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Synthesis of pyrimido[2,1-*b*][1,3]benzothiazoles and [1,3]benzothiazolo [3,2-*a*]quinazolines *via* one-pot three-component reactions from 2-aminobenzothiazole, arylglyoxals and 1,3-dicarbonyl compounds

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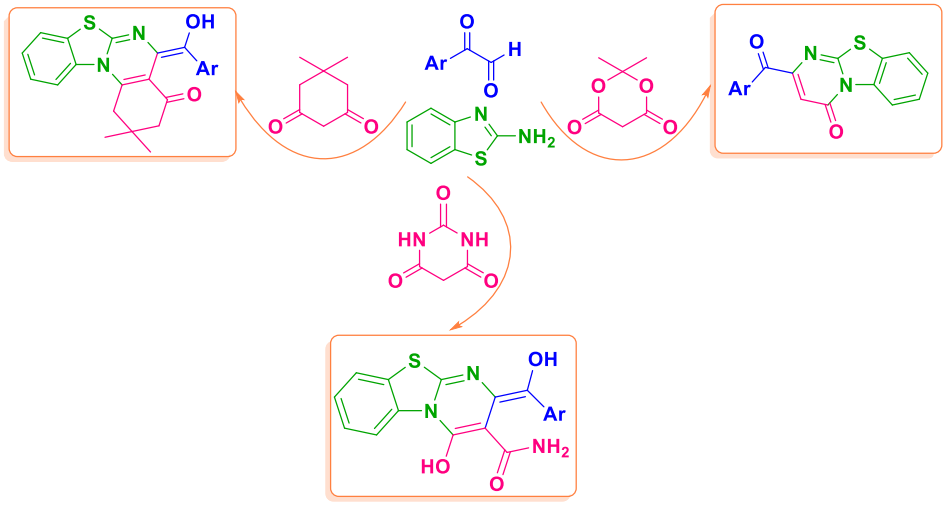
Abstract

A simple and efficient synthesis of pyrimido[2,1-*b*][1,3]benzothiazoles and [1,3]benzothiazolo[3,2-*a*]quinazolines has been developed by using a one-pot, three-component reaction between arylglyoxals, 2-aminobenzothiazole, and various 1,3-dicarbonyl compounds in acetic acid. All the products were obtained in good yields and their structures were established from their spectroscopic data.



Keywords: 2-Aminobenzothiazole, arylglyoxal, Meldrum's acid, dimedone, barbituric acid, fused pyrimidines, fused quinazolines, fused [1,3]benzothiazoles

Introduction

Fused pyrimidines heterocyclic compounds are ubiquitous in natural products, drug molecules, and functional materials.[1] Among them, especially pyrimido[2,1-*b*][1,3]benzothiazole and [1,3]benzothiazolo[3,2-*a*]quinazoline derivatives have been related to an extensive range of pharmacological activities, such as antibacterial **A**,[2] antimicrobial **B**,[3] antiallergy **C**,[4] antifungal **D**,[5] anticancer **E**,[6] antihistaminic **F**,[7] anticonvulsant **G**,[8] and anti-inflammatory activity **H** (Fig. 1).[9] Moreover, these compounds have cytotoxic activity against kidney, lung, colon, prostate or breast cancer cell lines.[10,11] As a result, the search for efficient syntheses of pyrimido[2,1-*b*][1,3]benzothiazole and [1,3]benzothiazolo[3,2-*a*]quinazoline derivatives have received much attention.

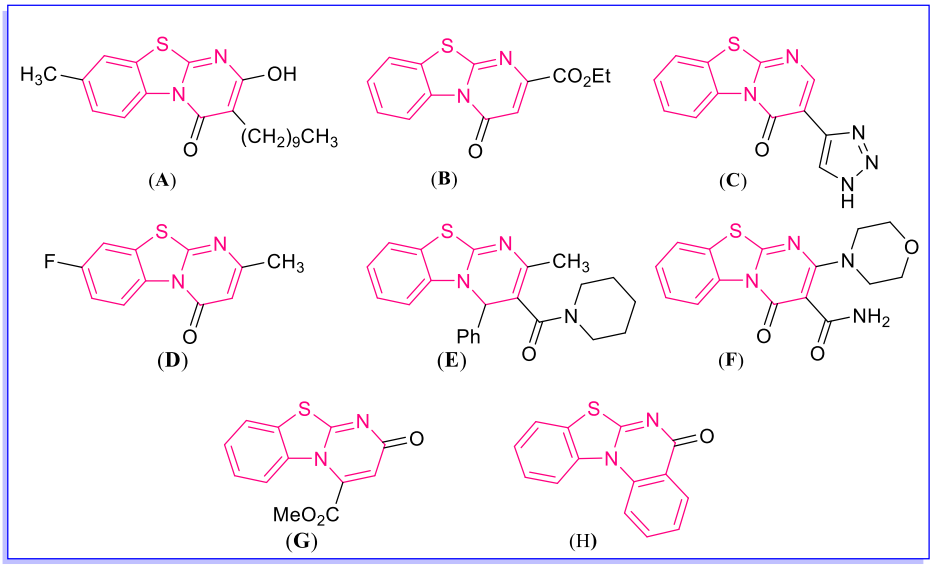


Figure 1. Selected bioactive molecules containing the pyrimido[2,1-*b*][1,3]benzothiazole and [1,3]benzothiazolo[3,2-*a*]quinazoline moieties.

