Research Article

NOVEL SYNTHETIC APPROACH OF SOME 3-AMINO-4-OXO-2-SUBSTITUTED BENZOTHIAZOLYL) PYRAZOLO [3,4-*B*] PYRIDO[1,2-*A*] PYRIMIDINE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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Accepted on: 07-07-2011; **Finalized on:** 20-10-2011.

ABSTRACT

Pyrazolo pyrimido pyrimidine (4a-k) were prepared by the reaction of compound 3-Amino-4-oxo-2-(methylthio) 4H-pyrido [1, 2-*a*] pyrimidine (3) with hydrazine hydrate, phenyl hydrazine, 2-hydrazino benzothiazole & 6-substuited hydrazine benzothiazole in N,N-dimethyl formamide (DMF) and anhydrous potassium carbonate. All these synthesized compounds were characterized by elemental analysis and spectral data.

Keywords: N,N-dimethyl formamide, Potassium carbonate, Pyrazolo pyrido pyrimidine.

INTRODUCTION

Interest in the synthesis of pyrimidine derivatives are reported to exhibit antimycobacterial[1], antitumor[2], antiviral[3], anticancer, anti-inflammatory, analgesic[4], antifolate[5], antimicrobial[6], anti-fungal[7], antiproliferative[8] and antihistaminic[9] activities. They are also effective as antiplatelet agents with analgesic activity[10] and as a new drug for treatment of insomnia[11] anti-AIDS[12] and antinociceptive[13]. Fused pyrimidines are extensively used in neurology, particularly in the treatment of neurodegenerative disorders such as Parkinson's disease[14], antianxiety disorders[15], and depression[16], Fused pyrimidines are selective inhibitors for multidrug resistance (MDR)[17]. Cyclization using phosphorus oxychloride or ethanol in sodium ethoxide furnished the pyrido[1,2-*a*]pyrimidines[18].

MATERIALS AND METHODS

Melting points were determined by open capillary tubes and were uncorrected. All the reactions monitored by thin layer chromatography, carried out on 0.2 mm silica gel-C plates using iodine vapors for detection. Infrared spectra were recorded in Nujol or as potassium bromide pallets on infrared spectrophotometer, nuclear magnetic resonance spectra were obtained on brukner advance spectrophotometer 400 MHz mass spectra were recorded on FT-VC-7070 H Mass spectrometer using the EI technique at 70 ev. All the reactions were carried out under ambient atmosphere. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

General procedure

3-Cyano-4-oxo-2-(methylthio) 4H-pyrido [1, 2-*a*] pyrimidine (3): A mixture of 2-aminopyridine **(1)** (0.01 mol) and ethyl di cyano (methylthio) acrylate **(2)** (0.01 mol) in 15 mL of N, N'- dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 5 hours. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystallized from a N, N'- dimethyl formamide-ethanol mixture to give pure **(3).**

3-Amino-4-oxo-2-(6'-substituted benzothiazolyl)pyrazolo [3,4-*b*]pyrido[1,2-*a*]pyrimidine (4a-k): A mixture of **3** (0.001 mol) and independently with hydrazine hydrate (80 %), phenyl hydrazine, 4-nitro phenyl hydrazine, 2,4-dinitro phenyl hydrazine, 2-hydrazino benzothiazole, 6-methyl 2-hydrazino benzothiazole, 6-methoxy 2-hydrazino benzothiazole, 6-chloro 2-hydrazino benzothiazole, 6-nitro 2-hydrazino benzothiazole, 2,4-dimethyl 2-hydrazino benzothiazole, 6,7-chloro,fluoro 2-hydrazino benzothiazole (0.001mol) in 15 mL of N, N'-dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 6 hours. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystallized from a N, N'- dimethyl formamide- ethanol mixture to give pure **(4a-k).**

3-Cyano4-oxo-2-(methylthio)4H-pyrido[1,2-*a*]pyrimidine (3): Orange powder, yield 78 %, mp 233-238°C (dec.). IR (KBr / cm^{-1}) 1702 (C=O), 2225 (CN); 1H NMR (400 MHz, DMSO-d_6) 2.59 (s, 3H, SCH_3), 7.3-7.4 (d, 2H), 7.8-7.9 (d, 2H), 9.2 (br s, 1H, =NH). EI-MS (m/z: RA %): 217 (M+I), 100%), 215 (35). Anal. Calcd. For: $C_{10}H_8N_4S$; C, 60.35; H, 3.55; N, 24.85. Found: C, 60.30; H, 3.50; N, 24.80.

