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SHORT COMMUNICATION

FeF_3 catalyzed cascade C–C and C–N bond formation: synthesis of differentially substituted triheterocyclic benzothiazole functionalities under solvent-free condition

Amol B. Atar · Yeon Tae Jeong

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Abstract A series of diverse polyfunctionalized triheterocyclic benzothiazoles were easily prepared in excellent yields via the Biginelli reaction of 2-aminobenzothiazole with substituted benzaldehydes and α-methylene ketones using FeF_3 as an expeditious catalyst under solvent-free conditions. The protocol provides a practical and straightforward approach toward highly functionalized triheterocyclic benzothiazole derivatives in excellent yields. The reaction was conveniently promoted by FeF_3 and the catalyst could be recovered easily after the reaction and reused without any loss of its catalytic activity. The advantageous features of this methodology are high atom economy, operational simplicity, shorter reaction time, convergence, and facile automation.

Keywords 4*H*-pyrimido[2, 1-*b*]benzothiazoles · Iron (III) fluoride · Multicomponent reaction · Solvent free · MCRs

Introduction

Substituted benzothiazoles have received considerable attention in the field of synthetic organic chemistry due to their numerous applications in the pharmaceutical industry. Functionalized benzothiazoles have shown anticonvulsant [1], antitumor [2], antiinflammatory [3], and antitubercular [4] activities, and also act as chemosensitizers in chemotherapy and neuroprotectant-cerebral antischemic agents [5–7]. Furthermore, they are also extensively used in material science. The industrial applications such as antioxidants [8], vulcanization accelerators [9], and a dopant in light emitting organic electroluminescent devices [10] have also been reported. The important of chemical and pharmacological properties of benzothiazoles derivatives and the development of synthetic methods which enable a facile access to these heterocyclic compounds are desirable. Recently, many efforts have been devoted to develop novel and highly efficient synthetic protocols for the synthesis of functionalized benzothiazoles such as multicomponent coupling reactions, transition metal catalyzed cyclizations, and [3+2] cycloadditions [11–18]. In the midst of them, multicomponent coupling reactions (MCRs) are known as a powerful tool for the construction of novel and structurally complex molecules in a single pot ensuring high atom economy, good overall yields and high selectivity, lower costs, shorter reaction times, minimizing waste, labor, energy, and avoidance of expensive purification processes [19–21].

The best-known multicomponent reaction for 4*H*-pyrimido[2,1-*b*]benzothiazoles and related polyheterocycles is the Biginelli reaction [22–24]. The simple and straightforward procedure reported by Biginelli [25] in 1893 involves a three-component condensation reaction of β-ketoesters, arylaldehydes, and urea to give 3,4-dihydropyrimidin-2-(1*H*)one in one-pot procedure. The urea has been reported as 2-aminobenzimidazoles and 2-aminobenzothioazoles derivatives as alternates [26–28]. The Biginelli reaction can be promoted by acid or base catalysis or by heating. Very recently, catalysts such as $AlCl_3$ [29], TBAHS [30], hydrotalcite [31], and *N*,*N*-dichlorobis(2,4,6-trichlorophenyl) urea [32] have been shown to be effective for the synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazoles. Although these methods provide good results in many instances, there is still a great

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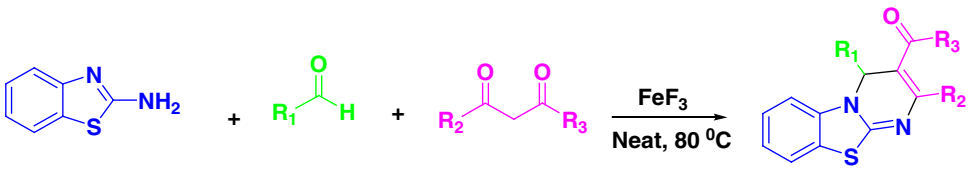
Scheme 1 Synthesis of fully substituted triheterocyclic benzothiazole functionalities catalyzed by FeF3 under solvent-free condition



demand for rapid and environment-friendly catalytic reaction conditions. We decided to find out the best environment-friendly catalytic system for this one-pot Biginelli reaction.

It is reported that FeF_3 is an efficient and inexpensive catalyst for the synthesis of polyhydroquinoline derivatives via unsymmetrical Hantzsch reaction [33]. We tested the three-component reaction of 2-aminobenzothiazole with substituted benzaldehydes and α-methylene ketones using FeF_3 as an expeditious catalyst under solvent-free conditions. We found FeF_3 to be an effective catalyst for the synthesis of triheterocyclic 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives in good to excellent yields and short reaction times. Based on our previous endeavors in exploring novel and practical multicomponent reactions to synthesize useful heterocyclic compounds [34–37], we proceeded to investigate the potential use of FeF_3 as a catalyst for the synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazoles. So herein we wish to report a tandem synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives by using FeF_3 as expeditious reusable catalyst in an excellent yield (Scheme 1).

