Novel Synthesis and Biological Activity of 2-Substituted Derivatives of 3-Cyano-4-imino-2-methylthio-8-methoxy-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole and 3-Amino-4-imino-8-methoxy-2*H*-pyrazolo[3′,4′:4,5]pyrimido[2,1-*b*][1,3]benzothiazole

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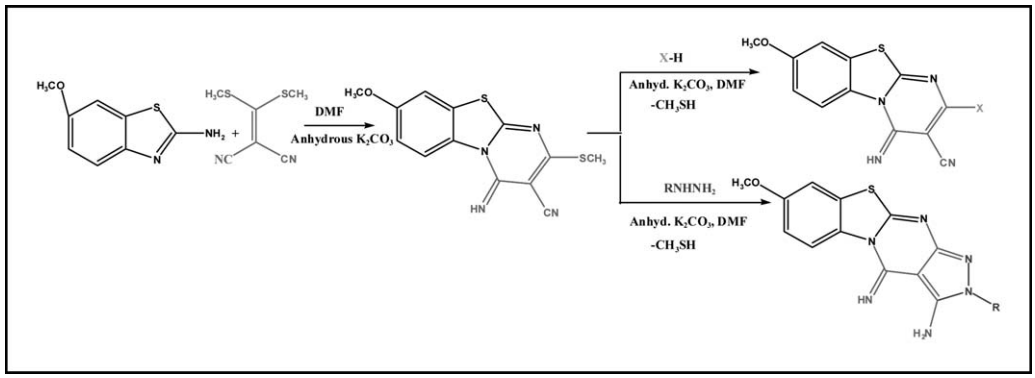

2-Amino-6-methoxybenzothiazole **1** on reaction with bis(methylthio)methylene malononitrile **2** in the presence of dimethyl formamide and catalytic amount of anhydrous potassium carbonate afforded 3-cyano-4-imino-8-methoxy-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole **3**. Under similar experimental conditions, compound **3** on treatment independently with arylamines/heterylamines/phenols/compounds containing active methylene group yielded corresponding 2-substituted derivatives of compound **3** (**4**$_{a–d}$, **5**$_{a–c}$, **6**$_{a–e}$, and **7**$_{a–e}$). Similarly, novel heterocyclic compounds, 3-amino-4-imino-8-methoxy-2*H* **8**$_{a}$/aryl **8**$_{b–c}$/heteryl **8**$_{d–f}$/pyrazolo[3′,4′:4,5]pyrimido[2,1-*b*][1,3]benzothiazoles, were prepared by heating compound **3** independently with hydrazine hydrate/arylhydrazines/heterylhydrazines, respectively. All these newly synthesized compounds were screened for antimicrobial activity.

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INTRODUCTION

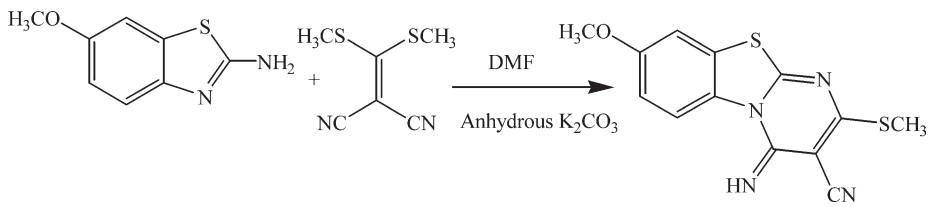
Fused pyrimidobenzothiazoles [1,2] are well known for their varied biological activities like antiallergic [3,4], antitumor [5], anti-inflammatory [6], antiparkinsonism [7], and phosphodiesterase inhibition [8]. In our recent publications [9–12], we have outlined convenient synthesis of new fused heterocyclic systems like oxopyrimidobenzothiazoles [9,10], pyrazolopyrimidobenzothiazoles [11], and benzothiazolotriazepines [12] and studied on their biological activities [12]. A literature survey revealed that very few refs. [13–15] are available on the synthesis of iminopyrimidobenzothiazoles and iminopyrazolopyrimidobenzothiazoles. These observations have stimulated our considerable interest to explore the synthesis of new fused heterocycles in which iminopyrimidine and pyrazolo iminopyrimidine rings are fused with another biologically active benzothiazole. In this work, we report one-pot synthesis of 3-cyano-4-imino-2-methylthio-8-methoxy-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole **3**, 3-amino-4-imino-8-methoxy-2*H*-pyrazolo[3′,4′:4,5]pyrimido [2,1-*b*][1,3]benzothiazole **8**$_{a}$ and their 2-substituted derivatives **4**$_{a–d}$, **5**$_{a–c}$, **6**$_{a–e}$, **7**$_{a–e}$, and **8**$_{b–f}$.

RESULTS AND DISCUSSION

Compound **3** was prepared from the reaction of bis (methylthio)methylene malonitrile **2** with 2-amino-6-methoxy benzothiazole in the presence of *N*,*N*′-dimethyl formamide and a catalytic amount of anhydrous potassium carbonate (Scheme 1). The structure of the compound **3** was assigned on the basis of elemental analysis and spectral data. IR (potassium bromide): =NH 3255, C≡N 2197 cm^{-1}; ^{1}H nuclear magnetic resonance (NMR; DMSO-d_6): δ 2.4 (s, 3H, SCH_3), 3.7 (s, 3H, OCH_3), 7.1–7.6 (m, 4H, Ar—H), 9.2 (s, 1H, =NH); ms: *m*/*z* 302 (M^+).

