Improved Synthesis and Efficient Chemoselective Reduction of Fused Tetrazoles under Phase-Transfer Conditions

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Received 24 April 2006; revised 7 June 2006

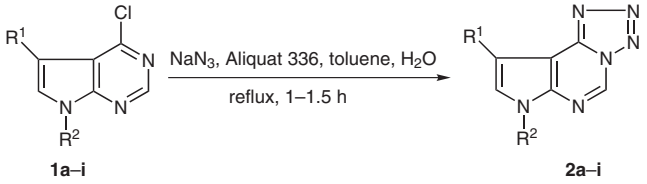
Dedicated to the memory of Dr. Chaitanya G. Dave

Abstract : Liquid–liquid phase-transfer conditions were employed in an improved synthesis of 7,9-substituted 7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines and 5,7-substituted 4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidines. The latter were obtained either by reductive ring cleavage of the former, or by one-pot synthesis from 5,7-substituted 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidines.

Key words: pyrrolotetrazolopyrimidines, reductive ring cleavage, phase-transfer catalyst, Aliquat 336, 18-crown-6

The investigation of fused tetrazolopyrimidines as a potent antagonist has shown that they have a wide range of biological activities such as anticancer,[1a,b] anticonvulsant,[1c] anti-ulcer,[1d] anti-inflammatory,[1e] antitumor,[1f] antihypertensive,[1g] antimalarial,[1h] antifolate,[1i] and antibacterial.[1j] Moreover, fused tetrazolopyrimidines are capable of undergoing reductive ring cleavage to form fused aminopyrimidines,[2] which are known for their valuable pharmacological properties and as intermediates in the construction of a variety of triheterocycles.[3] Phase-transfer catalysis (PTC) has been established as a widespread synthetic technique.[4] Reactions using phase-transfer catalysis can be readily scaled up and have been used particularly for clean and efficient processes involving high yields, operational simplicity, mild conditions, low cost, safety, and environmental profit. A literature survey reveals that phase-transfer conditions have been least exploited for the synthesis and reduction of fused tetrazoles.[5] These observations and pharmacological interest have led us to improve the synthesis of 7,9-substituted 7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines **2** and their transformation to 5,7-substituted 4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidines **3** via reductive ring cleavage under phase-transfer conditions. An efficient one-pot synthesis of **3** was also achieved for the first time to form 5,7-substituted 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidines **1** via in situ generation of pyrrolotetrazolopyrimidines **2**.

The chloro substituent present at C4 in the pyrrolo[2,3-*d*]pyrimidine ring system was found to be highly reactive towards nucleophilic substitution reactions with sodium azide and hydrazine hydrate. Our earlier publication exploited both reactions to synthesize pyrrolotetrazolopyrimidines **2**.[6] In one of the methods, 5,7-substituted 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidines **1** were reacted with sodium azide in the presence of ammonium chloride; the in situ generation of ammonium azide facilitated the reaction in dimethyl sulfoxide at 90 °C. Recovery of dimethyl sulfoxide from the reaction mixture is the main problem associated with such reactions and the use of other solvents was unsuccessful in generating the products in quantitative yield. With a view to this problem, the synthesis was improved by using liquid–liquid phase-transfer conditions with toluene and water as solvents and Aliquat 336 (methyltrioctylammonium chloride) as the catalyst (Scheme 1). This improved synthetic protocol enhanced the reaction rates and the products were obtained in good yields.



1a–i **2a–i**

Scheme 1

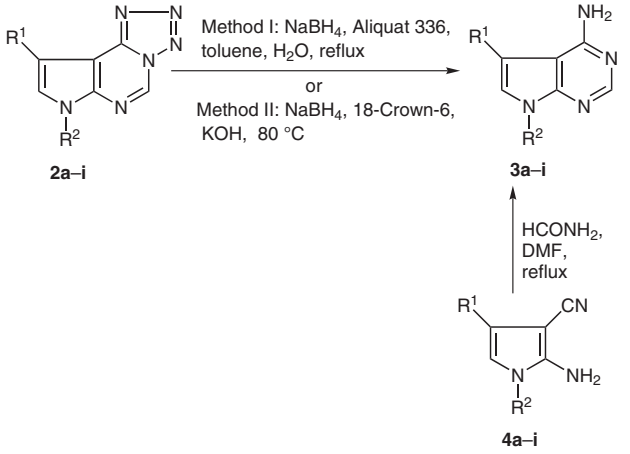
Table 1 Synthesis of 7,9-Substituted 7*H*-Pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines **2a–i**

