertensive agent, calcium channel blocker [7.8] analgesic[9], anti-cancer activity [10]. In addition, several marine natural products with interesting biological activities containing pyrimidine core have recently been isolated [11]. Most notably among these are the batzelladine alkaloids A and B which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy . Dihyropyrimidine is a bioisoster of Dihydropyridine which shows very good calcium channel blocking activity and antihypertensive activity.

4-thiazolidinones and its arylidene derivatives possess good pharmacological properties [12,13]. Also these compounds are known to exhibit antitubercular [14], antibacterial [15] and antifungal [16] activities. These heterocyclic systems find wide use in medicine, agriculture and industry. So in order to make effective biological drugs and having minimum of side effects it has been designed to make new derivatives of dihydropyrimidine-2-one having amide linkage. The pharmacological properties of 4-thiazolidinones encouraged our interest in synthesizing several new compounds featuring various heterocyclic rings, attached to 4-thiazolidinone moieties has not attracted

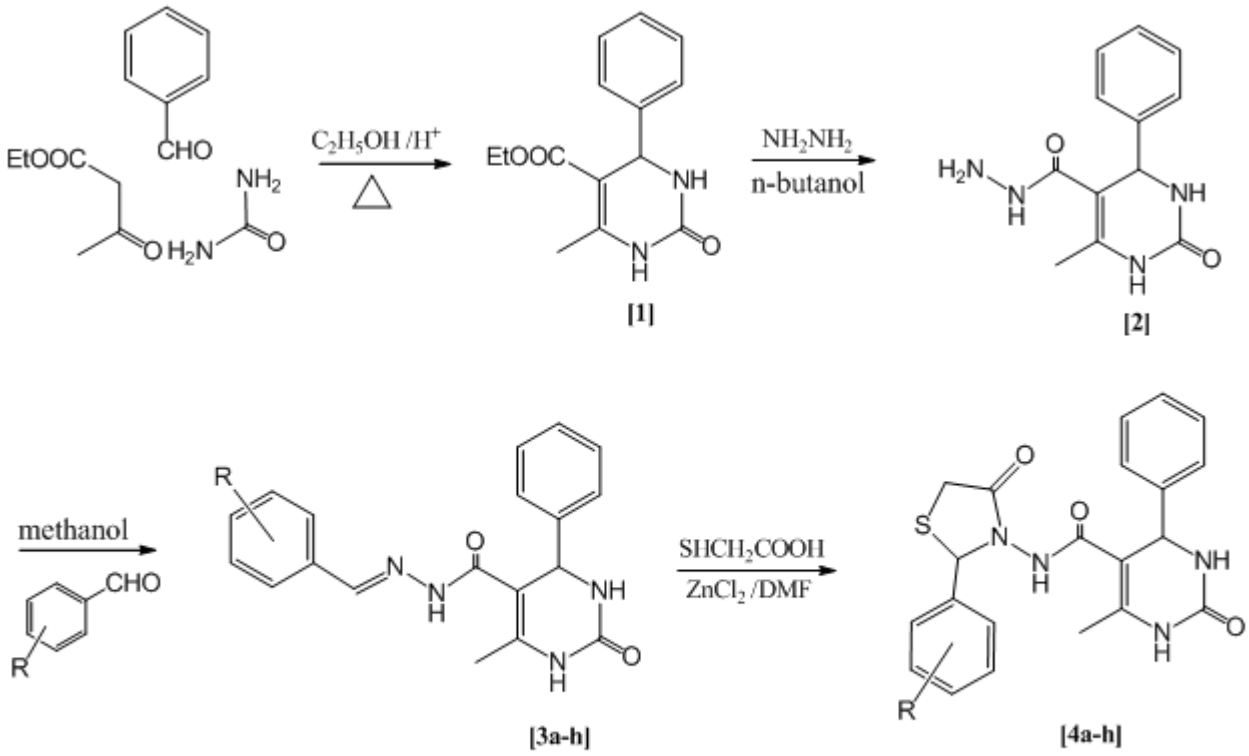
any attention. Hence, the work in this direction has been started. As a part of our aim to search for biologically active heterocycles containing sulfur and nitrogen, we have synthesized a series of 4-methyl-2-oxo-N-(4-oxo-2-phenylthiazolidin-3-yl)-6-phenylhexa hydropyrimidine-5-carboxamide and its derivatives (4a-h). The synthetic route is scan in scheme 1.

