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Synthesis, Characterisation of Some Novel Purine Derivatives

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ABSTRACT

The Reaction of 6-chloro purine hydro chloride with hydrazine hydrate and tri ethyl amine in presence of alcohol results in the formation of 6- hydrazinyl purine derivatives. Hydrazinyl purine derivatives react with substituted benzaldehydes in presence in ethanol form respective 6-bezylidene hydrazinyl purine derivatives. 6-chloro purine hydro chloride reacts with alcohol in presence of sodium alcoxide form 6-alkoxy purine derivatives. The structures of these compounds have been established by ^{1}H NMR studies, IR studies and Mass data.

KEY WORDS: 6- Chloro purines, hydrazine hydrate, substituted benzaldehydes, hydrazinyl purine derivatives and 6-bezylidene hydrazinyl purine derivatives.

1. INTRODUCTION

Purine, purine nucleosides and their analogues are important compound classes with different physiological and pharmacological properties (Szarka, 1997). Some purinyl derivatives have been extremely useful as anti-cancer agents (Montgomery, 1986; Elion, 1952; Birkett, 1993; Matsumoto, 1995). Some purinyl derivatives have been used as effective anti-retro virals (Hotl & Wong 1974). The chemotherapeutic uses of purines and purine analogues have prompted tremendous efforts towards their synthesis, both in academia and in the pharmaceutical industry. This article describes the preparation of novel aryl substituted purine derivatives. The structures of these compounds have been established by ^{1}H NMR, IR and mass studies and synthesis.

2. MATERIALS AND METHODS

Melting points were determined on Mel-temp apparatus, laboratory devices, Cambridge, MA, USA and are uncorrected. The purity of the compounds was checked by thin-layer chromatography. The infrared (IR) spectra were recorded using KBr pellets on Perkin-Elmer SPECTRUM 100 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz on a BRUKER avance-11 FT-NMR spectrometer. The electron spray ionisation MS (ESIMS) studies were performed on triple quadrupole mass spectrometer waters Quattro Micro API.

General procedure for the preparation of Pyrimidine derivatives (1-2): A solution of 4, 6-dichloropyrimidine-2,5-diamine hydro chloride (0.1020 moles) and substituted anilines (0.1122 moles) in n-Butanol (100 mL) was refluxed for 8-10 hrs .After the full conversion of the starting material was detected by TLC, the reaction mass cooled to room temperature. The reaction mixture stirred at room temperature for 1-2 h. The solid is filtered off, washed with n-Butanol (20 ml) and dried under suction.

General procedure for the preparation of Purine derivatives (2-4): A solution of the corresponding substituted pyrimidines (0.0796 moles) and conc. Hydrochloric acid (0.65 vol) in of triethylorthoformate (10 vol) was stirred for 8-10 hrs at room temperature .After the full conversion of the starting material was detected by TLC, The solid is filtered off, washed with methanol and dried under suction.

General procedure for the preparation of hydrazinyl purine derivatives (5-6): A solution of 6- chloro purine (0.04621 moles) , hydrazine hydrate (0.05545 moles) and triethyl amine (0.04621 moles) in ethanol was refluxed for 2-4 hrs .After the full conversion of the starting material was detected by TLC, the reaction mass cooled to room temperature. The reaction mixture stirred at room temperature for 1-2 h. The solid is filtered off, washed with ethanol (5 mL) and dried under suction.

General procedure for the preparation of benzylidene hydrazinyl Purine derivatives (7-13): A solution of the corresponding hydrazinyl purine derivatives (1.0 gms) (0.00312 moles) and substituted benzaldehyde (0.00312 moles) in ethanol was stirred for 2-4 hrs at reflux temperature .After the full conversion of the starting material was detected by TLC, The solid is filtered off, washed with ethanol and dried under suction.

General procedure for the preparation of 6-Alkoxy Purine derivatives (14-16): A solution of the 6-Chloro purine (1.0gms) and sodium alcoxide (0.00624 moles) in alcohol was stirred for 3-4 hrs at reflux temperature. After the full conversion of the starting material was detected by TLC, distilled out solvent under reduced pressure and the solid was isolated using ethanol and dried under suction.