2	R^1	R^2	Yield (%)	Mp (°C) Found	Lit.
2a	Ph	4-FC_6H_4	72	218–220	217–219[1j]
2b	Ph	3-Cl-4-FC_6H_3	68	212–214	212–214[1j]
2c	4-$MeOC_6H_4$	4-FC_6H_4	65	245–247	245–247[1j]
2d	4-$MeOC_6H_4$	3-Cl-4-FC_6H_3	58	219–221	219–221[1j]
2e	4-ClC_6H_4	4-FC_6H_4	70	228–229	226–228[1j]
2f	4-ClC_6H_4	3-Cl-4-FC_6H_3	69	222–224	220–222[1j]
2g	4-FC_6H_4	4-ClC_6H_4	60	226–228	226–228[6b]
2h	4-FC_6H_4	4-FC_6H_4	69	202–203	201–202[6b]
2i	4-FC_6H_4	3-Cl-4-FC_6H_3	75	234–236	234–236[6b]

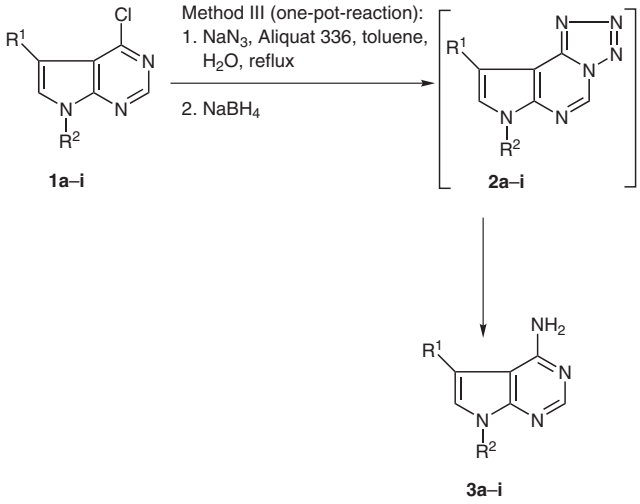
SYNTHESIS 2006, No. 19, pp 3275–3279
Advanced online publication: 21.08.2006
DOI: 10.1055/s-2006-950206; Art ID: Z08606SS

Azides and tetrazoles can be viewed as latent amino functionalities. While azides undergo chemoselective reduction using a novel system,[7] lithium aluminum hydride,[8] catalytic hydrogenation,[8a–d,9] or various other reagents[10] to yield amines, tetrazoles are highly resistant to reduction.[11] Dave et al.[6] successfully reduced pyrrolotetrazolopyrimidines **2** with zinc dust and acetic acid. With respect to the literature methods, the phase-transfer catalysis technique has the novelty of using sodium borohydride as an efficient reducing agent for tetrazoles. It affords pure products in high yields and offers the advantages of permitting a one-pot conversion of 4-chloropyrrolo[2,3-*d*]pyrimidines **1a–i** into 4-aminopyrrolo[2,3-*d*]pyrimidines **3a–i** with very simple operating conditions. Thus, in a modified procedure, two synthetic strategies based on phase-transfer catalysis were adopted for the reductive ring cleavage of pyrrolotetrazolopyrimidines **2** keeping sodium borohydride as the reducing agent. Under liquid–liquid phase-transfer conditions (Method I), Aliquat 336 was used as the catalyst and toluene and water were preferred as solvents whereas under solid–liquid phase-transfer conditions (Method II), 18-crown-6 was used as the catalyst along with powdered potassium hydroxide and acetonitrile as the solvent. The obtained compounds **3a–i** are identical with those synthesized by condensation of 2-amino-3-cyanopyrroles **4a–i** and formamide[12] (Scheme 2).

