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Novel synthesis and biological activity study of pyrimido[2,1-*b*] benzothiazoles

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A convenient and apparently simple procedure has been developed to prepare a series of substituted pyrimido [2,1-*b*]benzothiazoles by the conjugate addition of the imino nitrogen of 2-aminobenzothiazoles to alkyne β-carbon atom of acetylenic acid followed by ring closure. They are screened for antimicrobial activity and found to exhibit significant activities.

Keywords: Michael addition, fused nitrogen heterocycles, cyclocondensation

Condensed pyrimidine compounds[1-13] are reported to possess interesting pharmacological properties such as antibacterial, antifungal etc. As a part of an ongoing study of the synthesis of heterocyclic compounds of potential biological activity from allenic and acetylenic compounds[14,15], a series of substituted pyrimido[2,1-*b*]benzothiazoles are synthesized. The results of these studies along with the antimicrobial activities of these compounds are reported in this paper. The structure of these compounds are determined on the basis of their spectral data and elemental analysis **(Tables I** and **II)**.

Results and Discussion

The conjugate addition of the imino nitrogen of 2-aminobenzothiazole **1** to the alkyne β-carbon atom of acetylenic acids **2** in butanol followed by cyclo-condensation, gave the corresponding 2*H*-pyrimido-[2,1-*b*]benzothiazol-2-ones **6,7** in 59-75% yield **(Scheme I)**.

The structures of these compounds were determined by ^{1}H NMR and ^{13}C NMR spectra **(Table II)**.

When 2-aminobenzothiazoles **1a-1e** were allowed to react with phenyl propiolic acid **2a**, 4-phenyl-2*H*-pyrimido[2,1-*b*]benzothiazol-2-ones **6a-e** were obtained. The NMR spectra of the 8-chloro compound **6a** and 8,9-dimethyl compound **6c** showed singlets at δ 6.20 and δ 6.19, respectively, attributed to 3-H and doublets at δ 6.04 and δ 5.75, respectively, for 6-H. The shielding effects observed for the 6-H in the compounds **6a-c** is due to the diamagnetic effect of the phenyl group attached to C-4. The above data exclude the formation of the isomeric 2-phenyl-4*H*-pyrimido[2,1-*b*]benzothiazole-4-ones **8** which should exhibit a deshielded proton (6-H) near δ 9.00 resulting from the anisotropic effect of the carbonyl group. Further evidence for the formation of the 2-one derivatives was obtained from the fact that no shielding effect was noticed in compounds **7a-e** where phenyl group was replaced by 1-pentyl respectively.

The reaction of 2-aminobenzothiazoles **1** with acetylenic acids **2** is rationalized as shown **(Scheme I)**, where the alkynoic acid is first attacked at the β-carbon atom by the ring nitrogen atom of the benzothiazole. An attack of the 2-amino group of **1** on the β-carbon of **2** which eventually would generate the isomeric product **8** definitely does not occur[16,17] **(Scheme II)**.

Experimental Section

All the melting points were determined in open capillaries and are uncorrected. The purity of compounds was checked by TLC on silica gel G coated glass plates. IR spectra were recorded in KBr on a Shimadzu FT-IR 8400 spectrophotometer, ^{1}H and ^{13}C NMR in $CDCl_3$ were recorded on a JEOL AL-300 using TMS as internal standard. Mass