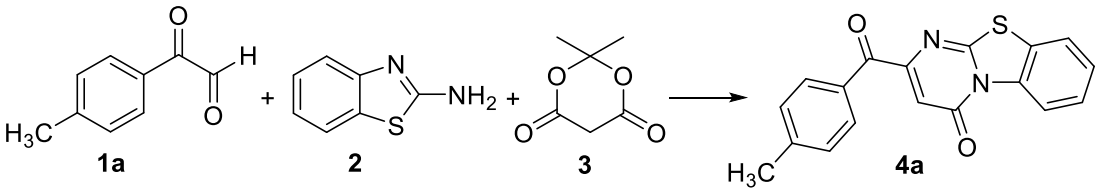
A variety of effective strategies for the synthesis of pyrimido[2,1-*b*][1,3]benzothiazole and [1,3]benzothiazolo[3,2-*a*]quinazoline derivatives have therefore been reported in literature. Most of the methods depict syntheses of pyrimido[2,1-*b*][1,3]benzothiazole and [1,3]benzothiazolo[3,2-*a*]quinazoline derivatives from intermolecular cyclization of 2-aminobenzothiazoles with malonic ester derivatives,[2,12] Meldrum's acid,[13] and β-ketoesters.[14] The reaction of 2-aminobenzothiazoles with various Michael acceptors, such as acetylenic compounds,[15,16] alkyl malonates,[8,17] and enaminones.[18] Moreover, organic and medicinal chemists have developed a series of multicomponent reactions (MCRs) for the synthesis of heterocyclic compounds and complex biologically-active compounds,[19-20] such as multi-component reaction of 2-aminobenzimidazole, benzaldehyde derivatives, and active methylene compounds,[6,21-22] and various other methods.[23-29] However, some of these modern methods have significant limitations such as tedious workup procedures, low yields, and longer reaction times. Therefore, a new and efficient method for synthesis of pyrimido[2,1-*b*]-[1,3]benzothiazole and [1,3]benzothiazolo[3,2-*a*]quinazoline derivatives remains an attractive goal.

We herein describe a new and efficient method for synthesis of pyrimido[2,1-*b*][1,3]benzothiazole and [1,3]benzothiazolo[[3,2-*a*]quinazoline derivatives *via* a one-pot, three-component reaction of an arylglyoxal, 2-amino benzothiazole, and 1,3-dicarbonyl compounds in acetic acid at reflux conditions.

Results and Discussion

To find the optimized conditions, we studied the synthesis of 2-(4-methylbenzoyl)-4*H*-benzo[4,5]thiazolo-[3,2-*a*]pyrimidin-4-one **4a** *via* the three-component reaction of 4-methylphenylglyoxal **1a**, 2-amino-benzothiazole **2**, and Meldrum's acid **3** under a variety of conditions (Table 1).

Table 1. Optimization of the reaction conditions in the synthesis of **4a**



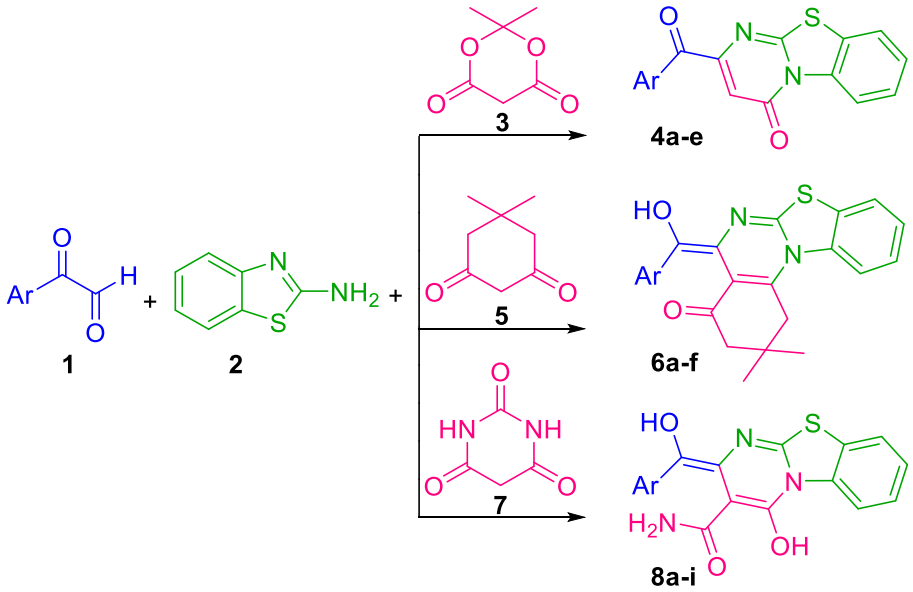
Entry	Solvent	Temp. (^{o}C)[a]	Mmol of **1a**:**2**:**3**	Yield (%)[b]
1	H_2O	r.t.	1:1:1	N.R.
2	EtOH	r.t.	1:1:1	N.R.
3	MeOH	r.t.	1:1:1	N.R.
4	CH_3CN	r.t.	1:1:1	N.R.
5	CH_3CO_2H	r.t.	1:1:1	12
6	H_2O	Reflux	1:1:1	N.R.
7	EtOH	Reflux	1:1:1	N.R.
8	MeOH	Reflux	1:1:1	N.R.
9	CH_3CN	Reflux	1:1:1	N.R.
10	CH_3CO_2H	Reflux	1:1:1	45
11	CH_3CO_2H	Reflux	0.9:1:1	36
12	CH_3CO_2H	Reflux	1:1:0.9	32
13	CH_3CO_2H	Reflux	1:0.9:1	58
14	CH_3CO_2H	Reflux[c]	1:0.9:1	58

[a] Reaction conditions: solvent was 5 mL, reaction time was 3 h.
[b] Isolated yields. [c] Reaction time was 12 h.

