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Research Article

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Synthesis and antimicrobial studies of fused heterocycles 'pyrimidobenzothiazoles'

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ABSTRACT

In the present work 2H-Pyrimido[2,1-b]benzothiazole-2-ones were synthesized by reacting 2-aminobenzothiazoles with alkynoic acid in butanol and 4H-Pyrimido[2,1-b]benzothiazole-4-ones were synthesized by the reaction of 2-aminobenzothiazoles with ethylacetoacetate in presence of polyphosphoric acid. The structures of synthesized compound were confirmed by IR, H^1NMR & mass spectrum analysis. Synthesized compounds shown biological activity against E. coli and B. Subtilis and anti-fungal activity against A. fumigates.

Keywords: 2-aminobenzothiazoles, 2-methyl-4H-pyrimido[2,1-b]benzothiazol-4-ones, 4-methyl-2H-pyrimido[2,1-b]benzothiazol-2-ones, alkynoic acid

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INTRODUCTION

Fusion of one heterocyclic system with other biodynamic heterocyclic system results in a molecule with structural diversity and with enhanced pharmacological activity. The fusion of hetero-systems has proved to be an attractive and useful method to design new molecular framework of therapeutically interest. With the objective of exploring new heterocycles, we had synthesized pyrimidobenzothiazoles [1-11], by incorporating two pharmacologically interesting heterocyclic systems; benzothiazole and pyrimidine. Pyrimidobenzothiazole are nitrogen–sulphur containing compounds that have been reported to exhibit a wide spectrum of activities such as GABA receptor binding agents [12,13], antiviral, antitumour, anti-inflammatory, analgesic, anticonvulsant, muscle relaxant, sedative [14-17], etc. During the past few decades, interest has been rapidly growing in the properties and transformations of this sulphur-nitrogen heterocycles [18-21]. In the present investigation we had synthesize derivatives of pyrimidobenzothiazoles from 2-aminobenzothiazole [22-24] and screened for biological activity.

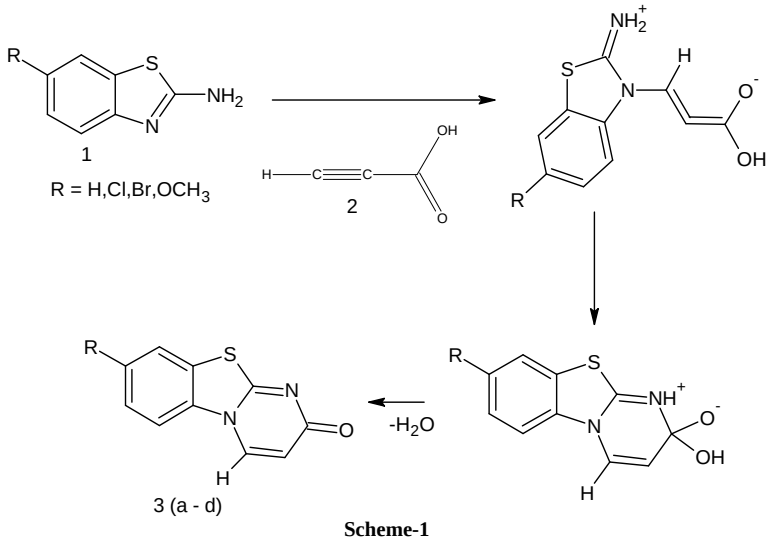
All the melting points are uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography using mixture of different proportions of polar and non-polar solvents. The infrared spectra were recorded in KBr on SHIMADZU-8400S FTIR, ^{1}H NMR spectra were recorded on an AV500 FT spectrometer operating in DMSO/$CDCl_3$ mixture with TMS as an internal reference. The physical data of the all synthesized compounds are given in table-1.