MATERIALS AND METHODS

All the chemicals and solvents used were of analytical grade and used directly, some of them are purified by reported methods [17]. The purity of all the synthesized compounds was checked by thin layer chromatography (TLC).

Measurements

Elemental analysis was carried out on a Thermofingan flash 1101EA (Italy). Infrared (IR) spectra of all the samples were scanned on a Nicolet-760 FTIR spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz Spectrometer (internal standard TMS) using DMSO-d_6 as the solvent. Antibacterial activity was studied against gram- negative and gram- positive bacteria e.g., Staphylococcus aureus (ATCC-25923), Bacillus subtilis (recultured), Escherichia coli (ATCC-25922), Pseudomonas picketti (recultured) and Micrococcus luteus (recultured). Plant pathogenic organisms used were Trichphyton longifusus, Candida albicans, Aspergillusflavus, Microsporum Canis, Fusarium Solani, Candida glabrata by using agar plate technique.



Scheme - 1

where R=(a)- C_6H_5, (b) 2-(-OCH_3-C_6H_4 (C)3,4-(OCH_3)$_2$-C_6H_3) (d) 4-0H-C_6H_4, (e) 4-0H-3-0CH_3.C_6H_3
(f) 3,4-(OC_2H_5)$_2$-C_6H_3 (g) 3,4- CH_2O_2-C_6H_3 (h) 2-OH-C_6H_4

Preparation of compound-(1): ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate

The (1) was prepared by method reported [18]. According to this method, A mixture of ethyl acetoacetate (0.15 mole, 19.7 gm, 99%), benzaldehyde (0.1 mole ,10.6 gm), Urea (0.1 mole, 6.0 gm) and in 250 ml ethanol was refluxed for 3 to 4 hours in presence of few drops of con.HCl. The mixture was frozen and the product was separated, filtered and dried. It was purified by column chromatography technique and recrystallized from ethanol.

Preparation of Compound-(2): 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide
An eqimolar mixture of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1) (0.01 mol) and hydrazine hydrate (0.01mol) was refluxed in 15 ml n-butanol for six hours. The solid separated was collected by filtration, dried, purified by column chromatography and recrystallized from ethanol, Color : Yellowish white; Yield : 83.32%; m.p. 187-188 ◦C; M Wt.: 248.28; Anal. calcd. for: $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57%; found :C 58.00,H 6.47, N22.55%; IR (νmax, KBr, cm^{-1}) : 3064(C-H str, aromatic), 2874 (C-H str,aliphatic),1594 (C=C, asymmetric str), 1488, 1468 (C=C str.ring),1228(C-N str), 748.6(C-H def, aromatic). 3378 (-$NHNH_2$), 1669 (>C=O of amide); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): (m, 5H,Ar-H = 7.22-7.41ppm) , (s, 3-H, CH_3 =2.3-2.73ppm), (4.18 s, 2H, -NH2), (7.67s,1H, -CONH-) ;^{13}C-NMR(400 MHz, DMSO-d6, δ / ppm): 14.1-CH_3)(158.2 c=o, urea), (126.9-128, benzene ring). (165.8 –NHCO).

General procedure for Preparation of 3a-h
An equimolar mixture of 4-methyl-2-oxo-6-phenylhexahydropyrimidine-5-carbohydrazide compound (2) (0.01mole/2.48gm) and the aromatic aldehydes (a-h) in ethanol (5 ml) were refluxed on a water bath for 2 hrs. The solid separated was collected by filtration, dried then it was purified by column chromatography technique and recrystallized from ethanol or chloroform.