The optimization of the reaction conditions, including the reaction solvent, the reaction temperature, and the equivalents of starting materials, was investigated. First, various solvents were examined (Table 1, entries 1–5), and acetic acid was proven to be the preeminent solvent for this reaction. Then, we examined the influence of different temperatures on this reaction. To our satisfaction, when the reaction was carried out at room temperature in 3 hr, the product was formed in only 12% yield, but under reflux conditions in the same time, the product was formed in 45% yield (Table 1, entries 5 and 10). Finally, we observed that the amount of starting materials also have an important influence on the reaction (Table 1, entries 10–13). A larger amount of 4-methylphenylglyoxal **1a**, and Meldrum's acid **3** (for example, 1.0 mmol) in acetic acid at reflux conditions resulted in a higher yield, 58% (Table 1, entry 13). It was found that a longer time of the reaction in acetic acid at reflux conditions did not improve the yield (Table 1, entry 14). A series of experiments revealed that the optimal results were obtained when the reaction of 4-methylphenylglyoxal **1a** (1.0 mmol) was conducted with

2-aminobenzothiazole **2** (0.9 mmol), and Meldrum's acid **3** (1.0 mmol) in acetic acid at reflux conditions. Under these optimized conditions, the yield of **4a** reached 58%.

Table 2. Synthesis of pyrimido[2,1-b][1,3]benzothiazole and [1,3]benzothiazolo[3,2-a]quinazoline derivatives

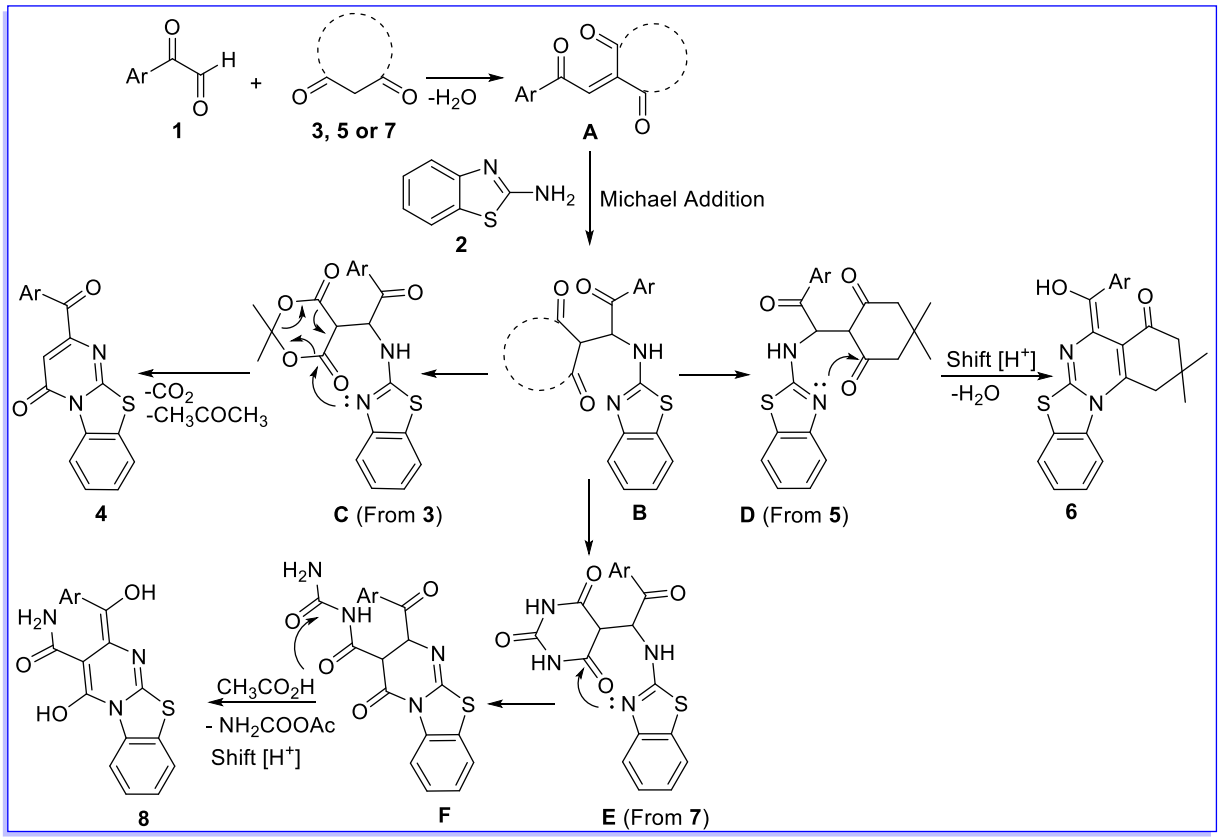


Entry	Product	Ar	Reagent **3, 5 or 7**	Time (min)	Yield (%)[a]
1	**4a**	4-$CH_3C_6H_4$	**3**	180	58
2	**4b**	4-ClC_6H_4	**3**	150	65
3	**4c**	4-BrC_6H_4	**3**	155	63
4	**4d**	C_6H_5	**3**	170	55
5	**4e**	4-FC_6H_4	**3**	130	68
6	**6a**	4-$CH_3C_6H_4$	**5**	75	73
7	**6b**	4-ClC_6H_4	**5**	62	79
8	**6c**	4-BrC_6H_4	**5**	65	77
9	**6d**	4-$CH_3OC_6H_4$	**5**	80	70
10	**6e**	4-FC_6H_4	**5**	58	81
11	**6f**	4-$NO_2C_6H_4$	**5**	50	85
12	**8a**	4-$CH_3C_6H_4$	**7**	35	82
13	**8b**	4-$OCH_3C_6H_4$	**7**	38	81
14	**8c**	3,4-$(OCH_3)_2C_6H_3$	**7**	40	80
15	**8d**	4-ClC_6H_4	**7**	21	89
16	**8e**	4-BrC_6H_4	**7**	25	87
17	**8f**	4-$NO_2C_6H_4$	**7**	16	95
18	**8g**	4-FC_6H_4	**7**	19	93
19	**8h**	3-$NO_2C_6H_4$	**7**	15	95
20	**8i**	C_6H_5	**7**	30	85

[a] Isolated yields.

