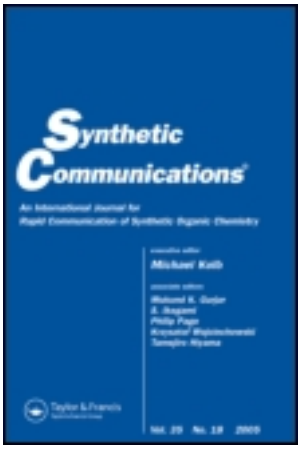

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Synthesis of Fused Tetrazolo[1,5-c] pyrrolo[3,2-e]pyrimidines and Their Reductive Conversion to New 4-Aminopyrrolo[2,3-d]pyrimidines

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Synthesis of Fused Tetrazolo[1,5-*c*] pyrrolo[3,2-*e*]pyrimidines and Their Reductive Conversion to New 4-Aminopyrrolo[2,3-*d*]pyrimidines

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Abstract: Some new 7,9-substituted 7*H*-1,2,3,4-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines **5** have been synthesized either by diazotization of 4-hydrazino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **4** obtained by hydrazinolysis of 4-chloro-5,7-disubstituted 7*H*-pyrrolo[2,3-*d*]pyrimidines **3** or via a substitution reaction between **3** and sodium azide. 5,7-Disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-ones **2** were obtained by cyclocondensation of 1,4-disubstituted 2-amino-3-cyanopyrroles **1** with formic acid, which, on chlorination using phosphorus oxychloride, afforded **3**. 2-Amino-3-cyanopyrroles **1** were synthesized from the reaction between (2-bromo-1-(4-fluorophenyl) ethylidene) propanedinitrile and substituted aromatic amines under Gewald reaction conditions. A novel route for the synthesis of 4-amino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **6** by the reductive ring cleavage of **5** has been reported.

Keywords: Aminopyrrolo[2,3-*d*]pyrimidine, reductive conversion, tetrazolopyrrolopyrimidine

INTRODUCTION

The investigation of fused tetrazolopyrimidine as a potent antagonist contributed to a wide range of biological activities such as analgesic,[1]

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antiinflammatory[1] anticonvulsant,[2] antiulcer,[3] antiallergic,[3] anticancer,[4,5] antifolate,[6] antihypertensive,[7] antimalarial,[8] and, antitumor[9] activities. Moreover, the capability of fused tetrazolopyrimidines to undergo reductive ring cleavage to form fused aminopyrimidines,[6,10] known for their valuable pharmacological properties and as intermediates in the construction of variety of triheterocycles, was also studied.[11] Therefore, we thought to undertake the synthesis of novel 7*H*-1,2,3,4-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines and to study their transformation to 4-amino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines via reductive ring opening of tetrazolopyrrolopyrimidines. The target triheterocyclic 7,9-disubstituted-7*H*-1,2,3,4-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines **5** were constructed by the annelation of the tetrazole ring onto the existing 4-chloro-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **3** and 4-hydrazino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **4**.

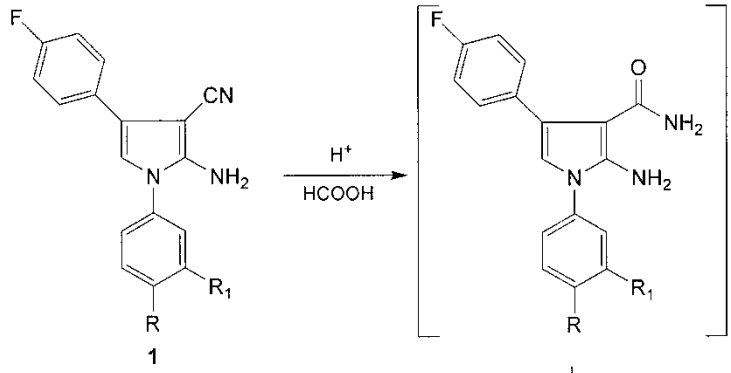
RESULTS AND DISCUSSION

2-Amino-3-cyanopyrroles **1** were obtained by the reaction of (2-bromo-1-(4-fluorophenyl)ethylidene)propanedinitrile and substituted aromatic amine under Gewald reaction conditions.[12]

Compounds **1** were refluxed in boiling formic acid to obtain 5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-(3*H*)-ones **2**. The reaction is believed to proceed through the formation of the corresponding 2-amino-3-carboxamidopyrroles followed by cyclization. Compounds **2** were refluxed in phosphorus oxychloride to obtain 4-chloro-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrmidines **3** (Scheme 1).

