Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 8157–8163

Synthesis of fused pyrimidines from amines and cyclic β-formylesters

Raghunath B. Toche,* Bhausaheb K. Ghotekar, Muddassar A. Kazi, Dhananjay B. Kendre and Madhukar N. Jachak

Organic Chemistry Research Centre, Department of Chemistry, K.T.H.M. College, Gangapur Road, Nashik 422002, Maharashtra, India

Received 5 March 2007; revised 15 May 2007; accepted 31 May 2007
Available online 6 June 2007

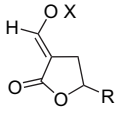
Abstract—A highly efficient method was successfully developed for the synthesis of fused pyrimidines via aminoheterocyclic dihydrofuranone intermediates obtained from 2-aminoheterocycles and cyclic β-formylesters by three different methods.

1. Introduction

Benzo- and hetero-fused pyrimidines are known to exhibit promising antiviral,[1] antibacterial,[2] anti-AIDS,[3] and antinociceptive[4] activities. Fused pyrimidines are selective inhibitors for multidrug resistance (MDR).[5] Folate metabolism has long been recognized as an attractive target for cancer chemotherapy because of the indispensable role of fused pyrimidine antifolates as antitumor agents.[6] Atherothrombotic coronary artery disease, giving rise to a number of cardio circulatory disorders such as myocardial infarction (MI), unstable angina (UA), or acute stroke associated with deep vein thrombosis (DVT), is one of the most important causes of death worldwide. The relevance of fused pyrimidines as antiplatelet and antithrombotic drugs[7] has been firmly established by clinical trials. Thus, further exploration of pyrimidine chemistry appears to be worthwhile.

Our ongoing interest in pyrimidine synthesis[8–11] and modifications to the Pechmann[12] reaction prompted us to develop a facile synthetic method for fused pyrimidines. Fused pyrimidines having 2-methyl and 3-chloro/hydroxyethyl-side chain are found to be biologically important compounds,[13–17] and were obtained from α-acetyl-γ-butyrolactone and 2-aminoheterocycles. However, mixture of products were observed in these cases[17] and the intermediates were not isolated.

In the present study, we report the synthesis of fused pyrimidines with 3-chloroethyl/chloropropyl side chain and the absence of a 2-methyl group. For this purpose, we have condensed 2-aminoheterocyclics with cyclic β-formylesters, i.e., sodium salt of α-formyl-γ-butyrolactone **1a** or α-ethoxyethylidene-γ-butyrolactone **2a** to obtain pyrimidines with a 3-chloroethyl side chain and the pyrimidines having a 3-chloropropyl side chain (Fig. 1).



1a-b, 2a-b

1a, R = H; **1b**, R = CH_3; X = Na+

2a, R = H; **2b**, R = CH_3; X = C_2H_5

Figure 1.

2. Results and discussion

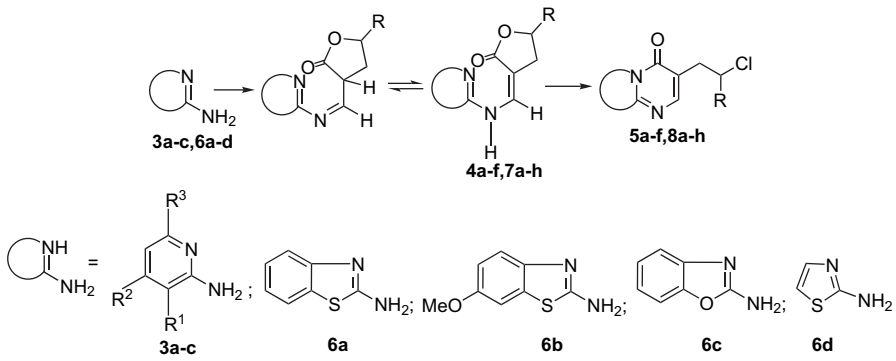
Synthesis of new pyrido[1,2-*a*]pyrimidin-4-(1*H*)-ones **5a–f** and benzohetero[3,2-*a*]pyrimidin-4(1*H*)-ones **8a–h** was obtained through aminoheterocyclic dihydrofuranones **4a–f**, **7a–h** as key intermediates (Scheme 1).

In the first method (Method A), the sodium salt of α-formyl-γ-butyrolactone **1a** or sodium salt α-formyl-γ-valerolactone **1b** was condensed with 2-aminopyridines **3a–c** in toluene and catalytic *p*-toluenesulfonic acid. The electrophilic formyl group is generated by protonation of **1a**, which reacts with $-NH_2$ to furnish aminoheterocyclic-4,5-dihydrofuran-2(3*H*)-ones **4a–f** in 65–70% yield.

In the second method (Method B), the condensation of **1a** or **1b** with 2-aminopyridines **3a–c** was carried out using ammonium acetate at 120 °C for 1 h to furnish **4a–f** in 70–75% yield (Scheme 1).

Keywords: Aminoheterocyclic dihydrofuranone; α-Formyl-γ-butyrolactone; Fused pyrimidines; Ammonium acetate.
* Corresponding author. Tel.: +91 253 2582876; fax: +91 253 2577341; e-mail: raghunath_toche@rediffmail.com

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.05.123



Scheme 1. Method A: toluene/*p*-TsOH; Method B: NH_4OAc/120 °C; Method C: CH_2Cl_2/rt.

The NH_4^+ reacts with the sodium salt of lactone **1a** or **1b** to furnish the α-formyl lactones in situ and the evolved ammonia can bring out condensation between $-NH_2$ and the formyl group of the lactone. This method gives higher yield (70–72%) and required a shorter time (1 h) than Method A. The ammonium acetate is easily available and non-hazardous and the aqueous work-up of the reaction made product isolation simple. Therefore, it may be useful for large-scale synthesis of enamines. In the third method (Method C), the intermediate products **4a–f** were obtained by stirring 2-aminopyridines **3a–c** with α-ethoxyethylene-γ-butyrolactone **2a** or α-ethoxyethylene-γ-valerolactone **2b** in dichloromethane at room temperature. Method C gives higher yields of **4a–f** (70–75%) at room temperature and the solvent used can be recycled after isolation of the products. But it is an inconvenient method as the preparation of **2a** or **2b** required stoichiometric amounts of ethylchloroformate, which is a lachrymator and cannot be used commercially. The results are tabulated in Table 1.