Under the optimized reaction conditions, were then used to synthesize and explore the scope of this novel transformation with various 1,3-dicarbonyl compounds such as Meldrum's acid **3**, dimedone **5** or barbituric acid **7** to give a series of pyrimido[2,1-*b*][1,3]benzothiazole derivatives (**4a-e**), (**8a-i**), and [1,3]benzothiazolo[[3,2-*a*]quinazoline derivatives (**6a-f**) (Table 2). As can be seen from Table 2, the kind of products **4**, **6** or **8** are dependent on the nature of the 1,3-dicarbonyl compounds. When the arylglyoxal especially with electron-withdrawing groups and the 1,3-dicarbonyl compounds such as barbituric acid were employed, a shorter reaction time was required, and also a higher yield was obtained.

All the synthesized compounds were previously unknown to the best of our knowledge and were characterized by ^{1}H and ^{13}C NMR, IR, CHN analysis and melting points. For instance, the ^{1}H NMR spectrum of the compound **4a** consisted of one singlet at δ = 2.46 ppm for the three hydrogens of the methyl group, and one signal at δ = 6.87 ppm for the alkenic hydrogen. The aromatic protons resonated in the region δ = 7.32–9.16 ppm. The ^{13}C NMR spectrum of compound **4a** exhibited 16 distinct signals in agreement with the proposed structure. In the IR spectrum, the carbonyl absorption was observed at 1676 cm^{-1}. Partial assignments of these resonances for the other products are given in the experimental section.



Scheme 1. The proposed mechanisms for the synthesis of pyrimido[2,1-*b*][1,3]benzothiazole and [1,3]benzothiazolo[[3,2-*a*]quinazoline derivatives.

A proposed mechanism for the formation of pyrimido[2,1-*b*][1,3]benzothiazole and [1,3]benzothiazolo-[3,2-*a*]quinazoline derivatives **4**, **8**, and **6** is described in Scheme 1. The reaction of Meldrum's acid **3**, dimedone **5** or barbituric acid **7** with arylglyoxal **1** gave the intermediates **A**. After the addition of 2-aminobenzothiazole **2**, the formation of intermediate **B** occurred *via* a Michael addition reaction of the nitrogen at the *sp*^{2} carbon atom of **A**. Intermediate **B** undergoes nucleophilic addition of the second nitrogen

to the carbonyl group affording the intermediates **C**, **D** or **E**. In the last step, the natures of the 1,3-dicarbonyl compounds were different, so that 2-benzoyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one **4** is formed by the cycloaddition and loss of one molecule of acetone and carbon dioxide and oxidative dehydrogenation in acetic acid under reflux conditions, 5-[(hydroxy)(aryl)methylene]-2,2-dimethyl-3,4-dihydro-1*H*-[1,3]benzothiazolo-[3,2-*a*]quinazolin-4(5*H*)-one **6** is formed by intramolecular cyclization from the carbonyl group of dimedone and elimination of H_2O and intramolecular H-shift in acetic acid under reflux, while 4-hydroxy-2-[(hydroxy)-(aryl)methylene]-2*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxamide **8** is formed *via* two step; at first, intermediate **F** is formed by intramolecular cyclization from the carbonyl group of barbituric acid; then, nucleophilic addition of acetic acid solvent to carbonyl group and elimination of acetic carbamic anhydride and intramolecular H-shift in acetic acid at reflux conditions.

Conclusions

In summary, we have successfully developed an efficient and one pot, three-component reaction for synthesis of pyrimido[2,1-*b*][1,3]benzothiazole and [1,3]benzothiazolo[[3,2-*a*]quinazoline derivatives by treatment of 1,3-dicarbonyl compounds such as Meldrum's acid, dimedone or barbituric acid with arylglyoxals and 2-aminobenzothiazole. Moreover, the method has advantages in terms of higher yields, low cost of the starting materials, shorter reaction time, easy work-up, and mild reaction conditions.

Experimental Section

General. All chemicals were purchased from Aldrich and Merck with high-grade quality, and used without any purification. All melting points were obtained by Barnstead Electrothermal 9200 apparatus and are uncorrected. The reactions were monitored by TLC and all yields refer to isolated products. NMR spectra were obtained on a Varian 500 MHz spectrometer (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz) in DMSO using TMS as an internal standard. Infrared spectra were recorded on a Bruker FT-IR Equinax-55 spectrophotometer in KBr with absorption in cm^{-1}. Elemental analyses were performed using a Carlo Erba EA 1108 instrument. All products were characterized by their spectral and physical data.

General procedure for the synthesis of compounds 4a-e. A mixture of arylglyoxal **1** (1.0 mmol), 2-aminobenzothiazole **2** (0.9 mmol), and Meldrum's acid **3** (1.0 mmol) was stirred in 5.0 mL of acetic acid under reflux conditions for 130-180 min. After completion of the reaction, determined by TLC, the solvent was removed under reduced pressure, and the viscous residue was purified by plate chromatography (20×20 cm) using n-hexane/EtOAc (2:1) as eluent to give the pure compounds **4a–e** (55–68%).

General procedure for the synthesis of compounds 6a-f. A mixture of arylglyoxal **1** (1.0 mmol), 2-aminobenzothiazole **2** (0.9 mmol), and dimedone **5** (1.0 mmol) was stirred in 5.0 mL of acetic acid under reflux conditions for 50-80 min. After completion of the reaction, determined by TLC, the solvent was removed under reduced pressure, and the resulting crude product was recrystallized from ethanol to give the pure compounds **6a–f** (70–85%).

General procedure for the synthesis of compounds 8a-i. A mixture of arylglyoxal **1** (1.0 mmol), 2-aminobenzothiazole **2** (0.9 mmol), and barbituric acid **7** (1.0 mmol) was stirred in 5.0 mL of acetic acid under reflux conditions for 15-40 min. After completion of the reaction, determined by TLC, the solvent was removed

under reduced pressure, and the resulting crude product was recrystallized from ethanol to give the pure compounds 8a-i (80–95%).