Compound-3a: N'-benzylidene-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide; Color: Light green; Yield: 86.02%; m.p.: 222-226ºC; M.Wt.: 334.37; Anal. calcd. for $C_{19}H_{18}N_4O_2$: C 68.25, H 5.43, N 16.76% Found: C 67.89, H 5.41, N 16.73%; IR (KBr, cm^{-1}): 3340(-NH st.), 3064(C-H aromatic st.), 2874(C-H aliphatic st.), 1668(>C=O, amide), 1626 (-N=CH-), 1588(C=C, asymmetric st.), 1468-1482(C=C ring), 1335(-NH-); ^{1}H-NMR(400MHz, DMSO-d6, δ ppm): 5.38(s,1H, -N=CH-), 8.07 (s, 1H,-CONH-), 6.91-7.68 (m, 5H, Ar-H), 2.2-2.70 (s, 3H, CH3 =); ^{13}C-NMR(400 MHz, DMSO-d6, δ ppm): 168.8(RCOO-), 146.8(-N=CH-), 126 -128.5 (benzene ring). 166.8 (–NHCO).

Compound-3b: N'-(2-methoxy benzylidene)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbo - hydrazide; Color : Green; Yield : 88.08 %; m.p. 240-245ºC; M.Wt.: 364.40; Anal. calcd. for $C_{20}H_{20}N_4O_3$: C 65.92, H 5.53; N 15.38% found: C 65.88,H 5.50, N 15.34%;IR(KBr, cm^{-1}): 3350(-NH st.), 1345 (-NH-), 3068(C-H str. aromatic), 2830 (Ar-OCH3), 2874 (C-H str. aliphatic), 1672 (>C=O amide), 1632 (-N=CH-), 1594 (C=C asymmetric str.), 1488, 1473 (C=C str. ring), ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 5.36(s,1H, -N=CH-), 8.12 (s, 1H,-CONH-), 6.86-7.72 (m, 5H, Ar-H), 2.26(s,3H, -OCH_3); (s, 3-H, CH_3 =2.4-2.7ppm); ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm): 146.3(-N=CH-), 64.8(-OCH_3), 168.8(RCOO-),126 -128.5 (benzene ring).

Compound-3c: N'-(3,4-dimethoxy benzylidene)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbo - hydrazide; Color : Light brown; Yield : 89.54%; m.p. : 22-256ºC; M Wt.: 394.42; Anal. Calcd.for $C_{21}H_{22}N_4O_4$: C 63.95, H 5.62, N 14.20 %; found :C 63.92,H 5.58,N 14.17%; IR(KBr, cm-1): 3380,1337 (-NH-), 3062(C-H str. aromatic), 2880 (Ar-OCH_3), 2878 (C-H str. aliphatic), 1480, 1473 (C=C str.ring), 1684 (>C=O amide), 1639 (-N=CH-), 1625 (C=C asymmetric str.),^{1}H-NMR(400 MHz, DMSO-d6, δ / ppm), 5.36(s,1H, -N=CH-), 8.34 (s, 1H,-CONH-),7.20-7.72 (m, 5H, Ar-H), 2.46(s,3H, -(OCH_3)$_2$); (s, 3-H, CH_3 =2.4-2.7ppm). ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm): 146.3(-N=CH-), 64.8(-OCH_3). 168.8(RCOO-), (126 -128.5, benzene ring).