Results and discussion

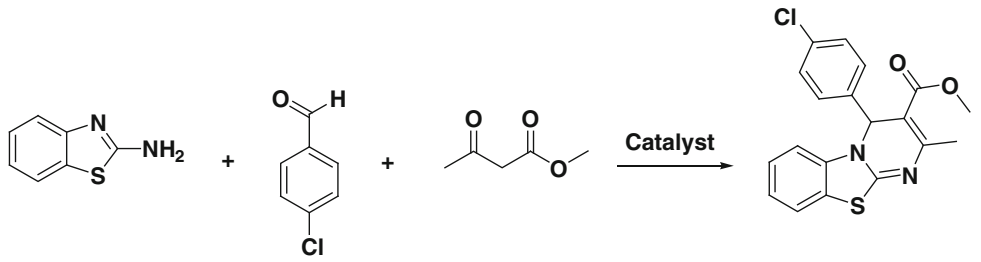
In order to optimize the reaction conditions, 2-aminobenzothiazole, 4-chlorobenzaldehyde, and methyl acetoacetate were taken as model reactants in the presence of different catalyst and solvent (Table 1). In order to establish the effectiveness of the catalyst for the synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives, a test reaction was performed without catalyst using 2-aminobenzothiazole, 4-chlorobenzaldehyde, and methyl acetoacetate in ethanol at reflux. It was found that only a trace amount of product was obtained in the absence of catalyst even after 10 h (Table 1, entry 1). In order to develop a viable approach, the model reaction was investigated using different catalysts including $CaCl_2$, SiO_2, $FeCl_3$, $Zn(OTf)_2$, $ZnCl_2$, $CuCl_2$, FeF_3, Li(OTf), $SnCl_2$. $2H_2O$, and CuF_2. Among all screened catalyst, FeF_3 gave the best result in view of yield and reaction time (Table 1, entry 8). In contrast $CaCl_2$, SiO_2, $Zn(OTf)_2$, $ZnCl_2$, Li(OTf), and $SnCl_2$. $2H_2O$ did not afford the desired product in good yields (Table 1, entries 2, 3, 5, 6, 10, and 11). FeF_3 was shown to be more effective than CuF_2 in terms of yield and time for completion of the reaction (Table 1, entries 8 and 13).

To assess the effect of solvents on this reaction, we screened different solvents such as toluene, EtOH, acetonitrile, DMF, ethylene glycol, methanol, water, and THF. It was observed that under solvent condition required longer times (2–4 h) to afford comparable yields (Table 1, entries 14–20). When the reaction was performed under solvent-free conditions, high yield of target product was obtained (Table 1, entry 8). Moreover, we found that the yields were affected by the amount of FeF_3 loaded. When 5, 10, and 20 mol% of FeF_3 were used, the yields were 90, 98, and 95 %, respectively (Table 1, entries 8, 21, and 22). Therefore, 10 mol% of FeF_3 was sufficient and optimal quantity for the completion of the reaction.

To explore the scope and limitations of this reaction further, we extended our studies to the use of various substituted aryl/aliphatic aldehydes and α-methylene ketones in the presence of 2-aminobenzothiazole. It was gratifying to observe that most of the tested substrates exhibited satisfactory reactivity profiles, in all cases leading to a heterocyclization sequence that readily afforded the target structures (Table 2). Compared with aromatic aldehydes, aliphatic aldehyde afforded relatively lower yields of the corresponding 4*H*-pyrimido[2,1-*b*]benzothiazole. A variety of α-methylene ketones like various substituted acetoacetates, 1,3 diketones, as well as isopropyl acetoactate reacted with 2-aminobenzothiazole and aldehydes under optimized conditions.

The reusability of the FeF_3 catalyst is one of the most important benefits and makes it useful for commercial applications as well. Thus, the recovery and reusability of the catalyst were investigated. The recyclability of the catalyst was checked with model reaction (Table 3, entries 1–4). The catalyst was recovered after completion of the first fresh run, the reaction mixture cooled to room temperature, and then water was added. The catalyst was dissolved in water and product was precipitated out. The precipitated crude product was separated by simple filtration and $FeF_3$was recovered by evaporating the aqueous layer under reduced pressure. The recovered FeF_3 (10 mol%) was dried at 90–100 °C for 12 h and tested in up to three more reaction cycles. The same catalyst (10 mol%) was reused for subsequent reactions (three runs) with fresh substrates under the same conditions. The catalyst showed excellent recyclability in all these reactions (Table 3), as the reaction times and yield remained almost the same without having a loss of catalytic activity.

Table 1 Optimization of catalysts, solvents, and temperature in the synthesis of **4aa**



1a **2a** **3a** **4aa**

No.	Catalyst (10 mol%)	Solvent	Condition	Time (h)	Yield[a] (%)
1	–	Ethanol	Reflux	10	22
2	$CaCl_2$	Ethanol	Reflux	8	35
3	SiO_2	Solvent free	100 °C	6	38
4	$FeCl_3$	Ethylene glycol	120 °C	3	65
5	$Zn(OTf)_2$	Methanol	80 °C	5	50
6	$ZnCl_2$	Ethanol	Reflux	4	55
7	FeF_3	Ethanol	Reflux	3	90
8	FeF_3	Solvent free	80 °C	0.5	98
9	$CuCl_2$	Solvent free	80 °C	3	75
10	Li(OTf)	Solvent free	80 °C	3	60
11	$SnCl_2{\cdot}2H_2O$	Solvent free	80 °C	2	65
12	$FeCl_3$	Solvent free	80 °C	3	85
13	CuF_2	Solvent free	80 °C	2	80
14	FeF_3	Water	Reflux	2	80
15	FeF_3	DMF	Reflux	3	82
16	FeF_3	Methanol	Reflux	4	85
17	FeF_3	Ethylene glycol	120 °C	3	82
18	FeF_3	CAN	100 °C	2	86
19	FeF_3	Toluene	100 °C	2.5	88
20	FeF_3	THF	Reflux	2	85
21	FeF_3 (5 mol%)	Solvent free	80 °C	0.5	90
22	FeF_3 (20 mol%)	Solvent free	80 °C	0.5	95

Reaction conditions: 4-Cl benzaldehyde (1 mmol), methyl acetoacetate (1 mmol), 2-aminobenzothiazole (1 mmol), catalyst (10 % mol)
[a] Isolated yield

Conclusion

In summary, we have described an efficient and environmentally benign protocol for the synthesis of fully substituted triheterocyclic benzothiazole functionalities via Biginelli reaction of 2-aminobenzothiazole with diversified α-methylene ketones and aldehydes using iron fluoride as a recyclable catalyst. The main advantages of this present methodology are the simple work up, easy recovery of catalyst, no need for anhydrous conditions, no base, or any additional activator required.