2-(4-Methylbenzoyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one (**4a**)**.** Yellow oil. IR ν/cm^{-1} (KBr): 1676, 1603, 1495; ^{1}H NMR (500 MHz, DMSO): δ 2.46 (s, 3H, CH_3), 6.87 (s, 1H, CH), 7.32 (d, *J* 7.5 Hz, 2H, ArH), 7.55-7.61 (m, 2H, A-H), 7.75 (d, *J* 7.5 Hz, 1H, ArH), 7.94 (d, *J* 7.5 Hz, 2H, ArH), 9.16 (d, *J* 7.5 Hz, 1H, ArH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 21.8, 109.8, 120.3, 121.3, 121.9, 122.7, 124.6, 127.2, 127.6, 129.2, 130.7, 132.3, 132.4, 144.9, 161.0, 191.5 ppm. Anal. Calcd for $C_{18}H_{12}N_2O_2S$ (320.37): C, 67.48; H, 3.78; N, 8.74. Found: C, 67.31; H, 3.75; N, 8.79%.

2-(4-Chlorobenzoyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one (**4b**)**.** Yellow oil. IR ν/cm^{-1} (KBr): 1682, 1583, 1494; ^{1}H NMR (500 MHz, DMSO): δ 6.93 (s, 1H, CH), 7.50 (d, *J* 7.5 Hz, 2H, ArH), 7.56-7.62 (m, 2H, ArH), 7.77 (d, *J* 7.5 Hz, 1H, ArH), 8.03 (d, *J* 7.5 Hz, 2H, ArH), 9.16 (d, *J* 7.5 Hz, 1H, ArH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 109.9, 109.9, 117.8, 120.3, 121.9, 123.2, 127.3, 127.7, 128.8, 132.0, 133.1, 133.3, 140.2, 179.1, 190.3 ppm. Anal. Calcd for $C_{17}H_9ClN_2O_2S$ (340.78): C, 59.92; H, 2.66; N, 8.22. Found: C, 60.07; H, 2.68; N, 8.19%.

2-(4-Bromobenzoyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one (4c). Yellow oil. IR ν/cm^{-1} (KBr): 1669, 1582, 1493; ^{1}H NMR (500 MHz, DMSO): δ 6.93 (s, 1H, CH), 7.57-7.62 (m, 2H, ArH), 7.67 (d, *J* 7.5 Hz, 2H, ArH), 7.76 (d, *J* 7.5 Hz, 1H, ArH), 7.94 (d, *J* 7.5 Hz, 2H, ArH), 9.16 (d, *J* 7.5 Hz, 1H, ArH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 109.9, 110.6, 119.1, 120.3, 121.9, 124.7, 127.3, 128.0, 129.5, 131.8, 132.0, 133.0, 139.0, 179.4, 191.6 ppm. Anal. Calcd for $C_{17}H_9BrN_2O_2S$ (385.24): C, 53.00; H, 2.35; N, 7.27. Found: C, 53.11; H, 2.36; N, 7.24%.

2-Benzoyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one (**4d**). Yellow oil. IR ν/cm^{-1} (KBr): 1683, 1596, 1506; ^{1}H NMR (500 MHz, DMSO): δ 6.89 (s, 1H, CH), 7.53 (d, *J* 7.5 Hz, 2H, ArH), 7.56-7.60 (m, 2H, ArH), 7.65 (t, *J* 7.5 1H, Hz, ArH), 7.75 (d, *J* 7.5 Hz, 1H, ArH), 8.04 (d, *J* 7.5 Hz, 2H, ArH), 9.16 (d, *J* 7.5 Hz, 1H, ArH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 106.5, 109.9, 120.3, 121.9, 124.6, 127.2, 127.6, 128.4, 130.5, 130.8, 133.7, 135.0, 135.7, 156.8, 191.8 ppm.

2-(4-Fluorobenzoyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one (4e). Yellow oil. IR ν/cm^{-1} (KBr): 1617, 1594, 1509; ^{1}H NMR (500 MHz, DMSO): δ 6.92 (s, 1H, CH), 7.20 (d, *J* 7.5 Hz, 2H, ArH), 7.56-7.62 (m, 2H, ArH), 7.76 (d, *J* 7.5 Hz, 1H, ArH), 8.12 (d, *J* 7.5 Hz, 2H, ArH), 9.15 (d, *J* 7.5 Hz, 1H, ArH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 109.9, 115.6, 115.8, 120.3, 121.9, 124.6, 127.3, 127.7, 127.8, 131.4, 133.4, 133.4, 135.6, 167.1, 190.1 ppm. Anal. Calcd for $C_{17}H_9FN_2O_2S$ (324.33): C, 62.96; H, 2.80; N, 8.64. Found: C, 62.91; H, 2.77; N, 8.70%.

5-[(Hydroxy)(*p*-tolyl)methylene]-2,2-dimethyl-1,2,3,5-tetrahydro-4*H*-[1,3]benzothiazolo[3,2-*a*]quinazolin-4-one (**6a**)**.** White solid. mp = 334-336 °C. IR ν/cm^{-1} (KBr): 1638, 1506, 1482; ^{1}H NMR (500 MHz, DMSO): δ 1.14 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.35 (bs, 2H, CH_2, 2.72 (bs, 2H, CH_2), 7.13 (d, *J* 7.5 Hz, 2H, ArH), 7.34 (t, *J* 7.5 Hz, 1H, ArH), 7.41 (t, *J* 7.5 Hz, 1H, ArH), 7.44 (d, *J* 7.5 Hz, 1H, ArH), 7.53 (d, *J* 7.5 Hz, 2H, ArH), 7.98 (d, *J* 7.5 Hz, 1H, ArH), 11.42 (bs, 1H, OH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 21.2, 27.3, 30.0, 31.9, 79.6, 105.1, 113.3, 116.3, 124.8, 125.1, 126.5, 126.9, 129.1, 129.6, 132.5, 133.2, 136.3, 144.5, 146.5, 191.1 ppm. Anal. Calcd for $C_{24}H_{22}N_2O_2S$ (402.51): C, 71.62; H, 5.51; N, 6.96. Found: C, 71.57; H, 5.50; N, 6.93%.

