ISSN (Print 0974-2115) (Online 2349-8552)
www.jchps.com Journal of Chemical and Pharmaceutical Sciences

Synthesis, characterization of N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoacetohydrazide and its derivatives

Vijaya Kumar Polem[1*], Y. N. Spoorthy[2], l. K. Rvindranath[2]
[1]Dept. of Chemistry, JNTU, Anantapur, Andhra Pradesh, India
[2]Dept. of chemistry, Sri Krishnadevaraya University, Anantapur, Andhra Pradesh, India
***Corresponding author: E-Mail ID: polem_vijay@yahoo.co.in, Ph.No: 09989160236**

ABSTRACT

N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoacetohydrazide on treatment with 1-Cyanoacetyl-3, 5-dimethylpyrazole using toluene as solvent affords N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoaceto hydrazide (3). The latter on reaction with different aromatic aldehydes form N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoacetohydrazides (4-13). A new sequence of analogues were prepared from N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoacetohydrazide and further confirmed by spectral data.

KEY WORDS: Ethyl cyano acetate, Acetyl acetone, cyano acetylating agent, cyano acetylation, different aromatic aldehydes.

1. INTRODUCTION

Purines are heterocyclic, organic, aromatic compounds consisting pyrimidine ring fused to imidazole ring. Purines and its analogues are very important in the field of synthetic organic chemistry. Cyanoacetamides are highly reactive compounds. They are extensively used as reactants or reaction intermediates because the cyano and carbonyl group of these analogues are suitably situated to enable reactions with common reagents to form a variety of hetero cyclic compounds. The active hydrogen on C-2 of cyanoacetamide derivatives can take part in variety of substitution and condensation reactions. Different biological activities reported for several cyanoacetamide derivatives. Some cyanoacetamide derivatives of heteroaryl amines have analgesic and antioxidant activity (Madhavi, 2013). Most of the cyanoacetamide derivatives shows different biological activities like antitubercular activity (Diptish Chakravarthy, 1964), anti-inflammatory activity (Mohamed, 2007), anticancer and radio sensitizing activity (Mostafa, 2016), antibacterial (Madhavi, 2016), antimitotic activity (Sundaresan, 2018), antimicrobial activity (Abu-Bakr, 2017). As cyanoacetamide derivatives were more biological active in different fields of medical sciences, it has been planned to synthesize a series of novel compounds of purine moiety using cyano acetylating agent. Present research work related to the preparation and isolation of N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoacetohydrazide using handy and cheap cyano acetylation reagent and some analogues of N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoacetohydrazide, further their structures were confirmed by spectral data.

2. MATERIALS AND METHODS

All reagents and starting material used for this work are commercial grade. These materials were used as it is without any further purification. Melting points of newly synthesized analogues were recorded in open-end capillaries and are uncorrected. All the synthesized analogues were confirmed by analytical methods like IR (using KBr pellets on Perkin-Elmer SPECTRUM 100 FT-IR), NMR (BRUKER avance 300MHz FT-NMR, DMSO-d_6 used as solvent for analysis) and mass (Mass spectrometer waters Quattro Micro API). The progress of the reaction was monitored using TLC system and observed under UV light.

Synthesis of Cyano acetic acid hydrazide (1): Cyano acetic acid hydrazide was obtained by careful addition of hydrazine hydrate to ethyl cyano acetate in ethanol at 0-5°C, maintained the reaction mass at 0-5°C for 1hr, filtered the product and washed the wet cake with chilled ethanol and dried the product at 55-60°C in hot air oven. (m.p 108-109°C; Litt.108-110°C).

Synthesis of 1-Cyanoacetyl-3, 5-dimethylpyrazole (2): To a mixture of cyano acetic acid hydrazide in water containing catalytic amount of Conc. HCl at ambient temperature, acetyl acetone was added slowly. The reaction mixture was stirred at ambient temperature for about 1hr, filtered the product and washed the wet material with water and dried at 55-60°C in hot air oven. (m.p 118-119°C; Litt.116-119°C).

Synthesis of N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoaceto hydrazide (3): A mixture of 9-(3-chloro-4-fluorophenyl)-6-hydrazinyl-9H-purin-2-amine (0.0510 moles) and 1-Cyanoacetyl-3, 5-dimethyl pyrazole (0.0510 moles) in 150 ml of toluene was maintained at refluxing temperature for 4 hrs .After completion of the reaction, cooled the reaction mass to ambient temperature. Maintained the reaction mass at ambient temperature for about 1 hr. Filtered the material, washed the wet material with toluene (25 mL) and dried at 55-60°C in hot air oven. Crude material was purified in ethyl alcohol to get N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoaceto hydrazide.

