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Synthesis and Characterization of Some Benzylidinehydrazinyl Derivatives of Newer Pyrimidine-5-carbonitrile Moiety

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ABSTRACT

Condensation of 2-hydrazinyl-1,6-dihydro-1-methyl-6-oxo-4-isobutylpyrimidine-5-carbonitrile (3) with different aromatic aldehyde gave the corresponding 2-(Benzylidinehydrazinyl)-1,6-dihydro-6-oxo-4-isobutylpyrimidine-5-carbonitrile (4). The reaction between 1,6-dihydro-1-methyl-2-(methylthio)-6-oxo-4-isobutylpyrimidine-5-carbonitrile (2) with hydrazine hydrate furnished (3). The condensation of 1,2,3,4-tetrahydro-4-oxo-6-isobutyl-2-thioxopyrimidine-5-carbonitrile (1) with methyl iodide yielded 2. Finally the products were characterized by ^{1}H NMR, Mass and IR Spectra.

***Keyword*:** Cyanopyrimidine; Benzylidinehydrazinyl; Isovaleraldehyde

1. INTRODUCTION

Schiff bases are an important class of organic compounds. They were first prepared by German chemist Hugo Schiff [1]. These compounds are prepared by condensation of primary amine with compound containing an active carbonyl group & elimination of water molecule. The structural feature of these compounds are the azomethine group having the general formula RHC=N-R_1, where R and R_1 are alkyl, aryl, cycloalkyl, or heterocyclic groups. They are known to exhibit a broad range of biological activities including antifungal, antibacterial, antimalarial, anti-inflammatory, antiviral, and antipyretic properties [2,3]. Imine or azomethine group present in various natural and synthetic compounds has been found to be critical to their biological activities [4-6]. Schiff's bases are important compounds also owing to their wide range of industrial applications [7]. They are well known intermediates for synthesis of pharmacologically active heterocycles like oxadiazolines, imidazolinones, azetidinones, thiazolidinones [8] and many other derivatives.

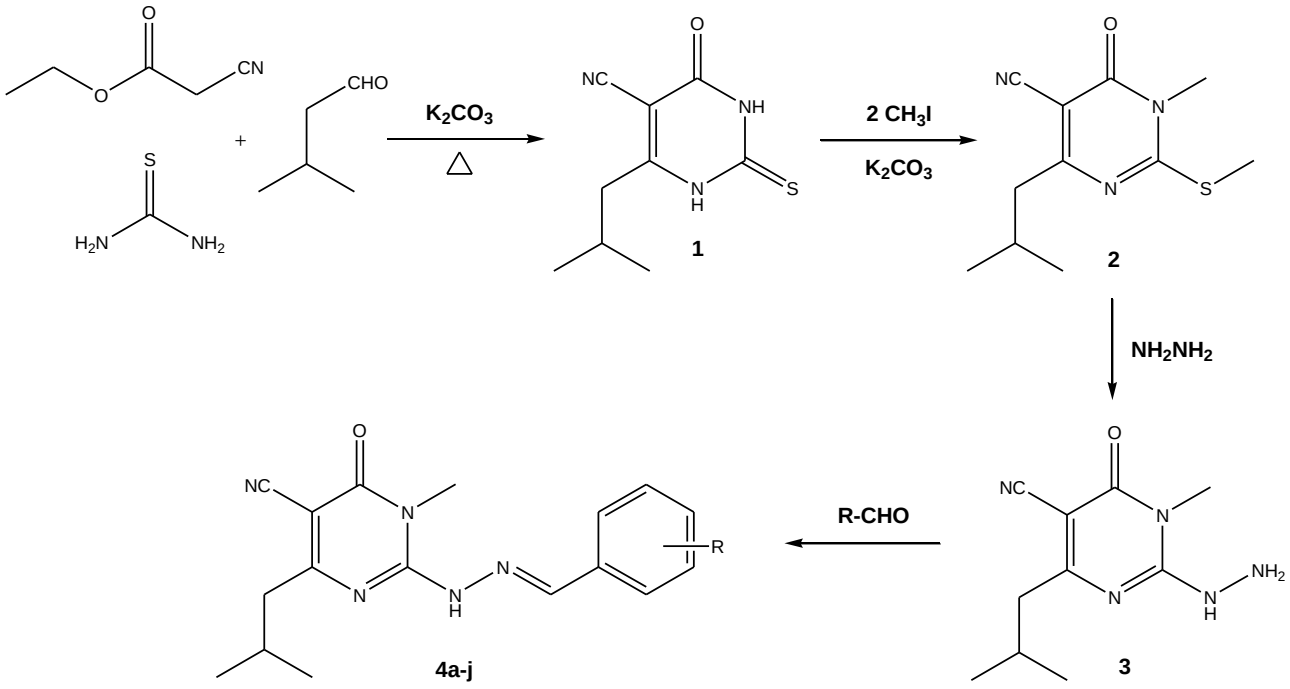
1,2,3,4-tetrahydropyrimidine-5-carbonitrile scaffold [9] have demonstrated biological activities like Calcium channel antagonist [10], Cardiovascular [11], Anti-inflammatory [12], Antimicrobial [13-15], and Immunomodulatory [16].

