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Research Article

SYNTHESIS AND CHARACTERIZATION OF SOME HETEROFUSED PYRIMIDINE DERIVATIVES

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ABSTRACT

In the present study, a novel series of thiadiazole and thiazolidinone incorporated dihydropyrimidine derivatives (5a-5g) were synthesized starting from different aromatic aldehydes, ethylacetoacetate and urea. The structures of all synthesized compounds were characterized by melting point determination, TLC, elemental analysis, IR, HNMR, C-NMR and LCMS. The LCMS and ^{13}C NMR spectra were recorded only for title compounds.

***Keywords**: Thiadiazole , Thiazolidinone , Dihydropyrimidine .*

INTRODUCTION

The resistance toward available drugs is rapidly becoming a major worldwide problem. Now a day's most of the viruses, fungi, and bacteria exhibit multiple drug resistance and this phenomenon is becoming increasingly prevalent amongst human, animal and plant pathogens.

Infections from bacterial biofilms cause high health costs as well as economic loss in agriculture. Deaths from acute respiratory infections, diarrhoeal diseases, measles, AIDS, malaria and tuberculosis account for more than 85 % of the mortality from infections worldwide. Resistance to firstline drugs in most of the pathogens causing these diseases ranges from zero to almost 100%. Hence, the need to design new compounds to deal with this resistance has become one of the most important areas of research today.

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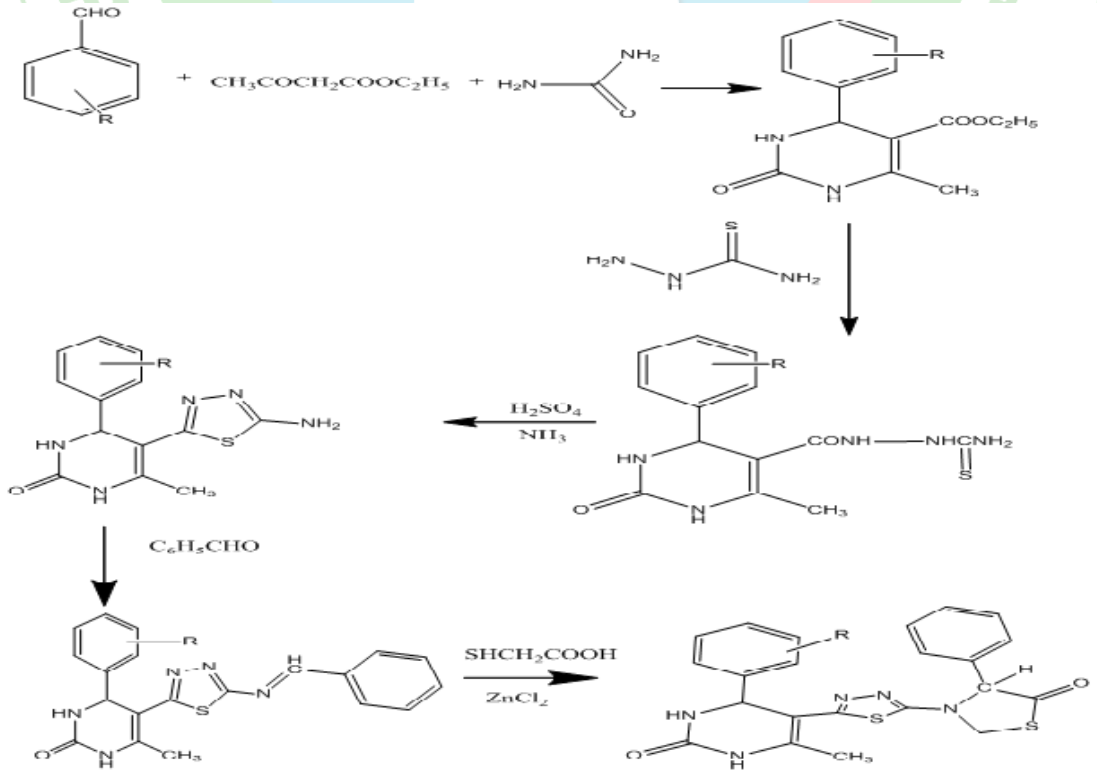
Pyrimidine derivatives and related fused heterocycles are important classes of heterocyclic compounds that exhibit a broad spectrum of biological activities such as anticancerous [1-3], antiviral [4], antibacterial [5], antioxidant [6], and anti-inflammatory[7]. The partially hydrogenated pyrimidine derivatives such as dihydropyrimidones and thiodihydropyrimidones have been used as key substrates to develop molecules as drug or potent leads in medicinal chemistry [8]. It was shown that substituted 1,3,4-thiadiazoles exhibit antimicrobial [9] and antitubercular [10-12] activities, while other compounds act on the CNS as anticonvulsants [13-14] or as antidepressant and anxiolitic [15] agents. 1,3,4-Thiadiazoles are thus a group of heterocycles whose derivatives are important in industry, medicine and agriculture [16-23]. Schiff bases form an important class of organic compounds with a variety of uses. Schiff bases were found to exhibit biological activities including antibacterial, antifungal and anti-inflammatory [24]. Moreover, Schiff

bases containing heterocycles have attracted much attention due to their diverse biological activity such as anticancerous, antiviral, fungicidal, bactericidal and anti- HIV [25]. Thiazolidin-4-one ring is a core substructure found in various synthetic pharmaceuticals which associate with diverse biological activities. A few of thiazolidine derivatives, for instance, pidotimod[26] and CGP52608[27] exhibited strong immunostimulating activity. Prompted by these literatures, it was planned to synthesize some novel dihydropyrimidine derivatives associated with thiadiazoles and thiazolidinone ring which has different potent pharmacophores and to explore their biological and pharmacological activities. Herein, the synthesis of some derivatives of some title structure compounds thiadiazoles and thiazolidinone ring moiety is reported in an attempt to significantly improve the biological spectrum of dihydropyrimidines. Overall 35 of compounds were synthesized which were subjected to spectral analysis for confirmation of structure.

