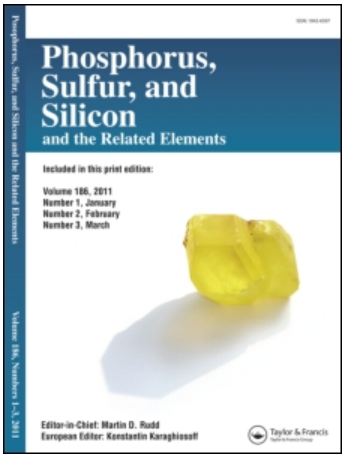

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One-Pot Three-Component Condensation Reaction in Water: An Efficient and Improved Procedure for the Synthesis of Pyrimido[2,1-b]benzothiazoles

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Industries are constantly in search of efficient and green chemistry protocols for the synthesis of pyrimido [2,1-b]benzothiazoles. One-pot reaction of 2-aminobenzothiazole, active methylene derivatives, and carbonyl compounds expeditiously annulate a pyrimidine ring on the benzothiazole nucleus to yield pyrimido [2,1-b]benzothiazole under microwaves or ultrasonic waves using water as energy transfer medium. The title compounds are easily accessible by various approaches; even waste-free procedures have been developed. The operational simplicity, environmentally friendly conditions, and high yield achieved in a very short reaction time are major benefits that meet the requirements of green production, including saving energy and high efficiency. The results are compared with conventional heating. Structural assignments are based on spectroscopic data.

Keywords Aqueous media and pyrimido [2,1-b]benzothiazoles; microwaves; ultrasonic waves

INTRODUCTION

Thiazole and pyrimidine nuclei are the active core of various bioactive molecules. In general, heterocycles encompassing a pyrimidine unit have found applications in a wide spectrum of biological and therapeutic areas.[1–6] Thus, the heterocyclic system resulting from the annulation of a pyrimidine ring on the biologically versatile thiazole nucleus is an attractive scaffold to be utilized for exploiting chemical diversity.

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Pyrimido [2,1-b]benzothiazoles have been widely recognized as biologically useful systems due to their structural similarities to purine bases and have been found to act as brain benzodiazepine receptor.[7]

For the preparation of the complex molecules large efforts have been directed towards the synthetic manipulation of pyrimido [2,1-b]benzothiazoles. As a result, a number of reports have appeared, which usually require drastic conditions, long reaction times and complex synthetic pathways and often react in organic solvents.[8–12] Thus, new routes for the synthesis of these molecules has prompted an extensive search for a rapid entry to these heterocycles.

The application of microwaves[13] and ultrasonic irradiations,[14] as a non-conventional energy source for activation of reactions, has now become a very popular and useful technology in organic chemistry. In this regard, the use of water[15] as a reaction solvent has also attracted great attention in the recent past and has become an active area of research in green chemistry.

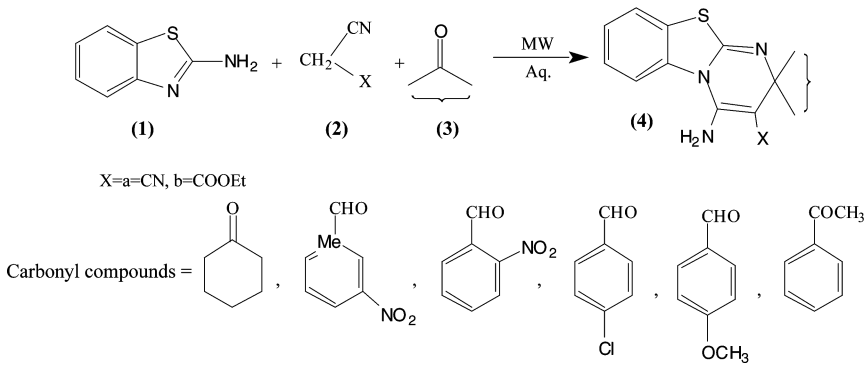
The diversity generating potential of multicomponent reactions has been recognized, and their utility in preparing libraries to screen for functional molecules is well appreciated.[16,17]

The combination of microwave irradiations, ultrasonic irradiations, and aqueous mediated conditions using multicomponent reactions lead to enhanced reaction rates, higher yields of pure products, easier work-up, and sometimes to selective conversions, with several advantages of the eco-friendly approach in the frame work of green chemistry. Consequently, this protocol should be welcome in these environmentally conscious days.

