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A novel ionic liquid mediated synthesis of 4(1*H*)-quinolones, 5*H*-thiazolo [3,2-*a*]pyrimidin-5-one and 4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones

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ABSTRACT

A new, convenient, environmentally benign two-step synthesis of 4(1*H*)-quinolones, 5*H*-thiazolo [3,2-*a*]pyrimidin-5-one and 4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones have been developed by first condensing substituted arylamine/2-aminothiazole/2-aminobenzenethiazole with Meldrum's acid and trimethylorthoformate in 1-butyl-3-methylimidazolium bromide at a moderate temperature to afford 5-{(substituted aryl/4-methylthiazolyl/substituted benzothiazolyl)methylene}-2,2-dimethyl-1,3-dioxane-4,6-dione. The resulting compounds upon cyclization in 1-butyl-3-methyl tetrafluoroborate/triflate at a moderate temperature gave the title compounds in excellent yields.

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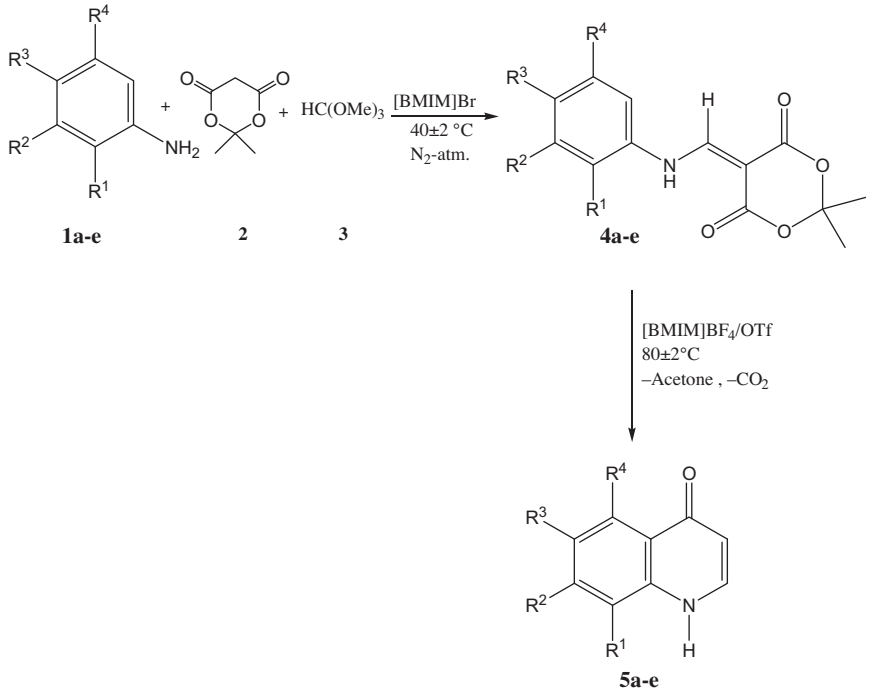
4(1*H*)-Quinolones constitute an important class of heterocyclic compounds because of their important pharmaceutical properties, such as anti-viral,[1,2] anti-platelet,[3] anti-tumor[4] and positive cardiac



Scheme 1. Synthesis of 4(1*H*)-quinolones.

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effects.[5] These compounds have been exploited as precursors for anti-cancer[6] and anti-malarial agents.[7]

The antibiotics, viz. norfloxacin and ciprofloxacin have been found to possess 4(1*H*)-quinolone nuclei, which inhibit topoisomerase II (Gyrase-*a* subunit).[8,9] Thiazolo[3,2-*a*]pyrimidine derivatives have demonstrated a variety of pharmacological activities, for example, anti-inflammatory,[10] as inhibitors of matrix metallo proteinases,[11] etc. Pyrimido[2,1-*b*]benzothiazol-4-one has exhibited potent pharmacological activities,[12] for example, anti-bacterial, anti-fungal, anti-inflammatory, etc. Various methods have been reported for the syntheses of 4(1*H*)-quinolones, viz. addition of (ethoxymethylene) malonates with anilines and subsequent cyclization,[13] addition of maleates to *o*-aminobenzoates followed by cyclization.[14] Conard–Limpach and Niementowski reactions[15] generally focus on the condensation of amines, carboxyl derivatives and subsequent cyclization. These methods, however, suffer serious disadvantages for the synthesis of 2,3-unsubstituted 4(1*H*)-quinolones as the removal of ester groups present at these positions involves several steps. Some elegant syntheses for the unsubstituted 4(1*H*)-quinolones have been reported, viz. addition of anilines to methylacetylene carboxylate and further cyclization,[16] thermolysis of aminomethylene Meldrum's acid derivatives[17] and reaction between polymer bound cyclic malonic ester with anilines.[18] The serious drawbacks of these methods form the necessity to employ harsh cyclization conditions, including temperatures above 200 °C or strong acids such as polyphosphoric acid or Eaton's reagent.[18] Also, the yield of the products were moderate to good. The thiazolo[3,2-*a*]pyrimidine derivatives have been synthesized by reacting 1,2,3,4-tetrahydropyrimidine-2-thione with chloroacetic acid and appropriate benzaldehyde.[10] In this method the cyclization step occurs at 220–40 °C.