EXPERIMENTAL

Thiadiazole and thiazolidinone incorporated dihydropyrimidine derivatives were synthesized as per Scheme 1 as below. The structure of synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, LCMS and elemental analysis. All chemicals were of AR grade (SD fine chemicals) and were procured from local market. Water used for present research was double distilled water. Thin layer chromatography (TLC) was performed on pre-coated silica gel G plates (Merck). IR absorption spectra were recorded on Bruker FT/ IR-470 PLUS, KBr diffuse reflectance (t_{max} in cm^{-1}), ^{1}H NMR and ^{13}C NMR spectra were recorded on the Bruker DPX-400 at 400 and 100 MHz, respectively. The ^{1}H and ^{13}C chemical shifts are reported as parts per million (ppm) downfield from TMS (Me_4Si). The LCMS of the compounds was recorded on Shimadzu 8201PC spectrometer. The LCMS and ^{13}C NMR spectra were recorded only for title compounds. The elemental analysis (CHN analysis) was performed on a CHN rapid analyzer. Compound 1(a-g) prepared as reported in the literature [28]. Target compounds were synthesized as outlined in Scheme 1.

Scheme:1



R= H(a); 2-NO_2(b); 4-NO_2(c); 3-NO_2(d); 4-OCH_3(e); 2-OH(f); 3-OH(g).

SYNTHESIS

Synthesis procedure for Step 1 compounds:
ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1a)

A mixture of benzaldehyde (1.06 gm, 10 mmol), urea (0.6 gm, 10 mmol), ethylaceto acetate (1.30 gm, 10 mmol) and phosphorus pentaoxide (0.5 gm, 3.54 mmol) in 250 ml round bottom flask were refluxed on water bath at 100 ^oC for 3 hours. The reaction mixture was cooled and poured into crushed ice. The separated solid was then filtered, washed with water, dried & recrystallized from ethanol. The completion of reaction was monitored by running T.L.C. Using solvent system: n-hexane: ethyl acetate (6:4) as detecting reagent.

Compounds **(1b-1g)** were also prepared in the similar way with minor modification in refluxed time and reaction mixture.

The spectral data of step1 synthesized compounds are as follows:

1(a): ethyl 6-methyl-2-oxo-4pheny1-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR (KBr): v cm^{-1}, 3234.09, 3117.03, 2980, 2882, 1693, 1660, 1659, 1465.06, 1422.51, 1291, 1227.46, 1090, 780.92, 699.77; ^1H NMR (DMSO-d6) δ: 9.12 (s, 1H, -NH), 7.73 (s, 1H, -NH), 7.21-7.29 (m, 5H, Ar-H), 5.13 (s, 1H, -CH-), 3.93 (q, 2H, -OCH_2-),2.27 (s, 3H, -CH_3), 1.15 (t, 3H, -OCH_2CH_3); Anal. Calcd. for $C_{14}H_{16}N_2O_3$ (260.29): C, 64.60; H, 6.20; N, 10.76; found: C, 63.59; H, 6.05; N, 9.73.

1(b): ethyl 6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR (KBr): v cm^{-1}, 3373.09, 3187.53, 2975, 2873.89, 1663.09, 1660, 1569, 1542.06, 1539.51, 1353, 1307.46, 1130,1075, 783.92, 693.77; 1H NMR (DMSO-d6) δ: 8.15 (s, 1H, -NH), 7.63 (s, 1H, -NH), 7.11-7.43 (m, 4H, Ar-H), 3.98 (q, 2H, -OCH_2-),2.25 (s, 3H, -CH_3), 1.73 (t, 3H, -OCH_2CH_3); Anal. Calcd. for $C_{14}H_{15}N_3O_5$ (305.29): C, 55.08; H, 4.95; N, 13.76; found: C, 53.59; H, 5.05; N, 12.73.

1(c): ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR (KBr): v cm^{-1}, 3243.09, 3117.54, 2993, 2975.83, 1720.05, 1710, 1665, 1530.09, 1463.51, 1350, 1299.36, 1230,1089, 785.93, 699.78; 1H NMR (DMSO-d6) δ: 9.25 (s, 1H, -NH), 8.19 (d, 2H, Ar-H), 7.83 (s, 1H, -NH), 7.45 (d, 2H, Ar-H), 5.29 (s, 1H, -CH-), 3.99 (q, 2H, -OCH_2-),2.27 (s, 3H, -CH_3), 1.23 (t, 3H, -OCH_2CH_3); Anal. Calcd. for $C_{14}H_{15}N_3O_5$ (305.29): C, 55.08; H, 4.95; N, 13.76; found: C, 53.59; H, 5.05; N, 12.73.

1(d): ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR (KBr): v cm^{-1}, 3441.15, 3237.53, 2973, 2799.93, 1699.95, 1663, 1615, 1531.05, 1451.50, 1353, 1297.33, 1230,1087, 735.93, 697.77; 1H NMR (DMSO-d6) δ: 9.33 (s, 1H, -NH), 7.77 (s, 1H, -NH), 7.61-8.17 (m, 4H, Ar-H), 5.39 (s, 1H, -CH-), 4.01 (q, 2H, -OCH_2-), 2.29 (s, 3H, -CH_3), 1.17 (t, 3H, -OCH_2CH_3); Anal. Calcd. for $C_{14}H_{15}N_3O_5$ (305.29): C, 55.08; H, 4.95; N, 13.76; found: C, 53.59; H, 5.05; N, 12.73.