Experimental

Chemicals were purchased from Aldrich and Alfa Aesar chemical companies and used as it is. The NMR spectra were recorded in $CDCl_3$ on a Jeol JNM ECP 400 NMR instrument using TMS as an internal standard. The HRMS was recorded on a Jeol JMS-700 mass spectrometer. Melting points were taken in open capillaries on an Electrothermal-9100 instrument (Japan).

General procedure for the synthesis of fully substituted triheterocyclic benzothiazole functionalities (Table 2)

A mixture of aldehydes (1 mmol), α-methylene ketone (1 mmol), and 2-aminobenzothiazole (1 mmol) was heated at 80 °C under solvent-free conditions using iron flouride as a catalyst (10 mol%). The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and the residue was diluted

Table 2 Synthesis of triheterocyclic benzothiazole functionalities catalyzed by FeF_3

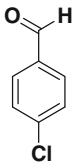
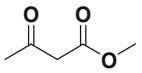
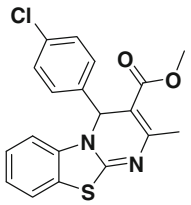
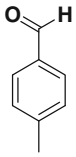
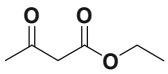
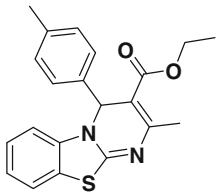
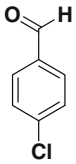
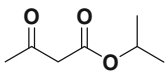
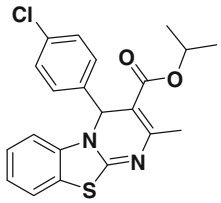
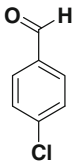
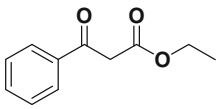
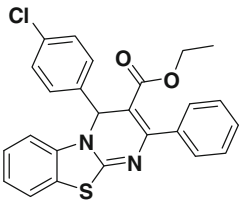
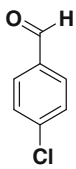
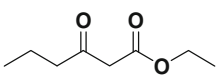
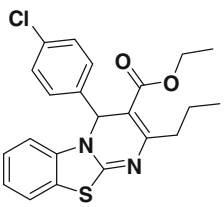
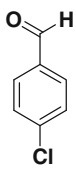
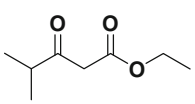
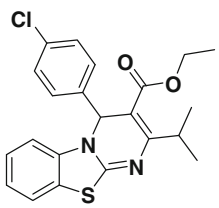
Entry	Aldehydes	α-Methylene ketone	Product	Time (h)	Yield[a] (%)	MP (°C)	References
1	 **2a**	 **3a**	 **4aa**	0.5	98	179–180	–
2	 **2b**	 **3b**	 **4bb**	1	95	153–154	–
3	 **2a**	 **3c**	 **4ac**	0.7	96	132–133	–
4	 **2a**	 **3d**	 **4ad**	0.5	97	83–84	–
5	 **2a**	 **3e**	 **4ae**	1.5	93	112–113	–
6	 **2a**	 **3f**	 **4af**	1	92	127–128	–

Table 2 continued

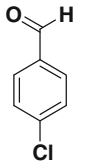
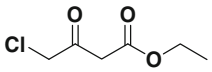
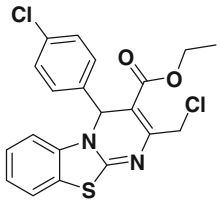
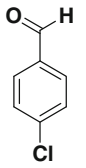
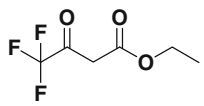
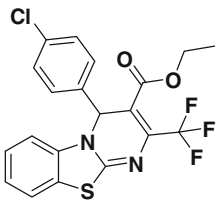
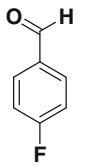
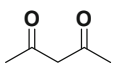
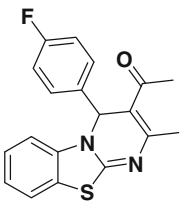
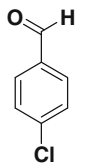
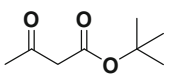
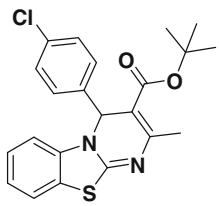
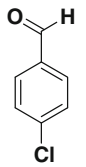
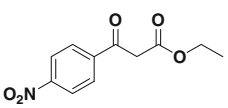
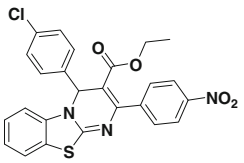
Entry	Aldehydes	α-Methylene ketone	Product	Time (h)	Yield[a] (%)	MP (°C)	References
7	 **2a**	 **3g**	 **4ag**	2	90	135–136	–
8	 **2a**	 **3h**	 **4ah**	2	88	143–144	–
9	 **2c**	 **3i**	 **4ci**	1	93	122–123	–
10	 **2a**	 **3j**	 **4aj**	1.5	90	102–103	–
11	 **2a**	 **3k**	 **4ak**	1.5	90	198–199	–