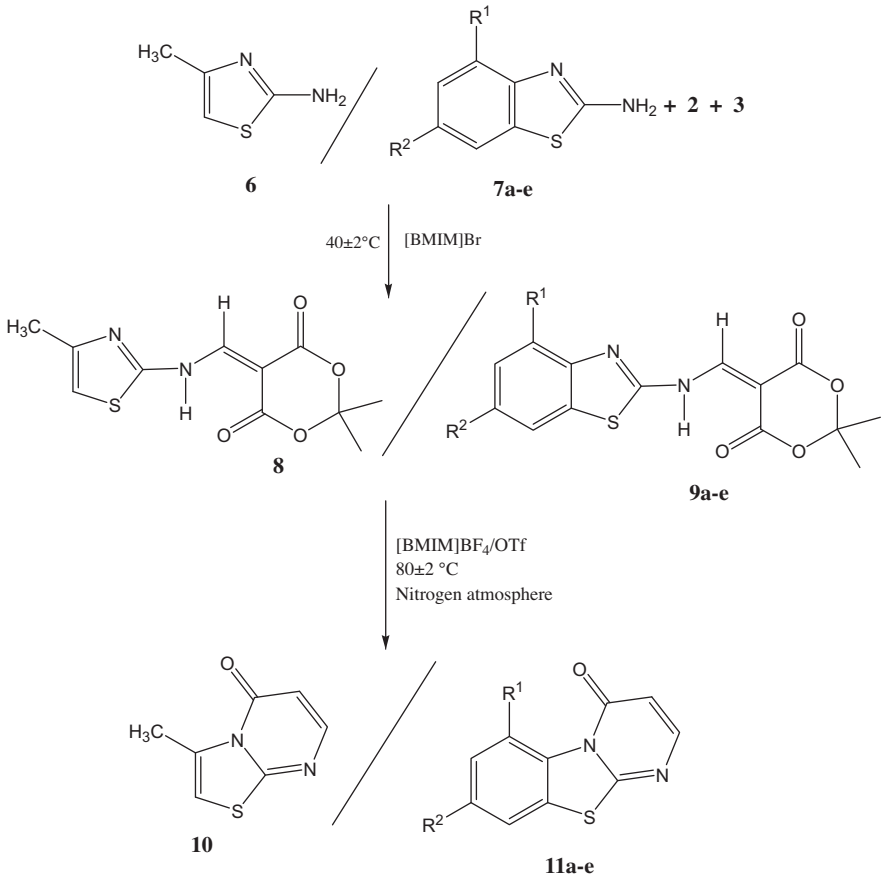
In view of diversified applications of 4(1*H*)-quinolones, thiazolo[3,2-*a*]pyrimidines and pyrimido[2,1-*b*]benzothiazoles and our interest in developing environmentally friendly room temperature ionic liquid mediated synthetic methodologies,[19] we herein report for the first time a clean, smooth and efficient two step synthesis of 4(1*H*)-quinolones, 5*H*-thiazolo[3,2-*a*]pyrimidine, and 4*H*-pyrimido[2,1-*b*]benzothiazoles at a moderate temperature.

In our strategy, we have performed the reaction between arylamine **1a–e** with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione, in which the nucleophilic attack occurs at C-4 and C-6 while the electrophilic attack occurs at C-5 position) **2** and trimethyl orthoformate **3** in the presence of ionic liquid, viz., 1-butyl-3-methyl imidazolium bromide [BMIM]Br. The reaction has been carried out by stirring the contents of the flask under nitrogen atmosphere at 40 ± 2 °C. The products obtained were arylaminomethylene-1, 3-dioxane-4,6-dione **4a–e**. Compounds **4a–e** were then cyclized under nitrogen current at 80 ± 2 °C in ionic liquids, viz. [BMIM]BF_4/OTf to afford 4(1*H*)-quinolones **5a–e** in excellent yields. (Scheme 1, Table 1).