A mechanism for the formation of parent compound **3** can be adduced as shown in Scheme 2.

Scheme 1

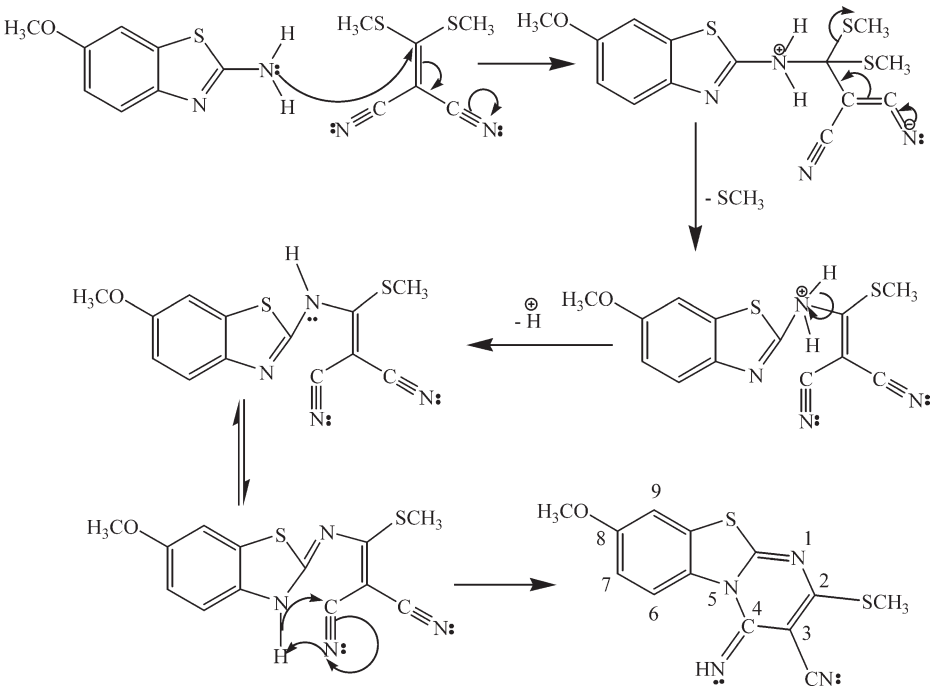


Compound **3** possesses a replaceable active methylthio group at the 2-position that is activated by the ring 1-nitrogen atom and the electron withdrawing 3-cyano group. Compound **3** was reacted with selected N-, O- and C-nucleophiles like arylamines, heterylamines, substituted phenols, and compounds containing an active methylene group. These reactions resulted in the formation of 2-substituted derivatives of compound **3**. According to this method, compound **3** on reaction independently with 4-nitroaniline, 4-methylaniline, 4-methoxyaniline, and 4-chloroaniline in the presence of *N*,*N*′-dimethyl formamide and a catalytic amount of anhydrous potassium carbonate afforded 3-cyano-4-imino-8-methoxy-2-(4′-nitroanilino/4′-methylanilino/4′-methoxyanilino/4′-chloroanilino-4*H*-pyrimido[2,1-*b*][1,3]benzothiazoles **4**$_{a-d}$, respectively (Scheme 3). Under similar experimental conditions, compound **3** reacted independently with heterylamines like morpholine, pyrrolidine, and piperidine to yield 3-cyano-4-imino-8-methoxy-2-(morphilino/pyrrolidino/piperidino)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazoles **5**$_{a-c}$, respectively (Scheme 3).