3-Amino-4-oxo-2-(2H) pyrazolo[3,4-*b*]pyrido [1, 2-*a*] pyrimidine (4a): Brown powder, yield 75 %, mp 187°C (dec.). IR (KBr/cm^{-1}) 3321cm^{-1} (NH_2 asym.)1705cm^{-1} (-C=O.). 1H NMR (400 MHz, DMSO-d_6) 4.9 (s, 1H), 7.3-7.4 (m, 4H), 5.4 (s, 2H),. EI-MS (m/z: RA %):, 201 (50%) Anal. Calcd. For $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81.

3-Amino-4-oxo -2-(phenyl) pyrazolo [3,4-*b*] pyrido [1,2-*a*] pyrimidine (4b): Brown powder, yield 62 %,mp 165°C (dec.). IR (KBr/cm^{-1}) 3221cm^{-1} (NH_2 asym.) 1700 cm^{-1} (-C=O.). 1H NMR (400 MHz, DMSO-d_6) 7.8-7.9 (m, 4H), 7.5 (S

5H),4.4 (s, 2H),. EI-MS (m/z: RA %): 277(M) , 80%), Anal. Calcd. For $C_{15}H_{11}N_5O$: C, 64.97; H, 4.00; N, 25.26

3-Amino-4-oxo-2-(4'-nitro phenyl) pyrazolo [3,4-*b*]pyrido [1,2-*a*] pyrimidine(4c): Brown powder, yield 79%, mp 169°C (dec.). IR (KBr/cm^{-1}) 3301cm^{-1} (NH_2 asym.)1690cm^{-1} (C=O.). 1H NMR (400 MHz, DMSO-d_6) , 6.9-7.2 (m, 4H), 6.1 (s, 2H),7.2(d 2H), 7.3(d 2H). EI-MS (m/z: RA %): 323(M+I), 70%), Anal. Calcd. For $C_{15}H_{10}N_6O_3$: C, 55.90; H, 3.13; N, 26.08.

3-Amino-4-oxo-2-(2',4'-dinitro phenyl) pyrazolo [3,4-*b*] pyrido [1,2-*a*] pyrimidine(4d): Brown powder, yield 68 %, mp 172°C (dec.). IR (KBr/cm^{-1}) 3300cm^{-1} (NH_2 asym.) 1685cm^{-1} (C=O.). 1H NMR (400 MHz, DMSO-d_6) 7.2(d 2H), 7.9(s 1H), 7.4-7.8 (m, 4H), 6.4 (s, 2H),. EI-MS (m/z: RA %): 367 (45) Anal. Calcd. For $C_{15}H_9N_7O_5$: C, 49.05; H, 2.47; N, 26.70.

3-Amino-4-oxo-2-(2-benzothiazolyl)pyrazolo[3,4-]pyrido [1,2-*a*] pyrimidine(4e): Brown powder, yield 74 %,mp 192°C (dec.). IR (KBr/cm^{-1}) 3340cm^{-1} (NH_2 asym.) 1675cm^{-1}(C=O.). 1H NMR (400 MHz, DMSO-d_6) 7.2(m 4H), 7.3-7.4 (m, 4H), 5.4 (s, 2H), EI-MS (m/z: RA %): 369(M+I), 50%), Anal. Calcd. For $C_{16}H_9N_6OCIS$: C, 52.11; H, 2.46; N, 22.79

3-Amino-4-oxo-2-(6'methyl-2'-benzothiazolyl) pyrazolo [3,4-*b*]pyrido[1,2-*a*] pyrimidine(4f): Brown powder, yield 68 %, mp 186°C (dec.). IR (KBr/cm^{-1}) 3380cm^{-1} (NH_2 asym.) 1690cm^{-1} (C=O.). 1H NMR (400 MHz, DMSO-d_6) 7.2(d 2H), 7.4(s 1H), 7.5-7.8 (m, 4H), 6.8 (s, 2H), 1.9(s3H). EI-MS (m/z: RA %): 348 (55%) Anal. Calcd. For $C_{17}H_{12}N_6OS$: C, 58.61; H, 3.47; N, 24.12;EI-MS (m/z: RA %): 349 (M+I) , 80%),

3-Amino-4-oxo-2-(6'methoxy-2'-benzothiazolyl) pyrazolo [3,4-*b*]pyrido[1,2-*a*]pyrimidine (4g): Brown powder, yield 72%, mp 183°C (dec.). IR (KBr/cm^{-1}) 3340cm^{-1} (NH_2asym.) 1689cm^{-1} (-C=O). 1H NMR (400 MHz, DMSO-d_6)7.1(d 2H), 6.2 (s1H), 7.5-7.9 (m, 4H), 5.9 (s, 2H),3.9(s3H). EI-MS (m/z: RA %): 364 (55%) Anal. Calcd. For $C_{17}H_{12}N_6O_2S$: C, 56.04; H, 3.32; N, 23.06.