Table 2 continued

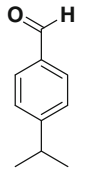
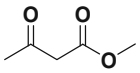
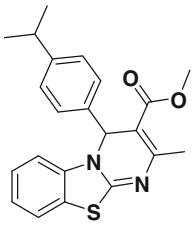
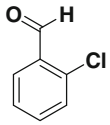
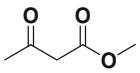
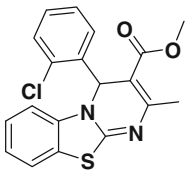
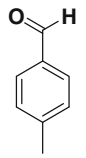
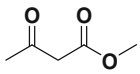
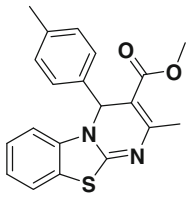
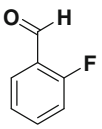
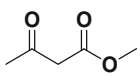
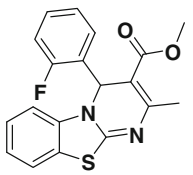
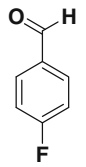
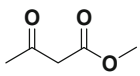
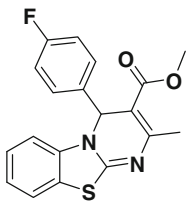
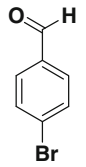
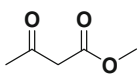
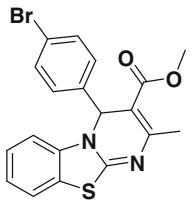
Entry	Aldehydes	α-Methylene ketone	Product	Time (h)	Yield[a] (%)	MP (°C)	References
12	 **2d**	 **3a**	 **4da**	1	93	146–147	–
13	 **2e**	 **3a**	 **4ea**	0.5	93	153–154	–
14	 **2b**	 **3a**	 **4ba**	1	90	154–155	–
15	 **2f**	 **3a**	 **4fa**	1.5	88	139–140	–
16	 **2c**	 **3a**	 **4ca**	2	91	160–161	–
17	 **2g**	 **3a**	 **4ga**	0.5	96	166–167	–

Table 2 continued

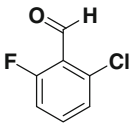
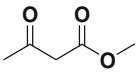
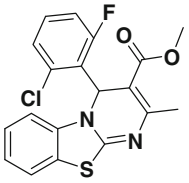
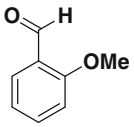
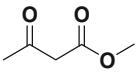
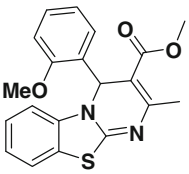
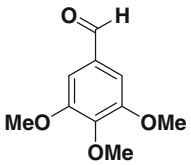
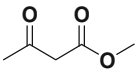
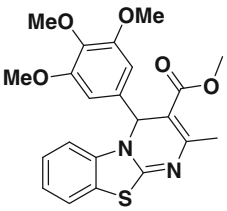
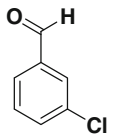
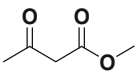
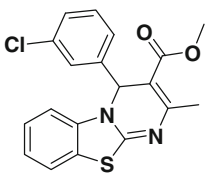
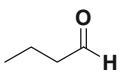
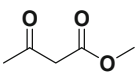
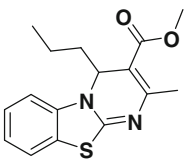
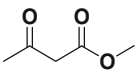
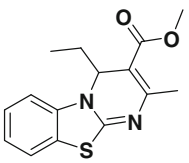
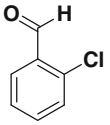
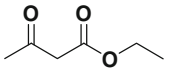
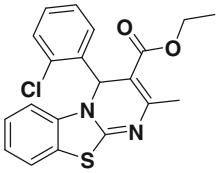
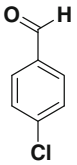
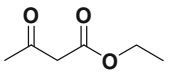
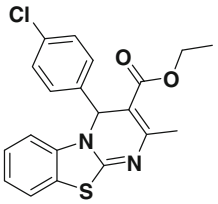
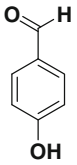
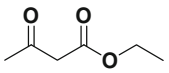
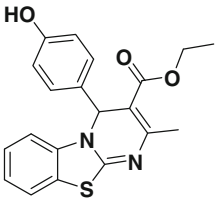
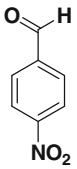
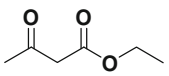
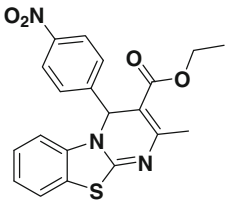
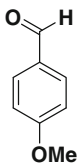
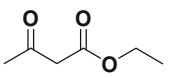
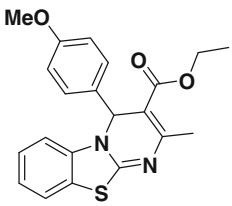
Entry	Aldehydes	α-Methylene ketone	Product	Time (h)	Yield[a] (%)	MP (°C)	References
18	 **2h**	 **3a**	 **4ha**	2.5	85	148–149	–
19	 **2i**	 **3a**	 **4ia**	1.5	89	145–146	–
20	 **2j**	 **3a**	 **4ja**	1.5	87	138–139	–
21	 **2k**	 **3a**	 **4ka**	0.5	95	139–140	–
22	 **2l**	 **3a**	 **4la**	2	85	123–124	–
23	 **2m**	 **3a**	 **4ma**	2.5	88	120–121	–

Table 2 continued

Entry	Aldehydes	α-Methylene ketone	Product	Time (h)	Yield[a] (%)	MP (°C)	References
24	 **2e**	 **3b**	 **4eb**	0.5	94	125–127	30
25	 **2a**	 **3b**	 **4ab**	0.5	93	142–143	–
26	 **2n**	 **3b**	 **4nb**	1.5	88	209–210	31
27	 **2o**	 **3b**	 **4ob**	2	85	155–156	30
28	 **2p**	 **3b**	 **4pb**	1.5	86	140–141	30

Reaction conditions: aldehyde (1 mmol), α-methylene ketone (1 mmol), 2-aminobenzothiazole (1 mmol), catalyst (10 mol%), solvent-free conditions, 80 °C

[a] Isolated yield

Table 3 Recycling and reuse of FeF_3

Entry	Reaction cycle	Yield[a] (%)
1	First (fresh run)	98
2	Second cycle	96
3	Third cycle	95
4	Fourth cycle	95

[a] Isolated yield

with water. The mixture was filtered and washed with water. The FeF_3 catalyst was dissolved in water and also recovered by evaporating the aqueous layer under reduced pressure. The solid crude product was easily purified by column chromatography over silica gel using hexane and ethyl acetate to get pure product **4**.