To the best of our knowledge, the one-pot tandem synthesis of pyrimido [2,1-b]benzothiazoles in aqueous medium has not been studied so far. Considering the abovementioned reports, and in continuation with the long lasting interest in this area,[18] and particular interest on the use of aqueous medium,[19] for heterocyclic synthesis, we report herein a new facile microwave or ultrasonic enhanced tandem reaction for annulation of a pyrimidine ring on benzothiazole to give pyrimido [2,1-b]benzothiazoles (**4**) in aqueous medium (Scheme 1).

RESULTS AND DISCUSSION

Multicomponent condensation reactions of 2-aminobenzothiazole (**1**) with malononitrile/ethylcyanoacetate (**2**) and carbonyl compounds (**3**) in aqueous media gave corresponding pyrimido [2,1-b]benzothiazoles (**4a–4l**). The envisaged annulation method in its entity involves irradiation of an intimate mixture of 2-aminobenzothiazole, malononitrile, and carbonyl compound in water for appropriate time and temperature



SCHEME 1

in a multimode microwave oven. The reaction was studied under different reaction conditions to find out the best method, giving the products in higher yields with operational simplicity (Table I).

Initially, we examined the reaction in ethanol with triethylamine catalyst under conventional method and observed that desired product was formed in low yield. Interestingly, no product was formed when the reaction was carried out in ethanol in absence of catalyst under conventional method; whereas the reaction proceeds very smoothly under microwaves without a catalyst. Further, all our attempts to improve the yield at elevated temperature and longer reaction times were met

TABLE I Comparative Study for Synthesis of 4′-Amino-spiro [cyclohexane-1,2′-2*H*- pyrimido[2,1-b]benzothiazole]-3′-carbonitrile (4a)

Entry	Reaction conditions	Method	Time (Min./h)	Yield (%)
i	Ethanol	Δ	24 h	Intermediate **(5)**
ii	Ethanol + Triethylamine	Δ	14 h	55
iii	Ethanol	MW	8 min	80
iv	Ethanol	Ultrasound	90 min	80
v	Water	Δ	8 h	75
vi	Water	MW	8 min	90
vii	Water	Ultrasound	1.5 h	88
viii	Water/PTC**	MW	5 min	80
ix	Water/PTC**	Ultrasound	1 h	82
x	Alkene nitrile + **1** (Ethanol)	MW	5+4*	80
xi	Alkene nitrile + **1** (Water)	MW	6+3	85

* = 5+4 indicates, first irradiation for 5 min gives intermediate (detected by TLC) and then further irradiation for 4 min after adding 2-aminobenzothiazole.

** = Cetyl trimethyl ammonium bromide is used as phase transfer catalyst for entry (viii) and (ix).

with unsuccessful results. To increase the efficiency, we decided to perform the reaction under mild condition in water and observed that the reaction proceeded uneventfully forming the desired product in good to excellent yields. To further improve the procedure, we also studied the reaction using cetyl trimethyl ammonium bromide as phase transfer catalyst (Table I, Entry-viii and ix); but, no change in yield was observed, although reaction time was reduced slightly. Hence, it may be concluded that the aqueous medium is the perfect method for the synthesis of pyrimido[1,2-a]benzothiazoles.