EXPERIMENTAL SECTION

Synthesis of substituted 2H-Pyrimido[2,1-b]benzothiazole-2/4-ones

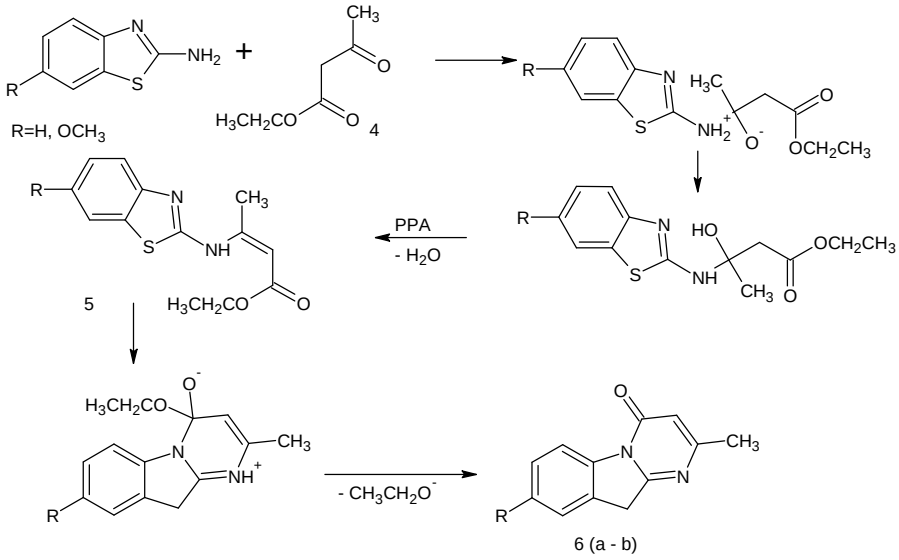
0.0033mole 2-amino-6-bromo/chloro/methoxybenzothiazole or 2-aminobenzothiazole and 0.0033mole propiolic acid were refluxed in 6ml butanol for about 22-23 hours and then filtered. The obtained solid were recrystallized.

The reaction mechanism has been given in **Scheme-1**. The structures of the synthesized heterocycles have been confirmed by their spectral characteristics.



Scheme-1

0.0033mol 2-aminobenzothiazole or 2-amino-6-methoxybenzothiazole and 2ml of ethylacetoacetate were refluxed in presence of polyphosphoric for 5 hours and then filtered. The obtained solid were recrystallized. The reaction mechanism has been given in **Scheme-2**. The structures of the synthesized heterocycles have been confirmed by their spectral data.



Scheme-2

Synthesis of 8-Bromopyrimidobenzothiazole-2-ones (3a)

Yield- 70%, **Melting point**- 300-310^{0}C, **IR** (KBr), 1637cm^{-1} (C=O) 1568cm^{-1} (C=C) 1587cm^{-1} (C=N), **MS:** m/z peak at 282(M^+) (100%) is base peak. The other peaks (m/z, I > 5%) relating to the fragments are: 150,165,203,230.9, 240.9, 254.9, 283.9, 284.9.

Synthesis of 8-Chloropyrimidobenzothiazole-2-ones (3b)

Yield- 72%, **Melting point:** 300^{0}C, **IR (KBr)** 1650cm^{-1} (C=O) 1568cm^{-1} (C=C) 1600cm^{-1} (C=N), **MS:** m/z peak at 237 (M^+) (100%) is the base peak and different fragmentations appear at 239, 259, 222, 240, 275, 185, 166 are proving the synthesis.

Synthesis of pyrimido [2,1-b]benzothiazol-2-one (3c)
Yield-33.3%, **Melting point:** 180-190^{0}C Thin Layer Chromatography solvent is $CHCl_3$: Hexane (6:4). Retention factor value for 2-aminobenzothiazole- 0.78 and for product is 0.60.

Synthesis of 8-methoxy-pyrimido [2,1-b]benzothiazol-2-one (3d)
Yield- 21.7%, **Melting point:** >300^{0}C Thin Layer Chromatography solvent is Diethylether: Hexane (7:3). Retention factor value for 2-amino-6-methoxybenzothiazole is 0.75 for product is 0.62.

Synthesis of 4H-pyrimido [2,1-b]benzothiazol-4-ones (6a)
Yield-69%, **Melting point:** 140-147^{0}C Thin Layer Chromatography solvent is Dichloromethanee. Retention factor value for 4H-pyrimido[2,1-b]benzothiazol-4-ones is 0.5

Synthesis of 8-methoxy-4H-pyrimido[2,1-b]benzothiazol-4-one (6b)
Yield-63%, **Melting point:** 150-160^{0}C Thin Layer Chromatography solvent is Dichloromethanee. Retention factor value for 8-methoxy-4H-pyrimido[2,1-b]benzothiazol-4-one is 0.6