Table 1
Yields of the compounds **4a–e** and **5a–e**

Product	R^1	R^2	R^3	R^4	Yield[a] (%)/Time (min)		
					[BMIM]Br **4**	[BMIM]BF_4 **5**	[BMIM]OTf **5**
a	H	H	H	H	87/120	85/120	90/120
b	Me	H	H	H	91/120	77/120	84/120
c	Me	H	H	Me	94/120	75/120	79/120
d	Cl	H	H	H	72/120	70/120	75/120
e	Cl	H	Cl	H	68/120	66/120	73/120

[a] Isolated yield after purification.



Scheme 2. Synthesis of 5*H*-thiazolo [3,2-*a*]pyrimidin-5-one/4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones.

Table 2
Yields of the compounds **9a–e** and **11a–e**

Product	R^1	R^2	Yield[a] (%)/Time (min)		
			[BMIM]Br **9**	[BMIM]BF_4 **11**	[BMIM]OTf **11**
a	H	H	87/120	90/90	93/90
b	CH_3	H	91/120	85/90	88/90
c	H	CH_3	94/120	83/90	85/90
d	H	OCH_3	72/120	78/90	80/90
e	H	Cl	78/120	75/90	77/90

[a] Isolated yield after purification.

Table 3
Recyclability data for product **4a** and **5a**

Product	Cycle	Yield[a] (%)/Time (min)		
		[BMIM]Br	[BMIM]BF_4	[BMIM]OTf
4a	0	87/120	—	—
	1	83/120	—	—
	2	79/120	—	—
5a	0	—	85/120	90/120
	1	—	79/120	85/120
	2	—	76/120	80/120

[a] Isolated yield after purification.

We have attempted the cyclization of **4a–e** in [BMIM]Br/BF_4/OTf at temperatures 40 ± 2 °C, 80 ± 2 °C with any of these three ILs. However at 80 ± 2 °C when cyclization was attempted with [BMIM]BF_4/OTf, we have obtained the products **5a–e** in excellent yields. This behavior appears to be due to the coordinating strength between the cation, viz. $[BMIM]^+$ and anion $Br^-/BF_4^-/OTf^-$. As BF_4^- and OTf^- are weakly coordinated[20] $Br^- > BF_4^- > OTf^-$, the cyclization occurs smoothly with [BMIM]BF_4/OTf. The better results of cyclization with anion OTf^- in comparison to BF_4^- are in consonance with this preposition.

Next, we have attempted this methodology with 2-aminothiazole **6**/2-aminobenzothiazole **7a–e**, reactant **2** and **3** in the presence of [BMIM]Br under nitrogen atmosphere at 40 ± 2 °C to afford thiazolo-2-amino/benzothiazolyl-2-aminomethylene-1,3-dioxane-4,6-dione **8**/**9a–e** in excellent yields. These compounds upon subsequent cyclization, as described above, afford 5*H*-thiazolo[3,2-*a*]pyrimidine-5-one **10** in an 88% yield/4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones **11a–e** in good yields (Scheme 2, Table 2).

A general method for the synthesis of these compounds is presented.[21] All these compounds **4a–e**, **5a–e**, **8**, **9a–e**, and **11a–e** were characterized by IR, ^1H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis.[22]

We have studied the recyclability of the regenerated ionic liquids for the products **4a** and **5a**. The yields of the products in two cycles are presented in Table 3.

From the data presented in Table 3, it is clear that the yields of the products **4a** and **5a** decrease in various cycles, yet the regenerated ionic liquid can be reused with reasonably good success. Thus, this procedure is advantageous over the reported conventional methods.

In conclusion, we have developed an environmentally benign efficient methodology for the clean synthesis of 4(1*H*)-quinolones, 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones and 4*H*-pyrimido[3,2-*a*]benzothiazol-4-ones.