As the starting point of our exploration, we chose the reaction of 2-aminobenzothiazole (**1**), malononitrile (**2**), and cyclohexanone (**3a**), and it has been found that when a mixture of **1**, **2**, and **3a** (0.01 equivalent) in water was irradiated in microwave for 8 min or in ultrasound for 1.5 h gave exclusively **4′-amino-spiro [cyclohexane-1,2′-2*H*-pyrimido[2,1-b]benzothiazole]-3′-carbonitrile** (**4a**) in 90% and 88% yield, respectively.

In order to extend our protocol and to explore the scope and limitations of this reaction, further other aromatic aldehyde bearing both electron withdrawing and donating group, as well as cyclic ketones were used successfully to give the corresponding pyrimido [2,1-b]benzothiazoles in good to excellent yields. Using the three-component one-pot procedure, we have synthesized a series of 12 compounds under microwaves in aqueous medium (Table II). A comparison of the time required for the reaction reported in (Table II) clearly indicates a tremendous reduction in the time of reaction in the microwave oven.

TABLE II Results of Synthesis of Compounds (4a–l) in Aqueous Medium

			Time /Yield (%)	
Entry	X	Carbonyl compounds	MW	Conventional
4a	CN	Cyclohexanone	8 min/90	8 h/75
4b	CN	m-Nitrobenzaldehyde	9 min/85	12 h/52
4c	CN	o-Nitrobenzaldehyde	8 min/85	14 h/50
4d	CN	p-chlorobenzaldehyde	7 min/88	11 h/62
4e	CN	p-Anisaldehyde	8 min/90	12 h/55
4f	CN	Acetophenone	9 min/85	10 h/58
4g	COOEt	Cyclohexanone	9 min/88	12 h/65
4h	COOEt	m-Nitrobenzaldehyde	8 min/85	10 h/54
4i	COOEt	o-Nitrobenzaldehyde	9 min/86	15 h/56
4j	COOEt	p-chlorobenzaldehyde	7 min/82	12 h/54
4k	COOEt	p-Anisaldehyde	6 min/85	14 h/55
4l	COOEt	Acetophenone	8 min/80	15 h/68

Reactions under microwave irradiation were faster than under standard thermal conditions, along with enhanced yields, cleaner reaction products, and easier workup.

Finally, to check the possible intervention of specific (non-thermal) microwave effects[20] on reactivity, the reactions (in case of compound **4a**) have been carried out using pre-heated oil-bath at the same time and same final temperature (which is 75°C in case of ethanol and 90°C in case of water) as measured at the end of the exposure during microwave experiment. It has been found that only traces of products (5–7%) were detected on TLC in case of reaction using water, while in case of ethanol no conversion to product **4a** occurs. The reaction time was then extended up to 2 h; lower yields were obtained demonstrates the effect of microwave irradiation is not purely thermal (Table III).

The formation of **4** is best explained by the conjugate addition of alkene-nitrile (**5**) (generated in situ by the reaction of malononitrile and cyclohexanone) to 2-aminobenzothiazole (**1**) to furnish Michael adduct (**6**) which undergoes intramolecular cyclization to yield **(4)**. The intermediate formation of (**5**) is confirmed by the TLC studies during the progress of reaction and also carrying out the reaction of pre-synthesized alkene-nitrile (**5**) with (**1**) under identical conditions (Scheme 2).

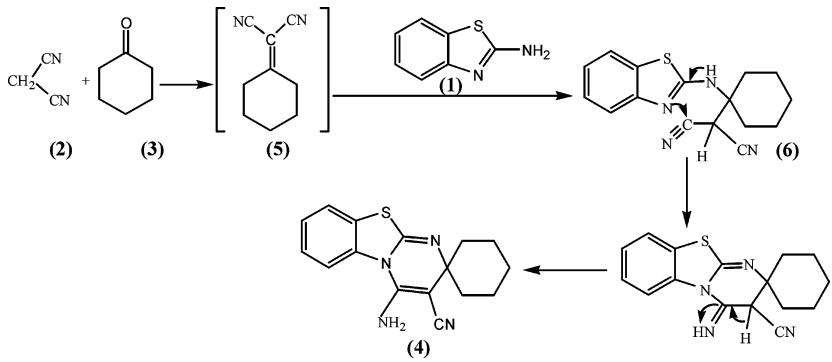
IR, ^{1}HNMR, and ^{13}CNMR spectra of the isolated compounds **4a–l** confirmed the expected structures. The IR spectra of **4a–4l** displayed characteristic absorptions in the region 3485–3215 (NH_2 stretching) and 1620–1640 cm^{-1} (C=N). Disappearance of C=O absorption band at 1740 cm^{-1} and C=C absorption band at 1620 cm^{-1} indicated the conversion of reactant **3** and also intermediate (**5**) into product **4**, further