The new compounds **4a–f** were characterized by IR, ^1H NMR, and ^{13}C NMR spectroscopies and elemental analysis. In the IR spectrum of **4a**, the C=O resonance was at 1718 cm^{-1} due to intermolecular hydrogen bonding between –NH and –CO.

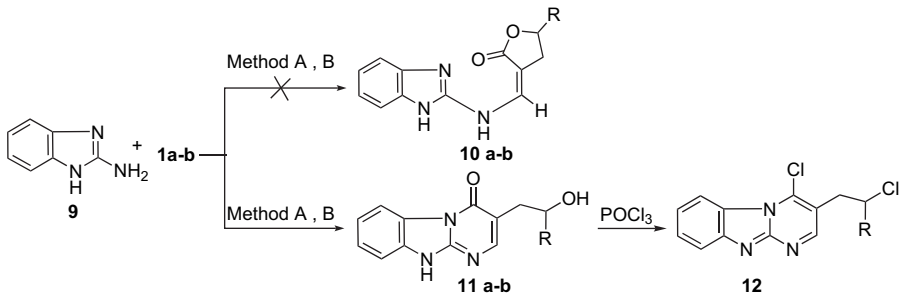
The key intermediates, **4a–f**, were cyclized using phosphorous oxychloride to pyrido[1,2-*a*]pyrimidin-4(1*H*)-one **5a–f** in 60–70% yield. The reactions were smooth and completed in a short time (Scheme 1). The results are tabulated in Table 1. The structures of **5a–f** were elucidated by IR and NMR spectroscopies, mass spectrometry and elemental analysis.

Our interest in this area was sparked by the unexpected results obtained with 2-aminopyridines **3a–c** by Method B and prompted us to generalize the use of ammonium acetate. We have selected 2-aminoheterocycles containing sulfur, oxygen, and nitrogen as heteroatoms. Thus, 2-aminobenzothiazole **6a**, 2-amino-6-methoxybenzothiazole **6b**, 2-aminobenzoxazole **6c**, and 2-aminothiazole **6d** were reacted with lactones **1a**,**b**, **2a**,**b** by Methods A, B, and C as discussed earlier. With heterocycles **6a–h**, it was observed that Method A (*p*-TsOH/toluene) gave higher yield (66–73%) than Method B (48–65%). Hence, Method A is the most useful for the synthesis of aminoheterocyclic dihydrofuranones **7a–h**. The reduction in yields were due to the formation of a salt between 2-aminoheterocycles **6a–h** and ammonium acetate used in excess. The salt formed with *p*-TsOH did not affect the yields of **7a–h** as it was used in small amounts. This type of salt was not observed in case of **3a–c** with ammonium acetate.

The key intermediates, **7a–h**, were cyclized using phosphorous oxychloride to fused pyrimidines **8a–h**. The reactions proceeded smoothly and gave facile ring closure reaction to furnish fused pyrimidines **8a–h** in 60–70% yields as single products (Scheme 1). The results are

Table 1. Comparative % yields of aminoheterocyclic dihydrofuranone **4a–f**, **7a–h** by Method A, B, and C and % yield of fused pyrimidines **5a–f**, **8a–h**

Amine	R	R^1	R^2	R^3	Aminoheterocyclic dihydrofuranone	Method A, PTSA/Toluene	Method B, NH_4OAc	Method C, rt, CH_2Cl_2	Fused pyrimidine	% Yield
3a	H	H	H	H	**4a**	65	70	71	**5a**	78
3b	H	H	CH_3	H	**4b**	68	71	71	**5b**	78
3c	H	H	H	CH_3	**4c**	70	72	72	**5c**	65
3a	CH_3	H	H	H	**4d**	69	70	68	**5d**	65
3b	CH_3	H	CH_3	H	**4e**	68	69	69	**5e**	64
3c	CH_3	H	H	CH_3	**4f**	65	69	70	**5f**	63
6a	H	—	—	—	**7a**	70	63	70	**8a**	60
6a	CH_3	—	—	—	**7b**	70	62	74	**8b**	66
6b	H	—	—	—	**7c**	70	66	70	**8c**	70
6b	CH_3	—	—	—	**7d**	70	64	71	**8d**	60
6c	H	—	—	—	**7e**	61	48	55	**8e**	61
6c	CH_3	—	—	—	**7f**	62	48	52	**8f**	60
6d	H	—	—	—	**7g**	65	49	49	**8g**	65
6d	CH_3	—	—	—	**7h**	60	48	47	**8h**	62



Scheme 2. Method A: toluene/PTSA; Method B: NH_4OAc; Method C: CH_2Cl_2/rt.

tabulated in Table 1. IR and NMR spectroscopies and elemental analysis were used to characterize the compounds **8a**–**h**.

We have made an interesting observation in the condensation of 2-aminobenzoimidazole **9** with the sodium salt of lactone **1a** or **1b**. Either Method A (*p*-TsOH/toluene) or Method B (NH_4OAc) did not afford aminoheterocyclic dihydrofuranones **10a**,**b**, but gave cyclized products 3-(2-hydroxyethyl)-1,3-benzimidazolo[3,2-*a*]pyrimidin-4(1*H*)-one **11a** and 3-(2-hydroxypropyl)-1,3-benzimidazolo[3,2-*a*]pyrimidin-4(1*H*)-one **11b** in 70% yield. The intermediates **10a**,**b** are presumably unstable due to the higher basicity of 2-aminobenzoimidazole **9**. Compound **11a** on refluxing in phosphorous oxychloride yielded the corresponding chloroderivatives **12**. All these compounds were characterized by ^{1}H NMR and IR spectroscopies and elemental analysis (Scheme 2). The neat reaction of lactone **1a**,**b** or **2a**,**b** with 2-aminoheterocycles **3a**–**c** or **6a**–**h** or with **9** yielded mixture of several products.

3. Conclusion

The methodology is useful to prepare fused pyrimidines with a 3-chloroethyl or a 3-chloropropyl side chain in high yield. The sodium salt of cyclic β-formylester can directly react with 2-aminoheterocycles in ammonium acetate or in *p*-TsOH/toluene to yield enamine intermediates. The limitations of the methods with 2-amino-*N*-heterocycles having heteroatom α to amine group were also discussed.