1(e): ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate

IR (KBr): v cm^{-1}, 3230.19, 3120.43, 2960, 2879.69, 1719.99, 1689, 1615, 1510.89, 1458.53, 1289.31, 1229, 1093, 789.91, 665.57; 1H NMR (DMSO-d6) δ: 9.10 (s, 1H, -NH), 7.63 (s, 1H, -NH), 6.85-7.13 (m, 4H, Ar-H), 5.19 (s, 1H, -CH-), 3.99 (q, 2H, -OCH_2-), 3.71 (s, 3H, -OCH_3), 2.25 (s, 3H, -CH_3), 1.13 (t, 3H, -OCH_2CH_3); Anal. Calcd. for $C_{15}H_{18}N_2O_4$ (290.31): C, 62.06; H, 6.25; N, 9.65; found: C, 61.09; H, 6.19; N, 9.73.

1(f): ethyl 4-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR (KBr): v cm^{-1}, 3323.17, 3190.23, 2985, 2975.39, 1721.89, 1610, 1569.09, 1513.89, 1459.33, 1287.35, 1257,1173, 1090, 766.91,

613.53; 1H NMR (DMSO-d6) δ: 10.19 (s, 1H, -OH), 9.60 (s, 1H, -NH), 9.12 (s, 1H, -NH), 6.73-7.21 (m, 4H, Ar-H), 4.59 (s, 1H, -CH-), 4.13 (q, 2H, $-OCH_2-$), 1.73 (s, 3H, $-CH_3$), 1.23 (t, 3H, $-OCH_2CH_3$); Anal. Calcd. for $C_{14}H_{16}N_2O_4$ (276.29): C, 60.86; H, 5.84; N, 10.14; found: C, 60.83; H, 5.73; N, 10.09.

1(g): ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR (KBr): v cm^{-1}, 3350.15, 3245.13, 3119, 2979.33, 1723.80, 1640,1610, 1449.99, 1427.59, 1311.33, 1230.15, 1090, 789.91, 709.53; 1H NMR (DMSO-d6) δ: 9.40 (s, 1H, -OH), 9.20 (s, 1H, -NH), 7.63(s, 1H, -NH),6.33-7.11(m, 4H, Ar-H),5.01(s, 1H, -CH-),4.09 (q, 2H, $-OCH_2-$),2.21 (s, 3H, $-CH_3$), 1.13 (t, 3H, $-OCH_2CH_3$); Anal. Calcd. for $C_{14}H_{16}N_2O_4$ (276.29): C, 60.86; H, 5.84; N, 10.14; found: C, 60.83; H, 5.73; N, 10.09.

Synthesis procedure for Step 2 compounds:

2-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonyl)hydrazinecarbothioamide 2(a)

A mixture of ethyl 6-methyl- 2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (2.60gm, 10 mmol) & thiosemicarbazide (0.91gm, 10mmol) were dissolved in sufficient amount of glacial acetic acid in 250ml round bottom flask. The reaction mixture was refluxed on water bath for 21 hours. The reaction mixture was cooled and poured into crushed ice. The separated solid was then filtered, washed with water, dried & recrystallized with ethanol. The completion of reaction was monitored by running T.L.C. Using solvent system: Benzene: ethylacetate (7:3) as detecting reagent.
The other compounds (2b-2g) were prepared by the same procedure with minor modification in refluxed time.

The spectral data of step 2 synthesized compounds are as follows:

2(a):2-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonyl)hydrazinecarbothioamide

IR (KBr): v cm^{-1}, 3378, 3234.09, 3117.03, 2980, 2882, 1724, 1660, 1659, 1465.06, 1422.51, 1291, 1227.46, 1090, 1070, 780.92, 699.77; 1H NMR (DMSO-d6) δ: 9.12 (s, 1H, -NH), 7.73 (s, 1H, -NH), 7.66 (s,1H, -CONH-), 7.21-7.29 (m, 5H, Ar-H), 4.17(s, 2H, $-NH_2$), 5.13 (s, 1H, -CH-), 2.27 (s, 3H, $-CH_3$); Anal. Calcd. for $C_{13}H_{15}N_5O_2S$ (305.36): C, 51.13; H, 4.95; N, 22.94; found: C, 50.59; H, 4.90; N, 22.70.

2(b): 2-(6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)hydrazinecarbothioamide

IR (KBr): v cm^{-1}, 3378, 3373.09, 3187.53, 2975, 2873.89,1724, 1660, 1569, 1542.06, 1539.51, 1353, 1307.46, 1130, 1069,1075, 783.92, 693.77; 1H NMR (DMSO-d6) δ: 8.15 (s, 1H, -NH), 7.65 (s,1H, -CONH-), 7.63 (s, 1H, -NH), 7.11-7.43 (m, 4H, Ar-H), 4.15 (s, 2H, $-NH_2$), 2.25 (s, 3H, $-CH_3$); Anal. Calcd. for $C_{13}H_{14}N_6O_4S$ (350.35): C, 44.57; H, 4.03; N, 23.99; found: C, 44.59; H, 4.05; N, 22.73.