Compound-3d: N'-(4-hydroxy benzylidene)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbo - hydrazide; Color : Green; Yield : 75.01%; m.p. 230-234ºC; M Wt.: 350.37; Anal. Calcd.for $C_{19}H_{18}N_4O_3$: C 65.13, H, 5.18, N 15.99 %; found :C 65.10,H 5.16,N 15.97%; IR(KBr, cm-1): 3372, 1337(-NH-),3580 (ArOH), 1672 (>C=O, amide), 1634 (-N=CH-), ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 5.30(s,1H, -N=CH-), 8.10 (s, 1H,-CONH-), 6.80-7.72 (m, 4H, Ar-H),4.20(s,H, -OH); ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm): 166.8(RCOO-),148.3 (-N=CH-), (126.9 -130.5, benzene ring).

Compound-3e: N'-(4-hydroxy-3-methoxybenzylidene)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide; Color : Brown; Yield : 69.17%; m.p.241-246ºC; M Wt.: 380.40; Anal. Calcd.for $C_{20}H_{20}N_4O_4$: C 63.15, H 5.30, N 14.73 %; found:C 63.12,H 5.26,N 14.69%; IR(KBr, cm-1): 3380,1337 (-NH-), 3565 (ArOH), 1684 (>C=O amide), 1637 (-N=CH-),^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm) 5.62(s,1H, -N=CH-), 8.12 (s, 1H,-CONH-), 6.85-7.75(m, 3H, Ar-H), 3.75(s,3H, -OCH_3), 5.80(s, H,-OH), ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm):170.4(RCOO-), 160.3(-N=CH-),66.8(-OCH_3).

Compound-3f: N'-(3,4-diethoxy benzylidene)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbo - hydrazide; Color : Light brown; Yield : 89.54%; m.p. : 253-257ºC; MWt.: 422.48; Anal. Calcd.for $C_{23}H_{26}N_4O_4$; C 65.39, H 6.20, N 13.26%; Found:C 65.37,H 6.17,N 13.21%; IR(KBr, cm^{-1}): 3380,1337 (-NH-), 1678 (>C=O amide),

1639 (-N=CH-);^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 5.66(s,1H, -N=CH-), 8.12 (s, 1H,-CONH-), 6.85-7.75(m, 3H, Ar-H), 4.32(q,2H,-OCH2CH_3), 1.80(t,3H,-OCH2CH3); ^{13}C-NMR(400 MHz, DMSOd_6,δ / ppm) : 173.8 (RCOO-), 164.6 (-N=CH-).

Compound-3g: N'-(benzo[d][1,3]dioxol-5-ylmethylene)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide; Color : Brown; Yield : 87.12%; m.p. 230-234ºC, MWt.: 378.38; Anal. Calcd.for $C_{20}H_{18}N_4O_4$;C 63.48, H 4.79 N 14.81%;found:C 63.44,H 4.77,N 14.78%; IR(KBr, cm^{-1}): 3370, 1340 (-NH-), 1672 (>C=O amide), 1632 (-N=CH-); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 5.60(s,1H, -N=CH-), 8.15 (s, 1H,-CONH-), 7.12-7.75 (m, 3H, Ar-H), 6.25(s,2H, O-CH_2-O); ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm): 172.8(RCOO-),168.3(-N=CH-),116.5(O-CH_2-O).

Compound-3h: N'-(2-hydroxy benzylidene)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbo -hydrazide; Color : Light green; Yield : 80.18%; m.p. 234-236ºC; M Wt.: 350.37 ; Anal. Calcd.for $C_{19}H_{18}N_4O_3$;C, 65.13; H, 5.18; N, 15.99%;found: C 65.09,H 5.14, N 15.95%;IR(KBr, cm^{-1}): 3584 (Ar-OH), 3380,1337 (-NH-), 1682 (>C=O amide), 1638 (-N=CH-); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 5.38(s,1H, -N=CH-), 8.10 (s, 1H,-CONH-),6.95-7.72 (m, 4H, Ar-H), 4.38(s,H, -OH), ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm): 166.8(RCOO-), 160.3(-N=CH-).