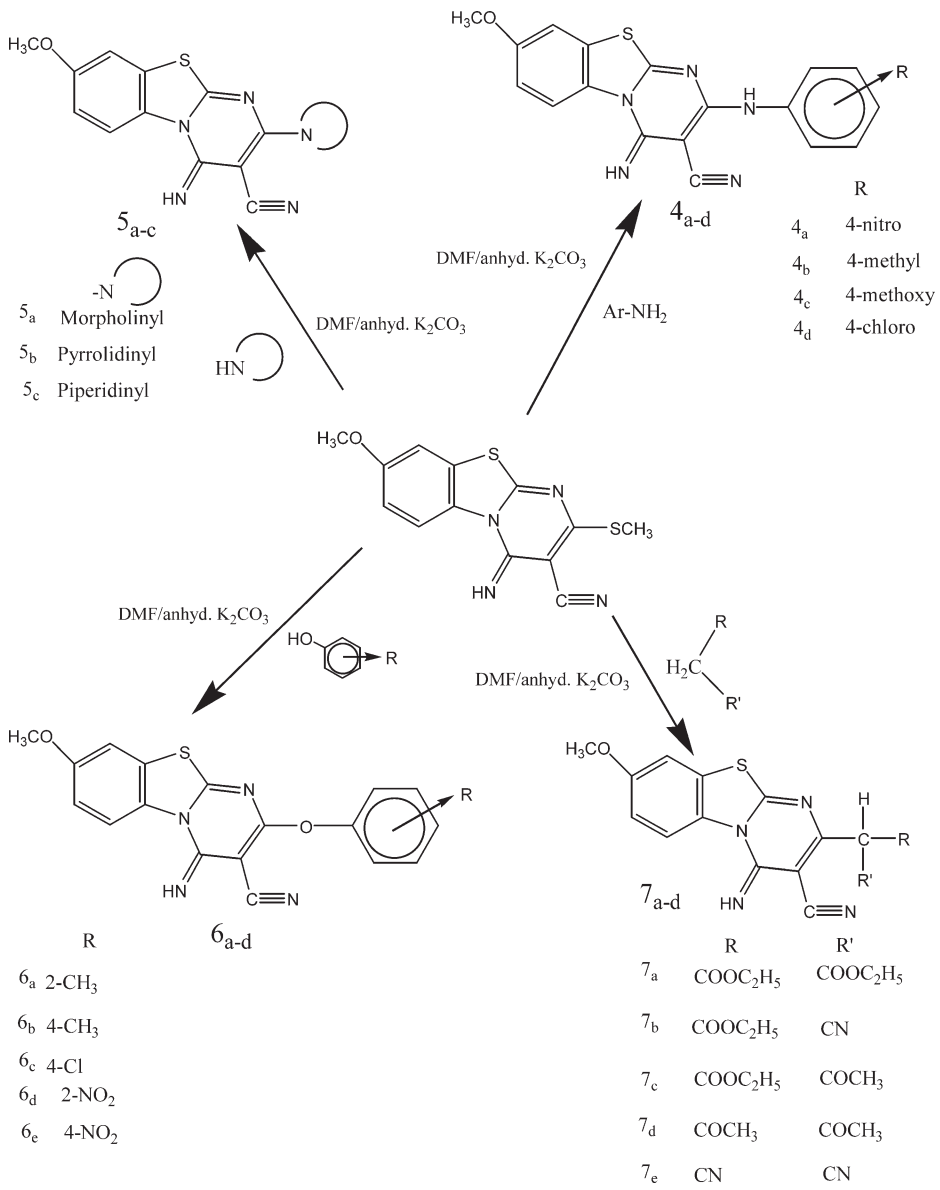
3-Cyano-4-imino-8-methoxy-2(2′-methylphenoxy/4′-methylphenoxy/4′-chlorophenoxy/2′-nitrophenoxy/4′-nitrophenoxy)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazoles **6**$_{a–e}$ were obtained by the condensation of compound **3** with 2-methyl phenol/4-methyl phenol/4-chlorophenol/2-nitrophenol/4-nitrophenol in *N*,*N*′-dimethyl formamide and a catalytic amount of anhydrous potassium carbonate independently (Scheme 3). Under similar experimental conditions, compound **3** reacted independently with diethyl malonate, ethyl cyanoacetate, ethyl acetoacetate, acetyl acetone, and malononitrile yielded compounds that were characterized on the basis of their analytical and spectral data as 3-cyano-4-imino-8-methoxy-2(diethylmalonyl/ethylcyanoacetyl/ethylacetoacetyl/acetylacetonyl/malononitrile)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazols **7**$_{a–e}$ (Scheme 3).

Compounds **4**$_{a–d}$, **5**$_{a–c}$, **6**$_{a–e}$, and **7**$_{a–e}$ exhibit absorption bands in their IR spectra in the range of 3300–3500 and 2180–2230 cm^{-1} due to =NH stretching and CN stretching, respectively. ^{1}H-NMR and mass spectral data are also in agreement with the structure assigned to compounds **4**$_{a–d}$, **5**$_{a–c}$, **6**$_{a–e}$, and **7**$_{a–e}$.

Scheme 2



Scheme 3

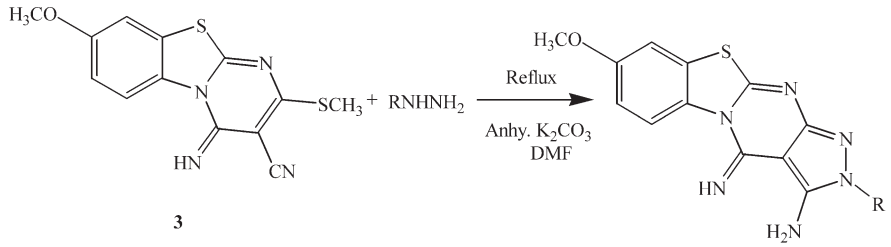


Similarly, novel heterocyclic compounds, 3-amino-4-imino-8-methoxy-2(*H*/phenyl/4′-nitrophenyl/2′-benzothiazolyl/6′-chloro-2′-benzothiazolyl/6′-methyl-2′-benzothiazolyl)pyrazolo[3′,4′:4,5]pyrimido[2,1-*b*][1,3]benzothiazoles **8a–f** were prepared by heating compound **3** under similar experimental conditions independently with hydrazine hydrate/phenyl hydrazine/4-nitrophenylhydrazine/2-hydrazinobenzothiazole/6-chloro-2-hydrazinobenzothiazole/6-methyl-2-hydrazinobenzothiazole, respectively (Scheme 4). The structures of compounds **8a–f** were confirmed on the basis of elemental analysis and spectral data.

