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Research Article

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Synthesis and Characterization of 3-Cyano- 9,12-Dimethyl -4,14-Dioxo-2-Methylthio- Pyrimido[2,3-b]Pyrazolo[3,4-e]Pyrimido[2,3-b][1,3]Benzothiazole and its 2-Substituted Derivatives

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Abstract A novel fused heterocyclic compound 3-cyano- 9, 12-dimethyl -4, 14-dioxo- 2-methylthio- Pyrimido[2,3-*b*] Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole (3) was prepared by the reaction of 3-amino - 6, 9-dimethyl-4-oxo pyrazolo[3,4-*e*]-pyrimido[2,1-*b*][1,3] benzothiazole (1) with Ethyl-2-cyano-3,3'-bis-methylthio acrylate (2) in presence of anhydrous K_2CO_3 in DMF. Moreover the compound (3) has thiomethyl functionality at 2- position act as best leaving group, which was get substituted different selected nucleophile like, p-chloro phenol, p-Toludine and pyrrolidine gives its 2-substituted derivatives (4a-c).

Keywords K_2CO_3, DMF, 2-amino- 4,7- dimethyl [1, 3] benzothiazole**,** Pyrimido Pyrazolo Pyrimido Benzothiazole

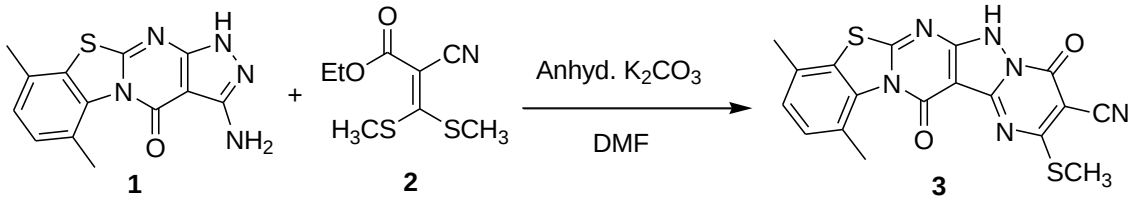
Introduction

Benzothiazole consist of sulfur-containing heterocycles and involves a benzene ring fused to a thiazole ring. Benzothiazole plays an important role in the field of medicinal chemistry and exhibited wide range of biological activities including anti-cancer [1-2], anti-bacterial [3-4], anti-tuberculosis [5-6], anthelmintic [7], anti-oxidant [8]. 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. K.G Baheti et al [9] reported Synthesis of 3-Amino-4-oxo-(2*H*)-pyrazolo[3′,4′:4,5]pyrimido-[2,1-*b*]benzothiazole and its 2- and 3-Substituted Derivatives. Kamlesh D. Niranjane *et al* [10] 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 [11] reported the drug Ibrutnib contain fused pyrazolo pyrimido exhibited activity against chronic lymphocytic leukemia cancer. Anil b. chidrawar et al [12] reported the multicomponent synthesis of new 2-substituted derivatives of 3-amino-4-imino-8- nitro-2H-pyrazolo [3,4-*e*]pyrimido[2,3- *b]*[1,3]benzothiazole. G.S Waghmare et al [13] reported the synthesis and *in-vitro* anticancer activity of 3-cyano-6,9-dimethyl-4-imino 2-methylthio 4H-pyrimido [2,1-*b*] [1,3] benzothiazole and its 2-substituted derivatives.

Present work, reported on the synthesis of novel fused heterocyclic compound 3-cyano- 9, 12-dimethyl -4, 14-dioxo-2-methylthio- Pyrimido[2,3-*b*] Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole (3). The compound (3) was synthesized by the reaction of 3-amino - 6, 9-dimethyl- 4-oxo pyrazolo[3,4-*e*]-pyrimido[2,1-*b*][1,3] benzothiazole (1) with Ethyl-2-cyano-3,3'-bis-methylthio acrylate (2) in presence of anhydrous K_2CO_3 in DMF. The compound 3 has thiomethyl functional group at 2- position which acts as better leaving group. Further reaction of compound 3