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References and notes

1. Llinas-Brunet, M.; Bailey, M. D.; Ghiro, E.; Gorys, V.; Halmos, T.; Poirier, M.; Rancourt, J.; Goureare, N. *J. Med. Chem.* **2004**, *47*, 6584.
2. Frutos, R. P.; Haddad, N.; Houpis, I. N.; Johnson, M.; Smith-Keenan, L. L.; Fuchs, V.; Yee, N. K.; Farina, V.; Faucher, A.-M.; Brochu, C.; Hache, B.; Duceepe, J.-S.; Beaulieu, P. *Synthesis* **2006**, 256. and the references cited therein.
3. Huang, L.-J.; Hsich, M.-C.; Teng, C.-M.; Lee, K.-H.; Kno, S.-C. *Bioorg. Med. Chem.* **1998**, *6*, 1657.
4. Gasparotto, V.; Castagliuolo, I.; Chiarelotto, G.; Pezzi, V.; Montanaro, D.; Brun, P.; Palu, G.; Viola, G.; Ferlin, M. G. *J. Med. Chem.* **2006**, *49*, 1910. and the references cited therein.
5. Osawa, T.; Ohta, H.; Akmoto, K.; Harada, K.; Soga, H.; Jinno, Y. EP 0343574, 1994.
6. Ruchelman, A. L.; Singh, S. K.; Ray, A.; Wu, X. H.; Yang, J.-M.; Li, T.-K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 2061.
7. (a) Theeraladanon, C.; Arisawa, M.; Nishidi, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017; (b) Nishida, A.; Sorimachi, H.; Iwaida, M.; Matsumizu, M.; Kawate, T.; Na Kagawa, M. *Synlett* **1998**, 389.
8. Wentland, M. P.; Perni, R. B.; Dorff, P. H.; Brundage, R. P.; Castaldi, M. J.; Bailey, T. R.; Carabatean, P. M.; Baeon, E. R.; Young, D. C.; Woods, M. G.; Rosi, D.; Drozd, M. L.; Kullnig, R. K.; Dutko, F. J. *J. Med. Chem.* **1993**, *36*, 1580.
9. Schmidt, R. D. *Taschenatlas der Biotechnologie and Gentechnik*; Wiley-VCH: Weinheim, 2002.
10. Tazkoparan, B.; Ertan, M.; Kelichen, P.; Demirdamar, R. *IL Farmaco* **1999**, *54*, 588. and the references cited therein.
11. Uwe, K.; Jochem, H. German patent Wo 2003089441A1 Oct 30, 2003.
12. Singh, H. P.; Sharma, C. S.; Gautam, C. P. *Middle East J. Scientific Res.* **2009**, *4*, 203.
13. Price, C. C.; Roberts, R. M. *J. Am. Chem. Soc.* **1946**, *68*, 1204.
14. Biere, H.; Seelen, W. *Liebigs Ann. Chem.* **1976**, 1972.
15. (a) Li, J. J. *Conard–Limpach Reactions in Name Reactions: A Collection of Detailed Reaction Mechanisms*, 2nd ed.; Springer: Berlin, 2003; (b) Zewge, D.; Chem, C.-Y.; Deer, C.; Domer, P. G.; Hughes, D. L. *J. Org. Chem.* **2007**, *72*, 4276. and the references cited therein.
16. Heindel, N. D.; Kennewell, P. D.; Fish, V. B. *J. Heterocyl. Chem.* **1969**, *6*, 77.
17. Rotzoll, S.; Reinke, H.; Fischer, C.; Langer, P. *Synthesis* **2009**, 69.
18. Huang, X.; Lia, Z. *J. Org. Chem.* **2002**, *67*, 6731. and the references cited therein.
19. Yadav, A. K.; Kumar, M.; Yadav, T.; Jain, R. *Tetrahedron Lett.* **2009**, *50*, 5031.
20. Bini, R.; Bortolini, O.; Chiappe, C.; Pieraccini, D.; Siciliano, T. *J. Phys. Chem. B.* **2007**, *111*, 598–604.