Table I — Characterization data of compounds **6, 7a-e**

Compd	R^1	R^2	R^3	R^4	R^5	m.p. (°C)	Yield (%)	Mol. Formula	Found (Calcd) (%) C	H	N
6a	H	Cl	H	H	Ph	78	62	$C_{16}H_9N_2OSCl$	61.51 (61.44	2.86 2.88	8.92 8.96)
6b	H	H	Br	H	Ph	61	69	$C_{16}H_9N_2OSBr$	53.99 (53.78	2.48 2.52	7.77 7.84)
6c	Me	Me	H	H	Ph	62	70	$C_{18}H_{14}N_2OS$	70.65 (70.58	4.56 4.57	9.12 9.15)
6d	H	Me	H	Me	Ph	160	74	$C_{18}H_{14}N_2OS$	70.46 (70.58	4.55 4.57	9.17 9.15)
6e	H	Cyclic C_4H_4-bonded at C-7 and C-8 position		H	Ph	49	67	$C_{20}H_{13}N_2OS$	72.90 (72.94	3.92 3.95	8.47 8.51)
7a	H	Cl	H	H	1-pentyl	48	59	$C_{15}H_{15}N_2OSCl$	58.89 (58.72	4.91 4.89	9.11 9.13)
7b	H	H	Br	H	1-pentyl	80	72	$C_{15}H_{15}N_2OSBr$	51.40 (51.28	4.25 4.27	7.92 7.97)
7c	Me	Me	H	H	1-pentyl	85	72	$C_{17}H_{20}N_2OS$	68.32 (68.00	6.62 6.66	9.31 9.33)
7d	H	Me	H	Me	1-pentyl	80	75	$C_{17}H_{20}N_2OS$	67.94 (68.00	6.61 6.66	9.30 9.33)
7e	H	Cyclic C_4H_4-bonded at C-7 and C-8 position		H	1-pentyl	51	68	$C_{19}H_{19}N_2OS$	70.70 (70.58	5.85 5.88	8.61 8.66)

Table II — Spectral data of compounds **6, 7a-e**

Compd	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	Mass *m/z* (%)	IR *v* (cm^{-1})
6a	6.04 (1H, d, 6-H), 6.20 (1H, s, 3-H), 7.21 (1H, dd, 7-H), 7.9 (1H, s,9-H), 7.5 (2H, d, 2′-H, 6′-H), 7.71 (2H, dd, 3′-H, 5′-H), 7.64 (1H, dd, 4′-H)	117.2 (C-6), 126.1 (C-7), 132.4 (C-8), 123.0 (C-9), 133 (C-5a), 124.9 (C-9a), 163.0 (C-10a), 166.7 (C-2), 99.6 (C-3), 149.0 (C-4), 128.5 (C-2′, C-6′), 129.6 (C-3′, C-5′), 130.9 (C-4′), 131.9 (C-1′)	312.54 (M^+, 74%), 314.5(M+2, 25%), 284(34%) 277 (15%), 275 (39%), 271 (45%), 210 (20%), 182 (100%) etc.	1650 (C = O) 1612 (C=N) 1590 (C=C)
6b	6.14 (1H, s, 6-H), 6.10 (1H, s, 3-H), 7.32 (1H, dd, 8-H), 7.84 (1H, d, 9-H), 7.49 (2H, d, 2′-H, 6′-H), 7.65 (2H, dd, 3′-H, 5′-H), 7.62 (1H, dd, 4′-H)	119.6 (C-6), 120.5 (C-7), 129.4 (C-8), 125.0 (C-9), 122.9 (C-9a), 137.2 (C-5a), 164.9 (C-10a), 167.0 (C-2), 99.7 (C-3), 149.2 (C-4), 128.3 (C-2′, C-6′), 129.5 (C-3′,C-5′), 130.8 (C-4′), 131.7 (C-1′)	357 (M^+, 50%), 359 (M+2, 49%), 328 (78%), 315 (42%), 277 (100%), 275 (25%), 254 (20%), 226 (10%) etc.	1645 (C = O) 1605 (C=N) 1585 (C=C)
6c	1.89 (3H, s, 8-CH_3), 2.18 (3H, s, 9-CH_3), 5.75 (1H, d, 6-H), 6.19 (1H, s, 3-H), 6.9 (1H, d, 7-H), 7.37 (2H,d, 2′-H, 6′-H), 7.53 (2H, dd, 3′-H, 5′-H), 7.60 (1H, dd, 4′-H)	113.2 (C-6), 126.5 (C-7), 136.0 (C-8), 132.8 (C-9), 124.5 (C-9a), 132.0 (C-5a), 164.8 (C-10a), 19.4 (8-CH_3), 20.0 (9-CH_3), 167.1 (C-2), 112.7 (C-3), 148.8 (C-4),128.3 (C-2′, C-6′), 129.1 (C-3′, C-5′), 130.6 (C-4′), 132.0 (C-1′)	306 (M^+, 100%), 278 (52%), 265 (10%), 204 (49%), 189 (14%) etc.	1635 (C = O) 1600 (C=N) 1565 (C=C)
6d	1.81 (3H, s, 6-CH_3), 1.91 (3H, s, 8-CH_3), 6.92 (1H, d, 7-H), 7.36 (1H, d, 9-H), 6.21 (1H, s, 3-H), 7.35 (2H, d, 2′H, 6′-H), 7.55 (2H, dd, 3′-H, 5′-H), 7.61 (1H, dd, 4′-H)	125.4 (C-6), 127.3 (C-7), 135.2 (C-8), 120.6 (C-9), 123.7 (C-9a), 121.7 (C-5a), 165.0 (C-10a), 167.2 (C-2), 112.6 (C-3), 148.9 (C-4), 128.2 (C-2′, C-6′), 129.0 (C-3′, C-5′), 130.8 (C-4′), 131.6 (C-1′), 18.0(6-CH_3), 19.4 (8-CH_3)	306 (M^+,100%), 278 (53%), 265 (7%), 204 (50%), 189 (12%) etc.	1640 (C = O) 1600 (C=N) 1568 (C=C)