Yield 16.84 g (92%). IR (ν, cm^{-1}):3419&3327(-NH_2), 3265(N-H),2260(-C≡N) 1350(C-H), 1514(N-H). ^{1}HNMR, δ(ppm): 3.76 (s, 2H, CH_2), 6.23 (b, 2H, NH_2), 7.60-8.30 (m, 3H, ArH), 8.25 (s, 1H, CH), 9.42 (s, 1H, NH) 10.26 (s, 1H, NH). Mass, m/z (%) =361.1(M+1), m.p 221-223°C.

General procedure for the preparation of N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoaceto hydrazide derivatives (4-13): A mixture of N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoaceto hydrazide (0.0028 mol) and ethyl alcohol (10 ml) taken in round bottom flask and slowly added substituted aromatic aldehydes (0.0028 mol) followed by catalytic amount of piperidine at 25-30°C. Then the reaction mass was maintained for 4-7 hrs at refluxing temperature. Reaction was monitored by TLC and After completion of the starting material, filtered the solid and then washed the wet material with ethyl alcohol (5mL), dried in hot air oven. All the analogues were purified in suitable solvent.

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyano-3-phenylacrylohydrazide (4): Yield 1.14g (92%). IR (KBr, cm^{-1}): 3482&3340(-NH_2), 3211(N-H),2215(-C≡N) 1342(C-H), 1513(N-H). ^{1}HNMR, δ(ppm): 6.27 (b, 2H, NH_2), 7.30-8.35 (m, 8H, ArH), 7.66 (s, 1H, CH), 8.28 (s, 1H, CH), 9.49 (s, 1H, NH) 10.65 (s, 1H, NH). Mass: 449.2(M+1), mp 257-260°C.

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-3-(4-bromophenyl)-2-cyanoacrylohydrazide (5): Yield 1.30g (89%). IR (KBr, cm^{-1}):3479&3337(-NH_2), 3216(N-H), 1349(C-H), 1515(N-H). ^{1}HNMR, δ(ppm): 6.26 (b, 2H, NH_2), 7.29-8.24 (m, 7H, ArH), 7.62 (s, 1H, CH), 8.30 (s, 1H, CH), 9.54 (s, 1H, NH) 10.82 (s, 1H, NH), Mass: 527.1 (M+1), mp 249-251°C.

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-3-(2-bromophenyl)-2-cyanoacrylohydrazide (6): Yield 1.23g (84%). IR (KBr, cm^{-1}): 3421&3323(-NH_2), 3175(N-H),2216(-C≡N) 1347(C-H), 1511(N-H). ^{1}HNMR, δ(ppm): 6.28 (b, 2H, NH_2), 7.31-8.28 (m, 7H, ArH), 7.68 (s, 1H, CH), 8.32 (s, 1H, CH), 9.57 (s, 1H, NH) 10.80 (s, 1H, NH), Mass: 527.1(M+1), mp 248-250°C.

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-3-(3-bromophenyl)-2-cyanoacrylohydrazide (7): Yield 1.27g (87%). IR (KBr, cm^{-1}): 3483&3346(-NH_2), 3249(N-H),2218(-C≡N) 1340(C-H), 1512(N-H). ^{1}HNMR, δ(ppm): 6.28 (b, 2H, NH_2), 7.30-8.22 (m, 7H, ArH), 7.55 (s, 1H, CH), 8.46 (s, 1H, CH), 9.73 (s, 1H, NH) 10.81 (s, 1H, NH), Mass: 527.1(M+1), mp 237-240°C.

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyano-3-(3-hydroxy-4-methoxyphenyl) acrylohydrazide (8): Yield 1.08g (79%). IR (KBr, cm^{-1}): 3480&3344(-NH_2), 3215(N-H),2210(-C≡N) 1336(C-H), 1513(N-H). ^{1}HNMR, δ(ppm): 3.72 (s, 1H, OH), 3.88 (s, 3H, CH_3), 6.26 (b, 2H, NH_2), 7.12-8.21 (m, 6H, ArH), 7.66 (s, 1H, CH), 8.27 (s, 1H, CH), 9.64 (s, 1H, NH) 10.39 (s, 1H, NH), Mass: 495.2(M+1), mp 247-250°C.

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyano-3-(4-methoxyphenyl) acrylohydrazide (9): Yield 0.88g (66%). IR (KBr, cm^{-1}): 3483&3344(-NH_2), 3212(N-H),2213(-C≡N) 1343(C-H), 1513(N-H). ^{1}HNMR, δ(ppm): 3.88 (s, 3H, CH_3), 6.26 (b, 2H, NH_2), 7.15-8.21 (m, 7H, ArH), 7.66 (s, 1H, CH), 8.27 (s, 1H, CH), 9.49 (s, 1H, NH) 10.41 (s, 1H, NH). Mass: 479.2(M+1), mp 258-261°C.

