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A Convenient one pot synthesis and antimicrobial activity of 10-methyl 14,15-diimino benzothiazolo[2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,3-*b*] benzothiazole and their substituted derivatives

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ABSTRACT

2-amino-6-methyl benzothiazole ***(1)*** *and bis (methylthio) methylene malanonitrile* ***(2)*** *were refluxed in N,N-dimethyl formamide (DMF) in presence of catalytic amount of anhydrous potassium carbonate to afforded 3-cyano-4-imino-2-methylthio-8-methyl-4H-pyrimido[2,1-b] benzothiazole* ***(3)****. The latter were further reacted with different substituted 2-amino benzothiazole* ***(4)****. Afforded to form10-methyl-14, 15-diimino benzothiazolo[2, 3-b] pyrimido [5,6-e] pyrimido [2, 3-b] benzothiazole* ***(5)*** *and its substituted derivatives. All these synthesized compounds were characterized by elemental analysis and spectral data.*

Keyward : N,N'-dimethyl formamide, Potassium carbonate, Pyrimido benzothiazole.

INTRODUCTION

The synthesis of fused pyrimido benzothiazole and its derivatives [1,2],which exhibit a wide spectrum of activities like anti-inflammatory[3],antiallergic[4],anti-tumor[5], Phosphodiesterase inhabitation[6], antiparkinsonism[7] . In view of the reported biological activities of this system has attracted much attention in recent years, which might be more potent.

The researcher published articles on oxo-/imino – pyrimido benzothiazole and their substituted derivatives[8-11], A literature survey revealed that very few refs.[12], are available on the synthesis of imino pyrimido benzothiazoles. These observation have stimulated our considerable interest to explore the synthesis of novel heterocyclic system possessing six member rings, In the present work we report the details of the reaction of 10-methyl-14, 15-diimino benzothiazolo [2, 3-*b*] pyrimido [5,6-*e*] pyrimido[2, 3-*b*] benzothiazole and its substituted derivatives.

MATERIALS AND METHODS

Melting point 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 reaction were carried out under ambient atmosphere. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

3-cyano-4-imino-2-methylthio-8-methyl-4H-pyrimido[2,1-*b*] benzothiazole (3)

A mixture of 2-amino benzothiazole **(2)** (0.01 mol) and bis (methylthio) metylene malononitrile **(1)** (0.01 mol) in 30 mL of N, N'- dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 4 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).**

10-methyl 14,15-diimino benzothiazolo[2,3-*b*]pyrimido [5,6-*e*]pyrimido [2,3-*b*]benzothiazole and their1/2/3-substuited derivatives (5a-h)

A mixture of **(3)** (0.001mol)and independently with **(4)** 2-amino 6H-benzothiazole, 2-amino 6 hydroxy-benzothiazole,2-amino 6-methyl benzothiazole,2-amino 6-methoxy benzothia -zole-2-amino 6-chloro benzothiazole,2-amino 6-nitro benzothiazole,2-amino-4,6 dimethyl benzo -thiazole, 2-amino 6,7-chloro,floro benzothiazole, (0.001mol) 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 **(5a-h).**

3-cyano-4-imino-2-methylthio-8-methyl-4H-pyrimido[2,1-*b*] benzothiazole (3)

Brown powder, yield 50 %, mp 220 °C (dec.). IR (KBr / cm^{-1}) 3296 cm^{-1} (=NH), 2198 cm^{-1} (CN); 1H NMR (400 MHz,DMSO-d_6) : δ 2.4(s,3H,CH_3), 2.6(s,3H,SCH_3), 7.2-7.8 (m, Ar-H), 9.3(s, 1H, =NH) . EI-MS (m/z: RA %): 286 (M^+), 265, 239, 228, 212, 195, 186, 149, 122. Anal. Calcd. For: $C_{13}H_{10}N_4S_2$: 54.52; H, 3.52; N, 19.56. Found: C, 54.03; H, 3.01; N, 19.02.

10-Methyl-14, 15-diimino benzothiazolo[2,3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] benzothiazole 5a

Brown powder, yield 66 %, mp 196 °C (dec.). IR (KBr / cm^{-1}) 3350-3100 cm^{-1}(=NH) ; 1H NMR (400 MHz,DMSO-d_6, δ,ppm) : 2.6(s,3H,CH_3), 6.0-8.1 (m, 7H,Ar-H), 9.2 (s, 2H, =NH) . EI-MS (m/z: RA %): 388(M^+).Anal. Calcd. For: $C_{19}H_{12}N_6S_2$: C,58.76; H, 3.09; N, 21.64. Found: C,58.72;H,3.07;N,21.62.