TABLE III Comparative Results Obtained in the Synthesis of Compound (4a) Using Similar Conditions of Microwaves and Preheated Oil Bath

Entry	Medium	Method	Reaction time	Final[a] temp (°C)	Yield (%)
1	Ethanol	MW	8 min	75	80
2	Ethanol	Δ	8 min	75	Nil*
3	Ethanol	Δ	2 h	75	Nil*
4	Water	MW	8 min	90	90
5	Water	Δ	8 min	90	Traces
6	Water	Δ	2 h	90	25

* = Intermediate (**5**) is formed only, no conversion to product **4a** occurs.

a = Final temperature is measured by introducing a glass thermometer in the reaction mixture at the end of exposure to microwave to microwave irradiation and gives approximate temperature range.



SCHEME 2

eliminating the possibility of formation of Michael adduct (**6**). Presence of primary amino group as two bands in the region 3485–3215 cm^{-1} affirmed the existence of 4a instead of tautomeric form **4'** in which only one absorption band will appear in the region 3415–3138 cm^{-1} (NH).

^{1}HNMR spectrum of representative compound (**4a**) showed signals at δ1.28–1.35 (t, 4H, CH_2), 1.75–1.98 (m, 6H, CH_2), 5.85 (s, 2H, NH_2), 6.94–7.14 (m, 4H, Ar-H) ppm. The presence and position of NH_2 was confirmed on deutaration. Absence of singlet at δ5.03 (s, 1H, CH) due to methine proton rules out the possibility of the formation of tautomeric form **4**′ and intermediate Michael adduct (**6**).

Formation of the final compound **4a** was further confirmed on the basis of ^{13}CNMR (δ ppm) spectrum which showed sharp signals at 20.40 (CH_2,C_3), 24.57 (CH_2,C_4), 36.71 (CH_2,C_6), 39.23 (CH_2,C_2), 52.76 (spiro carbon), 68.36 (C'_3, C-C≡N), 112.06, (C'_6), 115.91 (C'_9), 118.54 (C'_7), 119.44 (C≡N), 122.96 (C'_8), 129.19 (C'_{5a}), 143.63 (C'_{9a}), 148.90 (C=N) and 151.58 (C'_4, C-NH_2).Absence of signal at 164.25 (C=O, cyclohexanone ring) and presence of signal at 52.76 (spiro carbon) further confirmed the structure **4a**.

The formation of **4a** instead of other possible intermediates was further confirmed by the mass spectrum of **4a** that showed molecular ion peak at m/z 296 $[M]^+$ (41.3%), 236 (100%) corresponding the molecular weight of the compound. Other relevant peaks were observed at 223 (23.8%), 198 (1.1%), 170 (2.4%), 159 (2.0%), 144 (2.8%), 133 (16.7%), 118 (5.4%), and so on.

CONCLUSION

The facile reaction involving Knoevenagel Condensation followed by Michael addition and cyclization in aqueous medium occurs smoothly in few minutes to give pyrimido [2,1-b]benzothiazoles exclusively. In

addition, high yields of the products, short reaction times, ease of work-up and low cost make the above method advantageous in comparison to the traditional heating method. The use of water gives environmental benefits, i.e., no atmospheric pollution by escaping solvents and easy waste treatment. For these reasons, this methodology represents an important improvement for the production of this kind of fine chemicals following environmental benign procedures.