*Methyl-2-methyl-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4aa**)*

Pale yellow solid, m.p. 179–180 °C; Yield 98 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, $J_1 = 8$ Hz, $J_2 = 1.84$ Hz, 1H), 7.37–7.34 (m, 2H), 7.24–7.20 (m, 3H), 7.14–7.10 (m, 1H), 7.04 (d, 8 Hz, 1H), 6.37 (s, 1H), 3.71 (s, 3H), 2.44 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.94, 164.57, 156.35, 140.96, 138.84, 135.24, 129.98, 129.49, 127.76, 125.20, 124.87, 123.94, 112.66, 103.65, 85.17, 52.26, 24.88 ppm. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}ClN_2O_2S$ (m/z) 370.0543. Found: 370.0543.

*Ethyl-2-methyl-4-(4-methylphenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4bb**)*

Brown solid, m.p. 153–154 °C; Yield 95 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, 8 Hz, 1 H), 7.31 (d, 8 Hz, 2H), 7.25–7.17 (m, 1H), 7.10–7.03 (m, 4H), 6.35 (s, 1H), 4.18–4.13 (m, 2H), 2.47 (s, 3H), 2.22 (s, 3H), 1.28 (t, 12 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.49, 163.35, 154.34, 154.31, 138.47, 138.10, 137.94, 129.98, 129.26, 128.98, 127.09, 126.54, 123.87, 123.81, 122.06, 111.77, 103.18, 60.02, 57.48, 23.42, 21.06, 14.33 ppm. HRMS (ESI, m/z): Calcd for $C_{21}H_{20}N_2O_2S$ (m/z) 364.1245 Found: 364.1245.

*Isopropyl-2-methyl-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4ac**)*

Brown solid, m.p. 132–133 °C; Yield 96 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.35 (m, 3H), 7.23–7.19 (m, 3H), 7.13–7.09 (m, 1H), 7.04 (d, 8Hz, 1H), 6.35 (s, 1H), 5.06–5.03 (m, 1H), 2.45 (s, 3H), 1.28 (d, 8 Hz, 3H), 1.21 (d, 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.88, 163.20, 154.74, 139.86, 137.77, 134.08, 128.75, 128.60, 126.59, 124.02, 123.73, 122.21, 111.52, 102.99, 67.62, 57.10, 23.75, 22.19, 21.97 ppm. HRMS (ESI, m/z): Calcd for $C_{21}H_{19}ClN_2O_2S$ (m/z) 398.0856 Found: 398.0856.

*Ethyl-2-phenyl-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4ad**)*

Yellow solid, m.p. 83–84 °C; Yield 97 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.47 (m, 3H), 7.39–7.33 (m, 5H), 7.29–7.25 (m, 3H), 7.19–7.15 (m, 1H), 7.10 (d, 8 Hz, 1H), 6.50 (s, 1H), 3.89–3.86 (m, 2H), 0.82 (t, 12 Hz, 3H) ppm. ^{13}C NMR(100 MHz, $CDCl_3$): δ 166.69, 163.42, 155.04, 140.56, 139.80, 137.69, 134.34, 129.07, 128.44, 128.38, 128.13, 127.70, 126.78, 124.23, 124.14, 122.30, 111.69, 102.74, 60.07, 57.60, 13.50 ppm. HRMS (ESI, m/z): Calcd for $C_{25}H_{19}ClN_2O_2S$ (m/z) 446.0856 Found: 446.0856.

*Ethyl-2-butyral-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4ae**)*

Brown solid, m.p. 112–113 °C; Yield 93 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, 8 Hz, 1H), 7.38–7.35 (m, 2H), 7.22–7.17 (m, 3H), 7.12–7.03 (m, 2H), 6.37 (s, 1H), 4.19–4.14 (m, 2H), 2.80–2.77 (m, 2H), 1.70–1.65 (m, 2H), 1.28 (t, 12 Hz, 3H), 0.99 (t, 12 Hz, 3H) ppm. ^{13}C NMR(100 MHz, $CDCl_3$): δ 166.24, 163.45, 158.90, 140.02, 137.82, 134.09, 128.82, 128.53, 128.36, 126.74, 126.56, 123.95, 123.82, 122.18, 11.45, 102.65, 60.15, 57.09, 38.20, 22.06, 14.29 ppm. HRMS (ESI, m/z): Calcd for $C_{22}H_{21}ClN_2O_2S$ (m/z) 412.1012 Found: 412.1012.

*Ethyl-2-4-isobutyryl-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4af**)*

Brown solid, m.p. 127–128 °C; Yield 92 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, 8 Hz, 1H), 7.37–7.30 (m, 2H), 7.22–7.18 (m, 3 H), 7.13–7.07 (m, 1H), 7.03 (d, 8 Hz, 1H), 6.34 (s, 1 H), 4.19–4.14 (m, 2H), 3.97–3.93 (m, 1H), 1.29–1.20 (m, 6H), 1.13 (t, 12Hz, 3H) ppm. ^{13}C NMR(100 MHz, $CDCl_3$): δ 166.28, 163.62, 163.34, 140.21, 137.87, 134.04, 129.41, 129.06, 128.81, 128.49, 126.44, 123.95, 123.78, 122.15, 111.24, 101.38, 60.08, 57.08, 30.67, 20.49, 20.37, 14.29ppm. HRMS (ESI, m/z): Calcd for $C_{22}H_{21}ClN_2O_2S$ (m/z) 412.1012 Found: 412.1012.