2(c): 2-(6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)hydrazinecarbothioamide

IR (KBr): v cm^{-1}, 3377, 3243.09, 3117.54, 2993, 2975.83, 1723.05, 1710, 1530.09, 1463.51,1350,1299.36,230,1089,1071,785.93, 699.78; 1H NMR (DMSO-d6) δ: 9.25 (s, 1H, -NH), 8.19 (d, 2H, Ar-H), 7.83 (s, 1H, -NH), 7.66 (s,1H, -CONH-),7.45 (d, 2H, Ar-H),5.29 (s,1H,-CH-),4.16 (s, 2H, $-NH_2$), 2.27 (s, 3H, $-CH_3$); Anal. Calcd. for $C_{13}H_{14}N_6O_4S$ (350.35): C, 44.57; H, 4.03; N, 23.99; found: C, 44.59; H, 4.05; N, 22.73.

2(d):2-(6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)hydrazinecarbothioamide

IR (KBr): v cm^{-1}, 3379, 3441.15, 3237.53, 2973, 2799.93, 1725, 1663, 1615, 1531.05, 1451.50, 1353, 1297.33, 1230,1087, 1071.05, 735.93, 697.77; 1H NMR (DMSO-d6) δ: 9.33 (s, 1H, -NH), 7.77 (s, 1H, -NH), 7.65 (s,1H, -CONH-), 7.61-8.17 (m, 4H, Ar-H), 5.39 (s, 1H, -CH-), 4.17 (s, 2H, $-NH_2$), 2.29 (s, 3H, $-CH_3$); Anal. Calcd. for $C_{13}H_{14}N_6O_4S$ (350.35): C, 44.57; H,

4.03; N, 23.99; found: C, 44.59; H, 4.05; N, 22.73.

2(e): 2-(4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-terahydropyrimidine-5carbonyl)hydrazinecarbothioamide

IR (KBr): v cm^{-1}, 3378.78, 3230.19, 3120.43, 2960, 2879.69, 1727, 1719.99, 1615, 1510.89, 1458.53, 1289.31, 1229, 1093, 1073.90, 789.91, 665.57; 1H NMR (DMSO-d6) δ: 9.10 (s, 1H, -NH), 7.65 (s,1H, -CONH-),7.63 (s, 1H, -NH), 6.85-7.13 (m, 4H, Ar-H), 5.19 (s, 1H, -CH-), 4.19 (s, 2H, $-NH_2$), 3.71 (s, 3H, $-OCH_3$), 2.25 (s, 3H, $-CH_3$),; Anal. Calcd. for $C_{14}H_{17}N_5O_3S$ (335.38): C, 50.14; H, 5.11; N, 20.88; found: C, 50.11; H, 5.09; N, 20.55.

2(f): 2-(4-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-terahydropyrimidine-5carbonyl)hydrazinecarbothioamide

IR (KBr): v cm^{-1}, 3377.69, 3323.17, 3190.23, 2985, 2975.39, 1725, 1721.89, 1569.09, 1513.89, 1459.33, 1287.35, 1257,1173, 1090, 1072, 766.91, 613.53; 1H NMR (DMSO-d6) δ: 10.19 (s, 1H, -OH), 9.60 (s, 1H, -NH), 9.12 (s, 1H, -NH), 7.68 (s,1H, -CONH-), 6.73-7.21 (m, 4H, Ar-H), 4.59 (s, 1H, -CH-), 4.17 (s, 2H, $-NH_2$), 1.73 (s, 3H, $-CH_3$); Anal. Calcd. for $C_{13}H_{15}N_5O_3S$ (321.35): C, 48.59; H, 4.70; N, 21.79; found: C, 48.50; H, 4.63; N, 21.69.

2(g): 2-(4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4- terahydropyrimidine-5carbonyl)hydrazinecarbothioamide

IR (KBr): v cm^{-1}, 3375, 3350.15, 3245.13, 3119, 2979.33, 1728, 1723.80, 1610, 1449.99, 1427.59, 1311.33, 1230.15, 1090, 1075.05, 789.91, 709.53; 1H NMR (DMSO-d6) δ: 9.40 (s, 1H, -OH), 9.20 (s, 1H, -NH), 7.67 (s,1H, -CONH-), 7.63(s, 1H, -NH), 6.33-7.11(m, 4H, Ar-H),5.01(s, 1H, -CH-), 4.15 (s, 2H, $-NH_2$), 2.21 (s, 3H, $-CH_3$); Anal. Calcd. for $C_{13}H_{15}N_5O_3S$ (321.35): C, 48.59; H, 4.70; N, 21.79; found: C, 48.50; H, 4.63; N, 21.69.

Synthesis procedure for Step 3 compounds:

5-(5-amino-1,3,4-thiadiazol-2-yl)-6-methyl-4-phenyl1-3,4-dihydropyrimidin-2(1H)-one

Hydrazinecarbothioamide **2(a-g) (**0.01mol) was dissolved in 4 ml Conc. H_2SO_4. The solution was stirred at room temp. for 1 hr. and left overnight. It was then poured on crushed ice. The resulting suspention was kept in ammonical water for 2 hr., solid obtained was filtered and recrystallised from ethanol. The completion of reaction was monitored by running T.L.C. Using solvent system: chloroform: methanol: acetic acid (6:3:1) as detecting reagent.
The other compounds **(3b-3g)** were prepared by the same procedure with minor modification in refluxed time.

The spectral data of step 3 synthesized compounds are as follows:

3(a):5-(5-amino-1,3,4-thiadiazol-2-yl)-6-methyl-4-phenyl1-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3234.09, 3117.03, 2980, 2882, 1660, 1659, 1643, 1465.06, 1422.51, 1227.46, 1090, 780.92, 711, 699.77; 1H NMR (DMSO-d6) δ: 9.12 (s, 1H, -NH), 7.73 (s, 1H, -NH), 7.21-7.29 (m, 5H, Ar-H), 4.16 (s, 2H, $-NH_2$), 5.13 (s, 1H, -CH-), 2.27 (s, 3H, $-CH_3$); Anal. Calcd. for $C_{13}H_{13}N_5OS$ (287.34): C, 54.34; H, 4.56; N, 24.37; found: C, 54.29; H, 4.27; N, 24.23.

