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MULTICOMPONENT SYNTHESIS AND EVALUATION OF ANTIBACTERIAL ACTIVITY OF BENZOTHIAZOLO PYRIMIDO -PYRIMIDO BENZOTHIAZOLE AND ITS DERIVATIVES

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ABSTRACT

One-pot multicomponent reactions constitute an especially attractive recent synthetic strategy since they provide easy and rapid access to a large number of organic compounds with diverse substitution pattern with short time. To synthesize fused condensed pyrimido benzothiazole possessing more than three rings which exhibit a wide spectrum of biological and pharmacological activities. We report the synthesis of 14, 15-diimino-10-nitro-benzothiazolo [2,3-b] pyrimido [5,6-e] pyrimido [2,1-b] [1,3] benzothiazole with condensation of 3-cyano-4-imino-2-methylthio-8-nitro-4H-pyrimido [2,1-b] [1,3] benzothiazole and 2-amino-6-substituted benzothiazole in the presence of DMF and catalytic amount of K_2CO_3 by refluxing 5-6 hours by one pot multicomponent synthesis. In conclusion a facile one pot synthesis has been developed for the title compounds using readily available starting materials. All the newly synthesized compounds were screened for antibacterial activity. These compounds were found to possess a broad-spectrum activity.

KEY WORDS

2-amino-6-substituted benzothiazole, DMF, Potassium carbonate, Pyrimido benzothiazole

INTRODUCTION

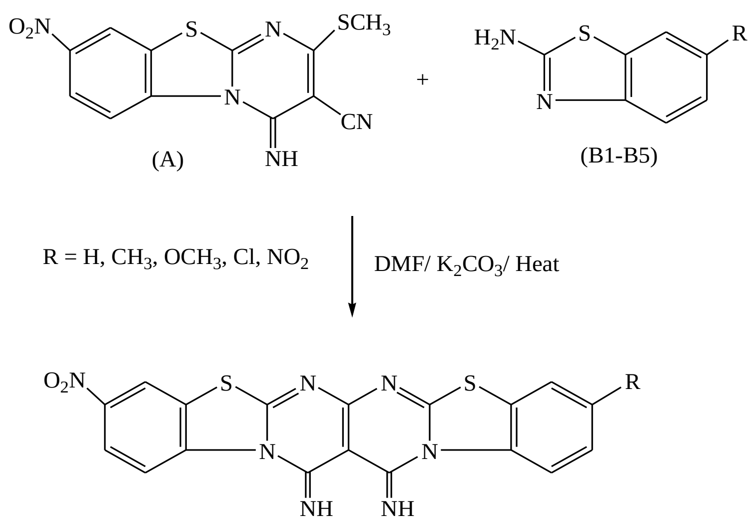
A survey of literature made it evident that, very little work has been carried out on the synthesis of fused pyrimido benzothiazole possessing three to four rings which exhibit a wide spectrum of biological and pharmacological activities like anti-allergic, antiparkinsonium[1], herbicidal[2], antiviral, phosphodiesterase inhibition, anti-parasitic activity [3], anti-inflammatory [4] and antitumor activity.

One pot synthesis is a green approach towards the synthesis of various heterocyclic compounds and for a researcher there is lot of scope to change the reaction condition, to change the catalyst, to change the solvent or to modify the catalyst. Pyrimidine, iminopyrimidine, pyrazole and fused benzothiazole heterocycles are reported to be effective pharmacophores [5-11]. Nair Mohan D. *et.al.* synthesized pyrimido [2,1-*b*] benzothiazole and its derivatives by refluxing diethyl ethoxy methyle nemalonate with respective 2-amino benzothiazole found to be antiviral activity.

A comprehensive review on the methods for the synthesis of iminopyrimidines has been published in the form of book, "The Pyrimidines" by Brown D.J. *et al*. [12-13]. Imino compounds are known to possess some sedative and hypnotic actions. Denny W.A. *et al.* [14] reported anticancer agents from fused pyrido-imidazo, -pyrazolo, -pyrazino and pyrollo heterocycles. Jimonet Patrick and his research group [15] reported synthesis of pharmacologically active 6-(trifluoromethoxy)- 3-substituted-2-imino benzothiazolines. Erlenmeyer and Von Meyenburg [16] reported moderate sedative activity of 5, 5-dialkyl-2-imino-4-thiazolidones which is in marked contrast to the lack of activity of the iminobarbituric acids [17-20]. In view of these reported biological activities of this system, synthesis of such condensed system has attracted much attention in recent years. In this note, we report one pot multicomponent synthesis of 14, 15-diimino-10-nitro-benzothiazolo [2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole and its derivatives.

