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Novel synthesis and antibacterial activity of 3-amino-8-chloro-4-oxo-(2H)/Aryl/Heteryl-pyrazolo [3′,4′: 4,5] pyrimido[2,1-*b*][1,3]benzothiazoles

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ABSTRACT

8-Chloro-3- cyano – 2 – methylthio - 4-oxo - 4H – pyrimido [2,1-b][1,3]benzothiazole ***(3)*** *on reaction in presence of dimethyl formamide and catalytic amount of anhydrous potassium with hydrazine hydrate / aryl hydrazine / heteryl hydrazine afforded 3-amino-8-chloro-4-oxo-(2H) / aryl/ heteryl-pyrazolo [3',4':4,5] pyrimido [2,1-b] [1,3] benzothiazoles (**4a-i**) in good yield. These newly synthesized compounds were evaluated for antibacterial activity.*

Key words: Ethyl-2-cyano-3 3-bismethylthioacrylate, hydrazine hydrate,aryl and heteryl hydrazines.

INTRODUCTION

Fused pyrimido benzothiazoles are reported to exhibit a broad spectrum of pharmacological activities like antibacterial, antiallergic, anti-inflammatary, antitumour, phsphodiesterase inhibition and antiparkinsonism[1-6]. In view of these reported pharmacological activities and in continuation of research work carried out by our research group[7-12], we report herein one pot synthesis of 3-amino-8-chloro-4-oxo-(2H) / aryl/ heteryl-pyrazolo [3',4':4,5] pyrimido [2,1-b] [1,3] benzothiazoles (**4a-i**).

EXPERIMENTAL SECTION

All melting points were determined in capillary tube and are uncorrected. IR spectra were recorded in potassium bromide pellets on Bomen MB 104 FT Infrared Spectrophotometer, ^{1}H-NMR spectra were

scanned on a FT Gemini 60 (200MHz) Spectrometer with Tetramethyl silane as an internal standard. Mass spectra were recorded on a FT VG – 7070 H Mass Spectrophotometer using the EI technique at 70 eV. Micro analysis were performed on a Heraeus CHN-O rapid analyzer. All the reactions were monitored by Thin layer chromatography, carried out on 0.25 mm thick silica gel-G plate using iodine vapour for detection.

General procedure for the synthesis of 3-Amino-8-chloro-4-oxo-2H/ aryl hydrazine/ heteryl hydrazine-pyrazolo[3',4':4,5]pyrimido-[2,1-*b*][1,3] benzothiazole (4a-i):

A mixture of of 8-chloro-3-cyano-2-methylthio-4-oxo-4H-pyrimido[2,1-*b*][1,3]benzothiazole (**3**) (0.001mole) and hydrazine hydrate / aryl hydrazine / heteryl hydrazine (0.002moles) was refluxed in the presence of catalytic amount of anhydrous potassium carbonate and 5ml of dimethylformamide for 3-4 hours. The reaction mixture was cooled to room temperature and poured into ice -cold water.The separated solid product was filtered,washed with water and recrystallized from DMF-ethanol mixture to give pure (**4a-i).**

3-Amino-8-chloro-4-oxo-(2H)-pyrazolo[3',4':4,5]pyrimido-[2,1-*b*][1,3]benzothiazole (4a):Yield: 52%, m.p.278°C; IR(KBr) : 3450, 3300cm^{-1} (NH_2), 1700 cm^{-1} (CO). ^{1}H-NMR($CDCl_3$): δ 5.2 (broad s, 2H, NH_2, exchangeable with D_2O), δ 7.3-7.7 (m, 3H, Ar-H), δ 10.9 (s, 1H, NH, exchangeable with D_2O. MS(m/z): 293 (M+2; 4%), 291(M$^{+\cdot}$,13%), 263, 234, 208, 180, 142. Anal. calcd. for: $C_{11}H_6N_5OSCl$: C, 45.36; H,2.06; N,24.05. Found:C,45.34; H,2.04; N,24.03.

3-Amino-8-chloro-4-oxo-2-phenyl pyrazolo [3',4':4,5] pyrimido-[2,1-*b*] [1,3] benzothiazole (4b): Yield : 51%. m.p. 290°C; IR(KBr) : 3371, 3320 cm^{-1} (NH_2), 1684 cm^{-1} (C=O). ^{1}H-NMR : ($CDCl_3$) δ 4.2 (s, 2H, NH_2, exchangeable with D_2O), δ 7.3 -7.9, (m, 8H, Ar-H). MS(m/z) : 369 (M+2; 3%), 367(M$^{+\cdot}$, 10%). Anal. calcd. For : $C_{17}H_{10}N_5OSCl$: C,55.58; H,2.72; N,19.07. Found: C,55.55; H,2.68; N,19.03.