N^4-(4-bromophenyl)-6-chloropyrimidine-2, 4, 5-triamine (1): The solid is purified in methanol to yield 27.3g (85.00%) of compound (1). IR (KBr pellet), ν, cm^{-1}: 3528&3400(-NH_2), 3143(N-H), 1305 (C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 4.23 (2H, S, NH_2), 5.94 (2H, S, NH_2), 7.45-7.42 (2H, db, ArH), 7.78-7.76 (2H, db, ArH), 8.44 (1H, S, CH), Mass: 314.0 (M+1), mp 258-261ºC.

N^4-(4-chlorophenyl)-6-chloropyrimidine-2, 4, 5-triamine (2): The solid is purified in methanol to yield 23.76g (87.00%) of compound (2). IR (KBr pellet), ν, cm^{-1}: 3397&3334(-NH_2), 3163(N-H), 2863 (Ar-H), 1365(C-H).

^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 6.78 (4H, b, 2NH_2), 7.87-7.84 (2H, db, ArH), 7.39-7.36 (2H, db, ArH), 9.71 (1H, S, CH), Mass: 270.0 (M+1), mp 245-250ºC.

9-(4-bromophenyl)-6-chloro-9H-purin-2-amine (3): The solid is purified in methanol to yield 20.34g (77.00%) of compound (3). IR (KBr pellet), ν, cm^{-1}: 3492&3303(-NH_2), 3117(Ar-H), 1639(C=N), 1328(C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 7.08 (2H, b, NH_2), 7.85-7.77 (4H, m, ArH), 8.55 (1H, S, CH), Mass: 324.0 (M+1), mp 300-302ºC.

6-chloro-9-(4-chlorophenyl)-9H-purin-2-amine (4): The solid is purified in methanol to yield 16.98g (73.00%) of compound (4). IR (KBr pellet), ν, cm^{-1}: 3500&3306(-NH_2), 3118(Ar-H), 1640(C=N), 1329(C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 7.08 (2H, S, NH_2), 7.68-7.64 (2H, m, ArH), 7.90-7.87 (2H, m, ArH), 8.54 (1H, S, CH), Mass: 380.1 (M+1), mp 271-273ºC.

9-(4-bromophenyl)-6-hydrazinyl-9H-purin-2-amine (5): The solid is purified in ethanol to yield 12.27g (83.00%) of compound (5). IR (KBr pellet), ν, cm^{-1}:3448&3307(-NH_2), 3202(N-H), 1361(C-H), 1533(N-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 4.85 (2H, b, NH_2), 6.20 (2H, S, NH_2), 7.75-7.72 (2H, m, ArH), 7.88-7.85 (2H, m, ArH), 8.19 (1H, S, CH), 8.74 (1H, b, NH), Mass: 320.1(M+1), mp 229-231ºC.

9-(4-chlorophenyl)-6-hydrazinyl-9H-purin-2-amine (6): The solid is purified in ethanol to yield 11.01g (86.00%) of compound (6). IR (KBr pellet), ν, cm^{-1}: 3455&3407(-NH_2), 3255(N-H), 3067(Ar-H), 1361(C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 4.65 (2H, S, NH_2), 6.12 (2H, S, NH_2), 7.62-7.59 (2H, m, ArH), 7.94-7.91 (2H, m, ArH), 8.17 (1H, S, CH), 8.72 (1H, S, NH), Mass: 276.0 (M+1), mp 243-245ºC.

6-((E)-2-(2-chloro benzylidene) hydrazinyl)-9-(4-bromophenyl)-9H-purin-2-amine (7): The solid is purified in ethanol to yield 1.26g (91.00%) of compound (7). IR (KBr pellet), ν, cm^{-1}: 3320&3203(-NH_2), 1631(C=N), 1358 (C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 7.00 (2H, b, NH_2), 7.87-7.41 (8H, m, ArH), 8.36 (1H, S, CH), 8.42 (1H, S, CH), 12.37 (1H, b, NH), Mass: 442.1 (M+1), mp 272-275ºC.