*Ethyl-2-4-chloro-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4ag**)*

Brown solid, m.p. 135–136 °C; Yield 90 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, $J_1 = 4Hz$, $J_2 = 8$Hz, 1H), 7.39-7.36 (m, 2H), 7.31 (s, 1H), 7.25–7.21 (m, 2H), 7.17–

7.13 (m, 1H), 7.07 (d, 8 Hz, 1H), 6.41 (s, 1H), 4.74–4.70 (m, 2H), 4.23–4.18 (m, 2H), 1.30 (t, 12 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.00, 164.37, 139.13, 137.41, 134.57, 129.77, 129.53, 129.02, 128.61, 128.43, 126.79, 126.35, 125.11, 124.38, 124.01, 122.35, 111.67, 104.17, 60.83, 57.14, 44.58, 14.20ppm. HRMS (ESI, m/z): Calcd for $C_{20}H_{16}Cl_2N_2O_2S$ (m/z) 418.031 Found: 418.031.

*Ethyl-2-4-trifluoro-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ah***)*

Pale yellow solid, m.p. 143–144 °C; Yield 88 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (dd, $J_1 = 4Hz$, $J_2 = 8$Hz, 1H), 7.35–7.32 (m, 2H), 7.28–7.17 (m, 4H), 7.07 (d, 8 Hz, 1H), 6.43 (s, 1H), 4.20–4.15 (m, 2H), 1.23 (t, 12 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.89, 163.66, 137.85, 136.99, 135.18, 129.74, 129.39, 128.27, 127.38, 127.02, 124.76, 124.07, 122.45 ppm. HRMS (ESI, m/z): Calcd for $C_{20}H_{14}ClF_3N_2O_2S$ (m/z) 438.0417 Found: 438.0417.

*2-Methyl-4-(4-fluorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-ethanone (***4ci***)*

Brown solid, m.p. 122–123 °C; Yield 93 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.38 (m, 3H), 7.24 (d, 8 Hz, 1H), 7.16–7.7.07 (m, 2H), 6.92–6.87 (m, 2H), 6.55 (s, 1H), 2.45 (s, 3H), 2.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.28, 163.69, 154.56, 137.89, 137.19, 128.88, 128.80, 126.85, 125.95, 125.95, 124.24, 123.90, 122.15, 115.61, 115.40, 114.18, 111.94, 56.24, 31.92, 25.19 ppm. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}FN_2OS$ (m/z) 338.0889 Found: 338.0889.

*T-Butyl-2-4-methyl-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4aj***)*

Brown solid, m.p. 102–103 °C; Yield 90 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, $J_1 = 4$Hz, $J_2 = 8Hz$, $1H$), 7.36–7.34 (m, 2H), 7.24–7.20 (m, 3H), 7.13–7.09 (m, 1H), 7.03 (d, 8 Hz, 1H), 6.33 (s, 1H), 2.41 (s, 3H), 1.46 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.79, 162.86, 153.67, 139.83, 137.85, 134.03, 128.75, 128.48, 126.55, 123.93, 123.76, 122.20, 111.42, 104.23, 80.69, 57.09, 28.40, 23.69 ppm. HRMS (ESI, m/z): Calcd for $C_{22}H_{21}ClN_2O_2S$ (m/z) 412.1012 Found: 412.1012.

*Ethyl-2-4-nitrophenyl-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ak***)*

Orange solid, m.p. 198–199 °C; Yield 90 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23–8.20 (m, 2H), 7.56–7.47 (m, 5H), 7.32–7.13 (m, 5H), 6.56 (s, 1H), 3.92–3.90 (m, 2H), 0.89 (t, 10 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.54, 164.02, 153.02, 147.54, 147.42, 139.43, 137.45, 134.65, 129.29, 129.22, 128.88, 128.40, 128.05, 127.04, 124.63, 124.06, 123.89, 122.97, 122.44, 111.94, 103.51, 60.42, 57.51, 13.66 ppm. HRMS (ESI, m/z): Calcd for $C_{25}H_{18}ClN_3O_4S$ (m/z) 491.0707 Found: 491.0707.

*Methyl-2-methyl-4-(4-isopropylphenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4da***)*

Brown solid, m.p. 146–147 °C; Yield 93 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 8 Hz, 1H), 7.32 (d, 8 Hz, 1H), 7.26–7.20 (m, 1H), 7.13–7.08 (m, 4H), 6.36 (s, 1H), 3.71 (s, 3H), 2.82–2.76 (m, 1H), 2.44 (s, 3H), 1.16 (d, 8 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.16, 164.57, 155.96, 149.96, 139.86, 139.20, 128.01, 127.82, 127.67, 124.92, 123.17, 112.87, 104.07, 58.45, 52.17, 34.79, 24.86, 24.76 ppm. HRMS (ESI, m/z): Calcd for $C_{22}H_{22}N_2O_2S$ (m/z) 378.1402 Found: 378.1402.

*Methyl-2-methyl-4-(2-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ea***)*

Yellow solid, m.p. 153–154 °C; Yield 93 %. Mp 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, $J_1 = 4$Hz, $J_2 = 8$Hz, 1H), 7.43 (d, 8 Hz, 1H), 7.38 (d, 8 Hz, 1H), 7.28–7.22 (m, 2H), 7.19–7.09 (m, 3H), 6.75 (s, 1H), 3.67 (s, 3H), 2.48 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.58, 163.47, 155.59, 139.67, 138.16, 131.45, 130.25, 129.65, 129.45, 128.16, 126.80, 124.09, 123.26, 121.99, 111.60, 102.47, 54.36, 50.97, 23.53 ppm. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}ClN_2O_2S$ (m/z) 370.0543 Found: 370.0543.