One-pot synthesis of 5,7-substituted 4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidines **3a–i** was achieved efficiently using liquid–liquid phase-transfer catalysis conditions using toluene and water as solvents and Aliquat 336 as the catalyst (Method III); however, a higher mol% of catalyst was required. Firstly, **1** was reacted with sodium azide to form **2**; on completion of the reaction, an equivalent quantity of powdered sodium borohydride was added portionwise to the same reaction mixture to give **3** (Scheme 3).



Scheme 2



Scheme 3

Table 2 Synthesis of 5,7-Substituted 4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidines **3a–i**

3	R^1	R^2	Yield[a] (%)			Mp (°C)	
			Method I	Method II	Method III	Found	Lit.
3a	Ph	4-FC_6H_4	54	56	50	183–185	183–185[12b]
3b	Ph	3-Cl-4-FC_6H_3	66	67	62	238–240	238–240[12b]
3c	4-$MeOC_6H_4$	4-FC_6H_4	58	58	54	153–154	154–156[12b]
3d	4-$MeOC_6H_4$	3-Cl-4-FC_6H_3	73	76	71	220–222	222–223[12b]
3e	4-ClC_6H_4	4-FC_6H_4	80	82	75	276–278	276–278[12b]
3f	4-ClC_6H_4	3-Cl-4-FC_6H_3	69	69	65	308–310	309–310[12b]
3g	4-FC_6H_4	4-ClC_6H_4	58	58	52	275–277	276–278[6b]
3h	4-FC_6H_4	4-FC_6H_4	61	65	54	163–165	165–166[6b]
3i	4-FC_6H_4	3-Cl-4-FC_6H_3	67	70	63	241–243	243–245[6b]

[a] Overall yields for Method I and Method II from compound **2** and for Method III from compound **1**.

In summary, we have described a convenient and practical synthesis of pyrrolotetrazolopyrimidines and their reductive ring cleavage using various phase-transfer conditions. We have also described, for the first time, a one-pot synthesis of 4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidines from 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidines using liquid–liquid phase-transfer catalysis without the need to work up every step. The operational simplicity of this synthetic route will be helpful to elaborate the chemistry and bioactivity of fused tetrazoles and aminopyrimidines.

Melting points were determined by electrothermal method in open capillary tube and are uncorrected. The IR spectra were recorded KBr pellets on a Buck-500 spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ or DMSO-d_6, using TMS as internal standard. MS spectra were recorded on a JEOL SX-102 mass spectrometer under electron-impact (EI) ionization. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar Vario EL III microanalyzer. The purity of the compounds was routinely checked by TLC using silica gel G and spots were exposed to iodine vapor.

Compounds **1a–i** were obtained according to procedures published in the literature.[6b,12b] All the other starting materials were obtained from commercial suppliers and were used without further purification.

7,9-Substituted 7*H*-Pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines 2a–i; General Procedure

To a well-stirred soln of 5,7-substituted 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **1** (5 mmol) and Aliquat 336 (0.202 g, 0.5 mmol) in toluene (25 mL) was added NaN_3 (0.390 g, 6 mmol) in H_2O (5 mL). The mixture was stirred under reflux for 1–1.5 h. The progress of the reaction was monitored by TLC. On completion, the two phases were separated. The aqueous phase was extracted with toluene (15 mL) and the combined organic layers were washed with H_2O (10 × 2 mL) and dried (anhyd Na_2SO_4). The solvent was recovered in vacuo and the oily residue obtained after distillation was treated with chilled MeOH. The solid thus obtained was filtered off, dried, and crystallized (DMF–EtOH, 6:4) (Table 1).

7-(4-Fluorophenyl)-9-phenyl-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (2a)[1j]
IR (KBr): 1604, 1516 cm^{-1} (C=C, C=N ring).

^{1}H NMR (DMSO-d_6): δ = 7.2–8.0 (m, 10 H, ArH), 8.41 (s, 1 H, H5).

MS: *m*/*z* = 330 (M$^+$).

Anal. Calcd for $C_{18}H_{11}FN_6$ (330.3): C, 65.45; H, 3.36; N, 25.44. Found: C, 65.66; H, 3.27; N, 25.19.