The chloro group present at position-4 in the pyrrolo[2,3-*d*]pyrimidine ring was found to be highly reactive toward nucleophilic substitution reactions with sodium azide and hydrazine hydrate. The desired tetrazolopyrrolopyrimidines **5** have been prepared by two different routes. In the first route, 4-chloro-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrmidines **3** were converted to 4-hydrazino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **4** by a substitution reaction with hydrazine hydrate (99%) in ethanol, which in turn was diazotized with sodium nitrite in glacial acetic acid to obtain tetrazolopyrrolopyrimidines **5** (method A). In the second route, 4-chloropyrrolo[2,3-*d*]pyrimidines **3** were reacted with sodium azide in the presence of ammonium chloride in which in situ generation of ammonium azide facilitated the reaction in dimethyl sulfoxide with stirring at 90°C (method B) (Scheme 2).

Because the reductive ring cleavage of the tetrazole moiety constituted a synthetically important process for the preparation of amines, 4-amino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **6** have been synthesized for the first time from tetrazolopyrrolopyrimidines **5**, employing zinc in acetic acid as a reducing agent under boiling conditions, and it was found that the compounds obtained were identical with those synthesized by condensation of 2-amino-3-cyanopyrroles **1** and formamide at reflux temperature[13] (Scheme 3).



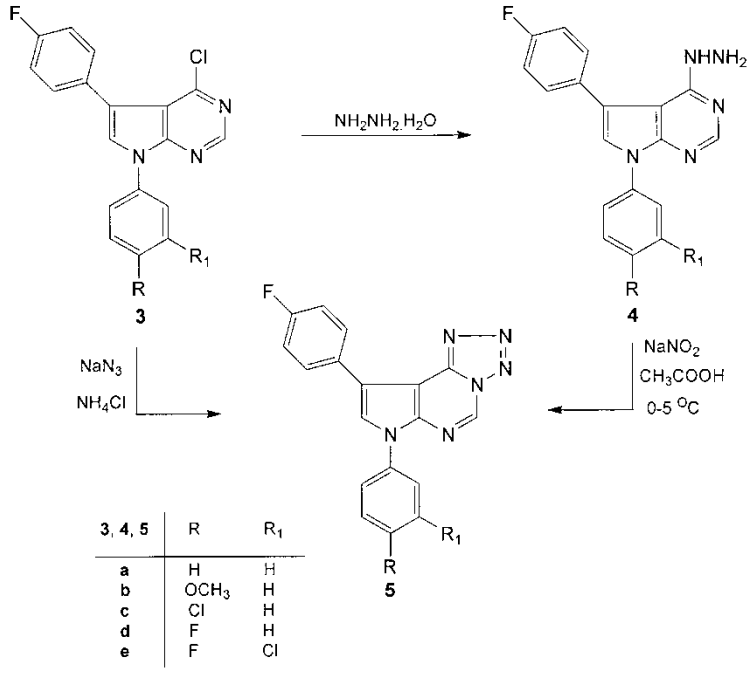
1, 2, 3	R	R_1
a	H	H
b	OCH_3	H
c	Cl	H
d	F	H
e	F	Cl

Scheme 1.

The attempted ring cleavage using agents such as sodiumborohydride[14] and zinc–nickel chloride hexahydrate[15] were unsuccessful, and in both the cases the starting compound **5** was recovered.

EXPERIMENTAL

Melting points were determined by the electrothermal method in an open capillary tube and are uncorrected. The IR spectra were recorded in cm^{-1} for KBr pellets on a Buck-500 spectrophotometer. The ^1H NMR spectra were recorded on Varian 300-MHz spectrophotometer in $CDCl_3$ or



Scheme 2.