—Contd

Table II — Spectral data of compounds **6, 7a-e** — *Contd*

Compd	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	Mass *m/z* (%)	IR *v* (cm^{-1})
6e	6.84 (1H, s, 6-H), 7.61 (1H, dd, 7-H) 7.30 (1H, dd, 8-H), 7.31 (1H, dd, 9-H), 7.66 (1H, d, 10-H), 7.00 (1H, s, 11-H), 5.68 (1H, s, 3-H), 7.30 (2H, d, 2′-H, 6′-H), 7.21 (2H, dd, 3′-H, 5′-H), 7.14 (1H, dd, 4′-H)	119 (C-6), 131 (C-6a), 128.3 (C-7), 125.6 (C-8), 124.6 (C-9), 126.2 (C-10), 123.7 (C-10a), 126.9 (C-11), 135.7 (C-11a), 132.6 (C-5a), 167.8 (C-12a), 163.0 (C-2), 99.8 (C-3), 150.2 (C-4), 128.2 (C-2′, C-6′), 128.4 (C-3′, C-5′), 128.4, 127.7 (C-4′), 134.9 (C-1′)	329 (M$^+$, 100%), 301 (38%), 288 (51%), 277 (20%), 199 (18%) etc.	1640 (C=O), 1590 (C=N), 1570 (C=C)
7a	7.59 (1H, d, 6-H), 6.13 (1H, s, 3-H), 7.62 (1H, dd, 7-H), 7.74 (1H, s, 9-H), 3.02 (2H, t, 1′-H), 1.75 (2H, tt, 2′H), 1.51 (2H, m, 3′-H), 1.42 (2H, m, 4′-H), 0.95 (3H, t, 5′-H)	117 (C-6), 126.2 (C-7), 133.3 (C-8), 123.3 (C-9), 133.6 (C-5a), 125.1 (C-9a), 164.8 (C-10a), 167.2 (C-2), 110.7 (C-3), 151.5 (C-4), 13.8 (C-5′), 22.5 (C-4′), 26.8 (C-2′), 31.2 (C-3′), 33.5 (C-1′)	306.52 (M$^+$, 75%), 308.5(M+2, 24%), 271 (20%), 269 (16%), 264 (39%), 250 (54%), 222 (43%), 210 (100%) etc.	1648 (C = O) 1584 (C=N) 1520 (C=C)
7b	6.15 (1H, s, 3-H), 7.62 (1H, s, 6-H), 7.56 (1H, dd, 8-H), 7.75 (1H, s, 9-H), 3.12 (2H, t, 1′-H), 1.70 (2H, tt, 2′H), 1.50 (2H, m, 3′-H), 1.41 (2H, m, 4′-H) 0.92 (3H, t, 5′-H)	119.5 (C-6), 120.4 (C-7), 129.5 (C-8) 124.9 (C-9), 123.0 (C-9a), 137.0 (C-5a), 164.8 (C-10a), 167.1 (C-2), 110.5 (C-3), 151.4 (C-4), 13.9 (C-5′), 22.4 (C-4′) 26.7 (C-2′), 31.2 (C-3′), 33.8 (C-1′)	351 (M$^+$, 50%), 353 (M+2, 48%), 308 (43%), 294 (28%), 271(16%), 269 (12%), 254 (100%) etc.	1644 (C = O) 1580 (C=N) 1510 (C=C)