7-(3-Chloro-4-fluorophenyl)-9-phenyl-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (2b)[1j]
IR (KBr): 1604, 1492 cm^{-1} (C=C, C=N ring).

^{1}H NMR (DMSO-d_6): δ = 7.2–8.0 (m, 9 H, ArH), 8.43 (s, 1 H, H5).

MS: *m*/*z* = 364 (M$^+$).

Anal. Calcd for $C_{18}H_{10}ClFN_6$ (364.8): C, 59.27; H, 2.76; N, 23.04. Found: C, 59.54; H, 2.50; N, 22.86.

7-(4-Fluorophenyl)-9-(4-methoxyphenyl)-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (2c)[1j]
IR (KBr): 1600, 1504 cm^{-1} (C=C, C=N ring).

^{1}H NMR (DMSO-d_6): δ = 3.91 (s, 3 H, OCH_3), 7.3–8.1 (m, 9 H, ArH), 8.41 (s, 1 H, H5).

MS: *m*/*z* = 360 (M$^+$).

Anal. Calcd for $C_{19}H_{13}FN_6O$ (360.3): C, 63.33; H, 3.64; N, 23.32. Found: C, 63.09; H, 3.45; N, 23.44.

7-(3-Chloro-4-fluorophenyl)-9-(4-methoxyphenyl)-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (2d)[1j]
IR (KBr): 1608, 1504 cm^{-1} (C=C, C=N ring).

^{1}H NMR (DMSO-d_6): δ = 3.89 (s, 3 H, OCH_3), 7.3–8.2 (m, 8 H, ArH), 8.44 (s, 1 H, H5).

MS: *m*/*z* = 394 (M$^+$).

Anal. Calcd for $C_{19}H_{12}ClFN_6O$ (394.8): C, 57.80; H, 3.06; N, 21.29. Found: C, 57.65; H, 3.25; N, 21.40.

9-(4-Chlorophenyl)-7-(4-fluorophenyl)-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (2e)[1j]
IR (KBr): 1612, 1496 cm^{-1} (C=C, C=N ring).

^{1}H NMR (DMSO-d_6): δ = 7.2–8.2 (m, 9 H, ArH), 8.41 (s, 1 H, H5).

MS: *m*/*z* = 364 (M$^+$).

Anal. Calcd for $C_{18}H_{10}ClFN_6$ (364.8): C, 59.27; H, 2.76; N, 23.04. Found: C, 59.06; H, 2.59; N, 23.36.

7-(3-Chloro-4-fluorophenyl)-9-(4-chlorophenyl)-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (2f)[1j]
IR (KBr): 1604, 1508 cm^{-1} (C=C, C=N ring).

^{1}H NMR (DMSO-d_6): δ = 7.2–8.23 (m, 8 H, ArH), 8.40 (s, 1 H, H5).

MS: *m*/*z* = 399 (M$^+$).

Anal. Calcd for $C_{18}H_9Cl_2FN_6$ (399.2): C, 54.16; H, 2.27; N, 21.05. Found: C, 54.01; H, 2.11; N, 20.88.

7-(4-Chlorophenyl)-9-(4-fluorophenyl)-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (2g)[6b]
IR (KBr): 1608, 1496 cm^{-1} (C=C, C=N ring).

^{1}H NMR ($CDCl_3$): δ = 7.24–8.12 (m, 9 H, ArH), 8.44 (s, 1 H, H5).

MS: *m*/*z* = 364 (M$^+$).

Anal. Calcd for $C_{18}H_{10}ClFN_6$ (364.8): C, 59.27; H, 2.76; N, 23.04. Found: C, 59.47; H, 2.81; N, 22.97.

7,9-Bis(4-fluorophenyl)-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (2h)[6b]
IR (KBr): 1600, 1504 cm^{-1} (C=C, C=N ring).

^{1}H NMR ($CDCl_3$): δ = 7.10–8.14 (m, 9 H, ArH), 8.42 (s, 1 H, H5).

MS: *m*/*z* = 348 (M$^+$).

Anal. Calcd for $C_{18}H_{10}F_2N_6$ (348.3): C, 62.07; H, 2.89; N, 24.13. Found: C, 62.20; H, 2.71; N, 23.98.