3-Amino-4-oxo-2-(6'chloro-2'-benzothiazolyl)pyrazolo [3,4-*b*] pyrido[1,2-*a*]pyrimidine(4h): Brown powder, yield 68 %,mp 194°C (dec.). IR (KBr/cm^{-1}) 3400cm^{-1} (NH_2 asym.) 1670cm^{-1} (C=O.). 1H NMR (400 MHz, DMSO-d_6) 6.9(d 2H), 6.4(s 1H), 7.0-7.1 (m, 4H), 4.9 (s, 2H), EI-MS (m/z: RA %): 368 (55%) Anal. Calcd. For $C_{16}H_9N_6ClOS$: C, 52.11; H, 2.46; N, 22.79.

3-Amino-4-oxo-2-(6'nitro-2'-benzothiazolyl)pyrazolo[3,4-*b*] pyrido[1,2-*a*]pyrimidine(4i): Brown powder, yield 68 %,mp 182°C (dec.). IR (KBr/cm^{-1}) 3300cm^{-1} (NH_2 asym.) 1685cm^{-1} (C=O.). 1H NMR (400 MHz, DMSO-d_6) 7.5(d 2H), 7.9(s 1H), 7.1-7.2 (m, 4H), 5.4(s, 2H),. EI-MS (m/z: RA %): 379 (55%) Anal. Calcd. For $C_{16}H_9N_7O_3S$: C, 50.66; H, 2.39; N, 25.85.

3-Amino-4-oxo-2-(4',6'dimethyl-2'-benzothiazolyl)pyrazolo[3,4-*b*]pyrido[1,2-*a*]pyrimidine (4j): Brown powder, yield 68 %,mp 167°C (dec.). IR (KBr/cm^{-1}) 3340cm^{-1} (NH_2 asym.) 1670cm^{-1} (C=O.). 1H NMR (400 MHz, DMSO-d_6) 7.6 (s2H), 7.0-7.4 (m, 4H), 5.8 (s, 2H), 1.9(s6H). EI-MS (m/z: RA %): 362 (55%) Anal. Calcd. For $C_{18}H_{14}N_6OS$: C, 59.65; H, 3.89; N, 23.19.

3-Amino-4-oxo-2-(6',7'-chloro,floro-2'benzothiazolyl) pyrazolo [3,4-*b*] pyrido [1,2-*a*] pyrimidine (4k): Brown powder, yield 68 %,mp 150°C (dec). IR (KBr/cm^{-1}) 3340cm^{-1} (NH_2 asym.) 1698cm^{-1} (-C=O.). 1H NMR (400 MHz, DMSO-d_6) 7.5(d 2H), 7.8-8.4 (m, 4H), 5.2 (s, 2H),. EI-MS (m/z: RA %): 386 (55%) Anal. Calcd. For $C_{16}H_8ClFN_6OS$: C, 49.68; H, 2.08; N, 21.73.