4. Experimental

4.1. General

Melting points were determined on a Gallenkamp melting point apparatus in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer (300 MHz). Chemical shifts are reported in parts per million from internal tetramethylsilane standard and are given in δ units. The solvent for NMR spectra were taken in deuteriochloroform, DMSO-d_6. Infrared spectra were taken on a Shimadzu FTIR-408 in potassium bromide pellets unless otherwise stated. The mass spectrum was recorded on QP-2010s. Elemental analyses were performed on a Hosli CH-Analyzer and are within ±0.4 of the theoretical percentages. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection. Column chromatography was carried out on silica gel (SD Fine Chemicals, 60–80 mesh). Starting materials were obtained from commercial suppliers and used without further purification. Common reagent-grade chemicals were either commercially available and used without further purification or prepared by standard literature procedures.

4.2. Synthesis of 4,5-dihydrofuranone intermediates

4.2.1. 3-[(2-Pyridylamino)-methylidene]-4,5-dihydrofuran-2-(3*H*)-one (4a–f), (7a–h) (Method A). A mixture of 2-aminopyridines **3a**–**c**, **6a**–**d** (0.01 mol) and sodium salt of α-formyl-γ-butyrolactone **1a** or sodium salt of α-formyl-γ-valerolactone **1b** (0.01 mol) in toluene (20 mL) containing catalytic amount (0.020 g) of *p*-toluenesulfonic acid was refluxed for 8 h. The solvent was evaporated in vacuum and the remaining solid was stirred with water (30 mL), filtered, dried, and recrystallized.

4.2.2. 3-[(2-Pyridylamino)-methylidene]-4,5-dihydrofuran-2-(3*H*)-one (4a–f), (7a–h) (Method B). A mixture of 2-aminopyridines **3a**–**c**, **6a**–**d** (0.01 mol) and sodium salt of α-formyl-γ-butyrolactone **1a** or sodium salt of α-formyl-γ-valerolactone **1b** (0.01 mol) in ammonium acetate (0.05 mol) was heated under Vigreux column at 120 °C for 1 h. Cold water (30 mL) was added to viscous reaction mixture and was stirred for 30 min to remove the excess of ammonium acetate. The precipitated solid product was filtered, washed with water, dried, and recrystallized.

4.2.3. 3-[(2-Pyridylamino)-methylidene]-4,5-dihydrofuran-2-(3*H*)-one (4a–f), (7a–h) (Method C). A mixture of 2-aminopyridines **3a**–**c**, **6a**–**d** (0.01 mol) and α-ethoxyethylidene-γ-butyrolactone **2a** or α-ethoxyethylidene-γ-valerolactone **2b** (0.01 mol) in dichloromethane (30 mL) was stirred for 1.5 h. The solvent was evaporated in vacuum. The solid product was isolated and recrystallized.

4.3. Synthesis of fused pyrido[1,2-*a*]pyrimidin-4-(1*H*)-one

4.3.1. 3-(2-Chloroethyl)/-3-(2-chloropropyl)pyrido[1,2-*a*]pyrimidin-4-(1*H*)-one (5a–f). A mixture of **4a**–**f** or (0.01 mol) and phosphorous oxychloride (30 mL) was refluxed for 2 h. The excess of phosphorous oxychloride was evaporated using rotary evaporator under reduced pressure. The ice-cold water (100 mL) was added to the reaction mixture, neutralized with solid sodium carbonate (6 g), and further stirred for 24 h. The precipitated product was filtered, washed with water, dried, and recrystallized.

4.4. General procedure for the synthesis of 8a–h

A mixture of **7a–h** (0.01 mol), phosphorous oxychloride (30 mL), and toluene (10 mL) was refluxed for 2 h. The excess of phosphorous oxychloride and toluene was evaporated using rotary evaporator under reduced pressure. The ice-cold water (100 mL) was added to the reaction mixture, neutralized with solid sodium carbonate (6 g), and further stirred for 24 h. The precipitated product was filtered, washed with water, dried, and recrystallized.

4.5. Synthesis of benzimidazolo[3,2-*a*]pyrimidin-4(1*H*)-one

4.5.1. 3-(2-Hydroxyethyl)-1,3-benzimidazolo[3,2-*a*]pyrimidin-4(1*H*)-one (11a,b) (Method A). A mixture of 2-aminobenzoimidazole **9** (0.01 mol) and sodium salt of α-formyl-γ-butyrolactone **1a** or sodium salt of α-formyl-γ-valerolactone **1b** (0.01 mol) was reacted and work-up as described in Section 4.2.1.

4.5.2. 3-(2-Chloroethyl)-pyrido[1,2-*a*]pyrimidin-4-(1*H*)-one (12a). A mixture of **11a** (0.01 mol) and phosphorous oxychloride (30 mL) was refluxed for 3 h. The excess of phosphorous oxychloride was evaporated using rotary evaporator under reduced pressure. The ice-cold water (100 mL) was added to the reaction mixture, neutralized with solid sodium carbonate (6 g), and further stirred for 24 h. The precipitated product was filtered, washed with water, dried, and recrystallized.

4.5.3. 3-[2-(2-Pyridylamino)-methylidene]-4,5-dihydrofuran-2-(3*H*)-one (4a). Recrystallized from acetonitrile as colorless needles: mp 216–216 °C; IR (KBr): 3290, 1718, 1660, 1636, 1605, 1576, 1502, 1472, 1414 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.95 (dt, *J*=7.0, 1.6 Hz, 2H, $–CH_2$), 4.35 (t, *J*=7.0 Hz, 2H, $–CH_2O$), 6.92 (m, 2H, C_4–H, C_5–H), 7.73 (d, *J*=7.0 Hz, 1H, C_3–H), 8.24 (d, *J*=7.0 Hz, 1H, C_6–H), 8.32 (dt, *J*=12.0, 1.6 Hz, 1H, =C–H), 9.76 (d, *J*=12.0 Hz, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 26.2, 35.6, 93.6, 113.9, 117.5, 137.6, 147.8, 152.4, 153.5, 173.7. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.19; H, 5.38; N, 14.73.