7-(3-Chloro-4-fluorophenyl)-9-(4-fluorophenyl)-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (2i)[6b]
IR (KBr): 1608, 1504 cm^{-1} (C=C, C=N ring).

^{1}H NMR ($CDCl_3$): δ = 7.16–8.24 (m, 8 H, ArH), 8.42 (s, 1 H, H5).

MS: *m*/*z* = 382 (M$^+$).

Anal. Calcd for $C_{18}H_9ClF_2N_6$ (382.8): C, 56.48; H, 2.37; N, 21.96. Found: C, 56.54; H, 2.50; N, 22.08.

5,7-Substituted 4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidines 3a–i : General Procedures

Method I: Liquid–Liquid Phase-Transfer Catalysis Conditions

A mixture of 7,9-substituted 7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine **2** (2 mmol) and Aliquat 336 (0.202 g, 0.5 mmol), toluene (15 mL), and H_2O (5 mL) was stirred on in a flat-bottom flask at 60 °C. Powdered $NaBH_4$ (0.302 g, 8 mmol) was added to this mixture portionwise cautiously over a period of 30 min. The mixture was then

refluxed for 1 h. On completion (TLC) the aqueous phase was separated. The aqueous phase was extracted with toluene (15 mL) and the combined organic layers were washed with H_2O (10 × 2 mL) and dried (anhyd Na_2SO_4). The solvent was recovered in vacuo, the residue was treated with *n*-hexane and the solid thus formed was filtered off, washed with cold MeOH, dried, and crystallized (EtOH–$CHCl_3$, 8:2) (Table 2).

Method II: Solid–Liquid Phase-Transfer Catalysis Conditions

A mixture of 7,9-substituted 7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine **2** (2 mmol), MeCN (25 mL), 18-crown-6 (0.132 g, 0.5 mmol), powdered KOH (0.841 g, 15 mmol) and powdered $NaBH_4$ (0.302 g, 8 mmol) was heated at 80 °C for 2–2.5 h, the supernatant reddish liquid was decanted from the solid residue and filter off. The solvent was recovered in vacuo and the resulting oily residue was treated with chilled MeOH. The solid thus obtained was filtered off, washed with MeOH, dried, and crystallized (Table 2).

Method III: One-Pot Reaction

To the well-stirred soln of 5,7-substituted 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **1a**–**i** (5 mmol) and Aliquat 336 (0.323 g, 0.8 mmol) in toluene (25 mL) was added NaN_3 (0.390 g, 6 mmol) in H_2O (5 mL). The mixture was stirred under reflux for 1–1.5 h. The progress of the reaction was monitored with TLC, after the formation of pyrrolotetrazolopyrimidine **2a**–**i** powdered $NaBH_4$ (0.302 g, 8 mmol) was added to the mixture in order to get the corresponding 4-aminopyrrolo[2,3-*d*]pyrimidine **3a**–**i**. The workup was effected according to Method I (Table 2).

4-Amino-7-(4-fluorophenyl)-5-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (3a)[12b]

IR (KBr): 3470, 3290 (NH), 1585, 1500 cm^{-1} (C=C, C=N ring).

^1H NMR ($CDCl_3$): δ = 5.30 (s, 2 H, NH_2), 7.10–8.38 (m, 11 H, ArH).

Anal. Calcd for $C_{18}H_{13}FN_4$ (304.3): C, 71.04; H, 4.31; N, 18.41. Found: C, 70.99; H, 4.11; N, 18.42.

4-Amino-7-(3-chloro-4-fluorophenyl)-5-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (3b)[12b]

IR (KBr): 3470, 3290 (NH), 1585, 1500 cm^{-1} (C=C, C=N ring).

^1H NMR ($CDCl_3$): δ = 5.32 (s, 2 H, NH_2), 7.10–8.38 (m, 10 H, ArH).

Anal. Calcd for $C_{18}H_{12}ClFN_4$ (338.8): C, 63.82; H, 3.57; N, 16.54. Found: C, 63.99; H, 3.78; N, 16.42.