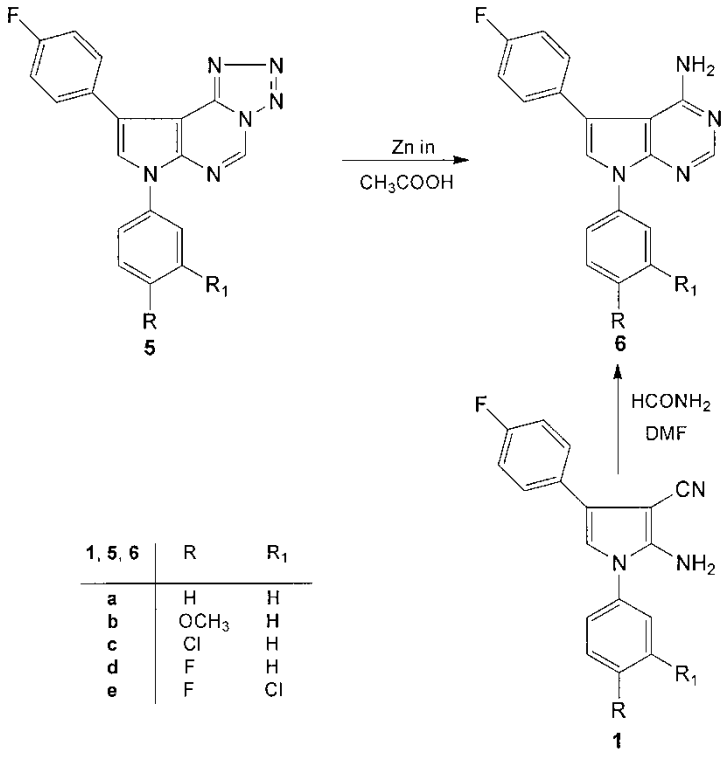
DMSO-d_6 using TMS as internal standard, and the chemical shifts are expressed in δ ppm. MS spectra were recorded on an LKB 9000 mass spectrophotometer. The purity of the compounds was routinely checked by TLC using silica gel G, and spots were exposed in iodine vapor.

General Procedure for the Synthesis of 1,4-Disubstituted 2-amino-3-cyanopyrroles[12,13] 1a–e

Substituted aromatic amine (0.02 mol) dissolved in n-propanol (10 ml) was added portionwise to the solution of (2-bromo-l-(4-fluorophenyl)ethylidene)-propanedinitrile (0.02 mol) in n-propanol (50 ml) with constant stirring at 60–65°C over a period of 40 min. After the completion of addition, the reaction mixture was stirred for 1 h at the same temperature and 1 h at room temperature. The reaction mixture was poured onto crushed ice, and the solid separated was filtered, dried, and crystallized from petroleum ether.

Data

1-Phenyl-2-amino-3-cyano-4-(4-fluorophenyl)pyrrole (**1a**): Yield, 58%, mp 142–144°C; IR (KBr): $\nu = 3480$, 3360 (NH), 2210 (CN), 1616, 1504 cm^{-1}



1, 5, 6	R	R_1
a	H	H
b	OCH_3	H
c	Cl	H
d	F	H
e	F	Cl

Scheme 3.

(C═C, C═N ring); ^{1}H NMR ($CDCl_3$): $\delta = 5.44$ (s, 2H, NH), 6.85 (s, 1H, H at C_5), 7.18–7.68 (m, 9H, Ar-H); anal. calcd. for $C_{17}H_{12}FN_3$ (277.30): C, 73.63; H, 4.36; N, 15.15%. Found: C, 73.56; H, 4.12; N, 15.31%.

1-(4-Methoxyphenyl)-2-amino-3-cyano-4-(4-fluorophenyl)pyrrole (**1b**): Yield, 62%, mp 122–124°C; IR (KBr): $\nu = 3460$, 3330 (NH), 2210 (CN), 1612, 150 cm^{-1} (C═C, C═N ring); ^{1}H NMR ($CDCl_3$): $\delta = 3.90$ (s, 3H, OCH_3), 5.46 (s, 2H, NH), 6.87 (s, 1H, H at C_5), 7.12–7.68 (m, 8H, Ar-H); anal. calcd. for $C_{18}H_{14}FN_3O$ (307.32): C, 70.35; H, 4.59; N, 13.67%. Found: C, 70.26; H, 4.77; N, 13.49%.