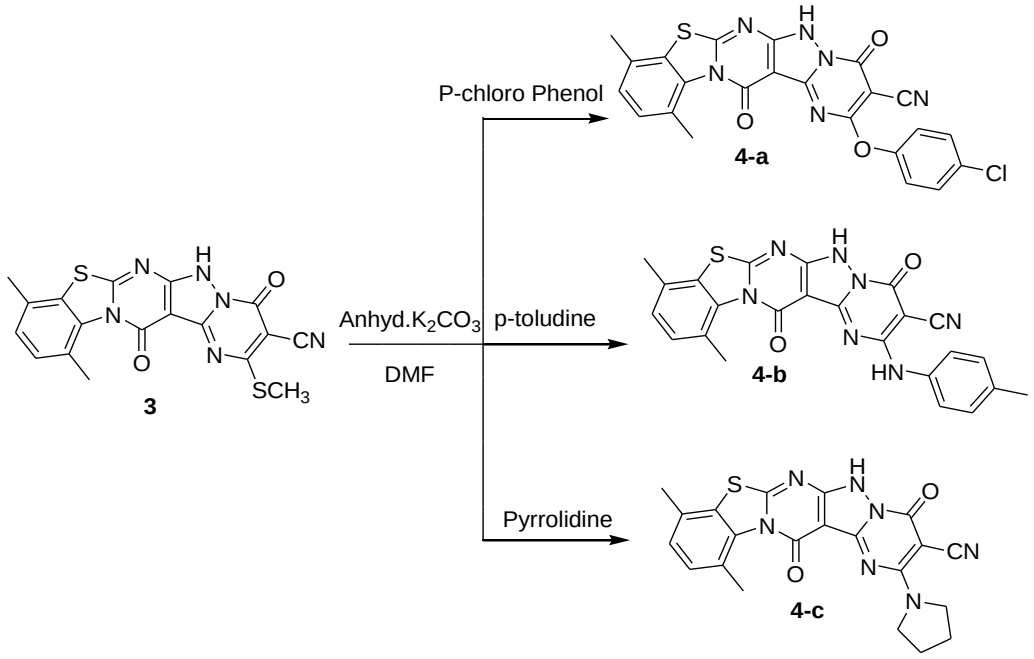
was carried out with different selected nucleophile like, p-chloro phenol, p-Toludine and pyrrolidine independently give 2-substituted derivatives (4a-c) as shown in reaction scheme-II.

Reaction Scheme I



1 **2** **3**

Reaction Scheme II



3 **4-a** **4-b** **4-c**

Result and Discussion

In continuation to earlier research reported [14] by our research group compound **1** was reported by the reaction of 3-cyano-6, 9-dimethyl- 4-oxo 2-methylthio-4H-pyrimido[2,1-*b*][1,3] benzothiazole with hydrazine hydrate in presence of anhydrous K_2CO_3 in DMF The compound **1** has four heterocyclic rings with amino functional group at 3- position, which proceeds further cyclization. Reaction of 3-amino - 6, 9-dimethyl- 4-oxo pyrazolo[3,4-*e*]-pyrimido[2,1-*b*][1,3] benzothiazole **1** with cyclising reagent Ethyl -2-cyano-3,3'-bis-methylthio acrylate **2** in presence of anhydrous K_2CO_3 in DMF as solvent to afford 3-cyano- 9, 12-dimethyl -4, 14-dioxo- 2-methylthio- Pyrimido[2,3-*b*] Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole **3.** The compound **3** possesses five heterocyclic rings fused with each other and has thiomethyl functionality at 2- position. The compound **3** shows absorption peak at 2210 cm^{-1} due to –CN stretching frequency in their IR spectrum. Anhydrous K_2CO_3 was used to maintain basic condition which favours cyclization reaction.

The derivatives **4a-c** of compound **3** (fused pyrimido pyrazolo pyrimido benzothiazole**)** were prepared by refluxing a mixture of 3-cyano- 9, 12-dimethyl -4, 14-dioxo- 2-methylthio- Pyrimido[2,3-*b*] Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole **3** with different selected nucleophile p-chlorophenol / p-toludine / pyrrolidine independently in presence of anhydrous K_2CO_3 in DMF as shown in reaction scheme-II. The progresses of reactions were monitored by TLC and reaction mixture was kept for overnight. Reaction mixture was poured in ice cooled water solid separate out and recrystallized from mixture of DMF/Ethanol. All the synthesized compounds were characterized by IR, NMR & Mass spectroscopy.

Experimental Section

The melting points of all synthesized compounds were determined in open capillary tubes and were uncorrected. The progress of reactions was monitored by thin layer chromatography. Infrared (IR) spectra of 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- 9, 12-dimethyl -4, 14-dioxo- 2-methylthio- Pyrimido[2,3-*b*] Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole 3

