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Note

Novel synthesis and antibacterial activity of 15-iminobenzothiazolo[2,3-*b*] pyrimido[5,6-*e*]pyrimido[2,3-*b*]benzothiazol-14(*H*)-one and its 3,10-disubstituted derivatives

K G Baheti[1], J S Jadhav[2], A T Suryavanshi[3] & S V Kuberkar*[3]

[1] Department of Pharmaceutical Chemistry, Nanded Pharmacy College, Nanded 431 605, India

[2]N.S. B. College, Nanded 431 601, India

and

[3] Department of Chemistry, Yeshwant Mahavidyalaya, Nanded 431 605, India

E-mail: *kuberkarsv@rediffmail.com*

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Novel heterocyclic compound 15-iminobenzothiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*] benzothiazol-14(*H*)-one and its 3,10-disubstituted derivatives **3a-l** have been synthesized by the reaction of 2-thiomethyl-3-cyano-8-H/substituted-pyrimido[2,1-*b*]benzothiazol-4(*H*)-one **1a-c** with 2-amino-6-H/ substituted benzothiazoles **2a-d**.

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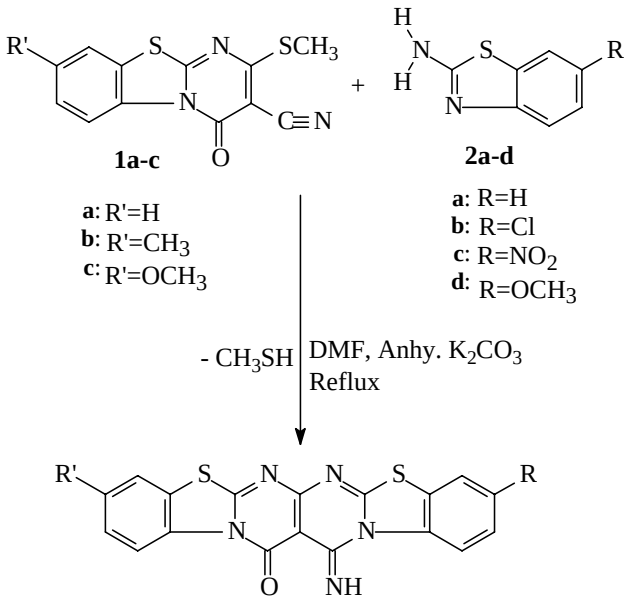
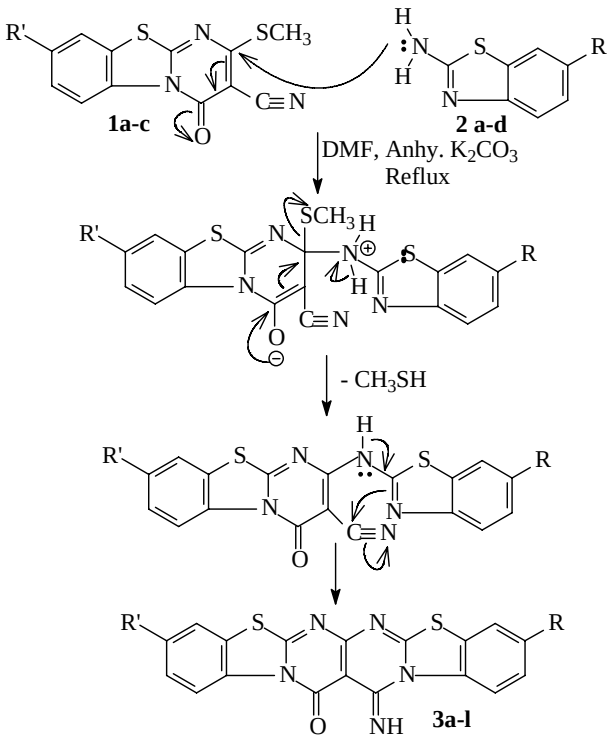
A survey of literature made it evident that very little work has been carried out on the synthesis of fused pyrimido benzothiazole possessing three to four rings[1-2] which exhibit a wide spectrum of activities like antitumor[3], phosphodiesterase inhibition[4], anti-allergic[5], anti-inflammatory[6] and antiparkinsonism[7]. In view of the reported biological activities of this system, synthesis of such condensed system has attracted much attention in recent years.