The IR spectra of compounds **8a–f** showed the absence of C≡N stretching absorption band in the range of 2180–2260 cm^{-1}. The presence of absorption bands in the region 3100–3350 cm^{-1} due to free NH_2 and =NH group indicate that the ring gets cyclized to form five-membered pyrazole ring. The ^{1}H-NMR spectra of compounds **8a–f** exhibited singlet in the region δ 3–3.5 due to —OCH_3 protons, broad peak in the region δ 3.7–5 due to —NH_2 proton, and singlet in the region δ 7.8–8.5 due to =NH proton. The mass spectra showed the molecular ion peaks which correspond to molecular weight of respective compounds. The mechanism for the formation of **8a–f** can be represented as shown in Scheme 5.

Antimicrobial activity. The synthesized compounds were tested for their antimicrobial activity by paper disc diffusion method against *S. aureus*, *B. subtilis*, *E. coli*, and *S. typhi* using Norflaxacin as a standard antimicrobial

Scheme 4



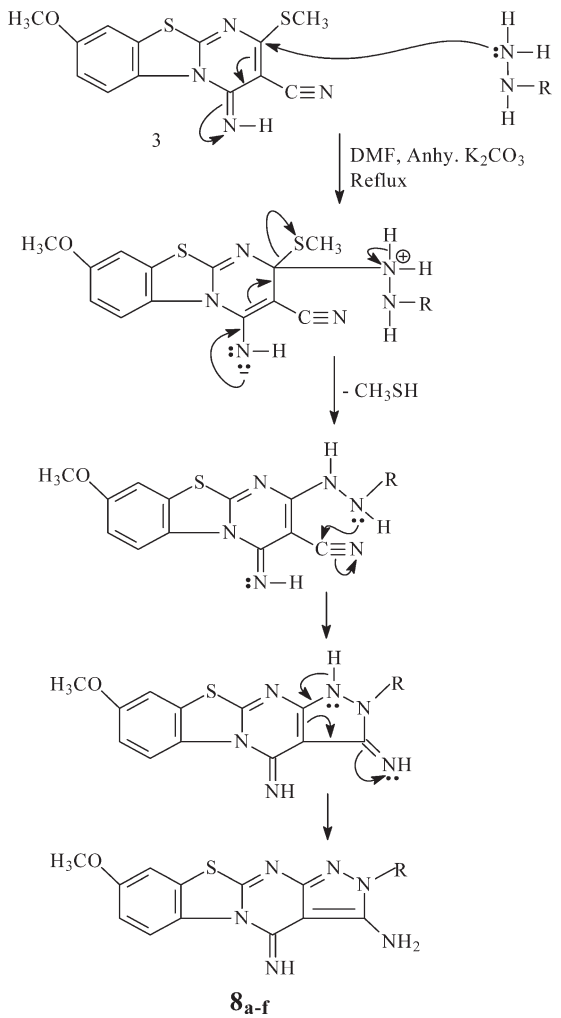
3

8a-f

R
8a-H
8b-Ph
8c-4'-nitrophenyl
8d-2'-benzothiazolyl
8e-6'-chloro-2'-benzothiazolyl
8f-6'-methyl-2'-benzothiazolyl

compound for comparison. The antimicrobial screening data of the compounds have been incorporated in Table 1. Dimethyl formamide was used as a control solvent.

Scheme 5



8a-f

The compounds **4a**, **4d**, **6a**, **6c**, and **6d** of the series of 3-cyano-4-imino-8-methoxy-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole and its 2-substituted derivatives were found to be more active and exhibited zone of inhibition 8–12 mm in diameter against all mentioned species of microorganisms. The compound **8a** of the series 3-amino-4-imino-8-methoxy-2*H*-pyrazolo[3′,4′:4,5]pyrimido[2,3-*b*][1,3] benzothiazole is more active and exhibited 8–11 mm

Table 1

Antimicrobial activity of **3**, **4a–d**, **5a–c**, **6a-e**, **7a–e**, and **8a–f**.

Comp. No.	Diameter in mm of zone of inhibition at 25 μg/disc			
	S. aureus	*B. subtilis*	*E. coli*	*S. typhi*
3	6	NA	6	8
4a	7	10	8	11
4b	7	NA	9	9
4c	8	7	NA	7
4d	8	9	8	12
5a	6	NA	8	10
5b	6	NA	6	7
5c	7	9	10	NA
6a	9	12	12	8
6b	8	NA	9	NA
6c	6	10	8	10
6d	7	11	9	7
6e	NA	NA	6	8
7a	10	NA	8	6
7b	9	NA	9	7
7c	9	NA	7	NA
7d	10	NA	6	6
7e	8	NA	7	10
8a	11	10	9	8
8b	8	NA	12	NA
8c	9	7	10	NA
8d	10	NA	9	7
8e	7	11	NA	NA
8f	11	NA	8	6
Norflaxacin	14	24	20	16

NA, no activity.