MATERIAL AND METHODS

Experimental: All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ^{1}H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by Thin layer chromatography.



(C1-C5)

General procedure

Multicomponent Synthesis of 3-substituted derivatives of 14,15-diimino-10-nitro-benzothiazolo [2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole (C1-C5).

It is prepared by condensation of 3-cyano-4-imino-2-methylthio-8-nitro-4H-pyrimido [2,1-*b*] [1,3] benzothiazole (A) independently with 2-amino benzothiazole (B1), 2-amino-6-methyl benzothiazole (B2), 2-amino-6-methoxy benzothiazole (B3), 2-amino-6-chloro benzothiazole (B4), and 2-amino-6-nitro benzothiazole (B5) in the presence of DMF and catalytic amount of K_2CO_3 reflux for 5-6 hours to get 14,15-diimino-10-nitro-benzothiazolo[2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole and its 3-substituted derivatives (C1-C5).

Multicomponent Synthesis of 14,15-diimino-10-nitro-benzothiazolo [2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole (C1).

Condensation of 3-cyano-4-imino-2-methylthio-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzothiazole (A) reflux with 2-amino benzothiazole (B1) in the presence of DMF and catalytic amount of K_2CO_3 for 5-6 hours to yields 14,15-diimino-10-nitro-benzothiazolo[2,3-*b*] pyrimido[5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole.

Yield : 59 %, IR:(KBr/cm^{-1}) : 3281 & 3322 (=NH), 3111 (Ar-H), 1615 (C=N), 1517 & 1350 (NO_2), ^{1}H-NMR: (DMSO): δ 4.01 (s 1H =NH), δ 4.11 (s 1H =NH), δ 7.10 (d 4H Ar-H), δ 7.11 (d 3H Ar-H), EI-MS: (m/z:RA%): 420 (M+1), Elemental analysis : $C_{18}H_9N_7O_2S_2$, Calculated: (%) C 51.54, H 2.16, N 23.28, O 7.63, S 15.29 Found (%) : C 51.51, H 2.11, N 23.20, O 7.60, S 15.24.

Multicomponent Synthesis of 3-methyl-14,15-diimino-10-nitro-benzothiazolo[2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole (C2).

Condensation of 3-cyano-4-imino-2-methylthio-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzothiazole (A) and 2-amino-6-methyl benzothiazole (B2) in the presence of DMF and small amount of potassium carbonate for 5 hours to give 3-methyl-14,15-diimino-10-nitro-benzothiazolo[2,3-*b*] pyrimido[5,6-*e*] pyrimido[2,1-*b*] [1, 3] benzothiazole.

Yield : 55 %, IR:(KBr/cm^{-1}) : 3310 & 3325 (=NH), 3110 (Ar-H), 1616 (C=N), 1522 & 1340 (NO_2), EI-MS: (m/z:RA%): 434 (M+1), Elemental analysis : $C_{19}H_{11}N_7O_2S_2$, Calculated: (%) C 52.65, H 2.56, N 22.62, O 7.38, S 14.79 Found (%) : C 52.61, H 2.50, N 22.60, O 7.31, S 14.75.

Multicomponent Synthesis of 3-methoxy-14, 15-diimino-10-nitro-benzothiazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 1-*b*] [1, 3] benzothiazole (C3).

Condensation of 3-cyano-4-imino-2-methylthio-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzothiazole (A) and 2-amino-6-methoxy benzothiazole (B3) in the presence of Dimethyl formamide and potassium carbonate for 6 hours to get 3-methoxy-14,15-diimino-10-nitro-benzothiazolo[2,3-*b*] pyrimido[5,6-*e*] pyrimido[2,1-*b*] [1,3] benzothiazole.

Yield : 57 %, IR:(KBr/cm^{-1}) : 3312 & 3313 (=NH), 3100 (Ar-H), 1620 (C=N), 1515 & 1332 (NO_2), 1160 (C-O), EI-MS: (m/z:RA%): 450 (M+1), Elemental analysis : $C_{19}H_{11}N_7O_3S_2$, Calculated: (%) C 50.77, H 2.47, N 21.81, O 10.68, S 14.27 Found (%) : C 50.70, H 2.44, N 21.76, O 10.62, S 14.25

Multicomponent Synthesis of 3-chloro-14,15-diimino-10-nitro-benzothiazolo[2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole (C4).