3-Hydroxy-10-methyl-14, 15-diimino benzothiazolo[2, 3-*b*]pyrimido [5, 6-*e*] pyrimido [2, 3-*b*]benzothiazole 5b

Brown powder, yield 48 %, mp 210 °C (dec.). IR (KBr / cm^{-1}) 3296cm^{-1} (-OH), 3211, 3126cm^{-1} (=NH) ; 1H NMR (400 MHz,DMSO-d_6, δ,ppm): 2.5(s,3H,CH_3), 5.2 (s,1H,OH), 6.0-7.9 (m,6H

Ar-H), 8.7 (s, 2H, =NH) . EI-MS (m/z: RA %): 404(M^+).Anal. Calcd. For: $C_{19}H_{12}N_6S_2O$: C, 56.43; H, 2.97; N, 20.78. Found: C, 56.04;H, 2.35; N, 20.16.

3, 10-Dimethyl-14, 15-diimino benzothiazolo[2, 3-*b*]pyrimido[5, 6-*e*]pyrimido [2, 3-*b*] benzothiazole 5c

Brown powder, yield 60 %, mp 125 °C (dec.). IR (KBr / cm^{-1}) 3400cm^{-1} and 3300cm^{-1} (=NH) ; 1H NMR (400 MHz,DMSO-d_6, δ,ppm): 2.6 (s, 6H, CH_3), δ 6.0-7.9 (m, 6H, Ar-H) , δ 9.1(s, 2H, =NH) . EI-MS (m/z: RA %): 402 (M^+). Anal. Calcd. For: $C_{20}H_{14}N_6S_2$: C, 59.70; H, 3.48; N, 20.89. Found: C, 59.69;H, 3.42; N, 20.84

3-Methoxy-10-methyl-14, 15-diimino benzothiazolo[2, 3-*b*]pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] benzothiazole 5d

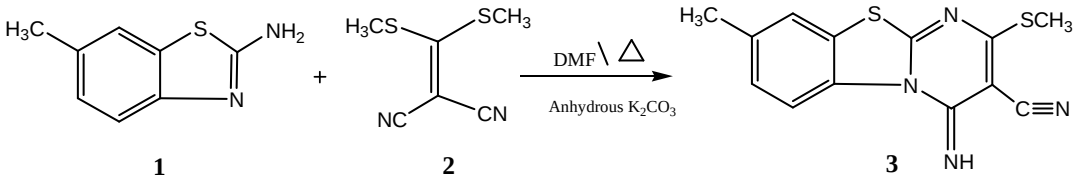
Brown powder, yield 52 %, mp 135 °C (dec.). IR (KBr / cm^{-1}) 3297-3171cm^{-1} (=NH); 1H NMR (400 MHz,DMSO-d_6, δ,ppm): 2.2(s, 3H, CH_3), δ 3.8 (s, 3H, OCH_3), δ 6.1-6.9 (m,6H, Ar-H), δ 9.1(s, 2H, =NH) . EI-MS (m/z: RA %): 418 (M^+).Anal. Calcd. For: $C_{20}H_{14}N_6OS_2$: C, 57.41; H, 3.34; N, 20.09. Found: C, 57.39;H, 3.32; N, 20.05 .

3-Chloro-10-methyl-14, 15-diimino benzothiazolo [2, 3-*b*] pyrimido [5, 6-*e*]Pyrimido [2, 3-*b*]benzothiazole 5e

Brown powder, yield 55 %, mp 190 °C (dec.). IR (KBr / cm^{-1}) 3413 cm^{-1} & 3299cm^{-1} (=NH); 1H NMR (400 MHz,DMSO-d_6, δ,ppm): 2.4 (s, 3H, CH_3), 6.0-8.1 (m, 6H Ar-H), 8.3(s, 2H, =NH) . EI-MS (m/z: RA %): 424(M^{+2}, 75%), 422 (M^+, 25%).Anal. Calcd. For: $C_{19}H_{11}N_6S_2Cl$; C, 54.02; H, 2.60; N, 19.90. Found: C, 54.00;H, 2.57; N, 19.85.

