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Research Article

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Synthesis, Characterization and Antibacterial Activity of 3-amino-6,9-dimethyl-4-oxo-Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole.

Gangadhar S Bhopalkar*

*Department of Chemistry, Rajiv Gandhi Mahavidyalaya Mudkhed, Dist. Nanded. (MS), India.431806
*Corresponding author. E-mail: gswagh.chem@gmail.com

Abstract
Novel fused heterocyclic compound 3-amino-6,9-dimethyl-4-oxo pyrazolo[3,4-*e*]-pyrimido[2,1-*b*][1,3] benzothiazole (4) was prepared by the reaction of 3-cyano-6, 9-dimethyl- 4-oxo 2-methylthio-4H-pyrimido[2,1-*b*][1,3] benzothiazole (3) with hydrazine hydrate in presence of anhydrous K_2CO_3 in DMF. The compound (3) was synthesized by the reaction of 2-amino- 4,7- dimethyl [1, 3] benzothiazole (1) with Ethyl -2-cyano-3,3'-bis-methylthio acrylate (2). All the synthesised compounds were characterised by spectral analysis and evaluated for their antibacterial activity against *E. coli* and *S. aureus* microorganism.

Keywords: 2-amino- 4,7- dimethyl [1, 3] benzothiazole, Pyrimido Benzothiazole, Hydrazine hydrate, K_2CO_3

1. Introduction

The heterocyclic compounds containing nitrogen and sulphur atom shows various pharmacological and biological activities [1]. A survey of the literature reveals that few references are available on the synthesis and biological activity of heterocycles containing a benzothiazole fused with the pyrimidine ring. Kamlesh D. Niranjane *et al* [2] reported some novel derivatives of 2-amino-3-cyano-14-imino-10-methoxy-4-methylthio pyrimido [2,1-*b*] pyrazolo [4,5-*d*] pyrimido [2,1-*b*] benzothiazole and its anti-inflammatory activity. Kaur R., Chaudhary [3] reported the drug Ibrutnib contain fused pyrazolo pyrimido exhibited activity against chronic lymphocytic leukemia cancer. Fatemeh Chadegani et al [4] reported an efficient one pot three component method for the synthesis of fused pyrimido benzothiazole and its derivatives. Abdel-Mohsen H T et al [5] synthesized fused pyrimido benzothiazole derivatives from catechols and 6-substituted 1, 2, 3, 4-tetrahydro-4-oxo-2-thioxo-5-pyrimidinecarbonitriles using aerial O_2 as the oxidant. Anil b. chidrawar et al [6] reported the multicomponent synthesis of new 2-substituted derivatives of 3-amino-4-imino-8- nitro-2*H*-pyrazolo [3,4-*e*]pyrimido[2,3- *b]*[1,3]benzothiazole. Mortimer et al. [7] reported in *vitro* antitumor properties of 2-(3, 4-dimethoxyphenyl)-5-fluorobenzothiazole. Benzothiazole containing phthalimide derivatives [8] also exhibited *in-vitro* cytotoxicity on human cancer cell lines. Vijay N. Bhosale et al [9] reported antibacterial activity of Aryl / Heteryl fused pyrazolo [3c,4c: 4,5] pyrimido[2,1-*b*][1,3]benzothiazoles and its 2-substituted derivatives and G.S Waghmare et al [10] reported the synthesis and *in-vitro* anticancer activity of 3-cyano-6,9-dimethyl-4-imino 2-methylthio 4*H*-pyrimido [2,1-*b*] [1,3] benzothiazole and its 2-substituted derivatives.

In view of the reported biological activities of fused heterocyclic compound ,the present work, reported on the synthesize of novel fused heterocyclic compound 3-amino - 6, 9-dimethyl- 4-oxo pyrazolo[3,4-*e*]pyrimido[2,1-*b*][1,3] benzothiazole (4) was synthesized by the reaction of 3-cyano-6, 9-dimethyl- 4-oxo 2-methylthio-4*H*-pyrimido[2,1-*b*][1,3] benzothiazole (3) with hydrazine hydrate in presence of anhydrous K_2CO_3 in DMF. The

compound 3-cyano-6, 9-dimethyl- 4-oxo 2-methylthio-4*H*-pyrimido[2,1-*b*][1,3] benzothiazole (3) was synthesized by the reaction of 2-amino- 4,7- dimethyl [1, 3] benzothiazole (1) with Ethyl -2-cyano-3,3'-bis-methylthio acrylate (2). All the synthesised compounds were characterized by spectral analysis and compound (3) and (4) were evaluated for their antibacterial activities.