6-((E)-2-(4-bromobenzylidene) hydrazinyl)-9-(4-bromophenyl)-9H-purin-2-amine (8): The solid is purified in ethanol to yield 1.41g (93.00%) of compound (8). IR (KBr pellet), ν, cm^{-1}: 3204(N-H), 2968(Ar-H) 1664(C=N), 1320 (C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 7.15 (2H, b, NH_2), 7.86-7.65 (8H, m, ArH), 8.40-8.43 (2H, S, 32CH), 12.30 (1H, b, NH), Mass: 486.0 (M+1), mp 292-296ºC.

6-((E)-2-(5-bromo-2-chlorobenzylidene) hydrazinyl)-9-(4-bromophenyl)-9H-purin-2-amine (9): The solid is purified in ethanol to yield 1.46g (90.00%) of compound (9). IR (KBr pellet), ν, cm^{-1}: 3367&3280(-NH_2), 3205(N-H), 3059 (Ar-H), 1619(C=N), 1356 (C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 7.16 (NH_2), 7.87-7.17 (7H, m, ArH), 8.51-8.46 (2H, S, 2CH), 12.61 (1H, b, NH), Mass: 520.0 (M+1), mp 274-277ºC.

6-((E)-2-(4-hydroxy benzylidene) hydrazinyl)-9-(4-bromophenyl)-9H-purin-2-amine (10): The solid is purified in ethanol to yield 1.15g (87.00%) of compound (10). IR (KBr pellet), ν, cm^{-1}: 3499(O-H), 3288&3173(-NH_2), 1608(C=N), 1309(C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 6.84 (2H, m, NH_2), 7.87-7.08 (8H, m, ArH), 8.37-8.33 (2H, S, 2CH), 9.96(OH), 12.03 (NH). Mass: 424.1(M+1), mp 290-292ºC.

6-((E)-2-(4-fluoro benzylidene) hydrazinyl)-9-(4-bromophenyl)-9H-purin-2-amine (11): The solid is purified in ethanol to yield 1.11g (83%) of compound (11). IR (KBr pellet), ν, cm^{-1}: 3257&3157(-NH_2), 3068(Ar-H), 1619(C=N), 1339 (C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 7.09 (NH_2), 7.97-7.29 (8H, m, ArH), 8.43 (1H, S, CH), 8.72 (1H, S, CH), 12.37 (NH), Mass: 426.1 (M+1), mp 279-280ºC.

6-((E)-2-(4-bromobenzylidene) hydrazinyl)-9-(4-chlorophenyl)-9H-purin-2-amine (12): The solid is purified in ethanol to yield 1.45g (89.00%) of compound (12). IR (KBr pellet), ν, cm^{-1}: 3489&3263(-NH_2), 3176(N-H), 3102(Ar-H), 1665(C=N), 1335 (C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 7.00 (2H, b, NH_2), 7.92-7.64 (8H, m, ArH), 8.41-8.39 (2H, S, 2CH), 12.32 (1H, b, NH), Mass: 442.1 (M+1), mp 294-298ºC.

6-((E)-2-(2-chlorobenzylidene) hydrazinyl)-9-(4-chlorophenyl)-9H-purin-2-amine (13): The solid is purified in ethanol to yield 1.21g (84.00%) of compound (13). IR (KBr pellet), ν, cm^{-1}: 3514&3307(-NH_2), 3182(N-H), 3111(Ar-H), 1622(C=N), 1331 (C-H). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 6.58 (2H, b, NH_2), 8.19-7.41 (8H, m, ArH), 8.41-8.36 (2H, S, 2CH), 8.75 (1H, S, CH), 12.31 (1H, b, NH), Mass: 398.1 (M+1), mp 239-241ºC.