5-[(Hydroxy)(4-chlorophenyl)methylene]-2,2-dimethyl-1,2,3,5-tetrahydro-4*H*-[1,3]benzothiazolo[3,2-*a*]quinazolin-4-one (**6b**)**.** White solid. mp = 333-335 °C. IR ν/cm^{-1} (KBr): 1657, 1595, 1509; ^{1}H NMR (500 MHz, DMSO): δ 1.14 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.40 (d, *J* 16.0 Hz, 2H, CH_2), 2.73 (d, *J* 16.0 Hz, 2H, CH_2), 7.35- 7.48 (m, 5H, ArH), 7.65 (d, *J* 7.5 Hz, 2H, ArH), 7.98 (d, *J* 7.5 Hz, 1H, ArH), 11.51 (bs, 1H, OH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 27.5, 29.8, 31.9, 77.9, 104.7, 113.5, 117.3, 125.1, 125.2, 127.0, 128.2, 128.6, 129.6, 131.7, 133.1, 134.2, 143.2, 146.9, 195.2 ppm.

5-[(Hydroxy)(4-bromophenyl)methylene]-2,2-dimethyl-1,2,3,5-tetrahydro-4*H*-[1,3]benzothiazolo[3,2-*a*]quinazolin-4-one (**6c**)**.** White solid. mp = 331-333 °C. IR ν/cm^{-1} (KBr): 1658, 1609, 1493; ^{1}H NMR (500 MHz, DMSO): δ 1.15 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 2.49 (d, *J* 16.0 Hz, 2H, CH_2), 2.72 (d, *J* 16.0 Hz, 2H, CH_2), 7.36 (t, *J* 7.5 Hz,

1H, ArH), 7.43 (t, *J* 7.5 Hz, 1H, ArH), 7.47 (d, *J* 7.5 Hz, 1H, ArH), 7.53 (d, *J* 7.5 Hz, 2H, ArH), 7.59 (d, *J* 7.5 Hz, 2H, ArH), 7.98 (d, *J* 7.5 Hz, 1H, ArH), 11.51 (bs, 1H, OH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 27.5, 29.8, 31.9, 72.2, 104.7, 113.5, 117.3, 120.2, 125.1, 125.2, 127.0, 128.5, 129.6, 131.5, 133.1, 134.5, 143.2, 146.9, 190.9 ppm. Anal. Calcd for $C_{23}H_{19}BrN_2O_2S$ (467.38): C, 59.11; H, 4.10; N, 5.99. Found: C, 59.17; H, 4.13; N, 5.97%.

5-[(Hydroxy)(4-methoxyphenyl)methylene]-2,2-dimethyl-1,2,3,5-tetrahydro-4*H*-[1,3]benzothiazolo[3,2-*a*]-quinazolin-4-one (**6d**). White solid. mp = 337-339 °C. IR ν/cm^{-1} (KBr): 1657, 1609, 1493; ^{1}H NMR (500 MHz, DMSO): δ 1.14 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 2.36 (bs, 2H, CH_2), 2.71 (bs, 2H, CH_2), 3.74 (s, 3H, OCH_3), 6.89 (d, *J* 8.5 Hz, 2H, ArH), 7.32- 7.44 (m, 3H, ArH), 7.56 (d, *J* 8.5 Hz, 2H, ArH), 7.96 (d, *J* 7.5 Hz, 1H, ArH), 11.36 (bs, 1H, OH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 27.4, 29.9, 31.9, 55.5, 73.8, 105.1, 113.2, 114.0, 115.7, 124.7, 125.1, 126.9, 127.8, 127.9, 129.5, 133.2, 144.3, 146.4, 158.6, 194.5 ppm. Anal. Calcd for $C_{24}H_{22}N_2O_3S$ (418.51): C, 68.88; H, 5.30; N, 6.69. Found: C, 68.71; H, 5.27; N, 6.65%.

5-[(Hydroxy)(4-fluorophenyl)methylene]-2,2-dimethyl-1,2,3,5-tetrahydro-4*H*-[1,3]benzothiazolo[3,2-*a*]quin-azolin-4-one (**6e**). White solid. mp = 339-341 °C. IR ν/cm^{-1} (KBr): 1688, 1595, 1510; ^{1}H NMR (500 MHz, DMSO): δ 1.12 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 2.48 (bs, 2H, CH_2), 2.73 (bs, 2H, CH_2), 7.17-7.98 (m, 8H, ArH), 11.52 (bs, 1H, OH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 27.4, 29.9, 31.9, 84.8, 104.8, 113.4, 115.5, 116.7, 125.0, 125.2, 127.0, 128.5, 129.6, 131.8, 133.1, 143.5, 146.7, 160.6, 192.9 ppm.

