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Synthesis and Characterization of Aroylhydrazino Derivatives of Pharmacologically Active Pyrimidine-5-carbonitrile

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ABSTRACT

The target compound N'-(5-Cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl)-4-methylbenzohydrazide have been synthesized by the condensation of 4-(4-Fluorophenyl)-2-hydrazinyl-1,6-dihydro-1-methyl-6-oxopyrimidine-5-carbonitrile with different aroylchlorides. The obtained products were characterized by ^{1}H NMR, Mass and IR Spectra.

***Keyword*:** Pyrimidine-5-carbonitrile; Aroylchlorides; Benzohydrazide

1. INTRODUCTION

A massive number of Heterocyclic compounds are known and are increasing rapidly. The literature on the subject is very wide. Heterocyclic systems are found in variety of naturally occurring and synthetic compounds and are essential to life. They are important components of alkaloids, antibiotics, hormones and large number of synthetic drugs and dyes [1]. The Nitrogen Heterocyclics are of great importance as they are present in nucleic acids, vitamins, proteins and other biologically important molecular systems [2].

Amide functional group is found widely in small or complex synthetic as well as natural molecules. It is ubiquitous in life as proteins play a crucial role in virtually all biological processes such as enzymatic catalysis (nearly all known enzymes are proteins), transport/storage (haemoglobin), immune protection (antibodies) and mechanical support (collagen). Amides also play a key role for medicinal chemists [3]. An in-depth analysis of the Comprehensive Medicinal Chemistry database revealed that the carboxamide group appears in more than 25 % of known drugs [4]. This can be expected, since carboxamides are neutral, stable and have both hydrogen-bond accepting and donating properties [5].

The 3,4-Dihydropyrimidine derivatives are known to exhibit traditional antithyroid activity of the 5-Fluoro-2-thiouracil[6]. Furthermore, Dihydropyrimidine derivatives are also reported to have showed different pharmacological activities like antitumor [7], analgesic [8], antineoplastic [9], cardiovascular [10], antiallergic [11] etc.

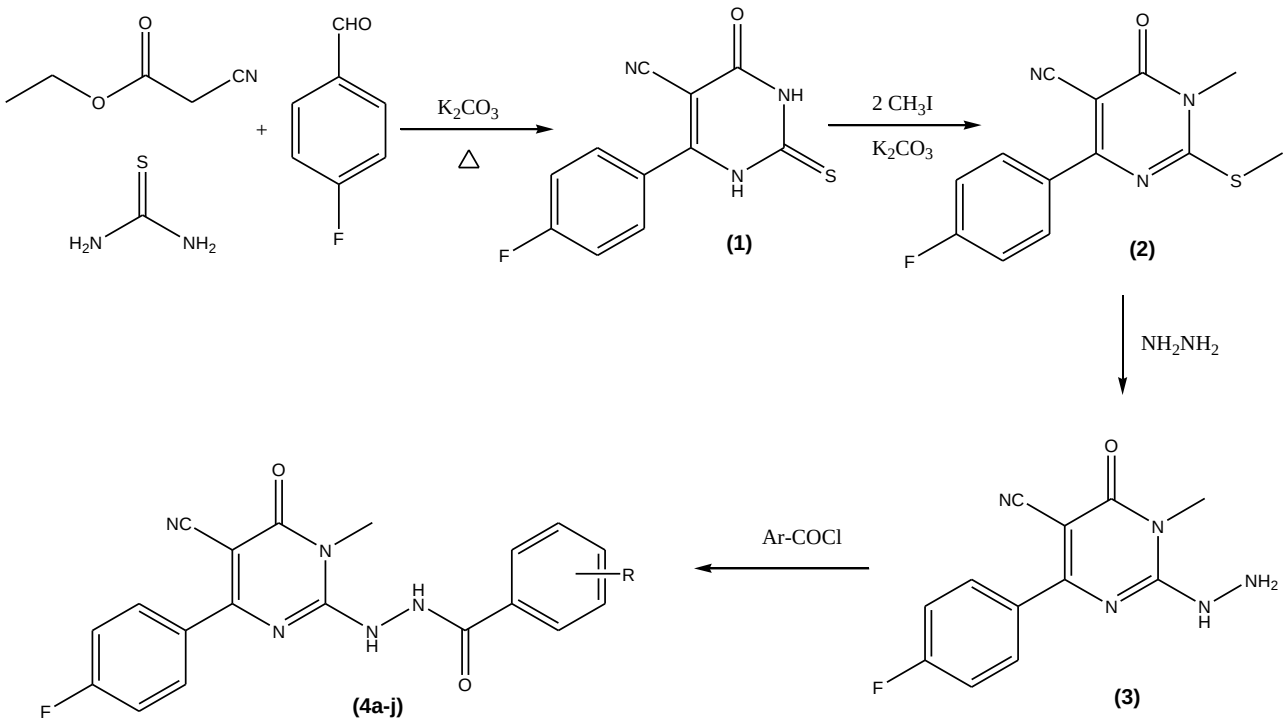
Many acyclic and cyclic amide derivatives have resulted into powerful central nervous depressant. The biological activity of arylamide derivatives have been reported as antitubercular [12], anticancer [13], antibacterial [14-15], CNS depressant [16-17].