2. Results and Discussion

The parent compound **(3)** was prepared by the reaction of 2-amino- 4,7- dimethyl [1, 3] benzothiazole **(1)** with Ethyl -2-cyano-3,3'-bis-methylthio acrylate **(2)** in presence of anhydrous K_2CO_3 in DMF as solvent. The anhydrous K_2CO_3 play an important role to maintain the basic condition which favour the cyclization during reaction progress. A new fused heterocyclic compound 3-amino - 6, 9-dimethyl- 4-oxo pyrazolo[3,4-e] -pyrimido[2,1-*b*][1,3] benzothiazole **(4)** was prepared by the reaction of 3-cyano-6, 9-dimethyl- 4-oxo 2-methylthio-4H-pyrimido[2,1-*b*][1,3] benzothiazole **(3)** with hydrazine hydrate in presence of anhydrous K_2CO_3 in DMF. The compound **(4)** possesses fused pyrazolo pyrimido benzothiazole moiety which has been reported as better pharmacophore to exhibit biological activities. The conversion of 2-amino- 4,7- dimethyl [1, 3] benzothiazole **(1)** into 3-amino - 6, 9-dimethyl- 4-oxo pyrazolo[3,4-*e*] -pyrimido[2,1-*b*][1,3] benzothiazole **(3)** exhibit the absence of peak between 3300-3600 cm^{-1} due to -NH_2 and presence of absorption peak at 2210 cm^{-1} due to –CN functional groups in compound **(3)** in their IR spectra. Consequently, the transformation of compound (**3)** in to **(4)** exhibited the absorption peak between 3300-3600 cm^{-1} due to -NH_2 functional group and absence of absorption peak at 2210 cm^{-1} in compound **(4)** in their IR spectra. The mechanism for the formation of compound fused pyrazolo pyrimido benzothiazole given in mechanism**.** All the synthesized compounds were characterized by IR, ^{1}H NMR, and Mass spectral analysis.

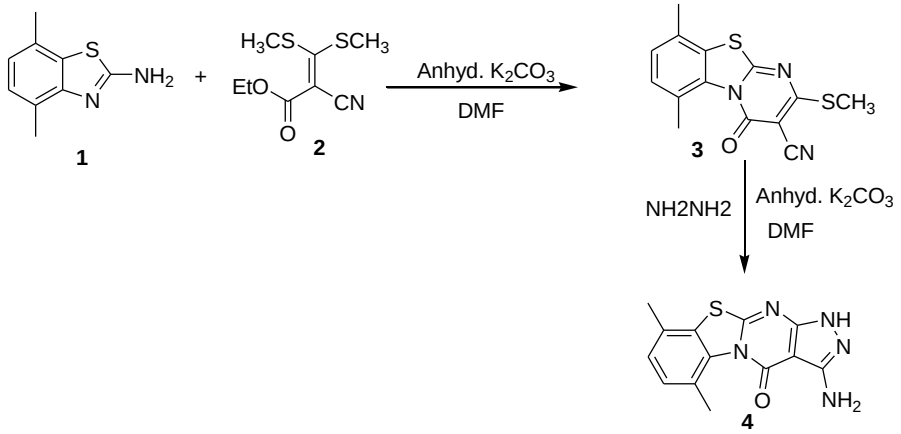
3.1 Antibacterial Activity

The synthesized compounds were screened for their antibacterial activity against *E. coli* and *S. aureus* microorganism which are characteristics type of gram –ve and gram +ve bacteria. Antibacterial activities of these compounds were performed by disc diffusion method [11]. Ceprofloxin was used to determine the zone of inhibition as standard which exhibited zone of inhibition 14 mm. These tested fused heterocyclic compounds exhibited potent antibacterial activity against gram +ve and gram-ve bacteria. The zones of inhibition exhibited by the compounds have been reported in table 1.