Antibacterial activity: The all synthesized pyrimidobenzothiazoles were investigated for their activity against bacterial and fungal strains. The anti-bacterial tests were conducted on two common microorganisms such as *Basillus subtilis* and *Escherichia coli*, which are the representative type of gram-positive and gram-negative organism respectively and anti fungal test, were conducted on one microorganism that specially used in lawns. The agar media prepared by using following ingredients

Nutrient agar	16 g	Pentose dextrose agar	17.5 g
Distilled water	500 ml	Distilled water	500 ml

Weighed-quantity of nutrient agar mix in the 500 ml distilled water to dissolve the agar solution. For complete dissolution the solution was heated in hot oven. Then the prepared nutrient agar media was sterilized by autoclave at 120˚C for 20 minutes at 15lbs/ in^2 pressure.

Preparation of test solution: 10 mg test compound were dissolved in 10 ml ethanol. From this 1ml solution was taken and dilute to 10 ml with ethanol. Now the concentration of test compound was 100 ppm or µg/ml. These sample solution were made in labeled sterilized test tubes.

Preparation of standard solution: The standard drug used for testing was Gentamicin (G^{20}) for anti bacterial and Flucanazole (FLC^{25}) for anti fungal. The concentration of these drugs was adjusted to 100µg/ml.

The sterilized media was cooled with gentle shaking to bring about uniform cooling. This was poured into sterilized Petri dishes and allows the media to set. The entire process of media pouring and inoculation was completed in laminar air flow unit. Then the discs which are previously prepared carefully kept on the solidified media by using sterilized forceps. These Petri dishes kept at room temperature for 1 hr and then for incubation at 37˚C for 24 hrs in incubator. The zone of inhibition was measured after 24 hrs for antibacterial and for antifungal after 4-5 days and result shown in table-2.

RESULTS AND DISCUSSION

The structures of the newly synthesized pyrimido [2,1-b]benzothiazol-2/4-ones were confirmed by spectral studies. The IR spectra of the synthesized compounds had shown characteristic absorption bands due to C=N, amidic C=O, and C=C stretching vibrations. The absorption band in range 1550–1600 cm^{-1} are due to C=N stretching vibrations and the absorption band in the region 1500–1550 cm^{-1} is assigned due to C=C stretching vibrations. The absence of stretching vibrations of the $–NH_2$ group and appearance of absorption band in the region 1680–1710 cm^{-1} corresponding to the C=O group of cyclic amide suggest that the heterocyclization has occurred.

The m/z peak at 282 (M^+) confirm the synthesis of (3a) and 237 (M^+) confirm the synthesis of (3b). Thin layer chromatography data (R_f value) also confirm the synthesis of 3c, 3d, 6a and 6b.

Table-1 Physical data of synthesized compounds

S. No.	Compound	Molecular formula	M.Pt. °C	%Yield
1	3a	$C_{10}H_5BrN_2OS$	300-310	70
2	3b	$C_{10}H_5ClN_2OS$	300	72
3	3c	$C_{10}H_6N_2OS$	180-190	33.3
4	3d	$C_{11}H_8N_2O_2S$	220-225	21.7
5	6a	$C_{11}H_8N_2OS$	140-147	69
6	6b	$C_{12}H_{10}N_2O_2S$	150-160	63

Table-2 Antibacterial activities of the compounds

S. No.	Compound	Zone of inhibition (in mm)				
		Antibacterial activity			Antifungal activity	
		***B. subtilis* (10ppm)**	***B. subtilis* (100ppm)**	***E.coli* (100ppm)**	***A. fumigates* (50ppm)**	***A. fumigates* (50ppm)**
1	**3c**	8±1(32%)	-	-	1.6± 0.57(14.3%)	3.3± 0.57(28.6%)
2	**3d**	-	-	7± 2(35%)	-	-
3	**6a**	-	4± 2.6(20%)	-	-	-
4	**6b**	-	-	2.6± 0.57(15%)	-	-
5	**Standard**	24.3±2.5	25±3	19±2	13.6±1.52	13.6± 1.52

CONCLUSION

In conclusion a new series of substituted pyrimido[2,1-*b*]benzothiazol-2-ones and 4-ones derivatives has been synthesized and evaluated for their anti microbial activities. Most of the new compounds shown appreciable activities.

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