EXPERIMENTAL

Melting points were determined on a Toshniwal apparatus and were uncorrected. The purity of compounds was checked on thin layers of silica gel in various non-aqueous solvent systems, for e.g., benzene: ethylacetate (9:1), benzene: dichloromethane (8:2). IR spectra (KBr) were recorded on a Shimadzu FT IR–8400S spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-300 using $CDCl_3$ at 300.15 and 75.47, respectively. TMS was used as internal reference. Mass spectrum of representative compound was recorded on Kratos 50 mass spectrometer at 70 eV. The microwave-assisted reactions were carried out in a multimode MW oven (Panasonic-NN-781JF) equipped with inverter technology (generating fixed frequency throughout the required time) for realistic control of the microwave operating at 1000 W generating 2450 MHz frequency and ultrasonic bath (Bandelin Sonorex) operating at 230 V generating 33 KHz output frequency.

General Procedure for the Preparation of Pyrimido [2,1-b]benzothiazoles (4a-l)

Conventional Method

A solution of 2-aminobenzothiazole (1.50 g, 10 mmol) (**1**), malononitrile (0.66 g, 10 mmol)/ethylcyanoacetate (1.13 g, 10 mmol) (**2**), and carbonyl compound (**3**) (10 mmol) in ethanol (25 ml) was refluxed for 20 h. However, no reaction occurred after intermediate stage (**5**). Then the reaction was continued after addition of 4–5 drops of triethylamine, immediately a color change occurred from yellow to red, and the mixture was further refluxed until the completion of reaction and progress is monitored by TLC. The reaction mixture was kept overnight at room temperature. The resulting precipitate was filtered, washed with ethanol, dried, and recrystallized from ethanol.

Microwave Activation Method

Using ethanol. An equimolar mixture (10 mmol) of **1**, **2**, and **3** was placed in a beaker and the minimum quantity of ethanol (sufficient to

make slurry) was added. The mixture was placed in the microwave oven and irradiated at power output 300 W. The product started to separate out immediately after cooling the reaction mixture at room temperature (or in some cases during the course of reaction) was filtered washed with cold aqueous ethanol and found to be pure on TLC with no need of further recrystallization.

Using water. An equimolar mixture (10 mmol) of **1**, **2**, and **3** in water (8–10 ml) in open borosil beaker (100 ml) was irradiated inside a microwave oven at 640 W until the completion of reaction (TLC control). The crystalline product started to separate out just after cooling the reaction mixture, which was washed with water and found to be pure by TLC, with no need of further purification process. All compounds **4a–4l** were synthesized similarly in comparatively high yields and reduced times using water under microwaves. For analytical and spectral data, compounds were recrystallized from ethanol.

Ultrasonic Irradiation Method

An equimolar quantity (10 mmol) of **1**, **2**, and **3** were added in a conical flask in water (10 ml). The mixture was introduced under ultrasonic waves using ultrasonic bath (operating at 230 V generating 33 KHz output frequencies) for 1.5 h at room temperature. The product started to separate out during the course of reaction. The crystalline solid was filtered and found pure on TLC with no need of further recrystallization.

4′-Amino-spiro [cyclohexane-1,2′-2H-pyrimido[2,1-b]benzothiazole]-3′-carbonitrile (4a). m.p. 170–172°C. Yield: 90%. IR (KBr)/cm^{-1} 3455-3245 (NH_2), 2235 (C≡N), 1640 (C=N). ^{1}HNMR ($CDCl_3$)δ =.28–1.35 (t, 4H, CH_2), 1.75–1.98 (m, 6H, CH_2), 5.85 (s, 2H, NH_2), 6.94–7.14 (m, 4H, Ar-H). ^{13}CNMR ($CDCl_3$)δ ppm 20.40, 24.57, 36.71, 39.23, 52.76, 68.36, 112.06, 115.91, 118.54, 119.44, 122.96, 129.19, 143.63, 148.90, and 151.58. Anal. Calcd. for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44; N, 18.90. Found: C, 64.64; H, 5.46; N, 18.95.