zone of inhibition in diameter against all mentioned species of microorganisms. The compounds $\mathbf{6_b}$, $\mathbf{7_a}$, and $\mathbf{7_b}$ of the series of 3-cyano-4-imino-8-methoxy-4*H*-pyrimido[2,-1*b*][1,3] benzothiazole and its 2-substituted derivatives found to be more active and exhibited 8–12 mm zone of inhibition in diameter against *S. aureus* and *E. coli*, whereas these compounds are less active against other species *B. subtilis* and *S. typhi*. Also the compounds of $\mathbf{8_b}$, $\mathbf{8_c}$, $\mathbf{8_d}$, and $\mathbf{8_f}$ of the series 3-amino-4-imino-8-methoxy-2*H*-pyrazolo[3′,4′:4,5]pyrimido[2,3-*b*][1,3]benzothiazole and its 2-substituted derivatives are more active against *S. aureus* and *E. coli* and exhibited 8–12 mm zone of inhibition in diameter, whereas these compounds are less active against other species *B. subtilis* and *S. typhi*. Standard Norflaxacin exhibited 14, 24, 20, and 16 mm zone of inhibition against *S. aureus*, *B. subtilis*, *E. coli*, and *S. typhi*, respectively.

EXPERIMENTAL

Melting points are determined in open capillary tubes and were uncorrected. All the reactions were monitored by thin layer chromatography, carried out on 0.2-mm silica gel-G plates using iodine vapor for detection. Infrared spectra were recorded in potassium bromide pellets on a Bomen MB 104 FT Infrared spectrophotometer. NMR spectra were obtained on a Gemini 200 MHz spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a FT VG-7070 H mass spectrophotometer using EI technique at 70 eV. Microanalysis was performed on a Herqeus CHN-O rapid analyzer.

3-Cyano-4-imino-2-methylthio-8-methoxy-4*H*-pyrimido[2,1-*b*][1,3]benzothiaole (3). A mixture of 2-amino-6-methoxy benzothiazole (1.80 g, 0.01 mol) and bis(methylthio)methylene malononitrile (1.58 g, 0.01 mol) was refluxed in the presence of 25–30 mL of dimethyl formamide and a pinch of anhydrous potassium carbonate for 4 h. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water, and recrystallized from *N*,*N*′-dimethyl formamide–ethanol to give pure **3**. Yield: 1.45 g (50%), m.p.: 210°C; IR (potassium bromide): C=NH 3255, C≡N 2197 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.4 (s, 3H, SCH_3), 3.7 (s, 3H, OCH_3), 7.1–7.6 (m, 3H, Ar—H), 9.2 (S, 1H, =NH); ms: *m/z* 302 (M^+ 100%), 255, 228, 202, 164, 138. Anal. Calcd. for $C_{13}H_{10}N_4S_2O$: C, 51.65; H, 3.31; N, 18.54. Found: C, 51.62; H, 3.29; N, 18.52.

General procedure for the preparation of 2-substituted derivatives of 3-cyano-4-imino-2-methylthio-8-methoxy-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole ($\mathbf{4_{a–d}}$, $\mathbf{5_{a–c}}$, $\mathbf{6_{a–e}}$, $\mathbf{7_{a–e}}$). A mixture of **3** (0.001 mol) and aromatic amines/heterylamines/phenols/compounds containing active methylene group (0.001 mol) in *N*,*N*′-dimethyl formamide (10 mL) and anhydrous potassium carbonate (10 mg) was refluxed independently for 4–6 h. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water, and recrystallized from *N*,*N*′-dimethyl formamide–ethanol mixture to give pure $\mathbf{4_{a–c}}$, $\mathbf{5_{a–c}}$, $\mathbf{6_{a–e}}$, and $\mathbf{7_{a–e}}$.

3-Cyano-4-imino-2-(4′-nitroanilino)-8-methoxy-4*H*-pyrimido[2,1-b][1,3]benzothiazole (4_a) Yield: 0.252 g (64%), m.p.: 120°C; IR (potassium bromide): —NH 3492, =NH 3379, CN 2199 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.2 (s, 1H, NH), 3.2 (s, 3H, OCH_3), 7.2–7.9 (m, 7H, Ar—H), 9.1 (s, 1H, =NH); ms: *m/z* 392 (M^+) Anal. Calcd. For $C_{18}H_{12}N_6O_3S$: C, 55.10; H, 3.06; N, 21.42. Found: C, 55.08; H, 3.02; N, 21.39.

3-Cyano-4-imino-2-(4′-methylanilino)-8-methoxy-4*H*-pyrimido[2,1-b][1,3]benzothiazole (4_b) Yield: 0.230 g (63%), m.p.: 227°C; IR (potassium bromide): —NH 3384, =NH 3280, CN 2215 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.3 (s, 1H, CH_3), 2.6 (s, 1H, NH), 3.5 (s, 3H, OCH_3), 7.3–8.0 (m, 7H, Ar—H), 9.3 (s, 1H, =NH); ms: *m/z* 361 (M^+). Anal. Calcd. for $C_{19}H_{15}N_5SO$: C, 63.15; H, 4.15; N, 19.39. Found: C, 63.12; H, 4.11; N, 19.36.