In this note, we report the synthesis of a novel heterocyclic system possessing six rings, 15-imino-benzothiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*]-benzothiazol-14(*H*)-one **3a** and its 3, 10-disubstituted derivatives **3a-l** . 2-Aminobenzothiazole in dimethyl-formamide on refluxing in the presence of anhydrous potassium carbonate with ethyl 2-cyano-3,3-bismethylthioacrylate afforded 2-thiomethyl-3-cyano-pyrimido[2,1-*b*]benzothiazol-4(*H*)-one[8] **1a**. Compounds **3a-d** were prepared by reaction of **1a** with 2-amino-6-H/substituted benzothiazole[9] **2a-d** in the presence of dimethylformamide and catalytic amount of anhydrous potassium carbonate in 40-70% yield **(Scheme I)**. The reaction proceeds with initial attack of amino group of benzothiazoles **2a-d** on carbon attached to SCH_3 group resulting in loss of thiomethyl group in the form of methyl mercaptan. The resulting secondary amine polarizes on to nitrile carbon to give cyclized product **(Scheme II)**. Similarly other 3,10-disubstituted derivatives of **3a** were prepared by heating **1b-c** independently with 2-amino-6-H/substituted-benzothiazoles **2a-d** in the presence of anhydrous potassium carbonate. The structures of these newly synthesized cyclized compounds **3a-l** were confirmed on the basis of elemental analysis **(Table I)** and IR, ^{1}H NMR and mass spectral data **(Table II)**.

The IR spectra of compounds **3a-l** showed the absence of CN stretching absorption band in the region 2200-2250cm^{-1}and showed the presence of absorption bands in the region 3300-3450 and 1680-1740cm^{-1} which can be assigned to -NH and C=O stretching, respectively. The ^{1}H NMR spectra exhibited a singlet at δ 8.4-8.9, exchangeable with D_2O,



Scheme I



Scheme II

which can be assigned to -NH proton. Mass spectra of compounds exhibited the molecular ion peaks which correspond to molecular weights.

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[10]. All the synthesized compounds were dissolved in dimethyl sulphoxide. The synthesized compounds exhibited zone of inhibition of 09-13 mm in diameter whereas standard Streptomycin exhibited zone of inhibition of 18 and 22 mm in diameter against *S. aureus* and *B. substilis* and Penicillin exhibited zone of inhibition of 15 and 16 mm in diameter against *E. coli* and *S. typhi* respectively. Amongst the synthesized compounds **3a-l**, compound **3j** (10,10,13, 10 mm) and **3k** (10,09,10,12) showed higher zone of inhibition against *S. aureus, B. substilis, E. coli* and *S. typhi* respectively. It seems that the presence of OCH_3 group at 10-position of **3a** increases antibacterial activity **(Table III)**.

Experimental Section

All melting points were determined in capillary tube and are uncorrected. IR spectra were recorded in

Table I — Physical data of compounds **3a-l**

Compd	R′	R	Mol. formula	Reaction time (hr)	m.p. °C	Yield (%)	Found % (Calcd) C	H	N
3a	H	H	$C_{18}H_9N_5OS_2$	03	>300	55	57.55 (57.60	2.30 2.40	18.42 18.66)
3b	H	NO_2	$C_{18}H_8N_6O_3S_2$	06	>300	48	51.37 (51.42	1.82 1.90	19.89 20.00)
3c	H	Cl	$C_{18}H_8N_5OS_2Cl$	04	>300	40	52.75 (52.81	1.85 1.95	17.09 17.11)
3d	H	OCH_3	$C_{19}H_{11}N_5O_2S_2$	04	285	50	56.25 (56.29	2.68 2.71	17.21 17.28)
3e	CH_3	H	$C_{19}H_{11}N_5OS_2$	05	250	68	58.60 (58.61	2.81 2.82	17.96 17.99)
3f	CH_3	NO_2	$C_{19}H_{10}N_6O_3S_2$	06	280	55	52.52 (52.53	2.20 2.30	19.33 19.35)
3g	CH_3	Cl	$C_{19}H_{10}N_5OS_2Cl$	05	240	50	53.85 (53.90	2.19 2.26	16.38 16.54)
3h	CH_3	OCH_3	$C_{20}H_{13}N_5O_2S_2$	05	233	48	57.25 (57.21	3.00 3.10	16.79 16.70)
3i	OCH_3	H	$C_{19}H_{11}N_5O_2S_2$	05	245	66	56.26 (56.30	2.68 2.72	17.23 17.28)
3j	OCH_3	NO_2	$C_{19}H_{10}N_6O_4S_2$	06	289	58	50.62 (50.66	2.19 2.22	18.63 18.66)
3k	OCH_3	Cl	$C_{19}H_{10}N_5O_2S_2Cl$	05	>300	47	51.90 (51.94	2.25 2.28	15.90 15.94)
3l	OCH_3	OCH_3	$C_{20}H_{13}N_5O_3S_2$	05	225	52	55.14 (55.17	2.95 2.99	16.06 16.09)