Schiff base associated with Pyrimidine-5-carbonitrile have also been reported to exhibit a wide range of biological activities like Antitubercular, Anticonvulsant, Neurotoxicity [17], Antitumor [18] and Antibacterial [19].

Going through the references and in search of newer pharmacologically active pyrimidine-5-carbonitrile derivatives, we have synthesized some new 2-(Benzylidinehydrazinyl)-1,6-dihydro-6-oxo-4-isobutylpyrimidine-5-carbonitrile by condensation of 2-hydrazinyl-1,6-dihydro-1-methyl-6-oxo-4-isobutylpyrimidine-5-carbonitrile with different aromatic aldehydes using 3-component heterocyclization method [20].

2. EXPERIMENTAL

Melting points were taken in open capillary and are not corrected. Purity of synthesized compounds have been checked by TLC. ^{1}H NMR spectra were recorded in Bruker-Avance-II (400 MHz) using DMSO-d6 as a solvent and TMS as an internal standard and the chemical shifts are reported as parts per million (ppm). Mass spectra were determined on Shimadzu-QP2010 spectrometer. IR spectra were recorded on Shimadzu-FTIR-8400 using KBr pallet.



Scheme 1

2. 1. Synthesis of 1,2,3,4-tetrahydro-6-isobutyl-4-oxo-2-thioxopyrimidine-5-carbonitrile (1)

A mixture of Thiourea (0.05 mol), ethylcyanoacetate (0.05 mol), isovaleraldehyde (0.05 mol) and potassium carbonate (0.05 mol) in absolute alcohol (100 ml) was refluxed for 4 hours. Reaction mixture was poured into minimum quantity of crushed ice and neutralized

with acetic acid. The product obtained was isolated and crystallized from water. Mass M^+ = 209: IR (KBr) v (cm^{-1}), 2965 (-CH_3, Asym.), 2877 (-CH_3, Sym.), 2235 (-CN), 1648 (-CO); 1H NMR (δ ppm) (400 MHz, DMSO), δ 0.9 (d, 6H, CH_3), δ 2.0 (m, 1H, CH), δ 2.4 (d, 2H, CH_2), δ 13 (s, 2H, NH).

2. 2. Synthesis of 1,6-dihydro-4-isobutyl-1-methyl-2-(methylthio)-6-oxopyrimidine-5-carbonitrile (2)

To a solution of (1) (0.05 mol) in DMF (70 ml), potassium carbonate (0.1 mol) and methyliodide (0.1 mol) were added and the mixture was stirred for 3 hours. The contents were poured into water, filtered, washed with water and crystallized from DMF. Mass M^+ = 237: IR (KBr) v (cm^{-1}), 2956 (-CH_3, Asym.), 2869 (-CH_3, Sym.), 2220 (-CN), 1673 (-CO), 663 (C-S-C); 1H NMR (δ ppm) (400 MHz, DMSO), δ 0.9 (d, 6H, CH_3), δ 2.1 (m, 1H, CH), δ 2.5 (d, 2H, CH_2), δ 2.6 (s, 3H, S-CH_3), δ 3.4 (s, 3H, N-CH_3).