9-(4-bromophenyl)-6-methoxy-9H-purin-2-amine (14): The solid is purified in ethanol to yield 0.77g (78.00%) of compound (14). IR (KBr pellet), ν, cm^{-1}: 3411&3341(-NH_2), 2963(Aliphatic C-H), 1605(C=N), 1331(C-H), 1284 (O-CH_3). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 4.00 (3H, S, CH3), 6.61 (2H, S, NH_2), 7.77-7.74 (2H, m, ArH), 7.86-7.83 (2H, m, ArH), 8.31 (1H, S, CH), Mass: 320.1(M+1), mp 202-204ºC.

9-(4-bromophenyl)-6-ethoxy-9H-purin-2-amine (15): The solid is purified in ethanol to yield 0.92g (88.00%) of compound (15). IR (KBr pellet), ν, cm^{-1}: 3403&3340(-NH_2), 2981(Aliphatic C-H), 1608(C=N), 1350(C-H), 1288(O-CH_2). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 1.38 (3H, t, CH_3), 4.50(2H, q, CH_2), 6.56 (2H, S, NH_2), 7.87-7.74 (4H, m, ArH), 8.31 (1H, S, CH), Mass: 334.1(M+1), m.p 238-241ºC.

9-(4-bromophenyl)-6-isopropoxy-9H-purin-2-amine (16): The solid is purified in ethanol to yield 0.87g (81.00%) of compound (16). IR (KBr pellet), ν, cm^{-1}: 3494&3312(-NH_2), 2977(Aliphatic C-H), 1616(C=N), 1334(C-H), 1282(O-CH). ^{1}HNMR (DMSO-d_6), δ, ppm (J, Hz): 1.37 (6H, db. 2CH_3), 5.0(1H, m, CH), 6.51 (2H, S, NH_2), 7.94-7.65 (4H, m, ArH), 8.28 (1H, S, CH), Mass: 348.1 (M+1), m.p. 288-291ºC.

3. RESULTS AND DISCUSSION

The synthetic pathway followed for the synthesis of purine derivatives is presented in Scheme 1 and 2. Aryl substituted derivatives (1&2) were synthesized by reaction of different substituted anilines with 4, 6-dichloropyrimidine-2, 5-diamine Hydro chloride in refluxing n-Butanol for 3-10 hrs. They were purified by using iso propyl alcohol as a solvent (Scheme-1).

6-Chloro Purinyl derivatives (3&4) were synthesized by reaction of aryl substituted pyrimidines with triethyl ortho formate in presence of Conc. HCl at room temperature for 8-12 hrs. They were purified by using methanol as a solvent (Scheme-1).

In the present article hydrazinyl substituted purine derivatives (4&6) were synthesized by the reaction of 6-chloro purines with hydrazine hydrate in presence tri ethyl amine in refluxing ethanol for 2-4 hrs (Scheme-2).

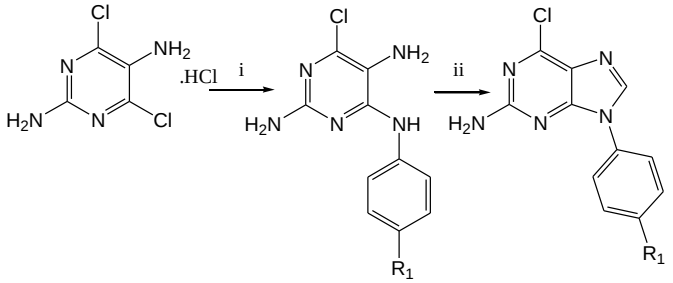
Schiff's bases of purinyl derivatives (7-13) were synthesized by reaction of hydrazinyl substituted purine derivative with different benzaldehyde derivatives in refluxing ethanol (Scheme-2). The IR spectra of 6-((E)-2-(2-chlorobenzylidene) hydrazinyl)-9-(4-bromophenyl)-9H-purin-2-amine exhibited intense bands at 3204, 1664 and 1320 cm^{-1} confirming the presence of NH, C=N and C-H groups respectively. ^1H NMR showed two singlets at δ 12.37(1H, NH) and 8.51(1H, N=CH) confirming the structure of the benzylidene derivative. Similarly, benzylidene derivatives 8-13 were synthesized from hydrazide by reacting with substituted benzaldehydes.