*Methyl-2-methyl-4-(4-methylphenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ba***)*

Brown solid, m.p. 154–155 °C; Yield 90 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.39 (m, 1H), 7.30 (d, 8 Hz, 2H), 7.22–7.18 (m, 1H), 7.11–7.04 (m, 4H), 6.35 (s, 1H), 3.69 (s, 3H), 2.44 (s, 3H), 2.23 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.11, 164.55, 155.95, 139.65, 139.21, 139.15, 130.44, 128.05, 127.66, 124.95, 124.90, 123.18, 112.83, 104.08, 58.53, 52.15, 24.80, 22.19 ppm. HRMS (ESI, m/z): Calcd for $C_{20}H_{18}N_2O_2S$ (m/z) 350.1089 Found: 350.1089.

*Methyl-2-methyl-4-(2-fluorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4fa***)*

Yellow solid, m.p. 139–140 °C; Yield 88 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.48 (m, 1H), 7.39 (d, 8 Hz, 1H), 7.25–7.22 (m, 2H), 7.20–7.09 (m, 2H), 7.06–6.95 (m, 2H), 6.67 (s, 1H), 3.67 (s, 3H), 2.49 (s, 3H) ppm. ^{13}C

NMR (100 MHz, $CDCl_3$): δ 167.67, 164.49, 160.88, 158.40, 157.06, 139.02, 130.84, 130.81, 127.92, 126.27, 126.23, 125.18, 124.62, 123.18, 116.39, 116.16, 112.11, 112.06, 102.85, 52.19, 51.85, 24.65 ppm. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}FN_2O_2S$ (m/z) 354.0838 Found: 354.0838.

*Methyl-2-methyl-4-(4-fluorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ca***)*

Yellow solid, m.p. 160–161 °C; Yield 91 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.37 (m, 3H), 7.25–7.20 (m, 1H), 7.14–7.05(m, 2H), 6.95–6.90 (m, 2H), 6.38 (s, 1H), 3.71 (s, 3H), 2.45 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.92, 163.66, 155.10, 137.80, 137.34, 128.84, 128.76, 126.63, 124.05, 123.80, 122.23, 115.72, 115.51, 111.62, 102.80, 57.00, 51.16, 23.76 ppm. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}FN_2O_2S$ (m/z) 354.0838 Found: 354.0838.

*Methyl-2-methyl-4-(4-bromophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ga***)*

Yellow solid, m.p. 166–167 °C; Yield 96 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 8 Hz, 1H), 7.37 (d, 8Hz, 2H), 7.30–7.27 (m, 2H), 7.22 (t, 12 Hz, 1H), 7.12 (t, 12 Hz, 1H), 7.03 (d, 8 Hz, 1H), 6.35 (s, 1H), 3.71 (s, 3H), 2.44 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.79, 163.44, 155.25, 140.33, 137.68, 131.81, 128.68, 126.65, 124.08, 123.72, 122.33, 122.22, 111.53, 102.44, 57.10, 51.16, 23.77 ppm. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}BrN_2O_2S$ (m/z) 414.0038 Found: 414.0038.

*Methyl-2-methyl-4-(2-chloro-6-fluorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ha***)*

Orange solid, m.p. 148–149 °C; Yield 85 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, J_1 = 2Hz, J_2 = 8Hz, 1H), 7.22–7.7.09 (m, 6H), 6.99 (s, 1H), 3.65 (s, 3H), 2.44 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.73, 164.42, 157.97, 139.23, 131.22, 131.12, 127.85, 125.07, 124.30, 123.14, 112.05, 51.93, 24.84 ppm. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}BrN_2O_2S$ (m/z) 388.0449 Found: 388.0449.

*Methyl-2-methyl-4-(2-methoxyphenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ia***)*

Yellow solid, m.p. 145–146 °C; Yield 89 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (dd, J_1 = 2Hz, J_2 = 8Hz, 1H), 7.35–7.7.31 (m, 2H), 7.20–7.13 (m, 2H), 7.07–7.03 (m, 1H), 6.87–6.80 (m, 2H), 6.71 (s, 1H), 3.91 (s, 3H), 3.63 (s, 3H), 2.46 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.00, 164.38, 156.99, 156.23, 139.47, 130.86, 130.79, 130.68, 127.44, 124.61, 124.35, 122.75, 122.13, 103.09, 56.66, 53.24, 51.85, 24.50 ppm. HRMS (ESI, m/z): Calcd for $C_{20}H_{18}N_2O_3S$ (m/z) 366.1038 Found: 366.1038.

*Methyl-2-methyl-4-(3,4,5-methoxyphenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ja***)*

Brown solid, m.p. 138–139 °C; Yield 87 %.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, J_1 = 2Hz, J_2 = 8Hz, 1H), 7.28–7.23 (m, 1H), 7.17–7.10 (m, 2H), 6.60 (s, 2H), 6.36 (s, 1H), 3.76 (t, 12 Hz, 12H), 2.44 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.08, 153.32, 136.97, 126.67, 124.05, 124.05, 123.72, 122.19, 111.80, 103.97, 102.81, 60.71, 57.70, 56.13, 51.13, 23.72 ppm. HRMS (ESI, m/z): Calcd for $C_{22}H_{22}N_2O_5S$ (m/z) 426.1249 Found: 426.1249.

*Methyl-2-methyl-4-(3-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ka***)*

Yellow solid, m.p. 139–140 °C; Yield 95 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.40 (m, 2H), 7.30–7.11 (m, 5H), 7.05 (d, 8 Hz, 1H), 6.37 (s, 1H), 3.72 (s, 3H), 2.45 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.87, 164.59, 156.52, 144.31, 138.80, 135.73, 131.04, 129.69, 128.21, 127.82, 126.30, 125.23, 124.87, 123.36, 112.64, 103.42, 58.32, 52.28, 24.89 ppm. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}ClN_2O_2S$(m/z) 370.0543 Found: 370.0543.