A mixture of 3-amino - 6, 9-dimethyl- 4-oxo pyrazolo[3,4-*e*]-pyrimido[2,1-*b*][1,3] benzothiazole **1** (0.01 mole) and Ethyl -2-cyano-3,3'-bis-methylthio acrylate **2** (0.01 mole) was refluxed for 4 hour in presence of anhydrous K_2CO_3 in DMF. The progress of reaction was monitored by TLC, cooled at room temperature and poured in to ice cold water, solid product was separate out , recrystallized from ethanol and DMF. Yield : 50 %, M.P = 310 ^{0}C; IR(KBr/cm^{-1}): 3320 cm^{-1} (-NH) , 3015, 2930 cm^{-1}(=C-H), 2210 cm^{-1} (CN), 1630 cm^1 (C=N). ^{1}HNMR:(DMSO-d^6): δ2.1 (s 3H -SCH_3), δ 2.2 (s 3H Ar-CH_3), δ 2.3 (s 3H Ar-CH_3), δ 6.5 (d 1H Ar-H), δ 6.9 (d 1H Ar-H). δ 13 (s 1H N-H). Mass : (m/z): 301 (50%), M.F: $C_{18}H_{12}N_6O_2S_2$: Found 408, Calculate (%):C 52.93, H 2.96, N 20.58,O 7.83, S 15.70.

General method for the synthesis of compounds 4a-c

Equimolar mixture of 3-cyano- 9, 12-dimethyl -4, 14-dioxo- 2-methylthio- Pyrimido[2,3-*b*] Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole **3** and selected nucleophile p-chlorophenol/ p-Toludine/ pyrrolidine independently refluxed for 5-6 hours in presence of anhydrous K_2CO_3 in DMF. Reaction mixture was monitored by Thin layer chromatography, cooled at room temperature, kept overnight and poured in ice cold water. Product was separate out recrystalized from methanol and DMF. Yield 40-50%.

3-cyano- 9, 12-dimethyl -4, 14-dioxo- 2-(4-chlorophenoxy) Pyrimido[2,3-*b*] Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole 4-a: yield 40%, M.P= 320^{0}C, IR(KBr/cm^{-1}): 3315 cm^{-1} (-NH) , 3025, 2910 cm^{-1}(=C-H), 2210 cm^{-1} (CN), 1635 cm^1 (C=N). ^{1}HNMR:(DMSO-d^6): δ 2.2 (s 3H Ar-CH_3), δ 2.3 (s 3H Ar-CH_3), δ 6.5-7.5 (m 6H Ar-H), δ 13 (s 1H N-H). Mass : (m/z): 488 (40%), M.F: $C_{23}H_{13}N_6O_3SCl$: Found 488, Calculate (%):C 56.50, H 2.68, N 17.19,O 9.82, S 6.56, Cl 7.25.

3-cyano- 9, 12-dimethyl -4, 14-dioxo- 2-(p-toludino) Pyrimido[2,3-*b*] Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole 4-b: yield 50%, M.P= 327^{0}C, IR(KBr/cm^{-1}): 3310 cm^{-1} (-NH) , 3015, 2915 cm^{-1}(=C-H), 2210 cm^{-1} (CN), 1630 cm^1 (C=N). ^{1}HNMR:(DMSO-d^6): δ 2.2 (s 6H Ar-CH_3), δ 2.3 (s 3H Ar-CH_3), δ 4.2 (s 1H NH) δ 6.6-7.0 (m 6H Ar-H), δ 13 (s 1H N-H). Mass : (m/z): 467 (50%), M.F: $C_{24}H_{17}N_7O_2S$: Found 467, Calculate (%):C 61.66, H 3.67, N 20.97,O 6.84, S 6.86.

3-cyano- 9, 12-dimethyl -4, 14-dioxo- 2-(Pyrrolidino) Pyrimido[2,3-*b*] Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole 4-c: yield 45%, M.P= 305^{0}C, IR(KBr/cm^{-1}): 3320 cm^{-1} (-NH) , 3025, 2910 cm^{-1}(=C-H), 2210 cm^{-1} (CN), 1629 cm^1 (C=N). ^{1}HNMR:(DMSO-d^6): δ 1.5 (t 4H -CH_2), δ 2.9 (t 4H -CH_2), δ 2.2 (s 3H Ar-CH_3), δ 2.3 (s 3H Ar-CH_3), δ 6.5 (d 1H Ar-H), δ 6.9 (d 1H Ar-H) δ 13 (s 1H N-H). Mass : (m/z): 431 (60%), M.F: $C_{21}H_{17}N_7O_2S$: Found 431, Calculate (%):C 58.46, H 3.97, N 22.72,O 7.42, S 7.43.

Conclusion

New heterocyclic compound 3-cyano- 9, 12-dimethyl -4, 14-dioxo- 2-methylthio- Pyrimido[2,3-*b*] Pyrazolo[3,4-*e*] Pyrimido[2,3-*b*][1,3] Benzothiazole was prepared and its-2- substituted derivatives were synthesized by using selected nucleophiles p-chlorophenol/ p-Toludine/ pyrrolidine independently.