3(b):5-(5-amino-1,3,4-thiadiazol-2-yl)-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3373.09, 3187.53, 2975, 2873.89, 1660, 1643, 1569, 1542.06, 1539.51, 1353, 1307.46, 1075, 783.92,715, 693.77; 1H NMR (DMSO-d6) δ: 8.15 (s, 1H, -NH), 7.63 (s, 1H, -NH), 7.11-7.43 (m, 4H, Ar-H), 4.14 (s, 2H, $-NH_2$), 2.25 (s, 3H, $-CH_3$); Anal. Calcd. for $C_{13}H_{12}N_6O_3S$ (332.34): C, 46.98; H, 3.64; N, 25.29; found: C, 46.59; H, 3.44; N, 25.23.

3(c):5-(5-amino-1,3,4-thiadiazol-2-yl)-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3243.09, 3117.54, 2993, 2975.83, 1720.05, 1665, 1645, 1530.09, 1463.51, 1350, 1230,1089, 785.93,733, 699.78; 1H NMR (DMSO-d6) δ: 9.25 (s, 1H, -NH), 8.19 (d, 2H, Ar-H), 7.83 (s, 1H, -NH), 7.45 (d, 2H, Ar-H),

5.29 (s, 1H, -CH-),4.13 (s, 2H, -NH_2), 2.27 (s, 3H, -CH_3); Anal. Calcd. for $C_{13}H_{12}N_6O_3S$ (332.34): C, 46.98; H, 3.64; N, 25.29; found: C, 46.59; H, 3.44;N,25.23.

3(d):5-(5-amino-1,3,4-thiadiazol-2-yl)-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3441.15, 3237.53, 2973, 2799.93, 1663,1643, 1615, 1531.05, 1451.50, 1353, 1230, 1087, 719, 735.93, 697.77; 1H NMR (DMSO-d6) δ: 9.33 (s, 1H, -NH), 7.77 (s, 1H, -NH), 7.61-8.17 (m, 4H, Ar-H), 5.39 (s, 1H, -CH-), 4.19 (s, 2H, -NH_2), 2.29 (s, 3H, -CH_3); Anal. Calcd. for $C_{13}H_{12}N_6O_3S$ (332.34): C, 46.98; H, 3.64; N, 25.29; found: C, 46.59; H, 3.44;N,25.23.

3(e):5-(5-amino-1,3,4-thiadiazol-2-yl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3230.19, 3120.43, 2960, 2879.69, 1719.99, 1632, 1615, 1510.89, 1458.53, 1229, 1093, 789.91, 733, 665.57; 1H NMR (DMSO-d6) δ: 9.10 (s, 1H, -NH), 7.63 (s, 1H, -NH), 6.85-7.13 (m, 4H, Ar-H), 5.19 (s, 1H, -CH-), 4.17 (s, 2H, -NH_2), 3.71 (s, 3H, -OCH_3), 2.25 (s, 3H, -CH_3); Anal. Calcd. for $C_{14}H_{15}N_5O_2S$ (317.37): C, 52.98; H, 4.76; N, 22.07; found: C, 52.49; H, 4.88; N, 22.13.

3(f):5-(5-amino-1,3,4-thiadiazol-2-yl)-4-(2-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3323.17, 3190.23, 2985, 2975.39, 1643, 1610, 1569.09, 1513.89, 1459.33, 1257,1173, 1090, 766.91, 743, 613.53; 1H NMR (DMSO-d6) δ: 10.19 (s, 1H, -OH), 9.60 (s, 1H, -NH), 9.12 (s, 1H, -NH), 6.73-7.21 (m, 4H, Ar-H), 4.59 (s, 1H, -CH-),4.13 (s, 2H, -NH_2), 1.73 (s, 3H, -CH_3); Anal. Calcd. for $C_{13}H_{13}N_5O_2S$ (303.34): C, 51.47; H, 4.32; N, 23.09; found: C, 51.30; H, 4.29; N, 23.15.

3(g):5-(5-amino-1,3,4-thiadiazol-2-yl)-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3350.15, 3245.13, 3119, 2979.33, 1640, 1610, 1599, 1449.99, 1427.59, 1230.15, 1090, 789.91,738, 709.53; 1H NMR (DMSO-d6) δ: 9.40 (s, 1H, -OH), 9.20 (s, 1H, -NH), 7.63(s, 1H, -NH),6.33-7.11(m, 4H, Ar-H),5.01(s, 1H, -CH-), 4.19 (s, 2H, -NH_2), 2.21 (s, 3H, -CH_3); Anal. Calcd. for $C_{13}H_{13}N_5O_2S$ (303.34): C, 51.47; H, 4.32; N, 23.09; found: C, 51.30; H, 4.29; N, 23.15.

Synthesis procedure for Step 4 compounds:

5-(5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one 4(a)

The compound **3(a-g)** (0.01 mol) was dissolved in ethanol (100 ml), sodium acetate (0.02 mol), benzaldehyde (2.1 ml) and two drops of conc. sulphuric acid was added and the reaction mixture was heated under reflux for 16 hr. The excess of solvent was distilled-off under reduced pressure. The residue so obtained was washed with dry diethyl ether and recrystallized from methanol. The completion of reaction was monitored by running T.L.C. Using solvent system: chloroform: methanol: (6:4) as detecting reagent.