2. 3. Synthesis of 2-hydrazinyl-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (3)

A mixture of (2) (0.01 mol) and Hydrazine hydrate (3.5 ml) in absolute alcohol (30 ml) was refluxed for 6 hours. The reaction mixture was poured into crushed ice and the solid product obtained after neutralization with acetic acid was kept in water overnight. The product was isolated and crystallized from absolute alcohol. Mass M^+ = 221: IR (KBr) v (cm^{-1}), 3304 (-NH, secondary) 2954 (-CH_3, Asym.), 2868 (-CH_3, Sym.), 2220 (-CN), 1676 (-CO); 1H NMR (δ ppm) (400 MHz, DMSO), δ 0.9 (d, 6H, CH_3), δ 2.2 (m, 1H, CH), δ 2.3 (d, 2H, CH2), δ 3.1 (s, 3H, N-CH_3).

2. 4. Synthesis of 2-(Substituted benzylidenehydrazinyl)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (4a-j)

A mixture of (3) (0.01 mol) and different aromatic aldehyde (0.01 mol) in absolute alcohol (20 ml) was refluxed for 3 hours in presence of catalytic amount of acetic acid. The reaction mixture was poured into sodium bisulfite solution. The product was isolated and crystalized from appropriate solvent.

Table 1. Physical constant.

Comp.	R	M.F.	MP °C	Yield %	% of C Found (Calcd.)	% of H Found (Calcd.)	% of N Found (Calcd.)
1	-	$C_9H_{11}N_3OS$	246	90	51.63 (51.65)	5.27 (5.30)	20.05 (20.08)
2	-	$C_{11}H_{15}N_3OS$	100	85	55.32 (55.37)	6.34 (6.37)	17.68 (17.71)
3	-	$C_{10}H_{15}N_5O$	168	60	54.25 (54.28)	6.79 (6.83)	31.61 (31.65)
4a	-H	$C_{17}H_{19}N_5O$	200	54	65.97 (66.00)	6.15 (6.19)	22.65 (22.64)
4b	-4-Cl	$C_{17}H_{18}N_5OCl$	206	55	59.36 (59.39)	5.23 (5.28)	20.35 (20.37)

4c	-4-OCH_3	$C_{18}H_{21}N_5O_2$	190	48	63.65 (63.70)	6.20 (6.24)	20.59 (20.64)
4d	-4-$N(CH_3)_2$	$C_{19}H_{24}N_6O$	212	53	64.76 (64.75)	6.87 (6.86)	23.83 (23.85)
4e	-3,4$(OCH_3)_2$	$C_{19}H_{23}N_5O_3$	186	56	61.74 (61.77)	6.24 (6.28)	18.96 (18.96)
4f	-3-OCH_3-4-OH	$C_{18}H_{21}N_5O_3$	206	49	60.82 (60.83)	5.94 (5.96)	19.68 (19.71)
4g	-4-CH_3	$C_{18}H_{21}N_5O$	190	52	66.86 (66.85)	6.56 (6.55)	21.63 (21.66)
4h	-4-F	$C_{17}H_{18}FN_5O$	170	58	62.35 (62.37)	5.51 (5.54)	21.40 (21.39)
4i	-4-OH	$C_{17}H_{19}N_5O_2$	242	60	62.71 (62.75)	5.88 (5.89)	21.50 (21.52)
4j	-2-Cl	$C_{17}H_{18}N_5OCl$	184	54	59.38 (59.39)	5.26 (5.28)	20.32 (20.37)