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References

[1]. Kok, S.H.L.; Gambari, R.; Chui, C.H.; Yuen, M.C.W.; Lin, E.; Wong, R.S.M.; Lau, F.Y.; Cheng, G.Y.M.; Lam, W.S.; Chan, S.H.; et al. (2008**)** Synthesis and anti-cancer activity of benzothiazole containing phthalimide on human carcinoma cell lines. *Bioorg. Med. Chem. 16*, 3626–3631.

[2]. Heo, Y.; Song, Y.S.; Kim, B.T.; Heo, J.N. (2006) A highly regioselective synthesis of 2-aryl-6-chlorobenzothiazoles employing microwave-promoted Suzuki–Miyaura coupling reaction. *Tetrahedron. Lett. 47*, 3091–3094.

[3]. Alaimo, R.J.; Pelosi, S.S.; Freedman, R. (1978). Synthesis and Antibacterial Evaluation of 2-(Substituted Phenylureido)-4-thiocyanatobenzothiazoles. *J. Pharm. Sci. 67*, 281–282

[4]. Singh, M.; Singh, S.K.; Gangwar, M.; Nath, G.; Singh, S.K. (2014) Design, synthesis and mode of action of some benzothiazole derivatives bearing an amide moiety as antibacterial agents. *RSC Adv. 4*, 19013–19023.

[5]. Ćaleta, I.; Grdiša, M.; Mrvoš-Sermek, D.; Cetina, M.; Tralić-Kulenovićd, V.; Pavelićb, K.; Karminski-Zamola, K. (2004) Synthesis, crystal structure and antiproliferative evaluation of some new substituted benzothiazoles and styrylbenzothiazoles. *Il Farmaco. 59*, 297–305.

[6]. Das, J.; Moquin, R.V.; Lin, J.; Liu, C.; Doweyko, A.M.; Defex, H.F.; Fang, Q.; Pang, S.; Pitt, S.; Shen, D.R.; et al. (2003). Discovery of 2-amino-heteroaryl-benzothiazole-6-anilides as potent p56lck inhibitors. *Bioorg. Med. Chem. 13*, 2587–2590.

[7]. Sreenivasa, G.M.; Jayachandran, E.; Shivakumar, B.; Jayaraj, K.K.; Vijay, K.M.M.J. (2009) Synthesis of bioactive molecule fluoro benzothiazole comprising potent heterocyclic moieties for anthelmintic activity. *Arch. Pharm. Sci. Res. 1*, 150–157

[8]. Cressier, D.; Prouillac, C.; Hernandez, P.; Amourette, C.; Diserbo, M.; Lion, C.; Rima, G. (2009) Synthesis, antioxidant properties and radioprotective effects of new benzothiazoles and thiadiazoles. *Bioorg. Med. Chem. 17*, 5275–5284.

[9]. K G Baheti, S V Kuberkar, (2003) Synthesis of 3-Amino-4-oxo-(2*H*)-pyrazolo[3′,4′:4,5]pyrimido-[2,1-*b*]benzothiazole and its 2- and 3-Substituted Derivatives: Journal of Heterocyclic communication , Volume 40, Issue3 ,Pages 547-551.

[10]. Kamlesh D. Niranjanea and Mayura A. Kale; (2011), Synthesis and anti-inflammatory activity of 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; *Der Pharmacia Lettre*, 3(2):276-283.

[11]. Kaur R., Chaudhary S., Kumar K., Gupta M.K., Rawal R.K. (2017), Recent synthetic and medicinal perspectives of dihydropyrimidinones: A review. *Eur. J. Med. Chem.* 132:108–134.

[12]. Anil B. Chidrawar* and Rajkumar U. Pokalwar; multicomponent synthesis and characterization of new 2-substituted derivatives of 3-amino-4-imino-8- nitro-2h-pyrazolo [3,4-e]pyrimido[2,3- b][1,3]benzothiazole; (2016), *world journal of pharmaceutical research*, vol 5, issue 3.

[13]. Gangadhar S. Waghmare, Anil B. Chidrawar, Vijay N. Bhosale, Giridhar R. Shendarkar , Sharad V. Kuberkar .(2013) "Synthesis and in-vitro anticancer activity of 3-cyano-6,9-dimethyl-4-imino 2-methylthio 4H-pyrimido [2,1-b] [1,3] benzothiazole and its 2-substituted derivatives. *Journal of pharmacy research*: 7, 823-827.

[14]. Gangadhar S Bhopalkar: (2022), Synthesis, Characterization and Antibacterial Activity of 3- amino-6,9-dimethyl-4-oxo-pyrazolo[3,4-e]Pyrimidine[2,3-b][1,3]Benzothiazole. *Chemistry Research Journal*, 7(3), 121-124.