3-Cyano-4-imino-2-(4′-methoxyanilino)-8-methoxy-4*H*-pyrimido[2,1-b][1,3]benzothiazole (4_c) Yield: 0.226 g (62%), m.p.: 116°C; IR (potassium bromide): —NH 3400, =NH 3375, CN 2200 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.6 (s, 1H, NH), 3.8 (s, 3H, OCH_3), 7–7.5 (m, 7H, Ar—H), 9.3 (s, 1H, =NH); ms: *m/z* 377 (M^+). Anal. Calcd. for $C_{19}H_{15}N_5O_2S$: C, 60.47; H, 3.97; N, 18.56. Found: C, 60.45; H, 3.95; N, 18.53.

3-Cyano-4-imino-2-(4′-chloroanilino)-8-methoxy-4*H*-pyrimido[2,1-b][1,3]benzothiazole (4_d) Yield: 0.224 g (59%), m.p.: 114°C; IR (potassium bromide): —NH 3380, =NH 3265, CN 2190 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.7 (s, 1H, NH), 3.5 (s, 3H, OCH_3), 7.2–8.1 (m, 7H, Ar—H), 9.2 (s, 1H, =NH); ms: *m/z* 383 (M^{+2}), 381 (M^+). Anal. Calcd. for $C_{18}H_{12}N_5OSCl$: C, 56.69; H, 3.14; N, 18.37. Found: C, 56.65; H, 3.11; N, 18.32.

3-Cyano-4-imino-2-morpholinyl-8-methoxy-4*H*-pyrimido[2,1-b][1,3]benzothiazole (5_a) Yield: 0.230 g (67%), m.p.: 197°C; IR (potassium bromide): =NH 3296, CN 2189 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.6 (t, 4H, two-N—CH^2), 3.8 (s, 3H, —OCH_3), 4.0 (t, 4H, —OCH_2), 7.0–7.5 (m, 3H, Ar—H), 9.2 (s, 1H, =NH); ms: *m/z* 341 (M^+). Anal. Calcd. for $C_{16}H_{15}N_5O_2S$: C, 56.30; H, 4.39; N, 20.52. Found: C, 56.28; H, 4.35; N, 20.49.

3-Cyano-4-imino-2-pyrrolidinyl-8-methoxy-4*H*-pyrimido[2,1-b][1,3] benzothiazole (5_b) Yield: 0.225 g (69%), m.p.: 145°C; IR (potassium bromide): =NH 3405, CN 2221 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.0 (quintet, 4H, two-CH_2), 2.5 (t, 4H, two-NCH_2), 6.8–7.3 (m, 3H, Ar—H), 8.9 (s, 1H, =NH); ms: *m/z* 325 (M^+). Anal. Calcd. for $C_{16}H_{15}N_5OS$; C, 59.07; H, 4.61; N, 21.53. Found: C, 59.05; H, 4.57; N, 21.49.

3-Cyano-4-imino-2-piperidinyl-8-methoxy-4*H*-pyrimido[2,1-b][1,3] benzothiazole (5_c) Yield: 0.240 g (71%), m.p.: 155°C; IR (potassium bromide): =NH 3360, CN 2186 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.5 (quintet, 2H, —CH_2), 2.4 (quintet, 4H, two-CH_2), 2.8 (t, 4H, two-CH_2), 6.8–7.3 (m, 3H, Ar—H), 8.9 (s, 1H, =NH); ms: *m/z* 339 (M^+). Anal. Calcd. for $C_{17}H_{17}N_5OS$: C, 60.17; H, 5.01; N, 20.64. Found: C, 60.14; H, 4.99; N, 20.60.

3-Cyano-4-imino-2-(4′-methylphenoxy)-8-methoxy-4*H*-pyrimido[2,1-b][1,3]benzothiazole (6_a) Yield: 0.180 g (50%), m.p.: 127°C; IR (potassium bromide): =NH 3296, CN 2203, C—O—C asymmetric and symmetric stretching 1267, 1227 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 3H, —CH_3), 3.9 (s, 3H, OCH_3), 7–7.9 (m, 8H, Ar—H), 9.1 (s, 1H, =NH); ms:

m/z 362 (M^+) Anal. Calcd. for $C_{19}H_{14}N_4O_2S$: C, 62.98; H, 3.86; N, 15.46. Found: C, 62.95; H, 3.84; N, 15.42.

3-Cyano-4-imino-2-(2′-methylphenoxy)-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole (6_b) Yield: 0.165 g (46%), m.p.: 130°C; IR (potassium bromide): =NH 3345, CN 2219, C—O—C asymmetric and symmetric stretching 1250, 1220 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.1 (s, 3H, Ar—CH_3), 3.5 (s, 3H, —OCH_3), 7.1–7.9 (m, 7H, Ar—H), 9.3 (s, 1H, =NH); ms: *m/z* 362 (M^+). Anal. Calcd. for $C_{19}H_{14}N_4O_2S$: C, 62.98; H, 3.86; N, 15.46. Found: C, 62.95; H, 3.84; N, 15.42.

3-Cyano-4-imino-2-(4′-chlorophenoxy)-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole (6_c) Yield: 0.180 g (47%), m.p.: 112°C; IR (potassium bromide): =NH 3383, CN 2195 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.6 (s, 3H, —OCH_3), 7.2–7.0 (m, 7H, Ar—H), 9.0 (s, 1H, =NH); ms: *m/z* 384 (M^{+2}), 382 (M^+). Anal. Calcd. for $C_{18}H_{11}N_4O_2SCl$: C, 56.54; H, 2.87; N, 14.65. Found: C, 56.52; H, 2.84; N, 14.61.