General procedure for Preparation of 4a-h

A mixture of of N'-benzylidene N'-benzylidene-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (3a-h) (0.01 mole) in THF (30ml) and mercapto acetic acid (thioglycolic acid) [0.01 mole] with apinch of anhydrous ZnCl2 [0.05gm] was refluxed for 12 hrs. The solvent was then removed to get a residue, which was dissolved in pet-ether and passed through a column of silica gel using pet-ether: chloroform (6:4; v/v) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol to give 4-thiazolidinones (4a-h).

Compound-4a:6-methyl-2-oxo-N-(4-oxo-2-phenyl thiazolidin-3-yl)-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxamide, Color : White crystals; Yield : 86.12%; m.p. 204-208ºC; M Wt.: 408.47; Anal. Calcd.for $C_{21}H_{20}N_4O_3S$;C, 61.75; H, 4.94; N, 13.72; S, 7.85%;found: C 61.73,H 4.98,N 13.69,S7.84%;IR(KBr, cm^{-1}): 3378,1339 (-NH-),1720 (>C=O thiazolidinone), 1672(>C=O amide); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 8.33 (s, 1H, -CONH-), 6.95-7.75 (m,5H, Ar-H, 4.52 (s, 2H, -CH_2-thiazolidinone); (s, 3-H, CH_3 =2.28-2.70)ppm,^{13}C-NMR(400 MHz,DMSO-d_6, δ / ppm): 162.5 (>C=O, thiazolidinone), 172(>C=O, amide), 45.8 (-CH2-thiazolidinone).

Compound-4b:N-(2-(2-methoxy phenyl)-4-oxo thiazolidin-3-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro -pyrimidine-5-carboxamide;Color : White crystals; Yield : 75.22%; m.p. 210-214ºC ; M Wt.: 438.50; Anal. Calcd.for $C_{22}H_{22}N_4O_4S$; C 60.26, H 5.06, N 12.78,S 7.31%; found: C 60.22,H 5.06,N 12.75, S7.28%; IR(KBr, cm-1): 3290,1338 (-NH-), 2818 (Ar-OCH_3), 1726 (>C=O thiazolidinone),1668 (>C=O amide); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 8.53 (s, 1H, -CONH-), 6.65-7.77 (m, 4H, Ar-H), 4.26 (s, 2H, -CH2-thiazolidinone), 3.59 (s, 3H, -OCH3); ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm): 64.65(-OCH_3), 164.5 (>C=O, thiazolidinone), 168(>C=O, amide), 48.2 (-CH_2-,thiazolidinone), 61.45(-OCH_3).

Compound-4c: N-(2-(3,4-dimethoxy phenyl)-4-oxothiazolidin-3-yl)-6-methyl-2-oxo-4-phenyl -1,2,3,4-tetrahy -dropyrimidine-5-carboxamide; Color : White crystals; Yield : 78.45%; m.p. 196-198ºC; M Wt.: 468.53 ; Anal. Calcd.for $C_{23}H_{24}N_4O_5S$: C 58.96, H 5.16, N 11.96, S 6.84%; found :C 58.94,H 5.13,N 11.63,S 6.81%; IR(KBr, cm^{-1}): 3290, 1338 (-NH-), 2830 (Ar-OCH_3), 1728 (>C=O thiazolidinone), 1670(>C=O amide); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm):8.44 (s, 1H, -CONH-),7.15-7.88 (m, 3H, Ar-H), 4.57 (s, 2H, S-CH_2-), 3.49 (s, 3H, -OCH_3); ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm): 33.8 (-S-CH2-),169 (>C=O thiazolidinone), 166.2(>C=O amide), 63.45(-OCH3, 16.56(-CH_3).