3-Amino-8-chloro-4-oxo-2(4'-nitrophenyl)pyrazolo[3',4':4,5]pyrimido-[2,1-*b*][1,3]benzothiazole (4c):

Yield: 53%. m.p. 284°C; IR(KBr) : 3380, 3315cm^{-1} (NH_2), 1695 cm^{-1} (CO). ^{1}H-NMR($CDCl_3$): δ4.8(broad s, 2H, NH_2, exchangeable with D_2O), δ7.1-7.8(m, 7H, Ar-H). MS(m/z) : 414 (M+2; 10%), 412(M$^{+\cdot}$, 30%) Anal. calcd. For : $C_{17}H_9N_6O_3SCl$: C,49.51; H,2.18; N,20.38. Found: C,49.48; H,2.15; N,20.36.

3-Amino-8-chloro-4-oxo-2 (2',4'-nitrophenyl) pyrazolo[3',4':4,5]pyrimido-[2,1-*b*][1,3] benzothiazole (4d):

Yield: 46%. m.p. 277°C; IR(KBr): 3480, 3390cm^{-1}(NH_2), 1710cm^{-1}(C=O), ^{1}H-NMR ($CDCl_3$): δ4.9 broad s, 2H, NH_2, exchangable with D_2O), δ7-7.8 (m, 6H, Ar-H). MS(m/z): 459 (M+2; 15%), 457(M$^{+\cdot}$, 45%), Anal. calcd. for: $C_{17}H_8N_7O_5SCl$: C, 44.63; H,1.75; N,21.44. Found: C,44.61; H,1.71; N,21.42.

3-Amino-8-chloro-4-oxo-2(2'-benzothiazolyl)pyrazolo[3',4':4,5]pyrimido[2,1-*b*] [1,3] benzothiazole (4e):

Yield: 56%. m.p. 251°C; IR(KBr) : 3470, 3400cm^{-1} (NH_2), 1690 cm^{-1} (C=O). ^{1}H-NMR($CDCl_3$): δ4.7(broads, -2H, NH_2, exchangable with D_2O), δ7.2-7.9(m, 7H, Ar-H). MS(m/e) : 426 (M+2; 32%), 424(M$^{+\cdot}$, 98%). Anal. calcd. for: $C_{18}H_9N_6OS_2Cl$: C,50.94; H,2.12; N,19.81. Found:C,50.90; H,2.12; N,19.80.

3-Amino-8-chloro-4-oxo-2(6'-methyl-2'-benzothiazolyl)pyrazolo[3',4':4,5]pyrimido[2,1-][1,3] benzothiazole (4f):
Yield: 52%. m.p. 280°C; IR(KBr) : 3470, 3410cm^{-1} (NH_2), 1710 cm^{-1} (C=O). ^{1}H-NMR($CDCl_3$): δ4.6 (broad s, 2H, NH_2, exchangeable with D_2O), δ7-7.8 (m, 6H, Ar-H). MS(m/z): 441(M+2; 12%), 439(M$^+$, 35%). Anal. calcd. for: $C_{19}H_{11}N_6OS_2Cl$: C,49.77; H,2.05; N,15.98. Found: C,49.69; H,1.99; N,15.93.

3-Amino-8-chloro-4-oxo-2(6'-methoxy-2'-benzothiazolyl)pyrazolo[3',4':4,5] pyrimido [2,1-*b*] [1,3] benzothiazole (4g):
Yield: 48%. m.p. 240°C; IR(KBr) : 3390, 3260cm^{-1} (NH_2), 1680 cm^{-1} (C=O). ^{1}H-NMR($CDCl_3$): δ4.8(broad s, 2H, NH_2, exchangable with D2O), δ7.3-8(m, 6H, Ar-H). MS(m/z): 456(M+2; 20%): 454(M$^+$, 60%) . Anal. calcd. for: $C_{19}H_{11}N_6O_2S_2Cl$: C,50.22; H,2.42; N,18.50. Found:C,50.20; H,2.42; N,18.47.