3-Cyano-4-imino-2-(2′-nitrophenoxy)-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole (6_d) Yield: 0.170 g (43%), m.p.: 138°C; IR (potassium bromide): =NH 3373, CN 2188, Ar—NO_2 1529 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.1 (s, 3H, —OCH_3), 7–7.8 (m, 7H, Ar—H), 8.9 (s, 1H, =NH); ms: *m/z* 393 (M^+). Anal. Calcd. for $C_{18}H_{11}N_5O_4S$: C, 54.96; H, 2.79; N, 17.81. Found: C, 54.92; H, 2.76; N, 17.77.

3-Cyano-4-imino-2-(4′-nitrophenoxy)-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole (6_e) Yield: 0.160 g (41%), m.p.: 132°C; IR (potassium bromide): =NH 3382, CN 2195, Ar—NO_2 1540 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.3 (s, 3H, —OCH_3), 7.2–7.9 (m, 7H, Ar—H), 9.2 (s, 1H, =NH); ms: *m/z* 393 (M^+). Anal. Calcd. for $C_{18}H_{11}N_5O_4S$: C, 54.96; H, 2.79; N, 17.81. Found: C, 54.94; H, 2.75; N, 17.78.

3-Cyano-4-imino-2-(diethylmalonyl)-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole (7_a) Yield: 0.30 g (73%), m.p.: 107°C; IR (potassium bromide): =NH 3296, CN 2201, C=O of ester 1727, C—O 1274 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.2 (t, 6H, two-CH_3), 3.8 (s, 3H, —OCH_3), 4.2 (q, 4H, two-CH_2), 6.8–7.3 (m, 3H, Ar—H), 9.2 (s, 1H, =NH); ms: *m/z* 414 (M^+). Anal. Calcd. for $C_{19}H_{18}N_4O_2S$: C, 55.07; H, 4.34; N, 13.52. Found: C, 55.02; H, 4.31; N, 13.49.

3-Cyano-4-imino-2-(α-ethylcyanoacetyl)-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole (7_b) Yield: 0.20 g (54%), m.p.: 182°C; IR (potassium bromide): =NH 3297, CN 2199, C=O of ester 1728 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 2.4 (t, 3H, —CH_3), 3.8 (s, 3H, —OCH_3), 3.9 (q, 2H, —OCH_2), 4.2 (s, 1H, —CH), 6.8–7.3 (m, 3H, Ar—H), 9.2 (s, 1H, =NH); ms: *m/z* 367 (M^+). Anal. Calcd. for $C_{17}H_{13}N_5O_3S$: C, 55.58; H, 3.54; N, 19.07. Found: C, 55.54; H, 3.51; N, 19.02.

3-Cyano-4-imino-2-(α-ethylacetoacetyl)-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole (7_c) Yield: 0.30 g (78%), m.p.: 115°C; IR (potassium bromide): =NH 3400, CN 2226, C=O of ester 1758, C—O 1248 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 1H, $COCH_3$), 2.8 (t, 3H, CH_3), 3.3 (s, 3H, —OCH_3), 4.0 (q, 2H, OCH_2), 4.3 (s, 1H, —CH), 7–7.4 (m, 3H, Ar—H), 9.0 (s. 1H, =NH); ms: *m/z* 384 (M^+). Anal. Calcd. for $C_{17}H_{13}N_5O_3S$: C, 56.25; H, 4.16; N, 14.58. Found: C, 56.22; H, 4.11; N, 14.54.

3-Cyano-4-imino-2-(α-acetylacetone)-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole (7_d) Yield: 0.20 g (56%), m.p.: 122°C; IR (potassium bromide): =NH 3402, CN 2210, C=O 1680 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 2.6 (s, 6H, two-$COCH_3$), 3.3 (s, 3H, OCH_3), 4.0 (s, 1H, —CH), 7.2–7.6 (m, 3H, Ar—H), 9.3 (s, 1H, =NH); ms: *m/z* 354 (M^+). Anal. Calcd. for $C_{17}H_{14}N_4O_3S$: C, 57.62; H, 3.95; N, 15.08. Found: C, 57.58; H, 3.92; N, 15.04.

3-Cyano-4-imino-2-(α-malononitrile)-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole (7_e) Yield: 0.20 g (65%), m.p.: 195°C; IR (potassium bromide): =NH 3400, CN 2215 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 3.5 (s, 3H, OCH_3), 4.2 (s, 1H, —CH), 7.1–7.5 (m, 3H); ms: *m/z* 320 (M^+). Anal. Calcd. for $C_{15}H_8N_6OS$: C, 56.25; H, 2.50; N, 26.25. Found: C, 56.23; H, 2.45; N, 26.22.

General procedure for the preparation of 2-substituted-3-amino-4-imino-8-methoxy-(2*H*)-pyrazolo[3′,4′:4,5] pyrimido[2,1-*b*][1,3]benzothiaoles ($8_{a–f}$). A mixture of **3** (0.001 mol) and hydrazine hydrate/phenyl hydrazine/4-nitrophenyl-hydrazine/2-hydrazine benzothiazole/6-chloro-2-hydrazino benzothiazole/6-methyl-2-hydrazino benzothiazole (0.002 mol) in *N*,*N*-dimethyl formamide (10 mL) and anhydrous potassium carbonate (10 mg) was refluxed independently for 4–6 h. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water, and crystallized from *N*,*N*-dimethyl formamide–ethanol mixture to give crystalline $8_{a–f}$.