Similarly, all the compounds **(4 b-4g)** were prepared by adopting same procedure.

The spectral data of step 4 synthesized compounds are as follows:

4(a): 5-(5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3234.09, 3117.03, 2980, 2882, 1660, 1659, 1643, 1544, 1465.06, 1422.51, 1227.46, 1090, 780.92, 711, 699.77; 1H NMR (DMSO-d6) δ: 9.12 (s, 1H, -NH), 7.73 (s, 1H, -NH), 7.69 (s,1H,-CH=N-), 7.21-7.29 (m, 5H, Ar-H), 5.13 (s, 1H, -CH-), 2.27 (s, 3H, -CH_3); Anal. Calcd. for $C_{20}H_{17}N_5OS$ (375.45): C, 63.98; H, 4.56; N, 18.65; found: C, 63.78; H, 4.27; N, 18.57.

4(b):5-(5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3373.09, 3187.53, 2975, 2873.89, 1660, 1643, 1619, 1569, 1542.06, 1539.51, 1353, 1307.46, 1075, 783.92,715,

693.77; 1H NMR (DMSO-d6) δ: 8.15 (s, 1H, -NH), 7.71 (s,1H,-CH=N-), 7.63 (s, 1H, -NH), 7.11-7.43 (m, 4H, Ar-H), 2.25 (s, 3H, -CH_3); Anal. Calcd. for $C_{20}H_{16}N_6O_3S$ (420.44): C, 57.13; H, 3.84; N, 19.99; found: C, 57.09; H, 3.44; N, 19.70.

4(c):5-(5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3243.09, 3117.54, 2993, 2975.83, 1720.05, 1665, 1645, 1550.78, 1530.09, 1463.51, 1350, 1230,1089, 785.93,733, 699.78; 1H NMR (DMSO-d6) δ: 9.25 (s, 1H, -NH), 8.19 (d, 2H, Ar-H), 7.83 (s, 1H, -NH), 7.73 (s,1H,-CH=N-), 7.45 (d, 2H, Ar-H), 5.29 (s, 1H, -CH-), 2.27 (s, 3H, -CH_3); Anal. Calcd. for $C_{20}H_{16}N_6O_3S$ (420.44): C, 57.13; H, 3.84; N, 19.99; found: C, 57.09; H, 3.44; N, 19.70.

4(d):5-(5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3441.15, 3237.53, 2973, 2799.93, 1663,1643, 1615, 1579, 1531.05, 1451.50, 1353, 1230, 1087, 719, 735.93, 697.77; 1H NMR (DMSO-d6) δ: 9.33 (s, 1H, -NH), 7.77 (s, 1H, -NH), 7.72 (s,1H,-CH=N-), 7.61-8.17 (m, 4H, Ar-H), 5.39 (s, 1H, -CH-), 2.29 (s, 3H, -CH_3); Anal. Calcd. for $C_{20}H_{16}N_6O_3S$ (420.44): C, 57.13; H, 3.84; N, 19.99; found: C, 57.09; H, 3.44; N, 19.70.

4(e): 5-(5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3230.19, 3120.43, 2960, 2879.69, 1719.99, 1632, 1615, 1569.78, 1510.89, 1458.53, 1229, 1093, 789.91, 733, 665.57; 1H NMR (DMSO-d6) δ: 9.10 (s, 1H, -NH), 7.75 (s,1H,-CH=N-), 7.63 (s, 1H, -NH), 6.85-7.13 (m, 4H, Ar-H), 5.19 (s, 1H, -CH-), 3.71 (s, 3H, -OCH_3), 2.25 (s, 3H, -CH_3); Anal. Calcd. for $C_{21}H_{19}N_5O_2S$ (405.47): C, 62.21; H, 4.72; N, 17.27; found: C, 62.49; H, 4.88; N, 17.13.

4(f):5-(5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)-4-(2-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3323.17, 3190.23, 2985, 2975.39, 1643, 1610, 1599, 1569.09, 1513.89, 1459.33, 1257,1173, 1090, 766.91, 743, 613.53; 1H NMR (DMSO-d6) δ: 10.19 (s, 1H, -OH), 9.60 (s, 1H, -NH), 9.12 (s, 1H, -NH), 7.78 (s,1H,-CH=N-), 6.73-7.21 (m, 4H, Ar-H), 4.59 (s, 1H, -CH-), 1.73 (s, 3H, -CH_3); Anal. Calcd. for $C_{20}H_{17}N_5O_2S$ (391.45): C, 61.37; H, 4.38; N, 17.89; found: C, 61.30; H, 4.29; N, 17.75.

4(g):5-(5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one

IR (KBr): v cm^{-1}, 3350.15, 3245.13, 3119, 2979.33, 1640, 1610, 1599, 1565.90. 1449.99, 1427.59, 1230.15, 1090, 789.91,738, 709.53; 1H NMR (DMSO-d6) δ: 9.40 (s, 1H, -OH), 9.20 (s, 1H, -NH), 7.73 (s,1H,-CH=N-),7.63(s, 1H, -NH),6.33-7.11(m, 4H, Ar-H),5.01(s, 1H, -CH-), 2.21 (s, 3H, -CH_3); Anal. Calcd. for $C_{20}H_{17}N_5O_2S$ (391.45): C, 61.37; H, 4.38; N, 17.89; found: C, 61.30; H, 4.29; N, 17.75.