3-Nitro-10-methyl-14, 15-diimino benzothiazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido[2, 3-*b*] benzothiazole 5f

Brown powder, yield 69 %, mp 220 °C (dec.). IR (KBr / cm^{-1}) 3325, 3280cm^{-1} (=NH); 1H NMR (400 MHz,DMSO-d_6, δ,ppm): 2.5 (s, 3H, CH_3), 6.0-7.9 (m, 6H, Ar-H), 9.3 (s, 2H, =NH) . EI-MS (m/z: RA %): 433(M^+).Anal. Calcd. For: $C_{19}H_{11}N_7O_2S$: C, 52.65; H, 2.54; N, 22.63. Found: C, 52.63;H, 2.51; N, 22.59.

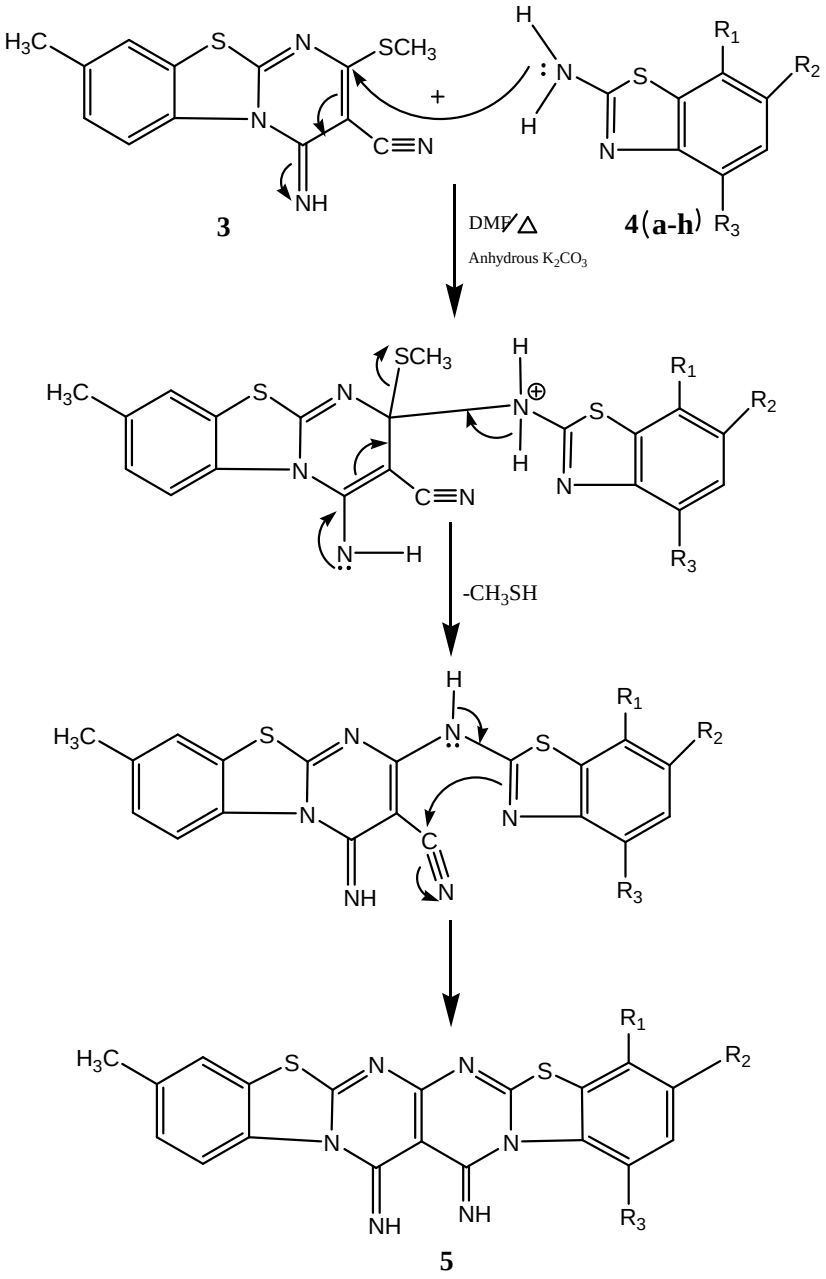


1 **2** **3**

Scheme -I

1,3,10-Trimethyl-14,15-diimino benzothiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*] benzothiazole 5g