1-(4-Chlorophenyl)-2-amino-3-cyano-4-(4-fluorophenyl)pyrrole (**1c**): Yield, 68%, mp 252–254°C; IR (KBr): $\nu = 3480$, 3340 (NH), 2220 (CN), 1612, 1508 cm^{-1} (C═C, C═N ring); ^{1}H NMR ($CDCl_3$): $\delta = 5.40$ (s, 2H, NH), 6.82 (s, 1H, H at C_5), 7.20–7.74 (m, 8H, Ar-H}; anal. cald. for $C_{17}H_{11}ClFN_3$ (311.74): C, 65.50; H, 3.56; N, 13.48%. Found: C, 65.38; H, 3.64; N, 13.61%.

1,4-Bis(4-fluorophenyl)-2-amino-3-cyanopyrrole (**1d**): Yield, 52%, mp 112–114°C; IR (KBr): $\nu = 3470$, 3380 (NH), 2210 (CN), 1620, 1512 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 5.47$ (s, 2H, NH), 6.85 (s, 1H, H at C_5), 7.14–7.68 (m, 8H, Ar-H); anal. calcd. for $C_{17}H_{11}F_2N_3$ (295.29): C, 69.15; H, 3.75; N, 14.23%. Found: C, 69.26; H, 3.98; N, 14.02%.

1-(3-Chloro-4-fluorophenyl)-2-amino-3-cyano-4-(4-fluorophenyl)pyrrole (**1e**): Yield, 66%, mp 196–198°C; IR (KBr): $\nu = 3460$, 3340 (NH), 2210 (CN), 1616, 1500 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 5.46$ (s, 2H, NH), 6.86 (s, 1H, H at C_5), 7.20–7.78 (m, 7H, Ar-H); anal. calcd. for $C_{17}H_{10}ClF_2N_3$ (329.73): C, 61.92; H, 3.06; N, 12.74%. Found: C, 61.86; H, 2.98; N, 12.67%.

General Procedure for the Synthesis of 5,7-Disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-ones 2a–e

A mixture of 1,4-disubstituted-2-amino-3-cyanopyrrole (**1**, 0.01 mol) and formic acid (25 ml) was stirred at reflux temperature for 7–8 h. The reaction mixture was then allowed to cool, poured onto crushed ice (50 g), neutralized with sodium hydroxide solution (5 N), filtered, dried, and crystallized from a mixture of *N*,*N*-dimethylformamide and ethanol (6 : 4 v/v).

Data

5-(4-Fluorophenyl)-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**2a**) nomenclature. Yield, 60%, mp 238–240°C; IR (KBr): $\nu = 3240$ (NH), 1680 (C═O), 1586, 1508 cm^{-1} (C═C, C═N ring); ^1H NMR (DMSO-d_6): $\delta = 7.20–8.10$ (m, 11H, Ar-H), 11.65 (s, 1H, NH); anal. calcd. for $C_{18}H_{12}FN_3O$ (305.31): C, 70.81; H, 3.96; N, 13.76%. Found: C, 70.66; H, 3.90; N, 13.67%.

5-(4-Fluorophenyl)-7-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**2b**). Yield, 60%, mp 286–288°C; IR (KBr): $\nu = 3250$ (NH), 1682 (C═0), 1590, 1504 cm^{-1} (C═C, C═N ring); ^1H NMR (DMSO-d_6): $\delta = 3.88$ (s, 3H, OCH_3), 7.16–8.14 (m, 10H, Ar-H), 11.58 (s, 1H, NH); anal. calcd. for $C_{19}H_{14}FN_3O_2$ (335.33): C, 68.05; H, 4.21; N, 12.53%. Found: C, 68.10; H, 4.44; N, 12.67%.

5-(4-Fluorophenyl)-7-(4-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**2c**). Yield, 70%, mp 297–299°C; IR (KBr): $\nu = 3260$ (NH), 1676 (C═O), 1584, 1512 cm^{-1} (C═C, C═N ring); ^1H NMR (DMSO-d_6): $\delta = 7.24–8.06$ (m, 10H, Ar-H), 11.63 (s, 1H, NH); anal. calcd. for $C_{18}H_{11}FN_3O$ (339.75): C, 63.63; H, 3.26; N, 12.37%. Found: C, 63.42; H, 3.12; N, 12.10%.