3. SPECTRAL ANALYSIS OF NOVEL BENZYLIDINEHYDRAZINYL DERIVATIVES

3. 1. 2-(Benzylidenehydrazinyl)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (4a)

Mass M^+ = 309: IR (KBr) v (cm^{-1}), 2966 (-CH_3, Asym.), 2872 (-CH_3, Sym.), 2222 (-CN), 1668 (-CO), 1496-1458 (C=C), 1084 (N-C); 1H NMR (δ ppm) (400 MHz, DMSO), δ 1.0 (d, 6H, CH_3), δ 2.0 (m, 1H, CH), δ 2.7 (d, 2H, CH_2), δ 3.2 (s, 3H, N-CH_3), δ 7.4-8.4 (m, 5H, Ar-H), δ 10.9 (s, 1H, NH).

3. 2. 2-(4-Chloro benzylidenehydrazinyl)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (4b)

Mass M^+ = 343: IR (KBr) v (cm^{-1}), 2962 (-CH_3, Asym.), 2875 (-CH_3, Sym.), 2224 (-CN), 1661 (-CO); 1H NMR (δ ppm) (400 MHz, DMSO), δ 1.1 (d, 6H, CH_3), δ 2.1 (m, 1H, CH), δ 2.8 (d, 2H, CH_2), δ 3.3 (s, 3H, N-CH_3), δ 7.4-8.4 (dd, 4H, Ar-H), δ 10.2 (s, 1H, NH).

3. 3. 2-(4-Methoxybenzylidenehydrazinyl)-1,6-dihydro-4-isobutyl-1-methyl-6-oxo pyrimidine-5-carbonitrile (4c)

Mass M^+ = 339: IR (KBr) v (cm^{-1}), 2954 (-CH_3, Asym.), 2868 (-CH_3, Sym.), 2220 (-CN), 1676 (-CO); 1H NMR (δ ppm) (400MHz, DMSO), δ 0.9 (d, 6H, CH_3), δ 2.1 (m, 1H, CH), δ 2.3 (d, 2H, CH_2), δ 3.1 (s, 3H, N-CH_3), δ 3.3 (s, 3H, -OCH_3), δ 7.2-7.8 (m, 4H, Ar-H) δ 9.8 (s, 1H, NH).

3. 4. 2-(4-N,N-dimethyl benzylidenehydrazinyl)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (4d)

Mass M^+ = 352: IR (KBr) v (cm^{-1}), 2965 (-CH_3, Asym.), 2877 (-CH_3, Sym.), 2218 (-CN), 1675 (-CO); 1H NMR (δ ppm) (400MHz, DMSO), δ 1.0 (d, 6H, CH_3), δ 2.0 (m, 1H, CH), δ 2.7 (d, 2H, CH_2), δ 3.0 (s, 6H, CH_3) δ 3.2 (s, 3H, N-CH_3), δ 7.4-8.4 (m, 5H, Ar-H), δ 10.4 (s, 1H, NH).

3. 5. 2-(3,4-Dimethoxy benzylidenehydrazinyl)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (4e)

Mass M^+ = 369: IR (KBr) v (cm^{-1}), 2956 (-CH_3, Asym.), 2868 (-CH_3, Sym.), 2225 (-CN), 1676 (-CO); 1H NMR (δ ppm) (400 MHz, DMSO), δ 0.9 (d, 6H, CH_3), δ 2.1 (m, 1H, CH), δ 2.3 (d, 2H, CH_2), δ 3.1 (s, 3H, N-CH_3), δ 3.5 (s, 6H, -OCH_3), δ 7.2-7.8 (m, 3H, Ar-H) δ 9.9 (s, 1H, NH).