Brown powder, yield 68 %, mp 136 °C (dec.). IR (KBr / cm^{-1}) 3422cm^{-1} and 3314cm^{-1} (=NH) ; 1H NMR (400 MHz,DMSO-d_6, δ,ppm): 2.6(s,9H,CH_3), δ 2.6(s,3H,SCH_3), δ 5.9-7.8 (m,5 Ar-H), δ 9.3 (s, 2H, =NH) . EI-MS (m/z: RA %): 416 (M^+).Anal. Calcd. For: $C_{21}H_{16}N_6S_2$; C, 59.55; H, 3.87; N, 20.18. Found: C, 59.01;H, 3.22; N, 19.84



Scheme -II :Plausible mechanism of formation of fused pyrimido benzothiazole

	R_1	R_2	R_3
5a	H	H	H
5b	H	OH	H
5c	H	CH_3	H
5d	H	OCH_3	H
5e	H	Cl	H
5f	H	NO_2	H
5g	H	CH_3	CH_3
5h	F	Cl	H

3,4-Chloro,Fluro,10methyl-14,15-diimino benzothiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido [2,3-*b*] benzothiazole 5h

Brown powder, yield 66 %, mp 138 °C (dec.). IR (KBr / cm^{-1}) 3435cm^{-1} and 3325cm^{-1} (=NH) ; 1H NMR (400 MHz,DMSO-d_6, δ,ppm): 2.4(s,3H,CH_3), 6.0-7.8 (m,5 Ar-H), 9.1(s, 1H, =NH) . EI-MS (m/z: RA %): 440 (M^+).Anal. Calcd. For: $C_{19}H_{10}ClFN_6S_2$: C, 51.76; H, 2.29; N, 19.06. Found: C, 51.09;H, 1.72; N, 18.64

Table-1: Antimicrobial activity of disc diffusion method of 10-methyl 14,15-diimino benzothiazolo [2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,3-*b*] benzothiazole and their1/2/3-substuited derivatives of newly synthesized compound (5a-h)

Comp. No.	R	Diameter in mm of zone of inhibition			
		S. Aureus	*B. Substilis*	*E. Coli*	*S. Typhi*
5a	H	06	----	06	05
5b	OH	10	12	06	----
5c	CH_3	06	----	08	08
5d	OCH_3	12	06	----	06
5e	Cl	12	12	----	08
5f	NO_2	11	12	05	----
5g	di-CH_3	08	07	----	08
5h	Cl, F	12	18	12	11
	Norflaxacin	**14**	**24**	**20**	**16**

Antimicrobial activity

All the newly synthesized compounds were tested for their antimicrobial activity using disc diffusion technique against *S. aureus*, *B.Substilis*, *E. Coli*,and *S. Typhi*, the standard antibiotics norflaxacin showed zones of inhibition 14-24 mm , against bacterial strains.

Among , all the newly synthesized compounds **5h** show very good activity against *B.Substilis* where as moderately active against *S. Aureus*, *E. Coli*,and *S. Typhi*. The compounds **5a-g** are less active against all bacterial strains.

RESULTS AND DISCUSSION

In the present investigation, we have reported the synthesis of 10-methyl 14,15-diimino benzothiazolo[2,3-*b*]pyrimido [5,6-*e*]pyrimido [2,3-*b*]benzothiazole and their substuited derivatives. **(5)** Our method gives single product with high yield. The reaction started with 2-amino-6-methyl benzothiazole **(1)** and bis (methylthio) methylene malanonitrile **(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 2-amino substituted benzothiazole**(4)** in presence of N,N-dimethyl formamide (DMF) and catalytic amount of anhydrous potassium carbonate afforded the compound (**5)** subsequently, compound **(3)** independently heating with 2-amino benzothiazole, 2-amino 6-methyl benzothiazole, 2-amino 6-methoxy benzothiazole, 2-amino 6-chlorobenzothiazole, 2-amino 6-

nitro benzothiazole,2-amino 6-hydroxy benzothiazole, 2-amino 6-chloro,7-floro benzothiazole, 2-amino 4,6-dimethyl benzothiazole to obtain 10-methyl 14,15-diimino benzothiazolo[2,3-*b*]pyrimido [5,6-*e*]pyrimido [2,3-*b*]benzothiazole and their1/2/3-substuited derivatives respectively **Scheme-2.**

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 this communication, we report convenient and practical procedure for the preparation of some new diimino benzothiazolo [2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,3-*b*] benzothiazole derivatives by using milder reaction conditions, simple workup with good yield. As well as their antimicrobial activity in which **5h** show very good activity against *B.Substilis,* remaining all derivatives are moderately active.

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