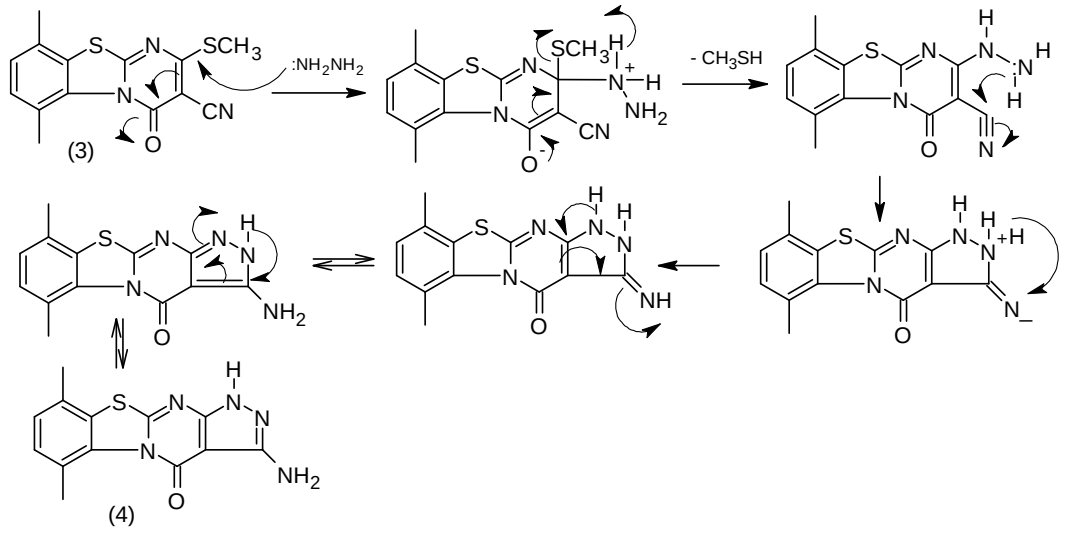
Table 1: Antibacterial activity: (Zone of inhibition in mm)

Compound	Zone of inhibition in mm	
	Gram+ bacteria	Gram –ve Bacteria
3	10	09
4	12	11

Reaction Scheme



Mechanism:



Experimental Section

The melting points of synthesized compounds were determined in open capillary tubes and are uncorrected. The reactions were monitored by thin layer chromatography. Infrared (IR) spectra compounds were recorded in KBr pallet on SHIMADZ-FTIR Spectrophotometer in cm^{-1}. The PMR spectra of compounds were recorded on FT Gemini 300MHz Spectrometer using DMSO-d^6/$CDCl_3$ and TMS as an internal reference. Chemical shift values are expressed in δ (ppm). Mass spectra were recorded on SCHIMADZU- GCMS Spectrometer using EI technique

General Method

Synthesis of 3-cyano-6, 9-dimethyl- 4-oxo 2-methylthio-4*H*-pyrimido[2,1-*b*][1,3] benzothiazole (3) : A mixture of 2-amino 4,7-dimethyl [1,3]benzothiazole (0.01 mole) and Ethyl 2-cyano 3,3' bis-methylthio acrylate (0.01 mole) was refluxed for 4-5 hours in presence of anhydrous K_2CO_3 in DMF as solvent. The reaction mixture was monitored with TLC, cooled at room temperature and poured in ice cold water. The solid product was separate out by filtration and recrystallized from ethanol. Yield:70%, M.P=240^{0}C, IR(KBr / cm^{-1}):3025, 2950 cm^{-1}(=C-H), 2202 cm^{-1} (CN), 1624 cm^1 (C=N). ^{1}HNMR:(DMSO-d^6): δ2.2 (s 3H -SCH_3), δ 2.3 (s 3H Ar-CH_3), δ 2.35 (s 3H Ar-CH_3), δ 6.6 (d 1H Ar-H), δ 7.1 (d 1H Ar-H). Mass : (m/z): 301 (50%), M.F: $C_{14}H_{11}N_3OS_2$ Found 301, Calculate (%):C 55.79, H 3.68, N 13.94,O 5.31 and S 21.28.

Synthesis of 3-amino-6, 9-dimethyl- 4-oxo pyrazolo[3,4-*e*] -pyrimido[2,1-*b*][1,3] benzothiazole (4): A mixture of 3-Cyano -6, 9-dimethyl -4-oxo 2-methylthi 4H-pyrimido [2, 1-*b*] [1, 3] benzothiazole **(**0.01mole) and Hydrazine hydrate 5 ml, was refluxed in the presence of 25ml of dimethyl formamide and a pinch of anhydrous potassium carbonate (0.5gm) for five hours. The reaction mixture was cooled to room temperature and poured in ice cold water. The separated solid product was filtered, washed with water and recrystallized from DMF-ethanol. Yield 40 %, M.P=284^{0}C, IR(KBr/cm^{-1}): 3406, 3329 cm^{-1} (-NH_2), 3025,2950 cm^{-1}(=C-H), 2210 cm^{-1} (CN), 1624 cm^1 (C=N). ^{1}HNMR:(DMSO-d^6): δ 2.3 (s 3H Ar-CH_3), δ 2.35 (s 3H Ar-CH_3), δ 4.2 (s 2H NH_2) δ 6.6 (d 1H Ar-H), δ 7.0 (d 1H Ar-H), δ 12.9 (s1H NH). Mass : (m/z): 284 (30%), M.F: $C_{13}H_{12}N_6S$ Found 284, Calculate (%):C 54.91, H 4.25, N 29.56, and S 11.28.

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