Synthesis procedure for Step 5 compounds:
6-methyl-5-[5-(5-oxo-4-phenyl-1,3-thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl]-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (5a)

A solution of **4**(**a-g**) **(**0.01mol) in DMF and mercaptoacetic acid (0.012 mol) was refluxed with a pinch of anhydrous $ZnCl_2$ for 10-14 hr. on a water bath. After completion of reaction, excess of DMF was distilled off. The resulting product was treated with 5% $NaHCO_3$ solution to remove unreacted mercaptoacetic acid. The separated product was washed with water, dried and recrystallized from DMF. The completion of reaction was monitored by running T.L.C.Using solvent system: ethylacetate:chloroform: (8:2) as detecting reagent.
Compound **(5b-5g)** was also prepared in a similar way with minor modification in refluxed time *etc*.

The spectral data of step 5 synthesized compounds are as follows:

5(a):6-methyl-5-[5-(5-oxo-4-phenyl-1,3-thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl]-4-phenyl-3,4- dihydropyrimidin-2(1*H*)-one

IR (KBr): v cm^{-1}, 3234.09, 3117.03, 2980, 2882, 1683, 1660, 1659, 1643, 1465.06, 1422.51, 1227.46, 1090, 780.92, 711, 699.77, 681; ^{1}H NMR (DMSO-d6) δ: 9.12 (s, 1H, -NH), 7.73 (s, 1H, -NH), 7.21-7.29 (m, 5H, Ar-H), 5.13 (s, 1H, -CH-), 4.63 (s, 1H, -CH), 2.27 (s, 3H, $-CH_3$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 195.5, 172.5, 157, 151.2, 143.1, 135.5, 129.5 (2C), 129.4 (2C) , 128.4 (2C), 127.4, 127.2, 126.8 (2C), 126.6, 113.4, 92.9, 60.7, 59.7, 14; LCMS m/z: $[M+1]^+$ 450.09, $[M]^+$ 449.09. Anal. Calcd. for $C_{22}H_{19}N_5O_2S_2$ (449.55): C, 58.78; H, 4.26; N, 15.58; found: C, 58.73; H, 4.29; N, 15.50.

5(b):6-methyl-5-[5-(5-oxo-4-phenyl-1,3-thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(2-nitrophenyl)-3,4- dihydropyrimidin-2(1*H*)-one

IR (KBr): v cm^{-1}, 3373.09, 3187.53, 2975, 2873.89,1693, 1660, 1643, 1569, 1542.06, 1539.51, 1353, 1307.46, 1075, 783.92,715, 693.77, 685; 1H NMR (DMSO-d6) δ: 8.15 (s, 1H, -NH), 7.63 (s, 1H, -NH), 7.11-7.43 (m, 4H, Ar-H), 4.73 (s, 1H, -CH), 2.25 (s, 3H, $-CH_3$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 195.5, 172.5, 157, 151.2, 147.1, 140.4, 135.5,130.7, 129.5 (2C), 129.4 (2C) , 127.7, 127.5, 127.4, 127.2, 113.4, 92.9, 60.7, 55.7, 14; LCMS m/z: $[M+1]^+$ 495.07, $[M]^+$ 494.06. Anal. Calcd. for $C_{22}H_{18}N_6O_4S_2$ (494.55): C, 53.43; H, 3.67; N, 16.99; found: C, 53.29; H, 3.64; N, 16.70.

5(c):6-methyl-5-[5-(5-oxo-4-phenyl-1,3-thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(4-nitrophenyl)-3,4- dihydropyrimidin-2(1*H*)-one

IR (KBr): v cm^{-1}, 3243.09, 3117.54, 2993, 2975.83, 1720.05, 1690, 1665, 1645, 1530.09, 1463.51,1350,1230,1089,785.93,733,705.98, 699.78; 1H NMR (DMSO-d6) δ: 9.25 (s, 1H, -NH), 8.19 (d, 2H, Ar-H), 7.83 (s, 1H, -NH), 7.45 (d, 2H, Ar-H), 5.29 (s, 1H, -CH-),4.83 (s, 1H, -CH), 2.27 (s, 3H, $-CH_3$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 195.5, 172.5, 157, 151.2, 149.2, 145.4, 135.5,130.7, 129.5 (2C), 129.4 (2C) , 128.3(2C), 127.2, 125.2(2C), 113.4, 92.9, 60.7, 59.7, 14; LCMS m/z: $[M+1]^+$ 495.07, $[M]^+$ 494.06. Anal. Calcd. for $C_{22}H_{18}N_6O_4S_2$ (494.55): C, 53.43; H, 3.67; N, 16.99; found: C, 53.29; H, 3.64; N, 16.70.

5(d):6-methyl-5-[5-(5-oxo-4-phenyl-1,3-thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one

IR (KBr): v cm^{-1}, 3441.15, 3237.53, 2973, 2799.93, 1715.65, 1663,1643, 1615, 1531.05, 1451.50, 1353, 1230, 1087, 735.93, 719, 685, 697.77; 1H NMR (DMSO-d6) δ: 9.33 (s, 1H, -NH), 7.77 (s, 1H, -NH), 7.61-8.17 (m, 4H, Ar-H), 5.39 (s, 1H, -CH-),4.89 (s, 1H, -CH), 2.29 (s, 3H, $-CH_3$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 195.5, 172.5, 157, 151.2, 147.6, 144.4,136.7, 133.5,129.7, 129.5 (2C), 129.3 (2C) , 127.5, 127.2, 121.7, 120.5, 113.4, 92.9, 60.7, 58.7, 14; LCMS m/z: $[M+1]^+$ 495.07, $[M]^+$ 494.06. Anal. Calcd. for $C_{22}H_{18}N_6O_4S_2$ (494.55): C, 53.43; H, 3.67; N, 16.99; found: C, 53.29; H, 3.64; N, 16.70.