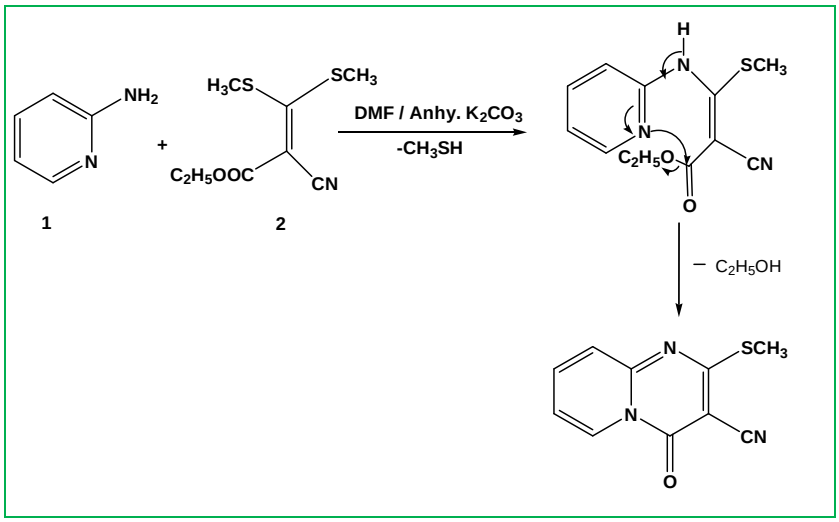
Antimicrobial activity

The synthesized compounds were evaluated for their antibacterial activity against gram-positive species *S. aureus* and *B. substilis* and gram-negative species *E. coli* and *S. typhi* by paper disc diffusion method[19]. All the synthesized compounds were dissolved in dimethyl sulphoxide. The synthesized compounds exhibited zone of inhibition of 09-13 mm in diameter whereas standard Streptomycin exhibited zone of inhibition of 18 and 22 mm in diameter against *S. aureus* and *B. substilis* and Penicillin exhibited zone of inhibition of 15 and 16 mm in diameter against *E. coli* and *S. typhi* respectively. Amongst the synthesized compounds **4,** compound **4g** (9, 12, 13, 10 mm) and **4h** (11, 11, 10, 12) showed higher zone of inhibition against *S. aureus, B. substilis, E. coli* and *S. typhi* respectively. It seems that the presence of OCH_3 & Cl group at 10-position **4a** increases antibacterial activity.