Also Incorporation of Aroylhydrazino group in 3,4-Dihydropyrimidine is reported to have increased the biological activity of Pyrimidine-5-carbonitrile [18].

Going through the references and in search of newer pharmacologically active Pyrimidine-5-carbonitrile derivatives, we have synthesized some new N'-(5-Cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl)-4-methylbenzohydrazide by condensation of 4-(4-Fluorophenyl)-2-hydrazinyl-1,6-dihydro-1-methyl-6-oxopyrimidine-5-carbonitrile with different Aroylchlorides using 3-component Heterocyclization method[19]. Compound **(1)** and **(2)** have been synthesized by reported method [20].

2. EXPERIMENTAL

Melting points were taken in open capillary and are not corrected. Purity of synthesized compounds have been checked by TLC. Mass spectra were determined on Shimadzu-QP2010 spectrometer. IR spectra were recorded on Shimadzu-FTIR-8400 using KBr pallet. ^{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).



Scheme – 1

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

A mixture of Thiourea (0.05 mol), ethylcyanoacetate (0.05 mol), 4-Fluorobenzaldehyde (0.05 mol) and potassium carbonate (0.05mol) in absolute alcohol (100 ml) was refluxed for 6 hours. Reaction mixture was poured into minimum quantity of crushed ice and neutralized with acetic acid. The product obtained was isolated and crystallized from absolute alcohol. Mass M^+ = 247: IR (KBr) v (cm^{-1}), 2943 (-CH_3, Asym.), 2855 (-CH_3, Sym.), 2208 (-CN), 1635 (-CO), 1245 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 7.2-7.3 (t, 2H, Ar-H), δ 7.7-7.8 (q, 2H, Ar-H) δ 11.6 (s, 2H, NH).

2. 2. Synthesis of 4-(4-Fluorophenyl)-1,6-dihydro-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 absolute alcohol. Mass M^+ = 275: IR (KBr) v (cm^{-1}), 2943 (-CH_3, Asym.), 2869 (-CH_3, Sym.), 2222 (-CN), 1680 (-CO), 663 (C-S-C), 1253 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 2.6 (s, 3H, S-CH_3), δ 3.2 (s, 3H, N-CH_3), δ 7.2-7.3 (t, 2H, Ar-H), δ 7.43-7.48 (q, 2H, Ar-H).

2. 3. Synthesis of 4-(4-Fluorophenyl)-2-hydrazinyl-1,6-dihydro-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 8 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^+ = 259 : IR (KBr) v (cm^{-1}), 3304 (-NH, secondary) 2954 (-CH_3, Asym.), 2868 (-CH_3, Sym.), 2216 (-CN), 1670 (-CO), 1250 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.2 (s, 3H, N-CH_3), δ 7.0-7.1 (d, 1H, Ar-H), δ 7.3-7.4 (t, 1H, Ar-H), δ 7.9-8.0 (q, 2H, Ar-H).

2. 4. Synthesis of N'-(5-Cyano-4-(4-fluorophenyl)-1,6-dihydro- 1-methyl-6-oxopyrimidin-2-yl)-benzohydrazide derivatives(4a-j)

A mixture of **(3)** (0.01 mol) and different aroylchloride (0.01 mol) in chloroform (20 ml) was refluxed for 3 hours in presence of catalytic amount of dry pyridine. The reaction mixture was poured into ice water. The product was isolated and crystalized from appropriate solvent.

3. SPECTRAL ANALYSIS OF NOVEL ARYLAMIDE DERIVATIVES

3. 1. N'-(5-Cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl)-4-methylbenzohydrazide (4a):

Mass M^+ = 377: IR (KBr) v (cm^{-1}), 3432 (-NH, secondary), 2925 (-CH_3, Asym.), 2830 (-CH_3, Sym.), 2204 (-CN), 1638 (-CO), 1092 (N-C), 1608 (-CO, Amide), 1259 (C-O-C), 1240 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.4 (s, 3H, N-CH_3), δ 2.38 (s, 3H, CH_3), δ 7.2-7.3 (q, 2H, Ar-H), δ 7.80-7.86 (m, 2H, Ar-H).