5(e):6-methyl-5-[5-(5-oxo-4-phenyl-1,3-thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one

IR (KBr): v cm^{-1}, 3230.19, 3120.43, 2960, 2879.69, 1719.99, 1689, 1632, 1615, 1510.89, 1458.53, 1229, 1093, 789.91, 733, 683, 665.57; 1H NMR (DMSO-d6) δ: 9.10 (s, 1H, -NH), 7.63 (s, 1H, -NH), 6.85-7.13 (m, 4H, Ar-H), 5.19 (s, 1H, -CH-),4.75 (s, 1H, -CH), 3.71 (s, 3H, $-OCH_3$), 2.25 (s, 3H, $-CH_3$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 196.5, 172.9, 158.7, 158.5, 150.1, 135.7, 127.7,127.2, 129.5 (2C), 129.1 (2C) , 125.5(2C), 114.2(2C), 113.5, 93.3, 61.7, 59.6, 55.5, 13.9; LCMS m/z: $[M+1]^+$ 480.10, $[M]^+$ 479.09. Anal. Calcd. for $C_{23}H_{21}N_5O_3S_2$ (479.57): C, 57.60; H, 4.41; N, 14.60; found: C, 57.29; H, 4.44; N, 14.70.

5(f):6-methyl-5-[5-(5-oxo-4-phenyl-1,3-thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(2-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one

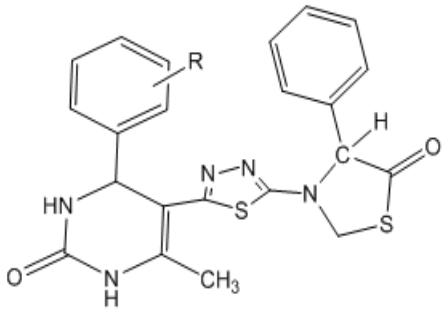
IR (KBr): v cm^{-1}, 3323.17, 3190.23, 2985, 2975.39, 1709, 1643, 1610, 1569.09, 1513.89, 1459.33, 1257,1173, 1090, 766.91, 743, 693.89, 613.53; 1H NMR (DMSO-d6) δ: 10.19 (s, 1H, -OH), 9.60 (s, 1H, -NH), 9.12 (s, 1H, -NH), 6.73-7.21 (m, 4H, Ar-H), 4.95 (s, 1H, -CH), 4.59 (s, 1H, -CH-), 1.73 (s, 3H, $-CH_3$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 196.4, 172.8, 158.7, 158.5, 154.1, 150.1, 136.7, 129.5 (2C), 129.1 (2C) , 128.2, 128, 127.7, 122.4, 121.2, 115.5, 93.7, 61.7, 59.6, 53.5, 14.8; LCMS m/z: $[M+1]^+$

466.09, $[M]^+$ 465.07. Anal. Calcd. for $C_{22}H_{19}N_5O_3S_2$ (465.55): C, 56.76; H, 4.11; N, 15.04; found: C, 56.79; H, 4.44; N, 15.10.

5(g):6-methyl-5-[5-(5-oxo-4-phenyl-1,3-thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl]-4-(3-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one

IR (KBr): v cm^{-1}, 3350.15, 3245.13, 3119, 2979.33, 1721, 1640, 1610, 1449.99, 1427.59, 1230.15, 1090, 789.91,738, 709.53, 689; 1H NMR (DMSO-d6) δ: 9.40 (s, 1H, -OH), 9.20 (s, 1H, -NH), 7.63(s, 1H, -NH),6.33-7.11(m, 4H, Ar-H),5.01(s, 1H, -CH-), 4.65 (s, 1H, -CH), 2.21 (s, 3H, $-CH_3$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 196.4, 172.9, 158.7, 156.5, 150.1, 144.6, 136.7, 129.8, 129.5 (2C), 129.1 (2C) , 127.7,127.2, 119.2, 113.5,112.5, 93.7, 61.7, 60.2, 14.9; LCMS m/z: $[M+1]^+$ 466.09, $[M]^+$ 465.07. Anal. Calcd. for $C_{22}H_{19}N_5O_3S_2$ (465.55): C, 56.76; H, 4.11; N, 15.04; found: C, 56.79; H, 4.44; N, 15.10.

Table: 1 Physico-chemical data of title compounds



Compound No.	Molecular formula	Molecular weight	R	Melting-range	Yield (%)	R_f
5 (a)	$C_{22}H_{19}N_5O_2S_2$	449.55	H	296-298	73	0.43
5 (b)	$C_{22}H_{18}N_6O_4S_2$	494.55	2-NO_2	333-339	70	0.23
5(c)	$C_{22}H_{18}N_6O_4S_2$	494.55	4-NO_2	345-347	56	0.21
5(d)	$C_{22}H_{18}N_6O_4S_2$	494.55	3-NO_2	310-313	64	0.31
5(e)	$C_{23}H_{21}N_5O_3S_2$	479.57	4-OCH_3	323-327	63	0.42
5(f)	$C_{22}H_{19}N_5O_3S_2$	465.55	2-OH	300-305	60	0.47
5(g)	$C_{22}H_{19}N_5O_3S_2$	465.55	3-OH	278-280	61	0.45

RESULTS AND DISCUSSION

The compounds were synthesized as per Scheme 1 and the structure was elucidated by physicochemical (Table 1) and spectroscopic data. IR, 1H-NMR, 13C-NMR and LCMS data for the synthesized compounds are reported in experimental protocols.

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