4.5.4. 3-[2-(4-Methyl-2-pyridylamino)methylidene]-4,5-dihydrofuran-2(3*H*)-one (4b). Recrystallized from *N*,*N*-dimethylformamide/ethanol (7:3) as colorless needles: mp 233–234 °C; IR (KBr): 3300, 1720, 1660, 1630, 1610, 1570, 1520, 1480, 1440 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.34 (s, 3H, C_3–CH_3), 2.90 (dt, *J*=7.0, 1.6 Hz, 2H, $–CH_2$), 4.36 (t, *J*=7.0 Hz, 2H, $–CH_2O$), 6.82 (d, *J*=7.0 Hz, 1H, C_5–H), 7.73 (s, 1H, C_3–H), 8.24 (d, *J*=7.0 Hz, 1H, C_6–H), 8.12 (dt, *J*=12.0, 1.6 Hz, 1H, =C–H), 9.76 (d, *J*=12.0 Hz, 1H, NH). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.54; H, 6.03; N, 13.84.

4.5.5. 3-[2-(6-Methyl-2-pyridylamino)-methylidene]-4,5-dihydrofuran-2(3*H*)-one (4c). Recrystallized from *N*,*N*-dimethylformamide/ethanol (8:2) as colorless needles: mp 207–208 °C; IR (KBr): 3380, 1720, 1660, 1630, 1600, 1580, 1480, 1440 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H, C_6–CH_3), 2.90 (dt, *J*=7.0, 1.6 Hz, 2H, $–CH_2$), 4.36 (t, *J*=7.0 Hz, 2H, OCH_2), 6.62 (d, *J*=7.0 Hz, 1H, C_3–H), 6.84 (d, *J*=7.0 Hz, 1H, C_5–H), 7.45 (t, *J*=7.0 Hz, 1H, C_4–H), 8.12 (dt, *J*=12, 1.6 Hz, 1H, =C–H), 9.62 (d, *J*=12.0 Hz, 1H, NH). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.70; H, 5.91; N, 13.65.

4.5.6. 3-[2-(2-Pyridylamino)-methylidene]-5-methyl-4,5-dihydrofuran-2(3*H*)-one (4d). Recrystallized from methanol as colorless needles: mp 175 °C; IR (KBr): 3300, 1720, 1660, 1630, 1600, 1580, 1480, 1420 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.36 (d, *J*=8.0 Hz, 3H, $CHCH_3$), 2.36, 2.96 (qd, dq, *J*=2.1, 5.9, 7.5 Hz, 2H, $–CH_2$), 4.67 (m, 1H, $CHCH_3$), 6.92 (m, 2H, C_4–H, C_5–H), 7.73 (d, *J*=7.0 Hz, 1H, C_3–H), 7.95 (d, *J*=12.0 Hz, 1H, NH exchangeable with D_2O), 8.24 (d, *J*=7.0 Hz, 1H, C_6–H), 8.32 (dt, *J*=12.0, 1.7 Hz, 1H, =C–H). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.66; H, 5.91; N, 13.67.

4.5.7. 3-[2-(4-Methyl-2-pyridylamino)-methylidene]-5-methyl-4,5-dihydrofuran-2(3*H*)-one (4e). Recrystallized from acetonitrile as colorless needles: mp 190–191 °C; IR (KBr): 3230, 2910, 1730, 1670, 1610, 1600, 1570, 1480 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.41 (d, *J*=8 Hz, 3H, CH–CH_3), 2.35 (s, 3H, C_4–CH_3), 2.45, 3.05 (qd, dq, *J*=2.1, 5.9, 7.5 Hz, 2H, $–CH_2$), 4.67 (m, 1H, $CHCH_3$), 6.82 (d, *J*=7.0 Hz, 1H, C_5–H), 6.91 (s, 1H, C_3–H), 7.88 (d, *J*=12.0 Hz, 1H, NH exchangeable with D_2O), 8.22 (dt, *J*=12.0, 1.7 Hz, 1H, =C–H), 8.24 (d, *J*=7.0 Hz, 1H, C_6–H). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.58; H, 6.70; N, 12.65.

4.5.8. 3-[2-(6-Methyl-2-pyridylamino)-methylidene]-5-methyl-4,5-dihydrofuran-2(3*H*)-one (4f). Recrystallized from methanol as colorless needles: mp 156–157 °C; IR (KBr): 3230, 3120, 2960, 1720, 1680, 1640, 1600, 1580, 1520, 1450 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.36 (d, *J*=8.0 Hz, 3H, C_6–CH_3), 1.38 (d, *J*=8.0 Hz, 3H, CH–CH_3), 2.45, 3.05 (qd, dq, *J*=2.1, 5.9, 7.5 Hz, 2H $–CH_2$), 4.75 (m, 1H, C_5–H), 6.65 (d, *J*=7.0 Hz, 1H, C_3–H), 6.78 (d, *J*=7.0 Hz, 1H, C_5–H), 7.45 (t, *J*=7.0 Hz, 1H, C_4–H), 7.99 (d, *J*=12.0 Hz, 1H, NH exchangeable with D_2O), 8.15 (dt, *J*=12.0, 1.7 Hz, 1H, =C–H). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.12; H, 6.68; N, 12.86.

4.5.9. 3-(2-Chloroethyl)-pyrido[1,2-*a*]pyrimidin-4(1*H*)-one (5a). Recrystallized from ligroin as colorless needles: mp 109–111 °C; IR (KBr): 2980, 1660, 1630, 1580, 1530, 1500, 1450 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.15 (t, *J*=7.0 Hz, 2H, CH_2), 3.85 (t, *J*=7.0 Hz, 2H, CH_2Cl), 7.15 (dt, *J*=7.0, 1.7 Hz, 1H, C_8–H), 7.75 (m, 2H, C_9–H & C_7–H), 8.35 (s, 1H, C_2–H), 9.05 (d, *J*=7.0 Hz, 1H, C_6–H). ^{13}C NMR: δ 26.5, 62.5, 111.4, 127.0, 135.3, 148.3, 157.8, 162.4, 171.0. Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.25; H, 4.80, N. 13.51.