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyano-3-(4-hydroxyphenyl) acrylohydrazide (10): Yield 1.10g (85%). IR (KBr, cm^{-1}): 3479&3346(-NH_2), 3212(N-H),2212(-C≡N) 1344(C-H), 1513(N-H). ^{1}HNMR, δ(ppm): 3.72 (s, 1H, OH), 6.25 (b, 2H, NH_2), 7.12-8.21 (m, 7H, ArH), 7.66 (s, 1H, CH), 8.27 (s, 1H, CH), 9.50 (s, 1H, NH) 10.58 (s, 1H, NH), Mass: 465.2(M+1), mp 266-268°C.

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyano-3-(4-fluorophenyl) acrylohydrazide (11): Yield 0.74 g (57%). IR (KBr, cm^{-1}): 3484&3349(-NH_2), 3289(N-H),2215(-C≡N) 1332(C-H), 15354(N-H). ^{1}HNMR, δ(ppm): 6.23 (b, 2H, NH_2), 7.45-8.34 (m, 7H, ArH), 7.66 (s, 1H, CH), 8.28 (s, 1H, CH), 9.75 (s, 1H, NH) 10.61 (s, 1H, NH), Mass: 467.2(M+1), mp 260-263°C.

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-3-(2-chlorophenyl)-2-cyanoacrylohydrazide (12): Yield 1.07g (80%). IR (KBr, cm^{-1}): 3483&3347(-NH_2), 3247(N-H),2218(-C≡N) 1341(C-H), 1513(N-H). ^{1}HNMR, δ(ppm): 6.27 (b, 2H, NH_2), 7.29-8.22 (m, 7H, ArH), 7.69 (s, 1H, CH), 8.26 (s, 1H, CH), 9.63 (s, 1H, NH) 10.83 (s, 1H, NH), Mass: 483.2(M+1), mp 260-262°C.

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-3-(5-bromo-2-chlorophenyl)-2-cyanoacrylo hydrazide (13): Yield 1.30g (83%). IR (KBr, cm^{-1}): 3495&3412(-NH_2), 3277(N-H), 2208(-C≡N) 1348(C-H), 1510(N-H). ^{1}HNMR, δ(ppm): 6.26 (b, 2H, NH_2), 7.32-8.26 (m, 6H, ArH), 7.69(s, 1H, CH), 8.56 (s, 1H, CH), 9.41 (s, 1H, NH) 10.85 (s, 1H, NH), Mass: 601.1(M+1), m.p 277-279°C.

3. RESULTS AND DISCUSSION

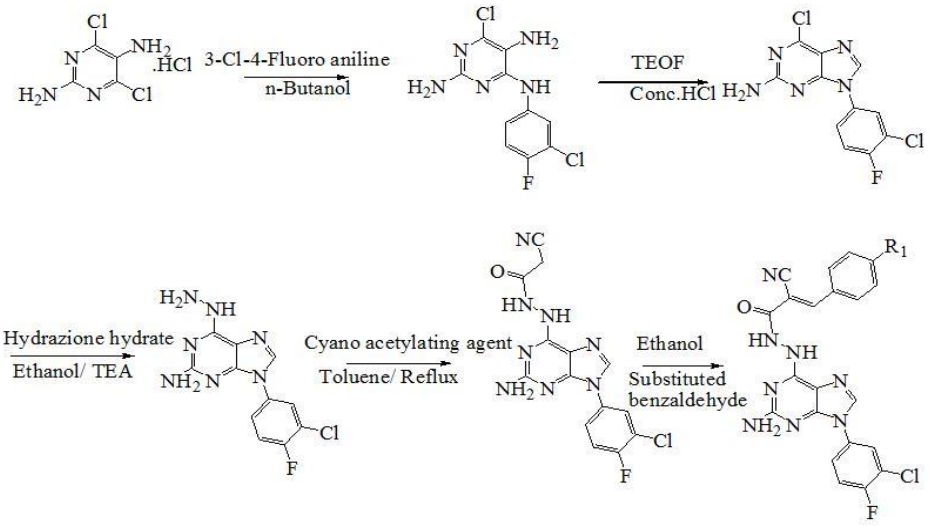
Cyano acetic acid hydrazide **(1)** was prepared using hydrazine hydrate and ethyl cyano acetate in ethanol as per literature procedure. Cyanoacetylating agent 1-Cyanoacetyl-3, 5-dimethylpyrazole (2) was prepared using Cyano acetic acid hydrazide, acetyl acetone and catalytic amount of Conc. HCl as per reported procedure.