Compound-4d: N-(2-(4-hydroxy phenyl)-4-oxothiazolidin-3-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro -pyrimidine-5-carboxamide; Color : White crystals; Yield : 70.33%; m.p. 174-178ºC; M Wt.: 424.47; Anal. Calcd.for $C_{21}H_{20}N_4O_4S$: C 59.42, H 4.75, N 13.20,S 7.55%; found:C 59.38,H 4.71,N 13.17,S 7.51%; IR(KBr, cm^{-1}): 3390, 1337 (-NH-), 3586 (Ar-OH), 1726(>C=O thiazolidinone), 1672 (>C=O amide); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 8.46 (s, 1H, -CONH-),7.28-7.90 (m, 4H, Ar-H), 4.60 (s, 2H,-CH_2-thiazolidinone), 8.26 (s, 1H,-OH), ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm): 30.5 (-S-CH_2-), 172 (>C=O thiazolidinone),167.2 (>C=O amide).

Compound-4e: N-(2-(4-hydroxy-3-methoxy phenyl)-4-oxo thiazolidin-3-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide; Color : White crystals; Yield : 69.22%; m.p. 164-166ºC; MWt.: 454.50; Anal.

Calcd.for $C_{22}H_{22}N_4O_5S$: C 58.14, H 4.88, N 12.33, S7.06%; found:C 58.11,H 4.85,N 12.29,S 7.06%;IR(KBr, cm^{-1}): 3285, 1340 (-NH-), 3582 (Ar-OH), 1722 (>C=O thiazolidinone),1668(>C=O amide); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 8.42 (s,1H, -CONH-), 7.20-7.90 (m, 3H, Ar-H), 4.63 (s, 2H, S-CH_2-), 3.82 (s,3H, -OCH_3), 6.82(s,H,-OH); ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm): 66.8(-OCH_3),33.8 (-SCH_2-),174(>C=O,thiazolidinone), 168.4(>C=O, amide),62.45(-OCH_3).

Compound-4f: N-(2-(3,4-diethoxyphenyl)-4-oxothiazolidin-3-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro -pyrimidine-5-carboxamide; Color : White crystals; Yield : 72.23%; m.p. 190-194ºC; M Wt.: 496.58; Anal. Calcd.for $C_{25}H_{28}N_4O_5S$:C 60.47, H 5.68, N 11.28, S 6.46%; found: C 60.44, H 5.64, N 11.85, S 645%;IR(KBr, cm^{-1}): 3280, 1336 (-NH-), 3590 (Ar-OH), 1726 (>C=O thiazolidinone), 1670(>C=O, amide); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 8.49 (s, 1H, -CONH-),7.30-7.90 (m, 3H, Ar-H), 5.32 (s, 1H, -N=CH-), 4.57 (s, 2H, S-CH_2-), 4.80 (q, 4H, -OCH2CH3),1.82(t,3H,-OCH_2CH_3); ^{13}C-NMR(400 MHz, DMSO-d_6, δ/ppm): 32.6 (-S-CH_2-), 172 (>C=O thiazolidinone), 167.2(>C=O,amide), 16.24(-CH=), 66.8(-CH_2-).

Compound-4g: N-(2-(benzo[d][1,3]dioxol-5-yl)-4-oxo thiazolidin-3-yl)-6-methyl-4-phenyl-1,2,3,4-tetrahydro -pyrimidine-5-carboxamide; Color : White crystals; Yield : 82.23%; m.p. 178-180ºC ; M Wt.: 438.50; Anal. Calcd.for $C_{22}H_{22}N_4O_4S$: C 60.26, H 5.06, N 12.78,S 7.31%; found: C 60.22, H 5.06, N 12.74,S7.28%; IR(KBr, cm^{-1}): 3288, 1335 (-NH-), 2364(-CH_2-O-CH_2-), 1724(>C=O thiazolidinone), 1670(>C=O amide); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 8.40 (s,1H, -CONH-), 7.18-7.90 (m, 3H, Ar-H),4.61 (s, 2H, S-CH_2-), 6.28 (s, 2H,O-CH_2-O); ^{13}C-NMR(400 MHz, DMSO-d_6, δ / ppm): 102.2(O-CH_2-O), 31.6 (-S-CH_2-), 173(>C=Othiazolidinone), 168 (>C=O amide).