4.5.10. 3-(2-Chloroethyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4(1*H*)-one (5b). Recrystallized from ligroin as colorless needles: mp 108–109 °C; IR (KBr): 2980, 1670, 1640, 1580, 1500, 1450, 1440 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.51 (s, 3H, C_8–Me), 3.05 (t, *J*=7.0 Hz, 2H, CH_2), 3.88 (t, *J*=7.0 Hz, 2H, CH_2Cl), 7.15 (dd, *J*=7.0 Hz, 1H, C_7–H), 7.45 (s, 1H, C_9–H), 8.25 (s, 1H, C_2–H), 8.95 (d, *J*=7.0 Hz, 1H, C_6–H). Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58; Cl, 15.92. Found: C, 59.19; H, 4.89, N, 12.50; Cl, 15.77.

4.5.11. 3-(2-Chloroethyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4(1*H*)-one (5c). Recrystallized from cyclohexane as colorless needles: mp 89–90 °C; IR (KBr): 2900, 1670, 1630, 1480, 1440 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.50 (s, 3H, C_6–CH_3), 3.10 (t, J=7.0 Hz, 2H, CH_2), 3.87 (t, J=7.0 Hz, 2H, CH_2Cl), 6.75 (m, 1H, C_7–H), 7.40 (dd, J=7.0 Hz, 1H, C_8–H), 8.20 (s, 1H, =CH), 8.95 (d, J=8.0 Hz, 1H, C_9–H). Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58; Cl, 15.92. Found: C, 59.14; H, 5.02, N, 12.34; Cl, 15.80.

4.5.12. 3-(2-Chloropropyl)-pyrido[1,2-*a*]pyrimidin-4(1*H*)-one (5d). Recrystallized from cyclohexane as colorless needles: mp 91–92 °C; IR (KBr): 2900, 1670, 1630, 1480, 1440 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.65 (d, J=7.0 Hz, 3H, CH_3), 3.85, 3.15 (q, dd, J=3.0, 6.0, 8.0 Hz, 2H, CH_2), 4.45 (m, 1H, $CHCH_3$), 7.15 (dt, J=7.0, 2.0, 9.0 Hz, 1H, C_8–H), 7.75 (d, J=8.0 Hz, 2H, C_9–H, C_7–H), 8.25 (s, 1H, =CH), 9.05 (d, J=7.0 Hz, 1H, C_6–H). Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58; Cl, 15.92. Found: C, 59.15 H, 5.03, N, 12.34; Cl, 15.95.

4.5.13. 3-(2-Chloroethyl)-8-methyl-pyrido[1,2-*a*]pyrimidin-4(1*H*)-one (5e). Recrystallized from ligroin as colorless needles: mp 137–138 °C; IR (KBr): 3020, 2990, 1670, 1640, 1580, 1450 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.5 (d, J=8.0 Hz, 3H, CH_3), 2.45 (s, 3H, C_8–CH_3), 2.85, 3.25 (q, dd, J=3.0, 6.0, 8.0 Hz, 2H, CH_2), 4.49 (m, 1H, $CHCH_3$), 7.05 (dd, J=7.0, 3.0 Hz, 1H, C_7–H), 7.43 (s, 1H, C_9–H), 8.20 (s, 1H, C_2–H), 8.96 (d, J=7.0 Hz, 1H, C_6–H). Anal. Calcd for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.83. Found: C, 61.11; H, 5.57; N, 11.90.

4.5.14. 3-(2-Chloropropyl)-6-methyl-pyrido[1,2-*a*]pyrimidin-4(1*H*)-one (5f). Recrystallized from petroleum ether as colorless needles: mp 92–93 °C; IR (KBr): 3030, 2990, 1670, 1640, 1590, 1480, 1450, 1430 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (d, J=7.0 Hz, 3H, CH_3), 2.85, 3.05 (q, dd, J=3.0, 6.0, 8.0 Hz, 2H, CH_2), 3.05 (s, 3H, C_6–CH_3), 4.47 (m, 1H, CHMe), 6.65 (m, 1H, C_7–H), 7.40 (dd, J=8.0, 2.9 Hz, 1H, C_8–H), 7.65 (d, J=7.0 Hz, 1H, C_9–H), 8.05 (s, 1H, C_2–H). Anal. Calcd for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.83. Found: C, 61.17; H, 5.24; N, 11.77.

4.5.15. 2-[1-(2-Oxo-2,3,4,5-tetrahydrofuran-3-yl)-ethen-2-yl-amino]-1,3-benzothiazole (7a). Recrystallized from *N*,*N*-dimethylformamide as pale yellow needles: mp 249–2350 °C; IR (KBr): 3260, 1720, 1670, 1630, 1600, 1530, 1440 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.95 (dt, J=7.0, 3 Hz, 2H, CH_2), 4.43 (t, J=7.0 Hz, 2H, CH_2Cl), 7.15 (dt, J=8.0, 2.0 Hz, 1H, C_7–H), 7.25 (dt, J=8.0, 2.0 Hz, 1H, C_4–H), 7.75 (dd, J=8.0, 2.0 Hz, 1H, C_5–H), 7.90 (dd, J=8.0, 2.0 Hz, 1H, C_6), 8.02 (dt, J=12.0, 3.0 Hz, 1H, =CH), 11.05 (d, J=12.0 Hz, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 25.2, 67.0, 104.1, 121.7, 123.3, 124.8, 129.0, 132.9, 133.7, 152.6, 163.3, 174.2. Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.87; H, 3.92; N, 11.44; S, 13.20.

4.5.16. 2-[1-(5-Methyl-2-oxo-2,3,4,5-tetrahydrofuran-3-yl)-ethen-2-yl-amino]-1,3-benzothiazole (7b). Recrystallized from methanol as colorless needles: mp 200–201 °C; IR (KBr): 3200, 3040, 1720, 1670, 1640, 1600, 1540, 1440 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.45 (d, J=7.0 Hz, 3H, CH_3), 2.42, 3.15 (qd, dq, J=2.1, 5.9, 7.5 Hz, 2H, CH_2), 4.78 (m, 1H, CH–Me), 7.25 (dd, J=8.0, 2.0 Hz, 1H, C_7–H), 7.35 (dd, J=8.0, 2.0 Hz, 1H, C_4–H), 7.72 (dt, J=8.0, 2.0 Hz, 1H, C_5–H), 7.85 (dt, J=8.0, 2.0 Hz, 1H, C_6–H), 7.95 (dt, J=12.0, 3.0 Hz, 1H, =CH), 10.85 (br s, 1H, NH). Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76. Found: C, 60.12; H, 4.41; N, 10.80.