Condensation of 3-cyano-4-imino-2-methylthio-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzothiazole (A) and 2-amino-6-chloro benzothiazole (B4) in the presence of Dimethyl formamide and potassium carbonate for 5 hours to produce 3-chloro-14,15-diimino-10-nitro-benzothiazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido[2,1-*b*] [1,3] benzothiazole.

Yield : 70 %, IR:(KBr/cm^{-1}) : 3312 & 3280 (=NH), 3111 (Ar-H), 1627 (C=N), 1519 & 1335 (NO_2), EI-MS: (m/z:RA%): 454 (M+1), Elemental analysis: $C_{18}H_8ClN_7O_2S_2$, Calculated: (%) C 47.63, H 1.78, Cl 7.81, N 21.60, O 07.05, S 14.13 Found (%) : C 47.61, H 1.74, Cl 7.75, N 21.55, O 07.00, S 14.10

Multicomponent Synthesis of 3-nitro-14, 15-diimino-10-nitro-benzothiazolo [2, 3-*b*] pyrimido [5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole (C5).

Condensation of 3-cyano-4-imino-2-methylthio-8-nitro-4H-pyrimido[2,1-*b*] [1,3] benzothiazole (A) and 2-amino-6-nitro benzothiazole (B5) in presence of DMF and K_2CO_3 for 6 hours to produce 3-nitro-14,15-diimino-10-nitro-benzothiazolo [2,3-*b*] pyrimido[5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole.

Yield : 64 %, IR:(KBr/cm^{-1}) : 3300 & 3265 (=NH), 3121 (Ar-H), 1622 (C=N), 1511 & 1355 (NO_2), EI-MS: (m/z:RA%): 465 (M+1), Elemental analysis : $C_{18}H_8N_8O_4S_2$, Calculated: (%) C 46.55, H 1.74, N 24.13, O 13.78, S 13.81 Found (%) : C 46.51, H 1.70, N 24.10, O 13.74, S 13.74

Table-1: Antibacterial activity of 3-substituted derivatives of 14, 15-diimino-10-nitro-benzothiazolo [2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole (C1-C5).

Sample code	*Zone of inhibition (diameter in mm)			
	B. subtilis	***B. Megatenium***	***E. coli***	***P. aureginosa***
	100μ/ml	**100μ/ml**	**100μ/ml**	**100μ/ml**
C1	21	26	07	10
C2	27	23	10	09
C3	13	15	20	22
C4	10	09	25	19
C5	23	20	10	11
Streptomycin	31	35	28	27
DMSO	-	-	-	-

***Each value is an average of three independent determinations ± Standard deviation.**

Note: '-' denotes no activity, 7-12 mm poor activity, 13-17 mm moderate activity,18-27 mm and above good activity.

RESULT AND DISCUSSION

One pot reaction constitutes an especially attractive recent synthetic strategy since they provide easy and rapid access to a large number of organic compounds with diverse substitution pattern. In the present work, we report one-pot synthesis of a novel fused heterocyclic compound, 14,15-diimino-10-nitro-benzothiazolo [2,3-*b*] pyrimido [5,6-*e*] pyrimido [2,1-*b*] [1,3] benzothiazole and its 3-substituted derivatives (C1-C5). All newly synthesized derivatives (C1-C5) were evaluated in-vitro for antibacterial activity against gram positive and gram-negative bacterial strain such as

Bacillus subtilis, Bacillus Megatenium, *Escherichia coli* and *Pseudomonas aureginosa* at concentration 100µ/ml by disc diffusion method[24] by using DMSO as solvent control and nutrient agar was employed as culture media. After 24h of incubation at 37^{0}C, the zone of inhibition were measured in mm. The activity was compared with known antibiotic Streptomycin and the data was represented in Table-1.

CONCLUSION

In conclusion a facile one pot synthesis has been developed for the title compounds using readily available starting materials. All the newly synthesized compounds were screened for antibacterial activity. These compounds were found to possess a broad-spectrum activity. However, the activities of the tested compounds are much less than those of standard antibacterial agents used. All newly synthesized compounds were screened for antibacterial activity studies at a concentration of 100µ/ml using DMSO as a control and Streptomycin used as a standard against gram positive and gram-negative bacteria. The data in Table 1 indicates that compound C1, C2 and C5 was found to possess a broad-spectrum activity against gram-positive bacteria and compound C3 and C4 were found to possess a broad-spectrum activity against gram-negative bacteria. However, the activities of the tested compounds are less than those of standard antibacterial agents used.

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CONFLICTS OF INTERESTS

Author has none to declare.

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