3-Amino-8-chloro-4-oxo-2(6'-chloro-2'-benzothiazolyl)pyrazolo[3',4':4,5] pyrimido [2,1-*b*] [1,3] benzothiazole (4h):
Yield: 48%. m.p. 269°C; IR(KBr) : 3390, 3250cm^{-1} (NH_2), 1690 cm^{-1} (C=O). ^{1}H-NMR($CDCl_3$): δ5.1(broad s, 2H, NH_2, exchangable with D_2O), δ7.2-7.9(m, 6H, Ar-H). MS(m/z): 462(M+4), 460(M+2), 458(M$^+$ 50%) Anal. calcd. for: $C_{18}H_8N_6OS_2Cl$: C,47.16; H,1.74; N,18.34. Found:C,47.09; H,1.69; N,18.29.

3-Amino-8-chloro-4-oxo-2(6'-nitro-2'-benzothiazolyl)pyrazolo[3',4':4,5] pyrimido [2,1-*b*] [1,3] benzothiazole (4i):
Yield: 49%. m.p. 260°C; IR(KBr) : 3410, 3320cm^{-1} (NH_2), 1705 cm^{-1} (C=O). ^{1}H-NMR($CDCl_3$): δ4.7(broad s, 2H, NH_2, exchangable with D_2O), δ7.1-7.9(m, 6H, Ar-H). MS(m/e): 471(M+2; 13%); 469(M$^+$; 40%). Anal. calcd. for: $C_{18}H_8N_7O_3S_2Cl$: C,46.05; H,1.70; N,20.89. Found: C,46.01; H,1.67; N,20.87.

RESULTS AND DISCUSSION

The required starting compound to synthesize these fused pyrazolo pyrimido benzothiazoles (**4a-i)** is 8-chloro-3- cyano – 2 – methylthio - 4-oxo - 4H – pyrimido [2,1-*b*][1,3] benzothiazole **(3)** which was prepared by refluxing 2-amino-6-chloro benzothiazole (**1**) in the presence of dimethyl formamide and a pinch of anhydrous potassium carbonate with ethyl-2-cyano-3 3-bismethylthioacrylate (**2**) (**Scheme**- I).

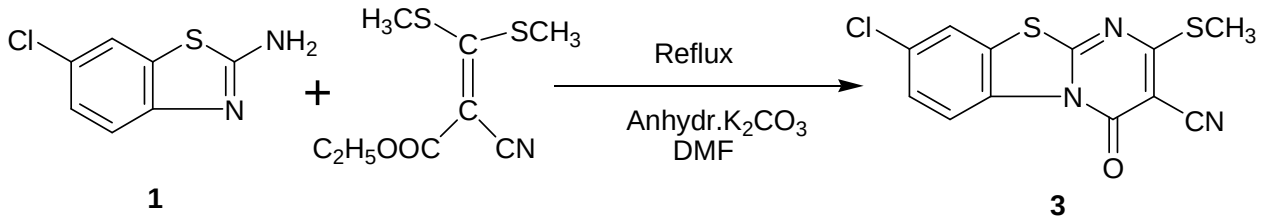
The compound(**3**) contains reactive methylthio group at 2-position and cyano group at 3-position.The compound (**3**) on heating in the presence of dimethyl formamide and a catalytic amount of anhydrous potassium carbonate with hydrazine hydrate afforded the compound (**4a**) to which on the basis of elemental analysis and spectral data was assigned the structure 3-amino-8-chloro-4-oxo-(2H)pyrazolo[3',4':4,5] pyrimido [2,1-*b*][1,3]benzothiazole(**4a)**.

Similarly ,compound (**3**) on heating independently under similar experimental conditions with phenyl hydrazine /4-nitro phenyl hydrazine /2,4-dinitrophenyl hydrazine /2-hydrazino benzothiazole /6-methyl-2-hydrazino benzothiazole /6-methoxy-2-hydrazino benzothiazole /6-chloro-2-hydrazino

benzothiazole / 6-nitro-2-hydrazino benzothiazole afforded respective 3-amino-8-chloro-4-oxo-2-phenyl (**4b**) /4'-nitrophenyl (**4c**) /2',4'-dinitrophenyl(**4d**) /2'-benzothiazolyl (**4e**) / 6'-methyl-2'-benzothiazolyl (**4f**) /6'-methoxy-2'-benzothiazolyl (**4g)** / 6'-chloro-2'-benzothiazolyl (**4h)** /6'-nitro-2'-benzothiazolyl (**4i)** -pyrazolo[3',4':4,5]pyrimido[2,1-*b*][1,3]benzothiazoles (**4b-i). (Scheme- II).** The structures to compounds (**4a-i**)were assigned on the basis of elemental analysis and spectral data.