4.5.17. 6-Methoxy-2-[1-(2-oxo-2,3,4,5-tetrahydrofuran-3-yl)-ethen-2-yl-amino]-1,3-benzothiazole (7c). Recrystallized from *N*,*N*-dimethylformamide/ethanol (8:2) as pale yellow needles: mp 254–255 °C; IR (KBr): 3280, 3020, 1725, 1670, 1630, 1600, 1540, 1470 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.95 (dt, J=7.0, 3.0 Hz, 2H, –CH_2), 3.82 (s, 3H, OCH_3), 4.42 (t, J=7.0 Hz, 2H, CH_2), 7.02 (d, J=2.0 Hz, 1H, C_7–H), 7.55 (d, J=8.0 Hz, 1H, C_4–H), 7.64 (dt, J=8.0, 2.0 Hz, 1H, C_5–H), 8.05 (dt, J=12.0, 3.0 Hz, 1H, =C–H), 11.8 (d, J=12 Hz, 1H, NH). Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.36; H, 4.25; N, 10.17; S, 11.36.

4.5.18. 6-Methoxy-2-[1-(5-methyl-2-oxo-2,3,4,5-tetrahydrofuran-3-yl)-ethen-2-yl-amino]-1,3-benzothiazole (7d). Recrystallized from methanol as colorless needles: mp 236–237 °C; IR (KBr): 3190, 2990, 2910, 1725, 1640, 1600, 1530, 1440 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.45 (d, J=7.0 Hz, 3H, CH_3), 2.41, 3.15 (qd, dq, J=2.1, 5.9, 7.5 Hz, 2H, CH_2), 2.82 (s, 3H, OCH_3), 4.70 (m, 1H, CH–Me), 7.05 (d, J=3.0 Hz, 1H, C_7–H), 7.35 (d, J=8.0 Hz, 1H, C_4–H), 7.55 (d, J=8.0 Hz, 1H, C_5–H), 8.05 (d, J=12.0 Hz, 1H, =CH), 10.85 (d, J=12.0 Hz, 1H, NH). Anal. Calcd for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65. Found: C, 57.82; H, 4.71; N, 9.58.

4.5.19. 2-[1-(2-Oxo-2,3,4,5-tetrahydrofuran-3-yl)-ethen-2-yl-amino]-1,3-benzoxazole (7e). Recrystallized from acetonitrile as colorless needles: mp 253–254 °C; IR (KBr): 3220, 1730, 1650, 1630, 1580, 1530, 1440 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.02 (dt, J=7.0, 3.0 Hz, 2H, CH_2), 4.43 (t, J=7.0 Hz, 2H, CH_2), 7.21–7.35 (m, 2H, C_4–H, C_5–H), 7.52 (dd, J=8.0, 2.5 Hz, 1H, C_6–H), 7.63 (dd, J=8.0, 2.5 Hz, 1H, C_7–H), 7.79 (dt, J=12.0, 3.0 Hz, 1H, =CH), 10.9 (br s, 1H, NH). Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.52; H, 4.38; N, 12.15.

4.5.20. 2-[1-(5-Methyl-2-oxo-2,3,4,5-tetrahydrofuran-3-yl)-ethen-2-yl-amino]-1,3-benzoxazole (7f). Recrystallized from methanol as colorless needles: mp 160–161 °C; IR (KBr): 3260, 3060, 1710, 1640, 1580, 1500, 1460 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.45 (d, J=7 Hz, 3H, CH_3), 2.55, 3.24 (qd, dq, J=2.1, 5.9, 7.5 Hz, 2H, CH_2), 4.75 (m, 1H, CHMe), 7.23 (dd, J=8.0, 2.0 Hz, 1H, C_7–H), 7.25–7.35 (m, 2H, C_4 & C_6–H), 7.45 (dd, J=8.0, 2.0 Hz, 1H, C_6–H), 7.53 (dt, J=12.0, 3.0 Hz, 1H, =CH), 9.92 (d, J=12.0 Hz, 1H, NH). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.95; H, 4.89; N, 11.55.

4.5.21. 3-[2-(2-Thiazoloamino)-methylidene]-4,5-dihydrofuran-2(3*H*)-one (7g). Recrystallized from ethanol as colorless needles: mp 213–214 °C; IR (KBr): 3380, 1720, 1670, 1630, 1520, 1470 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.95 (dt, J=7.0, 3.0 Hz, 2H, CH_2), 4.45 (t, J=7.0 Hz,

2H, CH_2O), 7.12 (d, J=8.0 Hz, 1H, C_4–H), 7.35 (d, J=8.0 Hz, 1H, C_5–H), 7.85 (dt, J=12.0, 3.0 Hz, 1H, =CH), 10.56 (d, J=12.5 Hz, 1H, NH). Anal. Calcd for $C_8H_8N_2O_2S$: C, 48.97; H, 4.11; N, 14.28. Found: C, 49.17; H, 3.91; N, 14.15.

4.5.22. 3-[2-(2-Thiazoloamino)-methylidene]-5-methyl-4,5-dihydrofuran-2(3*H*)-one (7h). Recrystallized from acetone/ligroin (1:2) as colorless needles: mp 168 °C; IR (KBr): 3280, 3040, 1720, 1660, 1640, 1520, 1470, 1440 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.32 (d, J=8.0 Hz, 3H, CH_3), 4.56 (m, 1H, –CHMe), 2.35, 3.15 (dq, qd, J=2.1, 5.9, 7.5 Hz, 2H, CH_2), 6.72 (d, J=8.0 Hz, 1H, C_4–H), 7.23 (d, J=8.0 Hz, 1H, C_5–H), 7.82 (dt, J=12.0, 3.0 Hz, 1H, =CH), 9.72 (br s, 1H, NH). Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.76; N, 13.32. Found: C, 51.67; H, 4.77; N, 13.44.