21. (a) Typical experimental procedure for the synthesis of **4a–e**: A mixture of appropriate aniline **1** (5 mmol), Meldrum's acid **2** (6 mmol), trimethyl orthoformate **3** (15 mmol) and [BMIM]Br (3 mL) is taken in a round bottomed flask with the provision to perform the reaction under nitrogen atmosphere. The contents of the flask were stirred magnetically at 40 ± 2 °C. The progress of the reaction was monitored on a TLC plate (Merck Silica gel $60F_{254}$) in pet.ether–ethyl acetate (8:2) and the visualization was accomplished in an iodine chamber/UV-light. After the completion of the reaction, water (10 mL) was added to it. The organic compound was precipitated, which was filtered on a Buckner funnel applying vacuum. The product, so obtained, was purified by crystallization with methanol/column chromatography (Merck Silica gel 60–120 mesh) and elution of the product was carried out by pet.ether–ethylacetate (8:2).
(b) Typical experimental procedure for the cyclization of **4a–e**: Compound **4a–e** (5 mmol) and [BMIM]BF_4/OTf (3 mL) were taken in a round bottomed flask having provision to carry out the reaction under nitrogen atmosphere. The contents of the flask were stirred magnetically at 80 ± 2 °C. The progress of the reaction was monitored on a TLC plate in pet.ether–ethyl acetate (8:2). After completion of the reaction, the product was extracted with ethyl acetate (3 × 10 mL). The solvent was recovered under reduced pressure (5 mm of Hg). The pasty mass thus obtained was extracted with diethyl ether (3 × 10 mL), dried over anhydrous sodium sulphate and ether was distilled. The product so obtained was purified by crystallization with ethanol/column chromatography (Merck Silica gel 60–120 mesh) and eluting TLC product with pet.ether–ethylacetate (8:2).
22. Details of analytical data of compounds **4a,b**, **5a,b,d,e**, **8**, **11a,b**; Compound **4a**. 5{(Phenylamino)methylene}-2,2-dimethyl, 1,3-dioxane-4,6-dione: Yellow solid, mp 135–136 °C, Characteristic IR (KBr pellet, cm^{-1}) 3169, 3067, 1728, 1675, 1630, 1608, 1440, 1270, 1028. ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 6H, 2 × CH_3), 7.18 (d, ^3J = 7.8 Hz, 2H, Ar), 7.15 (dd, ^3J = 7.6, 2H, Ar), 7.12 (dd, 1H, Ar), 8.68 (d, ^3J = 13.9 Hz, 1H, =CH), 11.43 (br d, ^3J = 13.8 Hz, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.1, 87.2, 105.4, 116.9, 125.2, 127.4, 131.5, 136.2, 137.6, 152.6, 163.6, 165.7. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.26, N, 5.66%. Found: C, 63.12; H, 5.18; N, 5.60%.
Compound **4b**. 5{[(2-Methylphenyl)amino]methylene}, 2,2-dimethyl-1,3-dioxane-4,6-dione: yellow solid, mp 142–143 °C, Characteristic IR (KBr pellet, cm^{-1}) 3165, 3058, 2985, 1722, 1672, 1640, 1609, 1440, 1270, 1025. ^1H NMR (300 MHz, $CDCl_3$) δ 1.76 (s, 6H, 2 × CH_3), 3.33 (d, 3H, CH_3), 7.02 (d, ^3J = 7.6 Hz, 1H, Ar), 7.15 (dd, 2H, Ar), 7.19 (d, ^3J = 7.6 Hz, 1H, Ar), 8.65 (d, ^3J = 13.9 Hz, 1H, –CH), 11.40 (d, ^3J = 13.9 Hz, 1H, NH). ^{13}CNMR (75 MHz, $CDCl_3$) δ 21.1, 27.1, 87.1, 105.3, 117.4, 124.8, 127.5, 131.3, 136.7, 137.5, 152.7, 163.6, 165.7. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.74; N, 5.36%. Found: C, 64.28; H, 5.79; N, 5.44%.
Compound **5a**. Quinolin-4(1*H*)-one: brownish solid, mp 190–191 °C, Characteristic IR (KBr pellet, cm^{-1}) 3240, 3080, 3150, 1640, 824. ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (d, ^2J = 7.5 Hz, 1H, CH), 7.37 (dd, ^3J = 7.5 Hz, 2H, Ar),