Formation of Schiff's base was not observed while using 9-(4-bromophenyl)-6-chloro-9H-purin-2-amine (3) instead of 9-(4-bromophenyl)-6-hydrazinyl-9H-purin-2-amine in same reaction conditions (5) and 1H NMR showing only starting material.

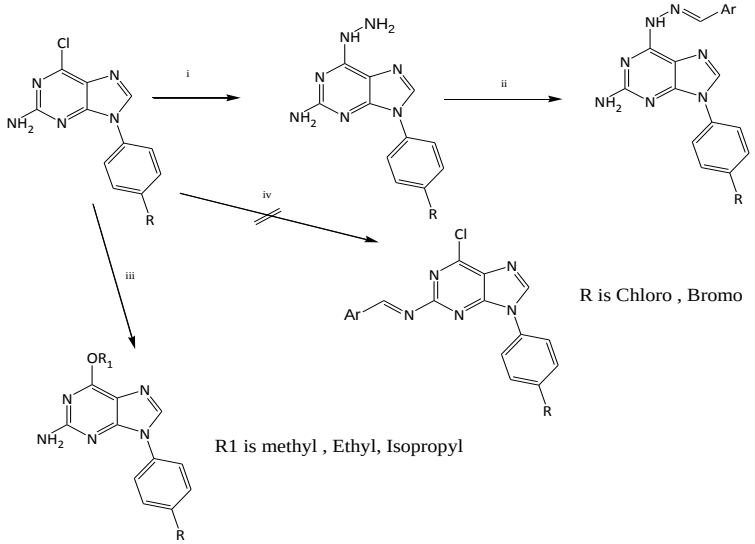
6-Alkoxy of purinyl derivatives (14-16) were synthesized by reaction 6-chloro purines with different alcohols in presence of sodium alcoxide (Scheme-2). The IR spectra of 9-(4-bromophenyl)-6-methoxy-9H-purin-2-amine (14) exhibited intense band at 1284 cm^{-1} confirming the presence of O-CH_3 group. ^1H NMR showed one singlet at δ 4.00 (3H, O-CH3) confirming the structure of the 6-methoxy derivative. Similarly, 6-Alkoxy derivatives 15-16 were synthesized from 6-chloro purine by reacting with sodium ethoxide and sodium isopropoxide respectively.

4. CONCLUSION

A new series of aryl substituted purine derivatives, the structure of these compounds was confirmed by IR, 1H NMR and MS spectral data.



Scheme 1:- Reagents and conditions: - i) Different substituted anilines/ n-Butanol, Reflux ii) Triethyl ortho formate / Conc. HCl, RT.



Scheme 2:- Reagents and conditions: - i) Hydrazine hydrate, Tri ethyl amine /Ethanol, Reflux ii) Substituted Benz aldehyde / Ethanol, Reflux iii) Alcohol/ Aq. Sodium hydroxide iv) Substituted Benz aldehyde / Ethanol Reflux.

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REFERENCES

Birkett P R, King H, Chapleo C B, Ewing D F and Mackenzie G, Synthesis of optically active-α-(imidazol-1-yl, purin-9-yl or uracil-1-yl) propanoic and succinic acid derivatives, Tetrahedron, 49,1993, 11029-11036.

Elion GB, Burg C and Hitchings GH, Studies on Condensed Pyrimidine Systems, IX. The Synthesis of Some 6-Substituted Purines, J Am Chem Soc., 74, 1952, 411.

Hotl & Wong C M, Reduction of Aromatic Nitro Compounds by Titanium (III) Chloride, Synthesis, 1, 45, 1974.

Matsumoto H, Hara S, Nagata N and Ikeda K, Synthesis of New 1-Chalcogenapurines by the Reaction of 5-Aminoimidazole-4-carbonitrile with Isochalcogenocyanates, Heterocycl., 1995, 41, 47-56.

Montgomery JA, The design of chemotherapeutic agents, Acc Chem Res., 19, 1986, 293-300.

Szarka, A murine model of pulmonary damage induced by lipopolysaccharide via intranasal instillation, J. Immunol. Methods, 202, 1997, 49-57.