4-Amino-7-(4-fluorophenyl)-5-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3c)[12b]

IR (KBr): 3470, 3290 (NH), 1585, 1500 cm^{-1} (C=C, C=N ring).

^1H NMR ($CDCl_3$): δ = 3.90 (s, 3 H, OCH_3), 5.32 (s, 2 H, NH_2), 7.10–8.38 (m, 10 H, ArH).

Anal. Calcd for $C_{19}H_{15}FN_4O$ (334.4): C, 68.25; H, 4.52; N, 16.76. Found: C, 68.10; H, 4.40; N, 16.52.

4-Amino-7-(3-chloro-4-fluorophenyl)-5-(methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3d)[12b]

IR (KBr): 3470, 3290 (NH), 1585, 1500 cm^{-1} (C=C, C=N ring).

^1H NMR ($CDCl_3$): δ = 3.89 (s, 3 H, OCH_3), 5.33 (s, 2 H, NH_2), 7.10–8.38 (m, 9 H, ArH).

Anal. Calcd for $C_{19}H_{14}ClFN_4O$ (368.8): C, 61.88; H, 3.83; N, 15.19. Found: C, 61.99; H, 3.78; N, 15.32.

4-Amino-5-(chlorophenyl)-7-(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3e)[12b]

IR (KBr): 3470, 3290 (NH), 1585, 1500 cm^{-1} (C=C, C=N ring).

^1H NMR ($CDCl_3$): δ = 5.32 (s, 2 H, NH_2), 7.10–8.38 (m, 10 H, ArH).

Anal. Calcd for $C_{18}H_{12}ClFN_4$ (338.8): C, 63.82; H, 3.57; N, 16.54. Found: C, 64.03; H, 3.66; N, 16.75.

4-Amino-7-(3-chloro-4-fluorophenyl)-5-(chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3f)[12b]

IR (KBr): 3470, 3290 (NH), 1585, 1500 cm^{-1} (C=C, C=N ring).

^1H NMR ($CDCl_3$): δ = 5.30 (s, 2 H, NH_2), 7.10–8.38 (m, 9 H, ArH).

Anal. Calcd for $C_{18}H_{11}Cl_2FN_4$ (373.2): C, 57.93; H, 2.97; N, 15.01. Found: C, 57.99; H, 2.78; N, 15.12.

4-Amino-7-(4-chlorophenyl)-5-(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3g)[6b]

IR (KBr): 3465, 3280 (NH), 1580, 1510 cm^{-1} (C=C, C=N ring).

^1H NMR ($CDCl_3$): δ = 5.24 (s, 2 H, NH_2), 7.12–8.36 (m, 10 H, ArH).

Anal. Calcd for $C_{18}H_{12}ClFN_4$ (338.8): C, 63.82; H, 3.57; N, 16.54. Found: C, 63.90; H, 3.43; N, 16.42.

4-Amino-5,7-bis(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3h)[6b]

IR (KBr): 3480, 3300 (NH), 1580, 1485 cm^{-1} (C=C, C=N ring).

^1H NMR ($CDCl_3$): δ = 5.28 (s, 2 H, NH_2), 7.20–8.38 (m, 10 H, ArH).

Anal. Calcd for $C_{18}H_{12}F_2N_4$ (322.3): C, 67.08; H, 3.75; N, 17.38. Found: C, 66.89; H, 3.50; N, 17.40.

4-Amino-7-(3-chloro-4-fluorophenyl)-5-(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3i)[6b]

IR (KBr): 3460, 3280 (NH), 1580, 1500 cm^{-1} (C=C, C=N ring).

^1H NMR ($CDCl_3$): δ = 5.30 (s, 2 H, NH_2), 7.18–8.34 (m, 9 H, ArH).

Anal. Calcd for $C_{18}H_{11}ClF_2N_4$ (356.8): C, 60.60; H, 3.11; N, 15.70. Found: C, 60.54; H, 3.24; N, 15.69.

Acknowledgment

We wish to thank the Regional Sophisticated Instrumentation Center, Central Drug Research Institute, Lucknow and Chandigarh, India, for the ^1H NMR and mass spectral analyses and the Director of the Loyola Center for R & D, St. Xavier's College, Ahmedabad, for the facility to carry out this work.

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