5-[(Hydroxy)(4-nitrophenyl)methylene]-2,2-dimethyl-1,2,3,5-tetrahydro-4*H*-[1,3]benzothiazolo[3,2-*a*]quin-azolin-4-one (**6f**). White solid. mp = 343-345 °C. IR ν/cm^{-1} (KBr): 1657, 1595, 1509; ^{1}H NMR (500 MHz, DMSO): δ 1.18 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.45 (bs, 2H, CH_2), 2.72 (bs, 2H, CH_2), 7.39 (t, *J* 7.5 Hz, 1H, ArH), 7.45 (t, *J* 7.5 Hz, 1H, ArH), 7.50 (d, *J* 8.0 Hz, 1H, ArH), 7.90 (d, *J* 8.5 Hz, 2H, ArH), 8.02 (d, *J* 8.0 Hz, 1H, ArH), 8.22 (d, *J* 8.5 Hz, 2H, ArH), 11.73 (bs, 1H, OH) ppm. ^{13}C NMR (125 MHz, DMSO): δ 27.9, 29.6, 32.0, 85.7, 104.4, 113.8, 119.7, 124.1, 125.3, 125.5, 126.9, 127.1, 129.8, 132.9, 141.8, 142.1, 146.1, 147.7, 195.8 ppm. Anal. Calcd for $C_{23}H_{19}N_3O_4S$ (433.48): C, 63.73; H, 4.42; N, 9.69. Found: C, 63.82; H, 4.42; N, 9.65%.

4-Hydroxy-2-[(hydroxy(*p*-tolyl)methylene]-2*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxamide (**8a**)**.** White solid. mp = 374-376°C. IR ν/cm^{-1} (KBr): 3080, 2949, 1709, 1573; ^{1}H NMR (500 MHz, DMSO): δ 2.29 (s, 3H, CH_3), 7.18 (d, *J* 8.0 Hz, 2H, ArH), 7.38 (t, *J* 7.5 Hz, 1H, ArH), 7.48 (t, *J* 7.5 Hz, 1H, ArH), 7.59-7.60 (m, 3H, ArH), 7.99 (d, *J* 8.0 Hz, 1H, ArH), 10.88 (bs, 2H, NH_2) ppm. ^{13}C NMR (125 MHz, DMSO): δ 21.2, 79.7, 113.7, 125.2, 125.2, 126.3, 127.2, 129.3, 129.4, 129.6, 131.3, 133.3, 136.8, 146.7, 151.0, 163.3, 172.3 ppm. Anal. Calcd for $C_{19}H_{15}N_3O_3S$ (365.41): C, 62.45; H, 4.14; N, 11.50. Found: C, 62.57; H, 4.17; N, 11.47%.

4-Hydroxy-2-[(hydroxy(4-methoxyphenyl)methylene]-2H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxamide (**8b**)**.** White solid. mp = 385-387 °C. IR ν/cm^{-1} (KBr): 3184, 2946, 1709, 1568; ^{1}H NMR (500 MHz, DMSO): δ 3.75 (s, 3H, OCH_3), 6.95 (d, *J* 9.0 Hz, 2H, ArH), 7.38 (t, *J* 7.5 Hz, 1H, ArH), 7.48 (t, *J* 7.5 Hz, 1H, ArH), 7.60 (d, *J* 8.0 Hz,1H, ArH), 7.64 (d, *J* 9.0 Hz, 2H, ArH), 8.00 (d, *J* 8.0 Hz, 1H, ArH), 10.81 (bs, 2H, NH_2) ppm. ^{13}C NMR (125 MHz, DMSO): δ 55.5, 79.5, 109.9, 113.7, 114.3, 125.2, 125.2, 126.5, 127.3, 127.7, 129.5, 133.3, 146.5, 151.1, 159.0, 163.4, 172.4 ppm. Anal. Calcd for $C_{19}H_{15}N_3O_4S$ (381.41): C, 59.83; H, 3.96; N, 11.02. Found: C, 59.77; H, 3.94; N, 11.07%.

4-Hydroxy-2-[(hydroxy(3,4-dimethoxyphenyl)methylene]-2*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carbox-amide (**8c**)**.** White solid. mp = 348-350 °C. IR ν/cm^{-1} (KBr): 3403, 2835, 1698, 1590; ^{1}H NMR (500 MHz, DMSO): δ 3.74 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 6.96 (d, *J* 8.5 Hz, 1H, ArH), 7.23 (d, *J* 8.5 Hz, 1H, ArH), 7.36-7.41 (m, 2H, ArH), 7.49 (t, *J* 8.5 Hz, 1H, ArH), 7.64 (d, *J* 8.0 Hz, 1H, ArH), 8.01 (d, *J* 8.0 Hz, 1H, ArH), 10.86 (bs, 2H, NH_2) ppm. ^{13}C NMR (125 MHz, DMSO): δ 55.5, 55.9, 79.4, 110.2, 112.3, 113.9, 115.7, 118.8, 125.2, 125.3, 126.3, 127.3, 129.5, 133.2, 146.4, 148.6, 148.8, 151.1, 163.5, 172.4 ppm. Anal. Calcd for $C_{20}H_{17}N_3O_5S$ (411.43): C, 58.39; H, 4.16; N, 10.21. Found: C, 58.47; H, 4.17; N, 10.16%.

4-Hydroxy-2-[(hydroxy(4-chlorophenyl)methylene]-2*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxamide (**8d**)**.** White solid. mp = 367-369 ^{o}C. IR ν/cm^{-1} (KBr): 3419, 3072, 1687, 1588; ^{1}H NMR (500 MHz, DMSO): δ 6.52 (bs, 2H, 2OH), 7.37-7.49 (m, 4H, ArH), 7.59 (d, *J* 10.0 Hz, 1H, ArH), 7.73 (d, *J* 8.5 Hz, 2H, ArH), 8.01 (d, *J* 8.0 Hz, 1H, ArH), 11.07 (bs, 2H, NH_2) ppm. ^{13}C NMR (125 MHz, DMSO): δ 79.9, 113.6, 116.0, 125.2, 125.3, 127.2, 127.9, 128.9, 129.6, 132.0, 133.2, 133.4, 143.4, 147.3, 150.9, 163.2 ppm.