4.5.23. 3-(2-Chloroethyl)-1,3-benzothiazolo[3,2-*a*]-pyrimidin-4(1*H*)-one (8a). Recrystallized from ethanol as pale yellow needles: mp 190–191 °C; IR (KBr): 1670, 1630, 1580, 1500, 1450 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.02 (t, J=7.0 Hz, 2H, CH_2), 3.95 (t, J=7.0 Hz, 2H, CH_2O), 7.55–7.65 (m, 2H, C_8–H, C_9–H), 8.02 (dt, J=8.0, 2 Hz, 1H, C_6–H), 9.02 (dt, J=8.0, 2 Hz, 1H, C_7–H), 8.12 (s, 1H, C_2H). Anal. Calcd for $C_{12}H_9ClN_2OS$: C, 54.44; H, 3.43; N, 10.58, Cl, 13.39. Found: C, 54.54; H, 3.29; N, 10.61, Cl, 13.45.

4.5.24. 3-(2-Chloropropyl)-1,3-benzothiazolo[3,2-*a*]pyrimidin-4(1*H*)-one (8b). Recrystallized from ligroin as pale yellow needles: mp 100–101 °C; IR (KBr): 1670, 1590, 1500, 1450 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.55 (d, J=8.0 Hz, 3H, CH_3), 2.80 (qd, dq, 2H, J=3.0, 6.0, 8.0 Hz, CH_2), 4.71 (m, 1H, CHMe), 7.55–7.65 (m, 2H, C_8–H, C_9–H), 7.89 (s, 1H, C_3H), 8.04 (dt, J=8.0, 2.0 Hz, 1H, C_6–H), 9.02 (dt, J=8.0, 2.0 Hz, 1H, C_7–H). Anal. Calcd for $C_{13}H_{11}ClN_2OS$: C, 56.01; H, 3.98; N, 10.05; Cl, 12.72. Found: C, 56.11; H, 3.93; N, 10.06; Cl, 13.01.

4.5.25. 3-(2-Chloroethyl)-8-methoxy-1,3-benzothiazolo[3,2-*a*]pyrimidin-4(1*H*)-one (8c). Recrystallized from methanol as pale yellow needles: mp 156–157 °C; IR (KBr): 1660, 1630, 1600, 1570, 1520, 1480, 1440 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.02 (t, J=7.0 Hz, 2H, CH_2), 3.095 (t, J=7.0 Hz, 2H, CH_2), 3.92 (s, 3H, OCH_3), 7.15 (dt, J=8.0, 3.0 Hz, 1H, C_7–H), 7.72 (d, J=3.0 Hz Hz, 1H, C_9–H), 7.91 (s, 1H, C_2–H), 8.85 (d, J=8.0 Hz, 1H, C_6–H). Anal. Calcd for $C_{13}H_{11}ClN_2O_2S$: C, 52.97; H, 3.76; N, 9.50. Found: C, 52.81; H, 3.83; N, 9.60.

4.5.26. 3-(2-Chloropropyl)-8-methoxy-1,3-benzothiazolo[3,2-*a*]pyrimidin-4(1*H*)-one (8d). Recrystallized from ligroin as pale yellow needles: mp 141–142 °C; IR (KBr): 1660, 1600, 1510, 1470, 1440 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.5 (d, J=8.0 Hz, 3H, CH_3), 2.85, 3.15 (q, dd, J=3.0, 6.0, 8.0 Hz, 2H, CH_2), 3.92 (s, 3H, OCH_3), 4.72 (m, 1H, CHMe), 7.05 (dt, J=8.0, 3.0 Hz, 1H, C_7–H), 7.15 (d, J=3.0 Hz, 1H, C_9–H), 7.90 (s, 1H, C_2–H), 9.80 (d, J=8.0 Hz, 1H, C_6–H). Anal. Calcd for $C_{14}H_{13}ClN_2O_2S$: C, 54.46; H, 4.24; N, 9.07. Found: C, 54.15; H, 4.05; N, 8.95.

4.5.27. 3-(2-Chloroethyl)-1,3-benzoxazolo[3,2-*a*]pyrimidin-4(1*H*)-one (8e). Recrystallized from ligroin as colorless needles: mp 141–143 °C; IR (KBr): 1660, 1600, 1510, 1470, 1440 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.02 (t, J=7.0 Hz, 2H, CH_2), 3.95 (t, J=7.0 Hz, 2H, CH_2Cl), 7.30–8.25 (m, 4H, Ar–H), 7.95 (s, 1H, C_2–H). Anal. Calcd for $C_{12}H_9ClN_2O_2$: C, 57.96; H, 3.65; N, 11.27. Found: C, 58.12; H, 3.35; N, 11.3.

4.5.28. 3-(2-Chloropropyl)-1,3-benzoxazolo[3,2-*a*]pyrimidin-4(1*H*)-one (8f). Recrystallized from ligroin as pale yellow needles: mp 130–131 °C; IR (KBr): 1680, 1600, 1520, 1450 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (d, J=8.0 Hz, 3H, CH_3), 2.80 (q, dd, J=3.0, 6.0, 8.0 Hz, 2H, CH_2), 4.71 (m, 1H, –CHMe), 7.30–78.25 (m, 4H, Ar–H), 7.95 (s, 1H, C_2–H). Anal. Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66. Found: C, 59.21; H, 4.23; N, 10.62.

4.5.29. 6-(2-Chloroethyl)-1,3-thiazolo[2,3-*b*]pyrimidin-5(1*H*)-one (8g). Recrystallized from cyclohexane as pale yellow needles: mp 86–87 °C; IR (KBr): 1670, 1560, 1500, 1450, 1420 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.03 (t, J=7.0 Hz, 2H, –CH_2), 3.85 (t, J=7.0 Hz, 2H, CH_2Cl), 7.05 (d, J=8.0 Hz, 1H, C_4–H), 8.02 (s, 1H, =C–H), 8.03 (d, J=8.0 Hz, 1H, C_5–H). Anal. Calcd for $C_8H_7ClN_2O_2S$: C, 44.76; H, 3.29; N, 13.05. Found: C, 44.83; H, 3.11; N, 13.17.