Table II — Spectral data of compounds **3a-l**

Compd	^{1}H NMR(DMSO-d_6) (δ, ppm)	MS: m/z (%)
3a	7.0-7.6(m, 8H, Ar-H), 8.8(s, 1H, -NH, exch.D_2O)	375(M^+, 100), 349(30), 198(15), 177(35), 134(10), 73(20), 43(15).
3b	7.1-7.9 (m, 7H, Ar-H), 8.6 (s, 1H, -NH, exch. D_2O)	420(M^+, 100), 390(30), 374(50), 227(30)199(20), 194(30)173(25).
3c	7.2-7.9 (m, 7H, Ar-H), 8.6 (s, 1H, -NH, exch. D_2O)	411(M+2, 8), 409(M^+, 25), 368(10), 273(100), 240(25), 198(45), 160(10).
3d	3.7 (s, 3H, OCH_3), 7.0-7.8(m, 7H, Ar-H), 8.8(s, 1H, -NH, exch. D_2O)	405(M^+, 40), 390(20), 379(30), 227(40), 199(20), 179(100), 173(25), 135(30).
3e	2.2(s, 3H, CH_3), 7.2-7.8(m, 7H, Ar-H), 8.6 (s, 1H, -NH, exch. D_2O)	389(M^+, 100), 363(15), 241(20), 213, (40), 187(45), 149(20), 148(30), 123(25).
3f	2.5(s, 3H, CH_3), 7.1-7.9(m, 6H, Ar-H), 8.9(s, 1H, -NH, exch. D_2O)	434(M^+, 100), 430(20), 388(45), 241(30), 213(32), 193(50), 187(40), 149(30).
3g	2.4(s, 3H, CH_3), 7.0-7.8 (m, 6H, Ar-H), 8.6(s, 1H, -NH, exch. D_2O)	425(M+2, 7)423(M^+, 21), 368(100), 241(40), 214(45), 188(30), 149(30).
3h	1.9(s, 3H, CH_3), 3.5(s, 3H, OCH_3), 7.1-7.7(m, 6H, Ar-H), 8.8(s, 1H, -NH, exch. D_2O)	419(M^+, 35), 404(10), 303(10), 288(10), 228(10), 180(100), 164(80), 136(25).
3i	3.6(s, 3H, OCH_3), 7.2-7.8 (m, 7H, Ar-H), 9.0(s, 1H, -NH, exch. D_2O)	405(M^+, 40), 390(20), 362(30), 335(20), 257(50), 149(100), 122(60).
3j	3.5(s, 3H, OCH_3), 7.1-7.9 (m, 6H, Ar-H), 8.6(s, 1H, -NH, exch. D_2O)	450(M^+, 50), 435(20), 389(35), 361(30), 257(20), 194(100), 163(40).
3k	3.6(s, 3H, OCH_3), 7.0-7.8 (m, 6H, Ar-H), 8.8(s, 1H, -NH, exch. D_2O)	441(M+2, 10), 439(M^+, 30), 424(15), 396(35), 384(100), 369(40), 257(50).
3l	3.4(s, 3H, OCH_3), 3.7(s, 3H.OCH_3), 7.3-7.8 (m, 6H, Ar-H), 8.5 (s, 1H, -NH, exch. D_2O)	435(M^+, 30), 420(15), 357(55), 342(30), 303(40), 260(25), 228(30), 180(100).

Table III — Antibacterial activity of compound **3a-l**

Compd	Diameter in mm of zone of inhibition at 25 μg/disc			
	S. aureus	*B. substilis*	*E. coli*	*S. typhi*
3a	07	08	10	09
3b	08	07	11	10
3c	09	08	09	11
3d	07	08	12	10
3e	08	07	12	09
3f	09	08	10	09
3g	09	08	11	10
3h	07	08	11	09
3i	07	08	11	10
3j	10	10	13	10
3k	10	09	10	12
3l	08	07	10	09
Streptomycin	18	22	—	—
Penicillin	—	—	15	16

KBr pellets on Bomen MB 104 FT Infrared Spectrophotometer; ^{1}H NMR spectra on a FT Gemini 60 (200MHz) Spectrometer with TMS as an internal standard; and mass spectra 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 TLC, carried out on 0.25 mm thick silica gel-G plate using iodine vapour for detection.

General procedure

A mixture of 2-thiomethyl-3-cyano-8-H/substituted-pyrimido[2,1-*b*]benzothiazol-4(*H*)-one **1a-c,** (0.01 mole) and 2-amino-6-H/substituted-benzothiazole **2a-d** (0.01 mole) in 20-25mL DMF and pinch of anhydrous potassium carbonate was refluxed for 3-6 hr. The reaction mixture was cooled to room temperature and poured into ice-cold water. The separated solid product was filtered, washed with water and recrystallised from DMF-ethanol mixture to give pure **3a-l**. The physical and spectral data of synthesized compounds **3a-l** are given in **Tables I** and **II**.

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