7c	2.28 (3H, s, 8-H), 2.32 (3H, s, 9-CH_3), 6.11 (1H, s, 3-H), 7.45 (1H, d, 6-H), 7.42 (1H, d, 7-H), 2.98 (2H, t, 1′H), 1.71 (2H, tt, 2′-H), 1.43 (2H, m, 3′-H), 1.38 (2H, m, 4′-H), 0.88 (3H, t, 5′-H)	113.0 (C-6), 126.6 (C-7), 136.9 (C-8) 133.1 (C-9), 124.7 (C-9a), 132.6 (C-5a), 165 (C-10a), 167.3 (C-2), 110.6 (C-3), 151.3 (C-4), 33.5 (C-1′), 26.7 (C-2′) 30.8 (C-3′), 22.1 (C-4′), 13.7 (C-5′) 19.4 (CH_3-8), 20.0 (CH_3-9)	300 (M$^+$, 100%), 258 (18%), 244 (15%), 216 (12%), 204 (28%) etc.	1640 (C = O) 1570 (C=N) 1500 (C=C)
7d	1.99 (3H, s, 6-CH_3), 2.30 (3H, s, 8-CH_3), 7.45 (1H, d, 7-H), 7.65 (1H, d, 9-H), 6.12 (1H, s, 3-H), 2.97 (2H, t, 1′H), 1.72 (2H, tt, 2′-H), 1.41 (2H, m, 3′-H), 1.35 (2′H, m, 4′-H), 0.91 (3H, t, 5′-H)	125.2 (C-6), 127.4 (C-7), 125.3 (C-8), 121.0 (C-9), 124.3 (C-9a), 133.4 (C-5a), 165.2 (C-10a), 167.0 (C-2), 110.5 (C-3), 151.0 (C-4), 33.2 (C-1′), 26.6 (C-2′), 30.9 (C-3′), 22.0 (C-4′), 13.6 (C-5′), 18.0 (CH_3-68), 19.4 (CH_3-8)	300 (M$^+$, 100%), 258 (36%), 244 (39%), 216 (36%), 204 (85%) etc.	1645 (C = O) 1575 (C=N) 1510 (C=C)
7e	7.54 (1H, s, 6-H), 7.60 (1H, dd, 7-H), 7.32 (1H, dd, 8-H), 7.31 (1H, dd, 9-H), 7.62 (1H, d, 10-H), 7.02 (1H, s, 11-H), 5.62 (1H, s, 3H), 3.05 (2H, t, 1′-H), 1.72 (2H, tt, 2′-H), 1.50 (2H, m, 3′-H), 1.43 (2H, m, 4′-H), 0.92 (3H, t, 5′-H)	119.2 (C-6), 130.2 (C-6a), 128.1 (C-7), 125.9 (C-8), 123.8 (C-9), 125.4 (C-10), 122.8 (C-10a), 125.8 (C-11), 134.8 (C-11a), 131.8 (C-5a), 166.6 (C-12a), 163.8 (C-2), 103.6 (C-3), 149.8 (C-4), 13.5 (C-5′), 22.8 (C-4′), 26.9 (C-2′), 31.5 (C-3′), 33.8 (C-1′)	323 (M$^+$, 100%), 281 (38%), 267 (52%), 239 (45%), 227 (18%) etc.	1635 (C=O) 1578 (C=N) 1520(C=C)