Compound-4h: N-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide; Color : White crystals; Yield : 78.77%; m.p. 143-146ºC; M Wt.: 410.49; Anal. Calcd.for $C_{21}H_{22}N_4O_3S$: C 61.44, H 5.40, N 13.65, S 7.81%; found: C 61.41, H 5.37, N 13.62, S7.78%;IR(KBr, cm^{-1}): 3278,1338 (-NH-), 3587 (Ar-OH), 1722 (>C=O,thiazolidinone),1668(>C=O amide); ^{1}H-NMR(400 MHz, DMSO-d_6, δ / ppm): 8.48 (s, 1H, -CONH-), 7.20-7.90 (m, 4H, Ar-H), 4.58 (s, 2H, S-CH_2-), 4.78 (s, 1H, -OH); ^{13}CNMR(400 MHz, DMSO-d_6, δ / ppm): 32.2 (-S-CH_2-), 175 (>C=O, thiazolidinone), 167.6(amide, >C=O).

RESULTS AND DISCUSSION

Elemental analysis

The elemental analyses of all synthesized compounds are in good agreement with the proposed structures.

Spectral analysis

It was observed that, the IR spectra for compound (1) shows a strong an absorption band at 1722 for C=O cm-1 ester and 1HNMR spectra shows triplet-quartet pair at 1.35 and 4.28 ppm, it is indicate formation of compound (1); when ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4 tetrahydropyrimidine-5-carboxylate compound(1) on condensation with hydrazine hydrate gave 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (2) in good yield, and compound (2) was confirmed by elemental analysis and IR spectra showing an absorption band due to C=O of ester was disappeared and a new strong band at 1662 for C=O amide , it is indicated that respective amide formation take place, and also shows triplet-quartet pair at 1.35 and 4.28 ppm for ethoxy group was disappear and two singlet peaks at 4.22 s, for 2H, -NH2, and 7.67s,1H, for -CONH, shows the formation of amide with hydrazine take place .IR spectra for all (3a-h) compounds shows, the strong absorption band at 1626-1638 cm-1 for –N=CH- and disappearance of peak at 4.22 for free NH2 in 1HNMR spectra of compound (2) indicate to formation of Schiff's base. IR spectra for compounds (4a-h) shows that , the band at 1626-1638 cm-1 for –N=CH- was disappeared and new strong absorption band was appear at 1720-1728 cm-1, which indicate the formation of cyclic thiazolidinone ring (4a-h), also the formation of all(4a-h) was confirmed by 1HNMR spectra ~4.55 s for , 2H, -CH2-thiazolidinone, and in 13CNMR ,~163 for C=O of thiazolidinone.

Biological analysis

Antibacterial Activities.

All the newly synthesized compounds have been done in vitro for their antibacterial activity against gram- negative and gram- positive bacteria Staphylococcus aureus (ATCC-25923), Bacillus subtilis (recultured), Escherichia coli (ATCC-25922), Pseudomonas picketti (recultured) and Micrococcus luteus (recultured) at a concentration of 50µg/ml by agar well diffusion method [19]. DMSO was used as a control solvent. Under similar conditions Tetracycline was used as a standard drug for comparison. After 24 hr of incubation at 37°C, the zone of inhibition was measured in mm. The investigation on structure-activity relationship (SAR), showed that in general, the

presence of dioxale ring, 3,4-diethoxy group and 3-methoxy -4-hydroxy groups on benzene ring enhanced the antibacterial action ,showed in Table-1. The results showed that almost all sixteen compounds are active against bacteria some of them are highly active are shown in Table -1.