4-Amino-2-(3-nitrophenyl)-2H-pyrimido[2,1-b][1,3]benzothiazole-3-carbonitrile (4b). m.p. 190–192°C. Yield: 85%. IR (KBr)/cm^{-1} 3465–3235 (NH_2), 2215 (C≡N), 1630 (C=N), 1570, 1385 (NO_2). ^{1}HNMR ($CDCl_3$) δ = 3.56–3.60 (s, 1H, CH), 5.77 (s, 2H, NH_2^*), 6.90–7.24 (m, 8H, Ar-H). ^{13}CNMR ($CDCl_3$) δ ppm 48.8, 58.8, 112.12, 114.22, 118.26, 119.91, 120.22, 124.22, 126.08 128.22, 130.32, 134.22, 146.88, 152.66. Anal. Calcd. for $C_{17}H_{11}N_5O_2S$: C, 58.44; H, 3.17; N, 20.05. Found: C, 58.63; H, 3.16; N, 19.99.

4-Amino-2-(2-nitrophenyl)-2H-pyrimido[2,1-b][1,3]benzothiazole-3-carbonitrile (4c). m.p. 188–190°C. Yield: 85%. IR (KBr)/cm^{-1} 3465–3238 (NH_2), 2218 (C≡N), 1632 (C=N), 1575, 1380 (NO_2). ^{1}HNMR ($CDCl_3$)δ = 3.58–3.62 (s, 1H, CH), 5.79 (s, 2H, NH_2^*), 6.98–7.26 (m, 8H, Ar-H). ^{13}CNMR ($CDCl_3$)δ ppm 48.6, 58.2, 112.14, 114.32, 118.28, 119.90, 120.28, 124.18, 126.09 128.42, 130.52, 134.82, 146.68, 152.96. Anal. Calcd. for $C_{17}H_{11}N_5O_2S$: C, 58.44; H, 3.17; N, 20.05. Found: C, 58.25; H, 3.18; N, 20.11.

4-Amino-2-(4-chlorophenyl)-2H-pyrimido[2,1-b][1,3]benzothiazole-3-carbonitrile (4d). m.p. 185–187°C. Yield: 88%. IR (KBr)/cm^{-1}3450-3240 (NH_2), 2230 (C≡N), 1620 (C=N). ^{1}HNMR ($CDCl_3$) δ = 3.44–3.60 (s, 1H, CH), 6.98 (s, 2H, NH_2^*), 7.35–7.40 (m, 8H, Ar-H). ^{13}CNMR ($CDCl_3$)δ ppm 47.8, 56.8, 114.22, 118.32, 119.26, 120.22, 122.26, 124.32, 126.09 128.02, 130.32, 134.22, 146.98, 152.82. Anal. Calcd. for $C_{17}H_{11}ClN_4S$ C, 60.26; H, 3.27; N, 16.54. Found: C, 60.46; H, 3.26; N, 16.59.

4-Amino-2-(4-methoxyphenyl)-2H-pyrimido[2,1-b][1,3]benzothiazole-3-carbonitrile (4e). m.p. 210–212°C Yield: 90%. IR (KBr)/cm^{-1} 3435–3215 (NH_2), 2232(C≡N), 1625(C=N), 1130 (C-O). ^{1}HNMR ($CDCl_3$) δ = 3.52–3.66 (s, 1H, CH), 3.52–3.66 (s, 3H, OCH_3), 5.87 (s, 2H, NH_2^*), 6.74–7.04 (m, 8H, Ar-H). ^{13}CNMR ($CDCl_3$)δ ppm 49.2, 56.8, 118.12, 118.52, 119.91, 120.22, 122.22, 124.26, 126.08 128.22, 130.32, 134.22, 138.82, 146.88, 152.66. Anal. Calcd. for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75. Found: C, 64.44; H, 4.23; N, 16.80.