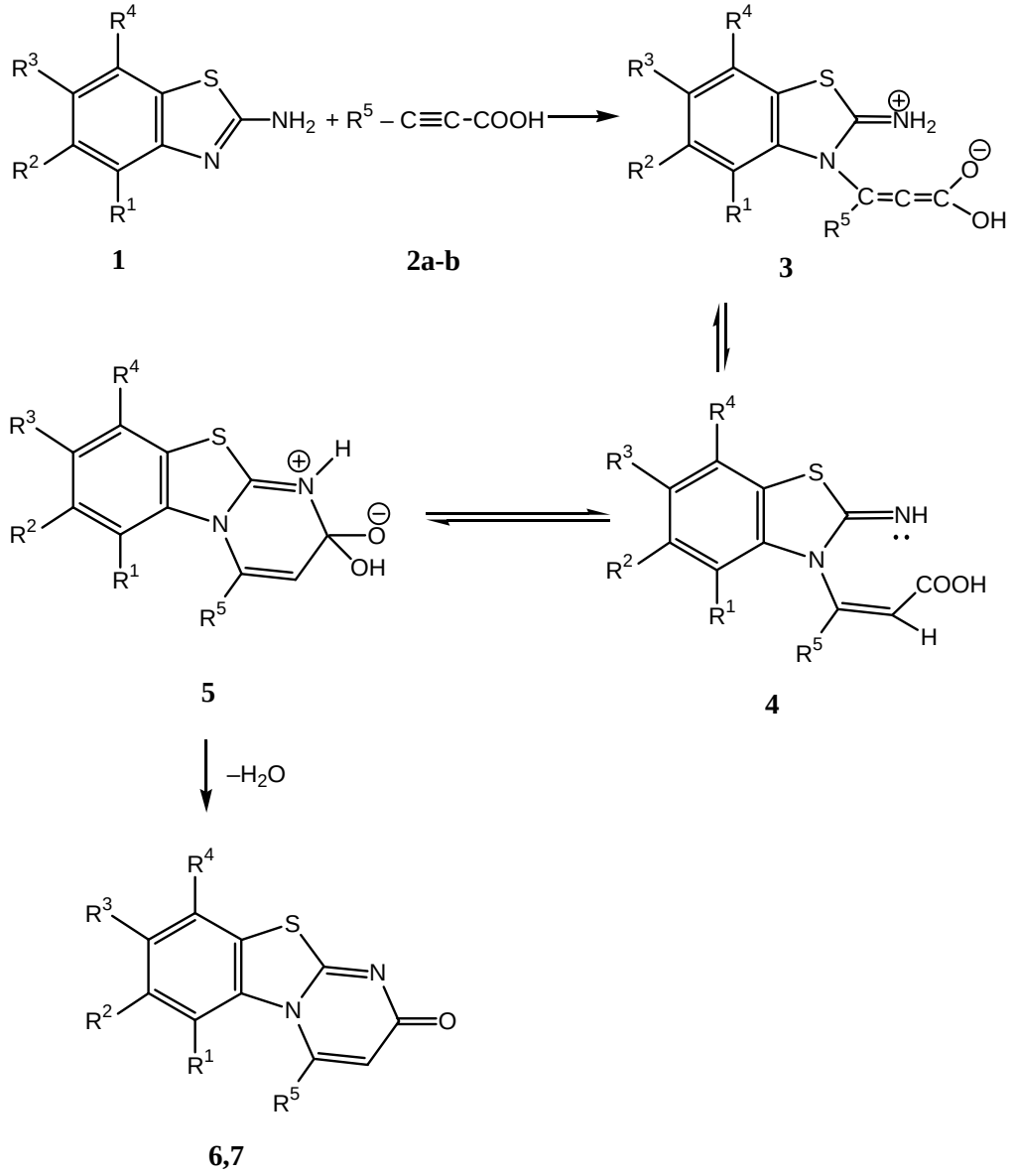
spectra were recorded on JEOL SX 102/DA-6000 using Argon/Xenon as FAB gas. All the compounds gave satisfactory elemental analysis.