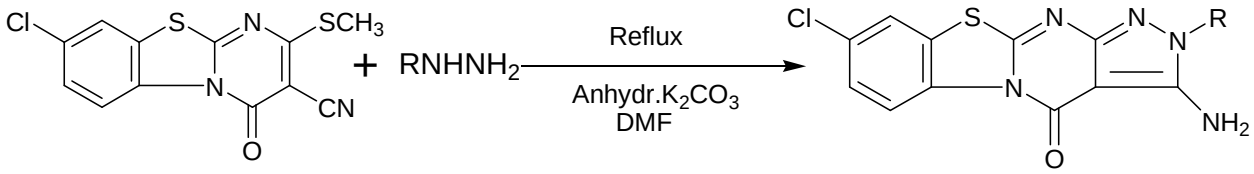
The IR spectra of compounds (**4a-i**) showed the presence of two absorption bands in the region 3400 cm^{-1}-3100 cm^{-1} due to asymmetric and symmetric stretching of -NH_2 group and showed the absence of absorption band in the range of 2250-2200 cm^{-1} due to CN stretching. The presence of absorption band in the region at 1740-1680cm^{-1} can be assigned to C=O group. All compounds (**4a-i**) in their PMR spectra exhibited peaks in the region δ7- δ7.9 and broad peak in the region δ4.0- δ5.5 which can be assigned to aromatic protons and –NH_2 protons respectively.Mass spectra of compounds(**4a-i**) exhibited molecular ion peaks which correspond to their molecular weights.

Scheme I

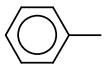
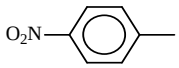
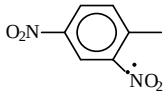
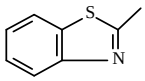
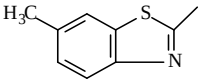
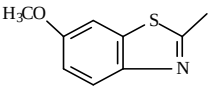
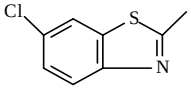
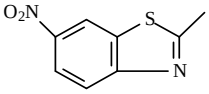