3. 2. 2-Chloro-N'-(5-cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl)-5-nitrobenzohydrazide (4b):

Mass M^+ = 442: IR (KBr) v (cm^{-1}), 3430 (-NH, secondary), 2922 (-CH_3, Asym.), 2828 (-CH_3, Sym.), 2200 (-CN), 1635 (-CO), 1090 (N-C), 1610 (-CO, Amide), 1257 (C-O-C), 764 (C-Cl), 1365 (C-NO_2), 1270 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.41 (s, 3H, N-CH_3), δ 8.44 (1H, Ar-H), δ 8.15 (1H, Ar-H), δ 7.38 (1H, Ar-H).

3. 3. 4-Chloro-N'-(5-cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl) benzohydrazide (4c):

Mass M^+ = 397: IR (KBr) v (cm^{-1}), 3432 (-NH, secondary), 2920 (-CH_3, Asym.), 2830 (-CH_3, Sym.), 2210 (-CN), 1630 (-CO), 1095 (N-C), 1620 (-CO, Amide), 1260 (C-O-C), 760 (C-Cl), 1255 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.38 (s, 3H, N-CH_3), δ 7.22-7.28 (q, 2H, Ar-H), δ 7.78-7.80 (m, 2H, Ar-H).

Table 1. Physical constant.

Comp.	R	M.F.	MP˚C	Yield %	% of C Found (Calcd.)	% of H Found (Calcd.)	% of N Found (Calcd.)
1	-	$C_{11}H_6FN_3OS$	290	60%	51.60 (51.65)	5.25 (5.30)	20.00 (20.08)
2	-	$C_{13}H_{10}FN_5O$	182	65%	55.34 (55.37)	6.30 (6.37)	17.65 (17.71)
3	-	$C_{12}H_{10}FN_5O$	240	55%	54.26 (54.28)	6.80 (6.83)	31.60 (31.65)
4a	-4-CH_3	$C_{20}H_{16}FN_5O_2$	260	66%	63.70 (63.65)	4.21 (4.27)	18.50 (18.56)
4b	-2-Cl-5-NO_2	$C_{19}H_{12}ClFN_6O_4$	225	64%	51.46 (51.54)	2.70 (2.73)	18.90 (18.98)
4c	-4-Cl	$C_{19}H_{13}ClFN_5O_2$	208	57%	57.30 (57.37)	3.25 (3.29)	17.54 (17.61)
4d	-H	$C_{19}H_{14}FN_5O_2$	220	60%	62.78 (62.81)	3.81 (3.88)	19.20 (19.27)
4e	-4-tert-Butyl	$C_{23}H_{22}FN_5O_2$	175	58%	65.80 (65.86)	5.24 (5.29)	16.65 (16.70)
4f	-3-NO_2	$C_{19}H_{13}FN_6O_4$	195	62%	55.85 (55.89)	3.16 (3.21)	20.50 (20.58)
4g	-4-NO_2	$C_{19}H_{13}FN_6O_4$	202	65%	55.86 (55.89)	3.18 (3.21)	20.55 (20.58)
4h	-4-OH	$C_{19}H_{14}FN_5O_3$	232	61%	60.11 (60.16)	3.69 (3.72)	18.40 (18.46)
4i	-4-NH_2	$C_{19}H_{15}FN_6O_2$	257	53%	60.28 (60.31)	3.95 (4.00)	22.18 (22.21)
4j	-2-Cl-4-Cl	$C_{19}H_{12}Cl_2FN_5O_2$	270	58%	52.75 (52.80)	2.76 (2.80)	16.15 (16.20)

3. 4. N'-(5-Cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl) benzohydrazide (4d):

Mass M^+ = 363: IR (KBr) v (cm^{-1}), 3436 (-NH, secondary), 2925 (-CH_3, Asym.), 2836 (-CH_3, Sym.), 2217 (-CN), 1636 (-CO), 1092 (N-C), 1625 (-CO, Amide), 1261 (C-O-C), 1251 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.41 (s, 3H, N-CH_3), δ 7.06 (1H, Ar-H), δ 7.14 (1H, Ar-H), δ 7.07 (1H, Ar-H), δ 7.14 (1H, Ar-H), δ 7.06 (1H, Ar-H).