Synthesis of 2*H*-pyrimido[2,1-*b*] benzothiazole-2-ones [6, 7a-e]

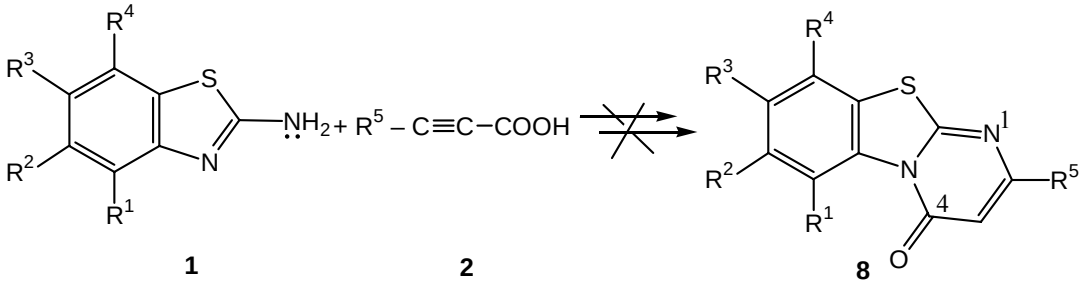
The alkynoic acid **2a,b** (20 mmole) and the appropriate 2-amino benzothiazole (**1a-e**, 10 mmole) were heated to reflux in 1-butanol (50 mL) for 48 hr. Evaporation of solvent under reduced pressure gave the crude product which was crystallized from hexane/ethyl acetate to give the 2*H*-pyrimido [2,1-*b*] benzothiazol-2-ones.

Antimicrobial activity

The synthesized compounds were tested for their antibacterial activity by using Paper Disc method by measuring the zone of inhibition on agar plates with *Escherichia coli, Staphyloccus aureus, Enterobacter* as test organisms at concentration of 100 µg per disc using vancomycin and meropenem as standard compounds and antifungal activity against various strains of *Candida albicans* at concentration of 100 µg/disc using flucanazole as standard compound **(Table III)**.



Scheme I



Scheme II

Table III — Antimicrobial activity of compounds **6, 7a-e**

Compd	Antibacterial activity (Zone of inhibition in mm)			Antifungal activity (Zone of inhibition in mm)	
	E. coli	*Entero-bacter*	*Staphylococcus aureus*	*Candida albicans* strain 1	*Candida albicans* strain 2
6a	15	14	-	12	15
6b	11	12	-	10	10
6c	7	7	7	12	7
6d	12	13	14	11	12
6e	-	-	-	24	24
7a	-	7	7	32	36
7b	-	-	-	-	6
7c	14	15	8	-	7
7d	-	-	-	18	18
7e	-	-	13	20	21
Meropenem	16	16	16	-	-
Vancomycin	-	-	15	-	-
Flucanazole	-	-	-	25	25
Note: < 7mm, inactive; 7-9 mm weakly active; 10-12 mm, moderately active; > 12 mm, active				< 7 mm, inactive; 7-11 mm, weakly active; 12-17 mm, moderately active; > 17 mm, active	

Conclusion

It is evident that the synthesized compounds are biologically active. The results of antibacterial screening indicated that good activity was shown by compounds **6a,7c** against *E. coli* and *Enterobacter* and compound **6d,7e** against *Staphylococcus aureus.* Moderate activity was shown by compound **6b, 6d** against *E. coli* and *Enterobacter.* Other compounds showed less or no activity against all bacterial strains.

Regarding antifungal activity, compounds **6e,7a,7d,7e** showed good activity against strains of *Candida albicans.* Other compounds showed moderate to less activity against strains of *Candida albicans* **(Table III)**.

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