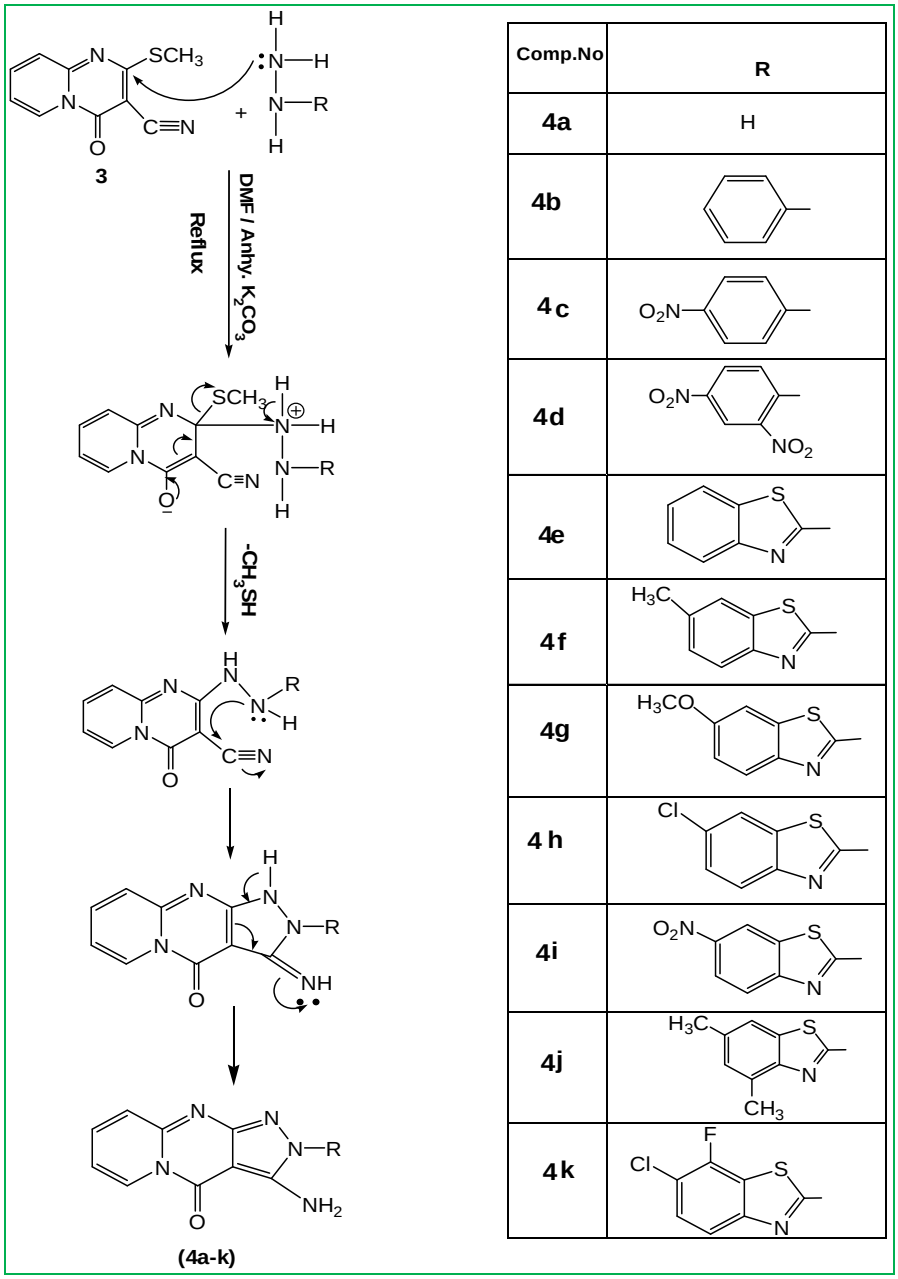
RESULTS AND DISCUSSION

In the present communication, we have developed new methodology towards the synthesis of 3-Amino -4-oxo-2-(6'-substituted benzothiazolyl) pyrazolo [3,4-*b*] pyrido [1, 2-*a*] pyrimidine **(4)** Our method gives single product with high yield. The reaction started with 2-aminopyridines (**1**) and ethyl dicyano (methylthio) acrylate **(2)** were refluxed in N,N-dimethyl formamide (DMF) in presence of catalytic amount of anhydrous potassium carbonate to afford **(3). Scheme-1**

The compound **(3)** possess replaceable active methylthio group at 2- position which is activated by the ring 1-nitrogen atom, electron withdrawing 3-cyano group. Compound **(3)** was reacting with hydrazine hydrate in presence of N,N-dimethyl formamide (DMF) and catalytic amount of anhydrous potassium carbonate afforded the compound 4a in 78 % yield . the subsequently compound **(3)** independently heating with phenyl hydrazine ,4-nitro phenyl hydrazine, 2,4-dinitro phenyl hydrazine, 2-hydrazino benzothiazole, 6-methyl 2-hydrazino benzothiazole, 6-methoxy 2-hydrazino benzothiazole, 6-chloro 2-hydrazino benzothiazole, 6-nitro 2-hydrazino benzothiazole,2,4- dimethyl 2-hydrazino benzothiazole, 6,7-chloro,fluoro 2-hydrazino benzothiazole to obtain 3-Amino -4-oxo-2-(6'-substituted benzothiazolyl) pyrazolo [3,4-*b*] pyrido [1, 2-*a*] pyrimidine derivatives **(4a-k)** respectively. **Scheme-2**



Scheme 1: Formation of fused pyrido [1, 2-*a*] pyrimidine.



Comp.No	R
4a	H
4b	
4c	
4d	
4e	
4f	
4g	
4 h	
4i	
4j	
4k	

Scheme 2: Formation of 3-Amino-4-oxo-2-(6'-substituted benzothiazolyl) pyrazolo[3,4-*b*]pyrido[1,2-*a*]pyrimidine derivatives.

Table 1: Antibacterial activity of compound (3-4k)

Diameter in mm of zone of inhibition at 25 µg/disc				
Compound No	***S.aureus***	***B.substilis***	***E. coli***	***S. typhi***
3	06	08	10	09
4a	09	07	11	10
4b	07	08	09	11
4c	06	08	12	10
4d	08	07	12	09
4e	07	08	10	09
4f	08	08	11	10
4g	09	**12**	**13**	10
4h	**11**	**11**	10	**12**
4i	**0**8	10	09	09
4j	07	09	10	10
4k	10	07	10	09
Streptomycin	18	22	-	-
Penicillin	-	-	15	16

The structure of these newly synthesized compounds were established on the basis of elemental analysis, IR, PMR and MASS Spectral data, spectral studies of all compounds shows that compounds are stable & do not exhibit any tautomerism.

CONCLUSION

In conclusion, we have described a convenient and practical procedure for the preparation of some novel pyrido[1,2-*a*] pyrimidine derivatives by the condensation of 2-amino-4,6,7-substuited benzothiazole catalyzed by anhy.K_2CO_3. The milder reaction conditions, simple workup, and good yields are the most significant advantages of this new procedure in synthesis of these potential biologically active compounds. The elemental and spectroscopy analysis of FTIR, 1H- and 13C-NMR were in good agreement with the proposed structure

Acknowledgements: The authors are grateful to Dr. N. V. Kalyankar, Principal, Yeshwant Mahavidyalaya, Nanded, for providing laboratory facilities, To UGC New Delhi for financial assistance under major research project (F.N 39-834/2010 SR) and Director, Indian Institute of Chemical Technology, Hyderabad, for providing spectra.

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