3. 6. 2-(3-Methoxy- 4-hydroxy benzylidenehydrazinyl)- 1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (4f)

Mass M^+ = 355: IR (KBr) v (cm^{-1}), 2957 (-CH_3, Asym.), 2870 (-CH_3, Sym.), 2223 (-CN), 1670 (-CO); 1H NMR (δ ppm) (400 MHz, DMSO), δ 0.9 (d, 6H, CH3), δ 2.1 (m, 1H, CH), δ 2.3 (d, 2H, CH2), δ 3.1 (s, 3H, N-CH_3), δ 3.5 (s, 3H, -OCH_3), δ 7.2-7.8 (m, 4H, Ar-H), δ 9.8 (s, 1H, NH), δ 10.1 (s, 1H, OH).

3. 7. 2-(4-Methyl benzylidenehydrazinyl)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (4g)

Mass M^+ = 323: IR (KBr) v (cm^{-1}), 2972 (-CH_3, Asym.), 2860 (-CH_3, Sym.), 2227 (-CN), 1671 (-CO); 1H NMR (δ ppm) (400 MHz, DMSO), δ 1.1 (d, 6H, CH_3), δ 2.1 (m, 1H, CH), δ 2.8 (d, 2H, CH_2), δ 2.3 (s, 3H, -CH_3), δ 3.2 (s, 3H, N-CH_3), δ 7.4-8.4 (m, 4H, Ar-H), δ 10.0 (s, 1H, NH).

3. 8. 2-(4-Fluro benzylidenehydrazinyl)- 1,6-dihydro-4-isobutyl-1-methyl- 6-oxo pyrimidine- 5-carbonitrile (4h)

Mass M^+ = 327: IR (KBr) v (cm^{-1}), 2972 (-CH_3, Asym.), 2860 (-CH_3, Sym.), 2227 (-CN), 1671 (-CO); 1H NMR (δ ppm) (400 MHz, DMSO), δ 1.1 (d, 6H, CH_3), δ 2.1 (m, 1H, CH), δ 2.8 (d, 2H, CH_2), δ 3.2 (s, 3H, N-CH_3), δ 7.4-8.2 (m, 4H, Ar-H), δ 10.0 (s, 1H, NH).

3. 9. 2-(4-Hydroxy benzylidenehydrazinyl)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (4i)

Mass M^+ = 325: IR (KBr) v (cm^{-1}), 2955 (-CH_3, Asym.), 2874 (-CH_3, Sym.), 2220 (-CN), 1678 (-CO); 1H NMR (δ ppm) (400MHz, DMSO), δ 0.9 (d, 6H, CH3), δ 2.1 (m, 1H, CH), δ 2.3 (d, 2H, CH_2), δ 3.1 (s, 3H, N-CH_3), δ 7.2-7.8 (m, 4H, Ar-H), δ 9.8 (s, 1H, NH), δ 10.1 (s, 1H, OH).

3. 10. 2-(2-Chloro benzylidenehydrazinyl)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (4j)

Mass M^+ = 343: IR (KBr) v (cm^{-1}), 2963 (-CH_3, Asym.), 2876 (-CH_3, Sym.), 2225 (-CN), 1668 (-CO); 1H NMR (δ ppm) (400 MHz, DMSO), δ 1.1 (d, 6H, CH_3), δ 2.1 (m, 1H, CH), δ 2.8 (d, 2H, CH_2), δ 3.3 (s, 3H, N-CH_3), δ 7.4-8.4 (m, 4H, Ar-H), δ 10.2 (s, 1H, NH).

4. CONCLUSION

Rarely reported Benzylidinehydrazinyl derivatives of 4-alkyl pyrimidine-5-carbonitrile were prepared using 2-hydrazinyl-1,6-dihydro-1-methyl-6-oxo-4-isobutylpyrimidine-5-

carbonitrile (3) with different aromatic aldehyde in presence of 1-2 ml of glacial acetic acid gave 2-(Substituted benzylidenehydrazinyl)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (4a-j) (Scheme 1). All synthesized compounds were obtained in good yield (Table 1). The synthesized compounds were characterized by IR, ^{1}H-NMR and Mass Spectroscopy and the obtained results are showing good agreement with the synthesized structure.

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