7.78 (d, ^3J = 7.5 Hz, 1H, CH), 8.27 (d, ^3J = 7.5 Hz, 2H, Ar), 10.97 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.1, 118.4, 121.2, 126.1, 128.4, 138.2, 138.7, 143.7, 171.8. Anal. Calcd for C_9H_7NO: C, 74.48; H, 4.82; N, 9.65%. Found: C, 74.43; H, 4.80; N, 9.75%.

Compound **5b**. 8-Methylquinolin-4(1*H*)-one: brownish solid, mp 196–197 °C, Characteristic IR (KBr pellet, cm^{-1}) 3168, 3110, 1610, 1560, 1519, 805. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H, CH_3), 6.21 (d, ^3J = 7.3 Hz, 1H, CH), 6.92 (d, ^3J = 7.4 Hz, 2H, Ar), 7.23 (dd, ^3J = 7.4 Hz, 1H, Ar), 7.73 (d, ^3J = 7.3 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2, 111.6, 124.8, 125.4, 127.1, 133.2, 138.7, 139.4, 141.4, 182.6. Anal. Calcd for $C_{10}H_9NO$: C, 75.47; H, 5.66; N, 8.81%. Found: C, 75.58; H, 5.72; N, 8.90%.

Compound **5d**. 8-Chloroquinolin-4(1H)-one: Brownish solid, mp 256–257 °C, Characteristic IR (KBr pellet, cm^{-1}): 3160, 3056, 2924, 1562, 1336, 1210, 1076. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (d, ^3J = 7.5 Hz, 1H, CH), 7.87 (d, ^3J = 7.5 Hz, 1H, CH), 7.96 (d, ^4J = 2.4 Hz, 2H, Ar), 7.01 (d, ^4J = 2.4 Hz, 1H, Ar), 11.52 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.9, 121.8, 122.7, 126.5, 126.9, 130.1, 134.2, 138.7, 176.8. Anal. Calcd for C_9H_6NOCl: C, 60.68; H, 3.36; N, 7.79%. Found: C, 60.72; H, 3.28; N, 7.70%.

Compound **5e**. 6,8-Dichloroquinolin-4(1*H*)-one: brownish solid, mp 287–288 °C, Characteristic IR (KBr pellet, cm^{-1}): 3140, 3082, 2926, 1620, 1560, 1511, 1337, 1215, 1080. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (d, ^3J = 7.5 Hz, 1H, CH), 7.90 (d, ^3J = 7.5 Hz, 1H, CH), 8.01 (d, ^4J = 2.4 Hz, 1H, Ar), 7.05 (d, ^4J = 2.4 Hz, 1H, Ar), 11.55 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.7, 122.5, 126.3, 126.9, 130.7, 134.9, 135.1,139.4, 177.2. MS (EI, 70 eV): m/z (%) = 213 $[M]^+$, (100), 185(55), 150(21), 123(14), 93(9) Anal. Calcd for $C_9H_5Cl_2NO$: C, 50.50; H, 2.35; N, 6.54%. Found: C, 50.40; H, 2.25; N, 6.63%.

Compound **8**. 3-Methyl 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one: Yellow solid, mp 124–125 °C. Characteristic IR (KBr pellet, cm^{-1}): 3114, 1665, 1618, 1590, 1482, 1419, 1285, 1235, 1148, 972, 815, 764. ^{1}H NMR (300 MHz, $CDCl_2$) δ 2.83(d, 3H, J = 1.35 Hz), 6.22 (d, 1H, J 6.55 Hz), 6.45 (t, 1H, J = 1.35 Hz), 7.87 (d, 1H, J = 6.55 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.66, 105.83, 107.45, 135.92, 152.7, 161.9, 166.1. MS (EI, 70 eV): m/z (%) = 166 (M^+, 100), 138 (74), 93 (19), 71 (28), 72 (19), 67 (16), 52 (11), 45 (33). Anal. Calcd. for $C_7H_6N_2OS$: C, 50.58; H, 3.63; N, 16.85%. Found: 50.50, H, 3.52; N, 16.76%.

Compound **11a**. 4*H*-Pyrimido[2,1-*b*]benzothiazol-4-one: Yellow solid, mp 165–166 °C. Characteristic IR (KBr pellet, cm^{-1}): 1681, 1578, 1503, 1258, 996, 826, 762. ^{1}H NMR (300 MHz, $CDCl_3$), δ 6.43 (d, 1H, J = 6.52 Hz), 7.52–7.59 (m, 2H), 7.72–7.74 (m, 1H), 7.98 (d, 1H, J = 6.52 Hz), 9.12–9.15 (m, 1H). MS m/z (%) = 202 (M^+, 100), 174 (98), 146 (15), 134 (13), 120 (11), 108 (9), 90 (13), 69 (16). Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.39; 2.98; N, 13.85%. Found 59.45; H, 2.91; N, 13.92%.

Compound **11b**. 6-Methyl-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one: Yellow solid, mp 105–106°. Characteristic IR (KBr pellet, cm^{-1}): 2932, 1695, 1578, 1498, 1476, 1386, 1278, 1245, 758. ^{1}H NMR (300 MHz, $CDCl_3$), δ 2.64 (s, 3H), 6.32 (d, J = 6.52 Hz), 7.32–7.42 (m, 2H), 7.46–7.48 (m, 1H), 7.87 (d, 1H, J = 6.52). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.26, 109.28, 119.24, 125.38, 126.93, 130.94, 132.01, 134.38, 151.25, 160.83, 163.15. Anal. Calcd. for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.95%. Found: C, 61.36; H, 3.93; N, 12.87%.