4-Amino-2-methyl-2-phenyl-2H-pyrimido[2,1-b][1,3]benzothiazole-3-carbonitrile (4f). m.p. 195–197°C. Yield: 85%. IR (KBr)/cm^{-1} 3455–3242 (NH_2), 2235(C≡N), 1630 (C=N). ^{1}HNMR ($CDCl_3$) δ = 1.42 (s, 3H, CH_3), 5.76 (s, 2H, NH_2^*), 6.78–7.06 (m, 9H, Ar-H) ppm. ^{13}CNMR ($CDCl_3$) 24.58, 49.22, 68.28, 118.22, 119.32, 120.22, 126.36, 128.38, 130.18, 132.20, 134.22, 136.24, 138.22, 142.68, 146.88, 152.66. Anal. Calcd. for $C_{18}H_{14}N_4S$: C, 67.90; H, 4.43; N, 17.60. Found: C, 68.10; H, 4.44; N, 17.65.

Ethyl-4′-amino-spiro [cyclohexane-1,2′-2H-pyrimido[2,1-b]benzothiazole]-3′-carboxylate (4g). m.p. 187–189°C. Yield: 88%. IR (KBr)/cm^{-1} 3480–3240 (NH_2), 2920–2880 (br, ali CH), 1728 (C=O), 1625 (C=N), 1120 (C-O). ^{1}HNMR ($CDCl_3$) δ = 1.28–1.35 (t, 4H, CH_2), 1.75–1.98 (m, 2H, CH_2), 1.84–1.89 (t, 3H, CH_3), 2.06–2.30 (t, 2H, CH_2), 4.31–4.36 (q, 2H, CH_2), 6.79 (s, 2H, NH_2^*), 6.94–7.14 (m, 4H, Ar-H). ^{13}CNMR ($CDCl_3$) δ ppm 14.86, 20.42, 24.52, 36.72, 39.54, 51.26, 59.88, 68.24, 87.88, 112.06, 115.82, 118.56, 119.44, 122.88, 129.80, 143.80,

148.92, 151.28, 166.26. Anal. Calcd. for $C_{18}H_{21}N_3O_2S$: C, 62.95; H, 6.16; N, 12.23. Found: C, 62.76; H, 6.18; N, 12.27.

Ethyl-4-amino-2-(3-nitrophenyl)-2H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (4h). m.p. 178–180°C. Yield: 85%. IR (KBr)/cm^{-1} 3470–3245 (NH_2), 1725 (C=O), 1622 (C=N),1578, 1380 (NO_2), 1125 (C-O). ^{1}HNMR ($CDCl_3$) δ = 1.22–1.36 (t, 2H, CH_2), 3.59–3.65 (s, 1H, CH), 4.33–4.38 (q, 2H, CH_2), 5.88 (s, 2H, NH_2^*), 6.92–7.22 (m, 8H, Ar-H). ^{13}CNMR ($CDCl_3$) δ ppm 14.82/50.2, 58.8, 112.32, 114.82, 118.84, 119.80, 120.26, 124.82, 126.88, 128.22, 130.32, 134.22, 138.44, 142.56, 148.28, 154.86. Anal. Calcd. for $C_{19}H_{16}N_4O_4S$: C, 57.57; H, 4.07; N, 14.13. Found: C, 57.38; H, 4.08; N, 14.09.