Table 1. Antibacterial activities and minimum inhibitory conc. (MIC)

Comp No.	EC (MIC)	PP (MIC)	BS (MIC)	SA (MIC)	MC (MIC)
3a	---	---	---	08.09 (0.8)	10.75 (0.8)
3b	11.05 (0.7)	9.30 (0.8)	---	---	---
3c	12.30 (0.7)	11.60 (0.8)	---	15.40 (0.8)	12.60 (0.8)
3d	13.45 (0.7)	---	12.05 (0.7)	---	---
3e	17.35 (0.7)	19.65 (0.8)	21.40 (0.7)	19.50	---
3f	16.68 (0.7)	15.05 (0.8)	---	17.55 (0.8)	13.30 (0.8)
3g	16.40 (0.7)	18.55 (0.8)	22.90 (0.7)	19.00 (0.8)	17.25 (.08)
3h	12.30 (0.7)	10.75 (0.8)	---	09.45 (0.8)	---
4a	08.25 (0.8)	---	05.65 (0.9)	07.35 (0.8)	---
4b	10.60 (0.8)	11.85 (1.0)	09.50 (0.9)	---	11.30 (1.0)
4c	13.75 (0.8)	11.65 (0.8)	---	15.85 (0.8)	13.40 (0.8)
4d	10.30 (0.8)	13.70 (1.0)	---	12.05 (0.8)	---
4e	18.50 (0.8)	16.30 (1.0)	15.55 (0.9)	17.80 (0.8)	16.05 (1.0)
4f	15.65 (0.8)	18.25 (0.8)	15.45 (0.9)	17.60 (0.8)	13.75 (1.0)
4g	17.78 (0.8)	20.40 (1.0)	22.60 (0.9)	19.25 (0.8)	17.20 (1.0)
4h	11.60 (0.8)	10.60 (1.0)	13.80 (0.9)	11.05 (0.8)	---
Tetracycline	14.00	18.46	23.50	17.85	15.00

***EC**: Escherichia Coli, **PP**: Pseudomonas picketti, **BS**: Bacillus Subtilis,**SA**: Staphylococcus aureus, **MC**: Micro coccluteus, **MIC:** Minimum Inhibitory Concentrations (mg/ml), ---: Not Active or Very minor active*

Antifungal Activities:

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were Trichphyton longifusus, Candida albicans, Aspergillusflavus, Microsporum Canis, Fusarium Solani, Candida glabrata by using agar plate technique [20], The percentage inhibition for fungi was calculated using the formula given below:

Percentage of inhibition = 100(X-Y) / X

Where, X = Area of colony in control plate
Y = Area of colony in test plate

Table 2. Antifungal activity of the newly synthesized compounds

Name of Fungi	Compd. No. and Inhibition Zones 1000 ppm (%)									Standard drug (%)
	3c	**3e**	**3f**	**3g**	**4c**	**4e**	**4f**	**4g**	**4h**	
Trichphyton longifusus	--	35	30	83	--	68	88	94	30	Miconazole (90)
Candida albicans	--	45	--	62	35	60	68	62	--	Miconazole (90)
Aspergillus flavus	34	--	42	45	--	54	76	45	43	Amphotericin (90)
Microsporum canis	--	34	58	58	42	74	44	58	--	Miconazole (90)
Fusarium solani	28	--	--	78	25	80	78	76	--	Miconazole (90)
Candida glabrata	--	52	--	86	--	88	93	88	24	Miconazole (90)

CONCLUSION

We have successfully synthesized N'-benzylidene-6-methyl-2-oxo-4-phenyl-1,2-di hydropyrimidine-5-carbohydrazide (3a-h) and various 6-methyl-2-oxo-N-(4-oxo-2-phenyl thiazolidin-3-yl)-4-phenyl-1,2-dihydro pyrimidine-5-carboxamide (4a-h). Compounds **3g, 3f, 4g and 4f** found to possess better antibacterial activity than its reference standard Tetracycline and in MIC also compounds **3g, 4e, 4f and 4g** found to possess better antifungal activity against Trichphyton longifusus and Candida glabrata than its reference standard Miconazole.

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