6-chloro-9-(3-chloro-4-fluorophenyl)-9H-purin-2-amine was prepared as per literature which is described in our previous article [Vijaya kumar, 2019]. 9-(3-chloro-4-fluorophenyl)-6-hydrazinyl-9H-purin-2-amine was prepared using 6-chloro-9-(3-chloro-4-fluorophenyl)-9H-purin-2-amine and hydrazine hydrate, triethyl amine as base in ethanol.

In the current research work N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoaceto hydrazide (3) and its analogues (4-13) were prepared.

N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoaceto hydrazide (3) was prepared using 9-(3-chloro-4-fluorophenyl)-6-hydrazinyl-9H-purin-2-amine and cyanoacetylating agent (2) in toluene. The Infra-Red spectrum of 3 exhibited intense band at 2260 cm^{-1} showing the presence of cyano group. ^1H NMR showed one singlet at δ 3.76 (2H, $-CH_2$), one singlet at δ 9.42 (s, 1H, NH) and another singlet at δ 10.26 (s, 1H, NH) confirming the structure of the cyanoacetylated derivative (3).

(E)-N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyano-3-phenyl acrylohydrazide (4) was synthesized by the reaction of N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoaceto hydrazide with benzaldehyde using piperidine in ethyl alcohol. The Infra-Red spectrum of 4 exhibited intense band at 2215 cm^{-1} showing the presence of cyano group. ^1H NMR showed absence of one singlet at δ 3.76 (2H, $-CH_2$) and presence of one singlet at δ 7.66 (s, 1H, CH) confirming the structure of the acrylohydrazide derivative (4). Similarly remaining analogues were prepared using different aromatic aldehydes. All structures of these derivatives were confirmed by IR, Mass, NMR spectral data and synthesis (See material and methods for data).



Scheme.1. Reaction path way for the synthesis of N'-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoacetohydrazide derivatives

4. CONCLUSION

In current research work few analogues of N^1-(2-amino-9-(3-chloro-4-fluorophenyl)-9H-purin-6-yl)-2-cyanoacetohydrazide were prepared and characterized successfully. We are planning to check biological activity for these compounds and the details will include in next article.

Acknowledgements: I sincerely thank my guide, co-workers and dept. of chemistry, (JNTU, Anantapur, Andhra Pradesh, India) and Laurus labs Limited (Hyderabad, Telangana) for providing laboratory and analytical facilities.

REFERENCES

Abu-Bakr A, El-Adasy, Synthesis and Biological Activity of Some Novel Heterocyclic Sulfonamides, Der Pharma Chemica, 9 (4), 2017, 1-9.

Diptish Chakravarty, Srun Bose, Samir Bose, Synthesis and Antitubercular Activity of Isonicotinoyl and Cyanoacetyl Hydrazones, Journal of Pharmaceutical Sciences, 53 (9), 1964, 1036-1039.

Madhavi K and Ramanamma K.V, Synthesis and Evaluation of Ethyl 2-(2-Cyano-3-(Substituted Phenyl) Acrylamido)-4, 5, 6, 7-Tetrahydrobenzo[b] Thiophene-3-Carboxyla -tes for Antioxidant and Antibacterial Activities, Int. J. Curr. Microbiol. App. Sci., 5 (1), 2016, 364-375.

Madhavi K and Sudeepthi P, Synthesis of cyano acetylated derivatives of some heteroaryl amines as analgesic and antioxident agents, International journal of pharmaceutical sciences and nanotechnology, 5 (4), 2013, 1879-1884.

Mohamed A.A, Radwan, Eman A, Ragab, Nermien M Sabry, Siham M EI-Shenawy, Synthesis and biological evaluation of new 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents, Bioorganic and Medicinal Chemistry, 15 (11), 2007, 3832-3841.

Mostafa Ghorab M, Fatma Ragab A, Helmy Heiba I, Aiten Soliman M, Design and synthesis of some novel 4-Chloro-*N*-(4-(1-(2-(2-cyanoacetyl)hydrazono) ethyl)phenyl) benzene sulfonamide derivatives as anticancer and radiosensitizing agents, European Journal of Medicinal chemistry, 117 (19), 2016, 8-18.

Sundaresan K, Umamatheswari S and Tharini K, Synthesis, Characterization and Antimitotic Activity of cyanoacetyl hydrazone derivatives, EJPMR, 5 (5), 2018, 314-320.

Vijaya kumar P, Yadati Narasimha Spoorthy, Ravindranath L.K, Synthesis, Characterisation and Biological evaluation of Some New Aryl Substituted Purine Derivatives, JCPS, 12 (4), 2019.