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SYNTHESIS AND CHARACTERIZATION OF NOVEL THIADIAZOLE AND THIAZOLIDINONE INCORPORATED DIHYDROPYRIMIDINE DERIVATIVES

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ABSTRACT

In the present study, a novel series of thiadiazole and thiazolidinone incorporated dihydropyrimidine derivatives were synthesized by treating Substituted aldehyde with ethylacetoacetate and urea to yield pyrimidine derivatives **(1)**, which on reaction with thiosemicarbazide followed by cyclization incorporated aminothiadiazole ring **(3)**. Compound **(3)** reacted with benzaldehyde to give Shiff bases **(4)** followed by reaction with thioglycollic acid to give title compound. The structures of all synthesized compounds were characterized by melting point determination, TLC, elemental analysis, IR, ^{1}H NMR, ^{13}C-NMR and LCMS.

Key words: Thiadiazole, Thiazolidinone, Dihydropyrimidine**,** Thiosemicarbazide.

INTRODUCTION

Pyrimidine derivatives and related fused heterocyclic are important classes of heterocyclic compounds that exhibit a broad spectrum of biological activities such as anticancerous[1-2], antiviral[3], antibacterial[4], antioxidant[5], and anti-inflammatory[6]. It was shown that substituted 1, 3, 4-thiadiazoles exhibit antimicrobial[7] and antitubercular[8] activities. 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[9] and CGP52608[10] 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.

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EXPERIMENTAL

Melting points of all synthesized compounds were taken in open capillaries and are uncorrected. IR spectra were recorded on Bruker FT-IR-470 PLUS, KBr diffuse reflectance (t_{max} in cm^{-1}) and ^1H NMR and ^{13}C NMR spectra were recorded on the Bruker DPX-400 at 400 and 100 MHz, respectively. The ^1H 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. All compounds gave satisfactory micro analytical results. Purity of the synthesized compound was checked by TLC using Silica gel-G Plates. Dihydropyrimidine derivatives **(1)** was prepared by reported method[11]. Target compounds were synthesized as outlined in **Scheme 1**.

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

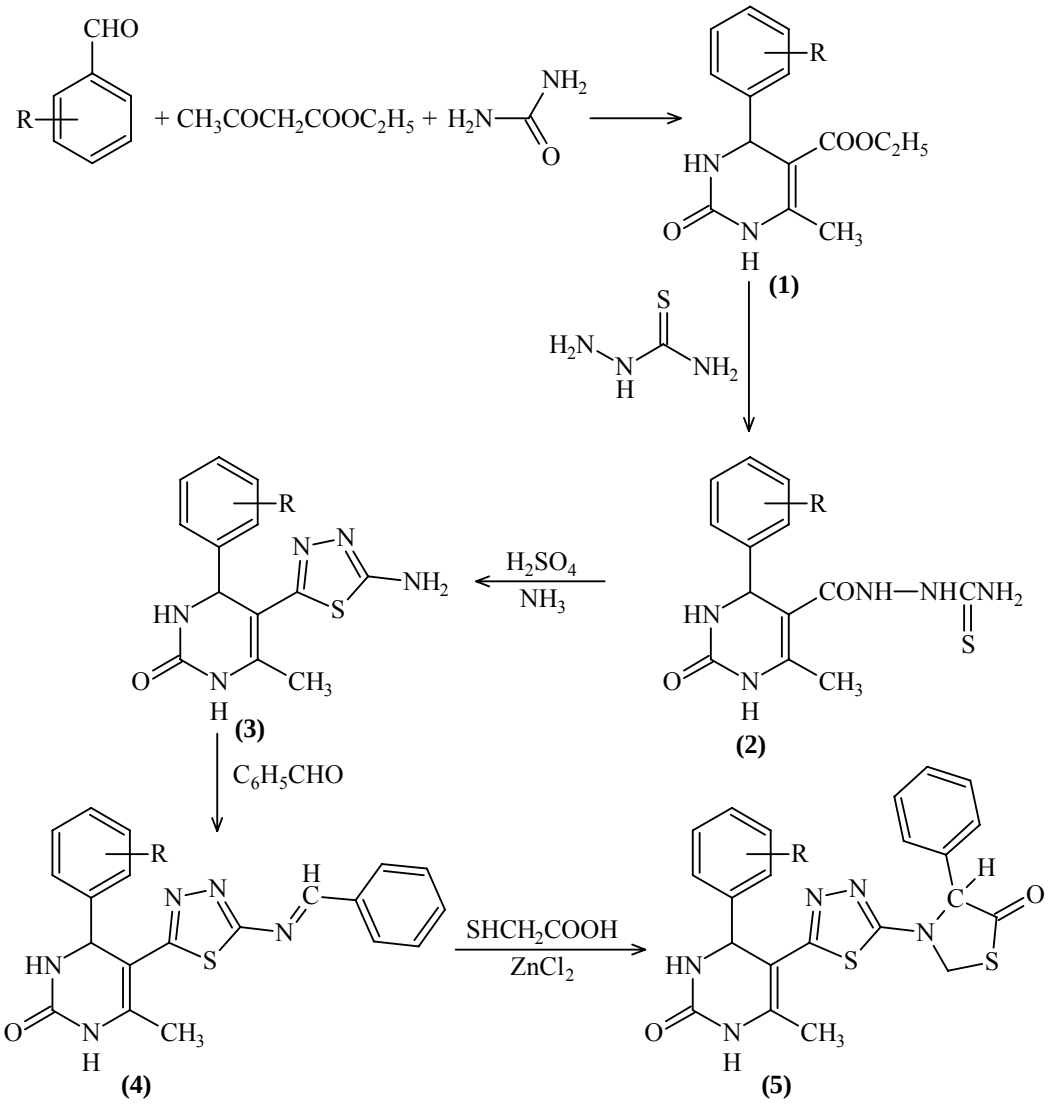
An equimolar mixture of compound **1** (0.01 mol) and thiosemicarbazide (0.01 mol) in glacial acetic acid were refluxed for 21 hrs and allow to cool to form a solid and it was recrystallized from alcohol. The completion of reaction was monitored by running T. L. C. using solvent system: Benzene: ethylacetate (7:3) as detecting reagent.

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, $-CH_3$).

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

Carbothioamide **2**. (0.01 mol) was dissolved in 5 mL conc. H_2SO_4. This solution was stirred at room temperature and left overnight. It was then poured into crushed ice. The resulting suspension was kept in ammonical water for 2 hrs, filtered and recrystallized from alcohol as white crystals. The completion of reaction was monitored by running T. L. C. using solvent system: chloroform: methanol: acetic acid (6:3:1) as detecting reagent.

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, $-CH_3$).



Scheme 1

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

The compound **3** (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.

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; ^{1}H 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).

Synthesis of 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(1H)-one (5)

A solution of **4 (**0.01 mol) 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.

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.

Table 1: Physico-chemical data of title compounds

Compd. No.	Molecular formula	Molecular weight	Melting-range (^{o}C)	Yield (%)	R_f
1	$C_{14}H_{16}N_2O_3$	260.29	203-206	74	0.26
2	$C_{13}H_{15}N_5O_2S$	305.36	242-247	80	0.25
3	$C_{13}H_{13}N_5OS$	287.34	275-279	66	0.21
4	$C_{20}H_{17}N_5OS$	375.45	310-313	64	0.31
5	$C_{22}H_{19}N_5O_2S_2$	449.55	323-327	63	0.27

RESULTS AND DISCUSSION

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

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