3-Amino-4-imino-8-methoxy-(2H)-pyrazolo[3′,4′:4,5]pyrimido-[2,1-b][1,3]benzothiazole (8_a) Yield 0.180 g (63%), m.p.: 267°C; IR (potassium bromide): NH_2 asymmetric 3317, NH_2 symmetric 3168 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.4 (broad s, 2H, NH_2, exchangeable with D_2O), 3.7 (s, 3H, OCH_3), 6.9–7.7 (m, 3H, aromatic-H), 7.9 (s, 1H, NH, exchangeable with D_2O), 8.3 (s, 1H, =NH exchangeable with D_2O); ms: *m/z* 286 (M^+,24%), 258, 229, 176, 138. Anal. Calcd. for $C_{12}H_{10}N_6OS$: C, 50.34; H, 3.49; N, 29.37. Found: C, 50.31; H, 3.46; N, 29.33.

3-Amino-4-imino-8-methoxy-2-phenylpyrazolo[3′,4′:4,5]pyri- mido-[2,1-b][1,3]benzothiazole (8_b) Yield: 0.182 g (50%), m.p.: 192°C; IR (potassium bromide): NH_2 3353, =NH, NH_2 symmetric 3159 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.4 (s, 2H, NH_2), 3.9 (s, 3H, OCH_3,), 6.9–7.7 (m, 8H, Ar—H), 8.5 (s, 1H, =NH); ms: *m/z* 362 (M^+). Anal. Calcd. for $C_{18}H_{14}N_6OS$: C, 59.66; H, 3.86; N, 23.20. Found: C, 59.64; H, 3.83; N, 23.16.

3-Amino-4-imino-8-methoxy-2-(4′-nitrophenyl)pyrazolo[3′,4′:4,5] pyrimido-[2,1-b][1,3]benzothiazole (8_c) Yield: 0.198 g (48%), m.p.: 168°C; IR (potassium bromide): NH_2 asymmetric and symmetric 3296, 3100, =NH 3116 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.1 (broad, 2H, NH_2), 3.7 (s, 3H, —OCH_3), 7–7.9 (m, 7H, Ar—H), 8.2 (s, 1H, =NH); ms: *m/z* 407 (M^+,100%). Anal. Calcd. for $C_{18}H_{13}N_7O_3S$: C, 53.07; H, 3.19; N, 24.07. Found: C, 53.04; H, 3.15; N, 24.05.

3-Amino-4-imino-8-methoxy-2-(2′-benzothiazolyl)pyrazolo[3′,4′:4,5]pyrimido[2,1-b][1,3]benzothiazole (8_d) Yield: 0.233 g (59%), m.p.: 165°C; IR (potassium bromide): NH_2 asymmetric and symmetric 3481, 3363, =NH 3240 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 3.2 (broad, 2H, NH_2), 3.8 (s, 3H, —OCH_3), 7.1–7.9 (m, 7H, Ar—H), 8.5 (s, 1H, =NH); ms: *m/z* 419 (M^+). Anal. Calcd. for $C_{19}H_{13}N_7OS_2$: C, 54.41; H, 3.10; N, 23.38. Found: C, 54.38; H, 3.05; N, 23.35.

3-Amino-4-imino-8-methoxy-2-(6′-chloro-2′-benzothiazolyl)pyrazolo[3′,4′:4,5] pyrimido [2,1-b][1,3]benzothiazole (8_e) Yield: 0.196 g (43%), m.p.: 145°C; IR (potassium bromide): NH_2 3370, 3250, =NH 3190 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 3.4 (broad, 2H, NH_2), 3.9 (s, 3H, —OCH_3), 7–7.7 (m, 6H,

Ar—H), 8.2 (s, 1H, =NH); ms: *m/z* 455 (M^{+2}, 3%), 453 (M^{+},10%). Anal. Calcd. for $C_{19}H_{12}N_7S_2OCl$: C, 50.33; H, 2.64; N, 21.63. Found: C, 50.30; H, 2.61; N, 21.59.

3-Amino-4-imino-8-methoxy-2-(6′-methyl-2′-benzothiazolyl)pyrazolo [3′,4′:4,5]pyrimido[2,1-b][1,3]benzothiazole (8_f) Yield: 0.208 g (51%), m.p.: 110°C; IR (potassium bromide): NH_2 asymmetric and symmetric 3342, 3309, =NH 3180 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 2.1 (s, 3H, Ar—CH_3), 3.1 (broad, 2H, NH_2), 3.9 (s, 3H, OCH_3), 7.2–7.9 (m, 6H, Ar—H), 8.4 (s, 1H, =NH); ms: *m/z* 433 (M^{+},100%) Anal. Calcd. for $C_{20}H_{15}N_7OS_2$: C, 55.42; H, 3.46; N, 22.63. Found: C, 55.40; H, 3.43; N, 22.60.

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