3. 5. 4-tert-Butyl-N'-(5-cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl) benzohydrazide (4e):

Mass M^+ = 419: IR (KBr) v (cm^{-1}), 3431 (-NH, secondary), 2922 (-CH_3, Asym.), 2830 (-CH_3, Sym.), 2221 (-CN), 1646 (-CO), 1089 (N-C), 1621 (-CO, Amide), 1254 (C-O-C), 1248 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.38 (s, 3H, N-CH_3), δ 3.38 (s, 3H, N-CH_3), δ 1.34 (9H, CH_3), δ 7.58 (1H, Ar-H), δ 7.56 (1H, Ar-H), δ 7.56 (1H, Ar-H), δ 7.58 (1H, Ar-H).

3. 6. N'-(5-Cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl)-3-nitrobenzohydrazide (4f):

Mass M^+ = 408: IR (KBr) v (cm^{-1}), 3428 (-NH, secondary), 2928 (-CH_3, Asym.), 2835 (-CH_3, Sym.), 2201 (-CN), 1635 (-CO), 1088 (N-C), 1625 (-CO, Amide), 1253 (C-O-C), 1370 (C-NO_2), 1253 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.38 (s, 3H, N-CH_3), δ 7.83 (1H, Ar-H), δ 7.43 (1H, Ar-H), δ 8.17 (1H, Ar-H), δ 8.39 (1H, Ar-H).

3. 7. N'-(5-Cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl)-4-nitrobenzohydrazide (4g):

Mass M^+ = 408 IR (KBr) v (cm^{-1}), 3430 (-NH, secondary), 2925 (-CH_3, Asym.), 2837 (-CH_3, Sym.), 2206 (-CN), 1638 (-CO), 1091 (N-C), 1627 (-CO, Amide), 1256 (C-O-C), 1360 (C-NO2), 1248 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.37 (s, 3H, N-CH_3), δ 7.29-7.3 (q, 2H, Ar-H), δ 7.80-7.86 (m, 2H, Ar-H).

3. 8. N'-(5-Cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl)-4-hydroxybenzohydrazide (4h):

Mass M^+ = 379: IR (KBr) v (cm^{-1}), 3430 (-NH, secondary), 2923 (-CH_3, Asym.), 2830 (-CH_3, Sym.), 2210 (-CN), 1640 (-CO), 1093 (N-C), 1630 (-CO, Amide), 1263 (C-O-C), 1400 (O-H), 1242 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.39 (s, 3H, N-CH_3), δ 7.32-7.35 (q, 2H, Ar-H), δ 7.81-7.85 (m, 2H, Ar-H).

3. 9. 4-Amino-N'-(5-cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl)benzohydrazide (4i):

Mass M^+ = 378: IR (KBr) v (cm^{-1}), 3432 (-NH, secondary), 2930 (-CH_3, Asym.), 2835 (-CH_3, Sym.), 2209 (-CN), 1640 (-CO), 1092 (N-C), 1612 (-CO, Amide), 1257 (C-O-C), 3400 (N-H, NH_2), 1260 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.42 (s, 3H, N-CH_3), δ 7.30-7.32 (q, 2H, Ar-H), δ 7.82-7.84 (m, 2H, Ar-H).

3. 10. 2,4-Dichloro-N'-(5-cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl)benzohydrazide (4j):

Mass M^+ = 331: IR (KBr) v (cm^{-1}), 3430 (-NH, secondary), 2927 (-CH_3, Asym.), 2831 (-CH_3, Sym.), 2205 (-CN), 1640 (-CO), 1088 (N-C), 1607 (-CO, Amide), 1259 (C-O-C), 763

(C-Cl), 1259 (C-F); 1H NMR (δ ppm) (400 MHz, DMSO), δ 3.38 (s, 3H, N-CH_3), δ 7.47 (1H, Ar-H), δ 7.06 (1H, Ar-H), δ 7.41 (1H, Ar-H).

4. CONCLUSION

Rarely reported Aroylhydrazino derivatives of 4-Arylpyrimidine-5-carbonitrile targeted to be prepared by condensing 4-(4-Fluorophenyl)-2-hydrazinyl-1,6-dihydro-1-methyl-6-oxopyrimidine-5-carbonitrile **(3)** with different aroylchlorides in presence of dry pyridine gave compound N'-(5-Cyano-4-(4-fluorophenyl)-1,6-dihydro-1-methyl-6-oxopyrimidin-2-yl)-4-methylbenzohydrazide **(4a-j) (Scheme 1)** in good yield **(Table 1)**. Result of constitutional characterization of the obtained products by IR, ^{1}H-NMR and Mass Spectroscopy showed good agreement with the constitution of the targeted molecules.

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