4-Hydroxy-2-[(hydroxy(4-bromophenyl)methylene]-2*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxamide (**8e**)**.** White solid. mp = 383-385 ^{o}C. IR ν/cm^{-1} (KBr): 3307, 2844, 1695, 1603; ^{1}H NMR (500 MHz, DMSO): δ 7.38 (t, *J* 8.5 Hz, 1H, ArH), 7.47 (t, *J* 8.5 Hz, 1H, ArH), 7.57-7.60 (m, 3H, AH), 7.66 (d, *J* 8.5 Hz, 2H, ArH), 8.01 (d, *J* 8.5 Hz, 1H, ArH), 11.30 (bs, 2H, NH_2) ppm. ^{13}C NMR (125 MHz, DMSO): δ 79.9, 113.6, 116.0, 120.6, 125.2, 127.2, 128.2, 129.7, 131.8, 133.2, 133.8, 143.4, 147.3, 150.9, 163.1, 172.4 ppm.

4-Hydroxy-2-[(hydroxy(4-nitrophenyl)methylene]-2*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxamide (**8f**). Yellow solid. mp = 382-384 ^{o}C. IR ν/cm^{-1} (KBr): 3207, 3022, 1706, 1598; ^{1}H NMR (500 MHz, DMSO): δ 5.79 (bs, 2H, 2OH), 7.41 (t, *J* 8.5 Hz, 1H, AH), 7.49 (t, *J* 8.5 Hz, 1H, ArH), 7.61 (d, *J* 8.5 Hz, 1H, ArH), 8.00 (d, *J* 9.5 Hz, 2H, AH), 8.03 (d, *J* 8.5 Hz, 1H, ArH), 8.26 (d, *J* 9.5 Hz, 2H, ArH), 11.82 (bs, 2H, NH_2) ppm. ^{13}C NMR (125 MHz, DMSO): δ 79.8, 113.8, 118.3, 124.4, 125.3, 125.5, 126.7, 127.3, 129.8, 133.1, 141.5, 142.8, 146.1, 148.1, 150.9, 163.1 ppm. Anal. Calcd for $C_{18}H_{12}N_4O_5S$ (396.38): C, 54.54; H, 3.05; N, 14.14. Found: C, 54.58; H, 3.06; N, 14.08%.

4-Hydroxy-2-[(hydroxy(4-fluorophenyl)methylene]-2*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxamide (**8g**). White solid. mp = 371-373 ^{o}C. IR ν/cm^{-1} (KBr): 3408, 3035, 1704, 1661; ^{1}H NMR (500 MHz, DMSO): 4.58 (bs, 2H, 2OH), 7.23 (t, *J* 7.5 Hz, 2H, ArH), 7.39 (t, *J* 8.0 Hz, 1H, ArH), 7.48 (t, *J* 8.0 Hz, 1H, ArH), 7.59 (d, *J* 8.0 Hz, 1H, ArH), 7.74 (dd, *J* 7.5 Hz, 2H, ArH), 8.02 (d, *J* 8.0 Hz, 1H, ArH), 11.84 (bs,2H, NH_2) ppm. ^{13}C NMR (125 MHz, DMSO): δ 79.8, 113.6, 115.8, 125.2, 127.2, 128.2, 128.3, 129.6, 131.1, 133.3, 143.6, 147.0, 150.9, 160.7, 162.7, 163.2 ppm. Anal. Calcd for $C_{18}H_{12}FN_3O_3S$ (369.37): C, 58.53; H, 3.27; N, 11.38. Found: C, 58.57; H, 3.29; N, 11.34%.

4-Hydroxy-2-[(hydroxy(3-nitrophenyl)methylene]-2*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxamide (**8h**). Yellow solid. mp = 375-377 ^{o}C. IR ν/cm^{-1} (KBr): 3118, 2961, 1676, 1574; ^{1}H NMR (500 MHz, DMSO): δ 7.40 (t, *J* 7.5 Hz, 1H, ArH), 7.49 (t, *J* 7.5 Hz, 1H, ArH), 7.63 (d, *J* 7.5 Hz, 1H, ArH), 7.69 (t, *J* 7.5 Hz,1H, AH), 8.03 (d, *J* 8.0 Hz, 1H, ArH), 8.10 (d, *J* 8.5 Hz, 1H, ArH), 8.14 (d, *J* 8.0 Hz, 1H, ArH), 8.57 (t, *J* 9.0 Hz, 1H, ArH), 11.18 (bs, 2H, NH_2) ppm. ^{13}C NMR (125 MHz, DMSO): 79.7, 113.8, 117.2, 120.4, 121.7, 125.2, 125.4, 127.2, 129.8, 130.6, 132.1, 133.1, 136.5, 142.5, 147.7, 148.5, 150.9, 163.2 ppm.

4-Hydroxy-2-[(hydroxy(phenyl)methylene]-2*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxamide (**8i**)**.** White solid. mp = 357-359 ^{o}C. IR ν/cm^{-1} (KBr): 3390, 2967, 1684, 1580; ^{1}H NMR (500 MHz, DMSO): δ 5.60 (bs, 2H, 2OH), 7.26 (t, *J* 7.5 Hz, 1H, ArH), 7.37-7.41 (m, 3H, ArH), 7.49 (t, *J* 7.5 Hz, 1H, ArH), 7.61 (d, *J* 7.5 Hz, 1H, ArH), 7.73 (d, *J* 7.5 Hz, 2H, ArH), 8.03 (d, *J* 8.0 Hz, 1H, ArH), 11.05 (bs, 2H, NH_2) ppm. ^{13}C NMR (125 MHz, DMSO): δ 79.9, 113.6, 116.0, 125.2, 125.2, 126.3, 127.2, 127.5, 128.8, 129.6, 133.3, 134.4, 144.1, 147.0, 151.0, 163.2 ppm. Anal. Calcd for $C_{18}H_{13}N_3O_3S$ (351.38): C, 61.53; H, 3.73; N, 11.96. Found: C, 61.62; H, 3.75; N, 11.94%.

Supplementary Material

The experimental procedures and ^{1}H NMR and ^{13}C NMR spectra associated with this article are available as supplementary data.

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