1 **3**

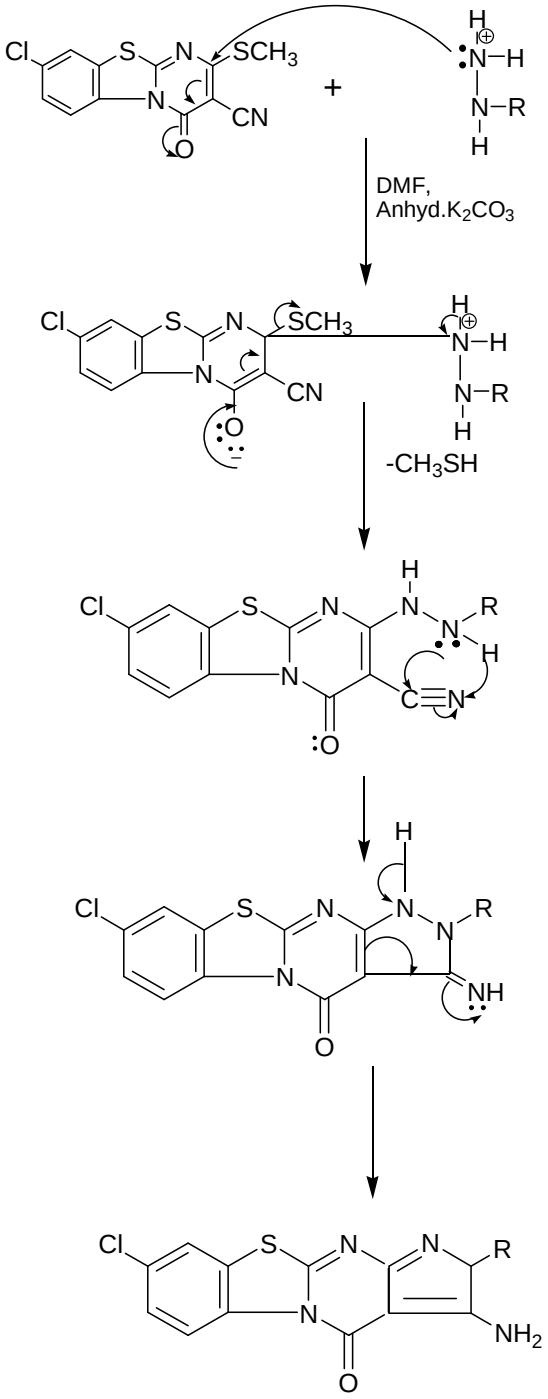
Scheme II



3 **4a-i**

	R
4a	**H**
4b	
4c	
4d	
4e	
4f	
4g	
4h	
4i	

The mechanism for the formation of compounds (4a-i**) can be adduced as in** (Scheme III).



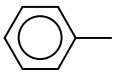
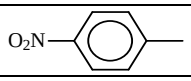
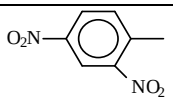
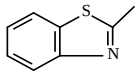
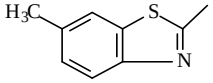
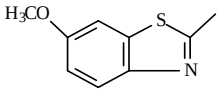
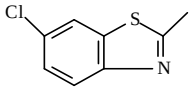
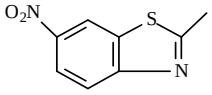
Scheme III

Antibacterial 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. All the synthesized compounds were dissolved in dimethyl sulphoxide. The synthesized compounds exhibited zone of inhibition of 07-14mm in diameter where as standard Norfloxin exhibited zone of inhibition of 14 and 24 in diameter against S. aureus and B. substilis and

20 and 16mm in diameter against E. coli and S. typhi respectively. Amongst the synthesized compounds , Compounds (**4b,c,d,i**) showed higher zone of inhibition against S. aureus, Compounds (**4a,b,c,g**),showed higher zone of inhibition against E.Coli and Compounds (**4e,g**) showed higher zone of inhibition against S.Typhi as compaired to other compounds.

Antimicrobial activity of compound (4a-i)

Compound	**R**	**Diameter in mm of zone of inhibition**			
		S. Aureus	*B. ubstilis*	*E. Coli*	*S. yphi*
4a	**H**	**08**	**-**	**12**	**05**
4b		**10**	**-**	**09**	**07**
4c		**10**	**-**	-	-
4d		**11**	**-**	**12**	**06**
4e		**07**	**-**	**-**	**08**
4f		09	-	-	06
4g		09	-	11	08
4h		06	**-**	08	05
4i		14	-	08	07
	Norfloxin	14	24	20	16

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REFERENCES

[1] Gupta S., Ajmera N., Gautam N., Sharma R. and Gautam D.C.,*Ind J.Chem*.,48B,**2009**,853.
[2] Dash B. Patra M. and Mahapatra P.K.,*J.Inst.Chem*.52[2],**1980**,92.
[3] Glennon R.A. , Gaines J.J. and Rogers M.E.,*J.Med.Chem*.24,**1981**,766.
[4] Heter H.L., Patent U.S.,3704303[1972];*Chem.Abstr*.78,**1972**,43513x.
[5] CovingtonR.R;TempleD.L.,YevichJ.P.*JGer.Patent* 918085,**1979**;*Chem.Abstrct*.94,**1979**,163993q.
[6] Wade J.J., Toso C.J. , Matson V.L.and Stelzer ,*J.Med.Chem*.26,**1983**,608.
[7] Baheti K.G., Kapratwar S.B. and Kuberkar S.V.,*Synth. Comm.*[UK],32,**2002**,2237.
[8] Baheti K.G.and Kuberkar S.V. *J.Het.Chem*.[USA],40,**2003**,547.

[9] Baheti K.G.and Kuberkar S.V.*Ind.J.Het.Chem*.12,**2003**,343.
[10] Baheti K.G., Jadhav J.S., Suryawanshi A.T.and Kuberkar S.V. ,*Ind.J.Chem*.,44B,**2005**,834.
[11] Pingle M.S., Vartale S.P., Bhosale V.N. and Kuberkar S.V. ,*Arkivoc*,X,**2006**,190.
[12] Vartale S.P., Jadhav J.S.,Kale M.A. and Kuberkar S.V.,*Ind.J.Chem*,January **2006**.