Ethyl-4-amino-2-(2-nitrophenyl)-2H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (4i). m.p. 195–197°C. Yield: 86%. IR (KBr)/cm^{-1} 3480–3240 (NH_2), 1730 (C=O), 1620 (C=N), 1570, 1385 (NO_2), 1110 (C-O). ^{1}HNMR ($CDCl_3$)δ = 1.26-1.38 (t, 2H, CH_2), 3.58-3.68 (s, 1H, CH), 4.32–4.39 (q, 2H, CH_2), 5.82 (s, 2H, NH_2^*), 6.98-7.29 (m, 8H, Ar-H). ^{13}CNMR ($CDCl_3$)δpm 14.62, 55.2, 59.2, 114.38, 116.82, 118.94, 119.80, 120.26, 124.92, 128.78, 129.22, 136.32, 138.22, 140.44, 142.56, 149.28, 154.86. Anal. Calcd. for $C_{19}H_{16}N_4O_4S$: C, 57.57; H, 4.07; N, 14.13. Found: C, 57.75; H, 4.06; N, 14.17.

Ethyl-4-amino-2-(4-chlorophenyl)-2H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (4j). m.p. 220–222°C. Yield: 82%. IR (KBr)/cm^{-1}3485–3230 (NH_2), 1720 (C=O), 1622 (C=N), 1120 (C-O). ^{1}HNMR ($CDCl_3$)δ = 1.24–1.38 (t, 2H, CH_2), 3.46–3.70 (s, 1H, CH), 4.34-4.38 (q, 2H, CH_2), 6.98 (s, 2H, NH_2^*), 7.35–7.40 (m, 8H, Ar-H). ^{13}CNMR ($CDCl_3$) δ ppm 14.42, 56.2, 114.22, 118.32, 119.26, 120.22, 122.26, 124.32, 126.09, 128.02, 130.32, 134.22, 146.98, 152.96. Anal. Calcd. for $C_{19}H_{16}ClN_3O_2S$: C, 59.14; H, 4.18; N, 10.89. Found: C, 59.33; H, 4.19; N, 10.91.

Ethyl-4-amino-2-(4-methoxyphenyl)-2H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (4k). m.p. 186–188°C. Yield: 85%. IR (KBr)/cm^{-1} 3470-3220 (NH_2), 1728 (C=O), 1625 (C=N), 1130 (C-O). ^{1}HNMR ($CDCl_3$) δ = 1.26–1.39 (t, 2H, CH_2), 3.52–3.66 (s, 1H, CH), 3.68 (s, 3H, CH_3), 4.32–4.36 (q, 2H, CH_2), 6.98 (s, 2H, NH_2^*), 6.76–7.06 (m, 8H, Ar-H). ^{13}CNMR ($CDCl_3$) δ ppm 14.48, 49.4, 58.2, 118.22, 119.52, 120.22, 122.22, 126.08, 128.22, 130.38, 134.26, 138.82, 146.88, 152.66. Anal. calcd. for $C_{20}H_{19}N_3O_3S$: C, 62.97; H, 5.02; N, 11.02. Found: C, 63.15; H, 5.04; N, 11.05.

Ethyl-4-amino-2-methyl-2-phenyl-2H-pyrimido[2,1-b][1,3]benzothia zole-3-carboxylate (4l). m.p. 180–182°C. Yield: 80%. IR

(KBr)/cm^{-1} 3478-3235 (NH_2), 1720 (C=O), 1622 (C=N), 1120 (C-O). ^{1}HNMR ($CDCl_3$) δ = 1.24–1.38 (t, 2H, CH_2), 3.48–3.78 (s, 3H, CH_3), 4.34–4.38 (q, 2H, CH_2), 6.98 (s, 2H, NH_2^*), 6.79–7.13 (m, 9H, Ar-H). ^{13}CNMR ($CDCl_3$) δ ppm 14.42, 24.58, 49.22, 68.28, 118.22, 119.32, 222, 126.46, 127.38, 130.18, 132.20, 134.72, 136.24, 138.22, 142.38, 146.98, 152.66. Anal. calcd. for $C_{20}H_{19}N_3O_2S$: C, 65.73; H, 5.24; N, 11.50. Found: C, 65.53; H, 5.26; N, 11.53.

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