4.5.30. 3-(2-Hydroxyethyl)-1,3-benzimidazolo[3,2-*a*]pyrimidin-4(1*H*)-one (11a). Recrystallized from acetonitrile as colorless needles: mp 203–204 °C; yield 70% (Method A), yield 68% (Method B); IR (KBr): 3350, 2900, 1740, 1670, 1610, 1570, 1500, 1490, 1420 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.85 (t, J=7.0 Hz, 2H, CH_2), 4.32 (t, J=7.0 Hz, 2H, CH_2), 7.32–7.56 (m, 3H, Ar–H), 7.95 (s, 1H, C_2–H), 8.42 (d, J=8.0 Hz, 1H, C_9–H), 12.6 (br s, 1H, NH). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.63; H, 4.86; N, 18.19.

4.5.31. 3-(2-Hydroxypropyl)-1,3-benzimidazolo[3,2-*a*]pyrimidin-4(1*H*)-one (11b). Recrystallized from methanol as colorless needles: mp 190–191 °C; yield 69% (Method A), yield 65% (Method B); IR (KBr): 3350, 3150, 2900, 1670, 1630, 1580, 1500, 1450 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.42 (d, J=7.0 Hz, 3H, CH_3), 2.55 (q, dd, J=3.0, 6.0, 8.0 Hz, 2H, CH_2), 4.45 (m, 1H, CHMe), 7.32–7.56 (m, 3H, Ar–H), 7.95 (s, 1H, C_2–H), 8.41 (d, J=8.0 Hz, 1H, C_9–H), 12.60 (br s, 1H, NH). Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.06; H, 5.51; N, 17.26.

4.5.32. 3-(2-Chloroethyl)-4-chloro-1,3-benzimidazolo[3,2-*a*]pyrimidine (12a). A mixture of **12a** (0.01 mol) and phosphorous oxychloride (30 mL) was refluxed for 3 h. The solvent was evaporated in vacuum and the remaining solid was stirred with water (50 mL) for 30 min, neutralized with sodium carbonate (6 g), stirred further for 5 h, filtered, dried, and recrystallized from ethanol as colorless needles: mp 220–221 °C; yield 62%; IR (KBr): 2980, 1640, 1600, 1520, 1480, 1450, 1410 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.52 (t, J=7.0 Hz, 2H, CH_2), 4.03 (t, J=7.0 Hz, 2H, CH_2Cl), 7.42–7.72 (m, 2H, C_7–H, C_8–H), 7.88 (d, J=8.0 Hz, 1H, C_6–H), 8.35 (d, J=8.0 Hz, 1H, C_9–H), 9.65 (s, 1H, C_2–H). Anal. Calcd for $C_{12}H_9Cl_2N_3$: C, 54.16; H, 3.41; N, 15.79. Found: C, 54.20; H, 3.47; N, 15.77.

Acknowledgements

Authors thank UGC, New Delhi for financial support under MRP. We also thank Professor Thomas Kappe, Department of Organic and Bio-organic Chemistry, University of Graz, Austria for encouragement and the higher authorities of NDMVP Samaj and KTHM College, Nashik.

References and notes

1. Hossain, N.; Rozenski, J.; Clercq, E. D.; Herdewijn, P. *J. Org. Chem.* **1997**, *62*, 2442.
2. Sabnis, R. W.; Rangnekar, D. W. *Indian J. Technol.* **1990**, *28*, 54.
3. Joseph, S.; Burke, J. M. *J. Biol. Chem.* **1993**, *268*, 24515.
4. Bookser, B. C.; Ugarkar, B. G.; Matelich, M. C.; Lemus, R. H.; Allan, M.; Tsuchiya, M.; Nakane, M.; Nagahisa, A.; Wiesner, J. B.; Erion, M. D. *J. Med. Chem.* **2005**, *48*, 7808.
5. Wang, S.; Folkes, A.; Chuckowree, I.; Cockcroft, X.; Sohal, S.; Miller, W.; Milton, J.; Wren, S. P.; Vicker, N.; Depledge, P.; Scott, J.; Smith, L.; Jones, H.; Mistry, P.; Faint, R.; Thompson, D.; Cocks, S. *J. Med. Chem.* **2004**, *47*, 1329.
6. Gangjee, A.; Jain, H. D.; Phan, J.; Lin, X.; Song, X.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **2006**, *49*, 1055.
7. Bruno, O.; Brullo, C.; Schenone, S.; Bondavalli, F.; Ranise, A.; Tognolini, M.; Impicciatore, M.; Ballabeni, V.; Barocelli, E. *Bioorg. Med. Chem.* **2006**, *14*, 121.
8. Toche, R.; Jachak, M.; Medhane, V.; Desai, A. *J. Indian Chem. Soc.* **2006**, *83*, 1.
9. Jachak, M.; Avhale, A.; Medhane, V.; Toche, R. *J. Heterocycl. Chem.* **2006**, *43*, 1.
10. Jachak, M.; Tantak, C.; Toche, R.; Badgujar, N. *Monatsh. Chem.* **2004**, *135*, 1529.
11. Toche, R.; Jachak, M.; Dalvi, T.; Kappe, T. *Org. Prep. Proced. Int.* **1998**, *30*, 367.
12. Toche, R.; Jachak, M.; Kappe, T. *J. Heterocycl. Chem.* **1999**, *36*, 467.
13. Josephine, K. L. E. Aloysius, P. S. M. Paul, B. F. (Janssen Pharmaceutica N.V., Belg.) PCT Appl. WO 2000020422 Al 20000413, 2000; *Chem. Abstr.* **2000**, *132*, 265188t.
14. Fujit, H.; Shimoji, Y.; Kojima, S.; Nishino, H.; Kamoshita, K.; Katsuo, K.; Endo, K.; Kobayashi, S.; Kumakura, S.; Sato, Y. Sanko Ltd, Tokyo, Japan. *Sankyo Kenkyusho Nenpo* **1977**, *29*, 75.
15. Kennis, J. E. L.; Bischoff, F. P.; Mertens, C. J.; Love, C. J.; Van den Keybus, F. A. F.; Pieters, S.; Braeken, M.; Megens, A. A.; Leysen, J. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 71.
16. Wamhoft, H.; Korte, F. *Synthesis* **1972**, 151.
17. Willenbrock, H. J.; Wamhoff, H.; Korte, F. *Justus Liebigs der Chemie* **1973**, *1*, 103.