*Methyl-2-methyl-4-(butyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4la***)*

Brown solid, m.p. 123–124 °C; Yield 85 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (t, 8Hz, 1H), 7.38–7.33 (m, 1H), 7.20 (d, 8Hz, 2H), 5.59 (t, 8Hz, 1H), 3.78 (s, 3H), 2.41 (s, 3H), 1.80–1.77(m, 1H), 1.55–1.52 (m, 1H), 1.40–1.36 (m, 1H), 1.12–1.07 (m, 1H), 0.79–0.78(m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.27, 164.16, 157.35, 137.98, 126.65, 124.04, 123.78, 122.36, 111.02, 100.06, 53.22, 51.13, 36.19, 23.45, 16.80, 13.97 ppm. HRMS (ESI, m/z): Calcd for $C_{16}H_{18}N_2O_2S$ (m/z) 302.1089 Found 302.1089

*Methyl-2-methyl-4-(propyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (***4ma***)*

Brown solid, m.p. 120–121 °C; Yield 88 %.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, 8Hz, 1H), 7.36–7.33 (m, 1H), 7.18 (t, 8Hz, 2H), 5.61 (t, 8Hz, 1H), 3.78 (s, 3H), 2.42 (s, 3H), 1.89–1.87(m, 1H), 1.63–1.61 (m, 1H), 0.79(t, 12Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.25, 164.29, 157.55, 137.96, 126.62, 123.98, 123.78, 122.35, 111.05, 99.36, 54.07, 51.12, 26.56, 23.47, 7.69 ppm. HRMS (ESI, m/z): Calcd for $C_{15}H_{16}N_2O_2S$ (m/z) 288.0932 Found 288.0932.

*Ethyl-2-methyl-4-(2-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4eb**)*

Yellow solid, m.p. 125–127 °C; Yield 94 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, $J_1 = 4$Hz, $J_2 = 8$Hz, 1H), 7.47 (d, 8 Hz, 1H), 7.38 (d, 8 Hz, 1H), 7.27–7.23 (m, 2H), 7.19–7.09 (m, 3H), 6.76 (s, 1H), 4.17–4.13 (m, 2H), 2.49 (s, 3H), 1.24 (t, 12 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.22, 163.33, 155.31, 139.58, 138.23, 131.46, 130.45, 129.68, 129.45, 128.08, 126.74, 124.04, 123.26, 121.98, 111.67, 102.77, 59.99, 54.46, 23.66, 14.42 ppm. HRMS (ESI, m/z): Calcd for $C_{20}H_{17}ClN_2O_2S$ (m/z) 384.0699 Found 384.0699.

*Ethyl-2-methyl-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4ab**)*

Brown solid, m.p. 142–143 °C; Yield 93 %.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.35 (m, 3H), 7.21–7.17 (m, 3H), 7.10–7.02 (m, 2H), 6.36 (s, 1H), 4.19–4.14 (m, 2H), 2.46 (s, 3H), 1.28 (t, 12 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.31, 163.28, 154.90, 139.83, 137.07, 134.07, 128.77, 128.50, 126.59, 124.03, 123.70, 122.18, 111.53, 102.69, 60.13, 57.06, 23.70, 14.34 ppm. HRMS (ESI, m/z): Calcd for $C_{20}H_{17}ClN_2O_2S$ (m/z) 384.0699 Found 384.0699.

*Ethyl-2-methyl-4-(4-hydroxyphenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4nb**)*

White solid, m.p. 209–210 °C; Yield 88 %.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.56–7.32 (m, 4H), 7.22–7.01 (m, 2H), 6.89–6.72 (m, 2H), 6.32 (s, 1H), 4.08–4.14 (m, 2H), 2.49 (s, 3H), 1.26 (t, 12Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.21, 163.24, 156.31, 153.58, 136.49, 132.65, 128.87, 126.38, 123.42, 122.85, 122.21, 116.01, 111.85, 102.36, 59.45, 56.21, 23.11, 14.32 ppm. HRMS (ESI, m/z): Calcd for $C_{20}H_{18}N_2O_3S$ (m/z) 366.1038 Found 366.1038.

*Ethyl-2-methyl-4-(4-nitrophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4ob**)*

Pale yellow solid, m.p. 155–156 °C; Yield 85 %.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.32 (m, 4H), 7.21–7.05 (m, 4H), 6.42 (s, 1H), 4.25–4.15 (m, 2H), 2.46 (s, 3H), 1.30 (t, 12Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.21, 163.45, 155.86, 148.23, 147.56, 137.69, 128.32, 126.19, 124.67, 123.89, 122.89, 122.01, 112.14, 102.09, 59.49, 57.23, 23.43, 14.66 ppm. HRMS (ESI, m/z): Calcd for $C_{20}H_{17}N_3O_4S$ (m/z) 395.0940 Found 395.0940.

*Ethyl-2-methyl-4-(4-methoxyphenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (**4pb**)*

Yellow solid, m.p. 140–141 °C; Yield 86 %.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.30 (m, 4H), 7.01–6.82 (m, 4H), 6.31 (s, 3H), 4.12–4.02 (m, 2H), 3.75 (s, 3H), 2.41 (s, 3H), 1.27 (t, 12Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.45, 163.28, 159.45, 153.87, 152.23, 138.69, 132.79, 128.31, 125.98, 123.47, 122.87, 122.06, 120.69, 118.92, 112.89, 103.56, 60.85, 58.36, 55.21, 23.45, 14.23 ppm. HRMS (ESI, m/z): Calcd for $C_{21}H_{20}N_2O_3S$ (m/z) 380.1195 Found 380.1195.

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