5,7-Bis(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**2d**). Yield, 52%, mp 217–219°C; IR (KBr): $\nu = 3290$ (NH), 1672 (C═O), 1588, 1496 cm^{-1} (C═C, C═N ring); ^1H NMR (DMSO-d_6): $\delta = 7.16–8.14$ (m, 10H, Ar-H), 11.67 (s, 1H, NH); anal. calcd. for $C_{18}H_{11}F_2N_3O$ (323.30): C, 66.87; H, 3.43; N, 13.00%. Found: C, 67.01; H, 3.50; N, 12.88%.

5-(4-Fluorophenyl)-7-(3-chloro-4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**2e**). Yield, 65%, mp 275–277°C; IR (KBr): $\nu = 3210$ (NH), 1680 (C═O), 1586, 1500 cm^{-1} (C═C, C═N ring); ^1H NMR (DMSO-d_6): $\delta = 7.16–8.14$ (m, 9H, Ar-H), 11.62 (s, 1H, NH); anal. calcd. for $C_{18}H_{10}ClF_2N_3O$ (357.74): C, 60.43; H, 2.82; N, 11.75%. Found: C, 60.12; H, 3.02; N, 11.69%.

General Procedure for the Synthesis of 4-Chloro-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines 3a–e

A mixture of 5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**2**, 0.01 mol) and phosphorus oxychloride (25 ml) was refluxed for 16–17 h. After the completion of reaction, the excess of phosphorus oxychloride was removed under vacuum. The cooled reaction mixture was then added to crushed ice (25 g). The resulting solid was filtered, washed with sodium bicarbonate (5% w/v) followed by cold water, dried, and crystallized from ethanol and chloroform (8 : 2 v\v).

Data

4-Chloro-5-(4-fluorophenyl)-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3a**): Yield 78%, mp 138–140°C; IR (KBr): $\nu = 1612$, 1504 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 7.16–8.14$ (m, 11H, Ar-H); anal. calcd. for $C_{18}H_{11}ClFN_3$ (323.75): C, 66.78; H, 3.42; N, 12.98%. Found: C, 66.52; H, 3.50; N, 12.88%.

4-Chloro-5-(4-fluorophenyl)-7-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3b**): Yield; 81%, mp 166–167°C; IR (KBr): $\nu = 1608$, 1512 cm^{-1} (C═C, C═N ring), ^1H NMR ($CDCl_3$): $\delta = 3.90$ (s, 3H, OCH_3); 7.20–8.22 (m, 10H, Ar-H); anal. calcd. for $C_{19}H_{13}ClFN_3O$ (353.78): C, 64.50; H, 3.70; N, 11.88%. Found: C, 64.38; H, 3.52; N, 12.03%.

4-Chloro-5-(4-fluorophenyl)-7-(4-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3c**): Yield, 75%, mp 179–181°C; IR (KBr): $\nu = 1616$, 1500 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 7.12–8.00$ (m, 10H, Ar-H); anal. calcd. for $C_{18}H_{10}Cl_2FN_3$ (358.20): C, 60.36; H, 2.81; N, 11.73%. Found: C, 60.18; H, 3.04; N, 11.96%.

4-Chloro-5,7-bis(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3d**): Yield, 68%, mp 118–119°C; IR (KBr): $\nu = 1604$, 1512 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 7.18–8.16$ (m, 10H, Ar-H); anal. calcd. for $C_{18}H_{10}ClF_2N_3$ (341.74): C, 63.26; H, 2.95; N, 12.30%. Found: C, 63.18; H, 3.04; N, 12.19%.

4-Chloro-5-(4-fluorophenyl)-7-(3-chloro-4-chlorophenyl)-7*H*-pyrrolo[2,3-*d*] pyrimidine (**3e**): Yield, 85%, mp 153–155°C; IR (KBr): $\nu = 1612$, 1504 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 7.12–8.08$ (m, 9H, Ar-H); anal. calcd. for $C_{18}H_9Cl_2F_2N_3$ (376.19): C, 57.47; H, 2.41; N, 11.17%. Found: C, 57.22; H, 2.24; N, 10.96%.

General Procedure for the Synthesis of 4-Hydrazino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines 4a–e

4-Chloro-5,7-disubstituted-7*H*-pyrrolo[2,3-d]pyrimidine (**3**, 0.01 mol) was added to a mixture of hydrazine hydrate (99%, 15 ml) and absolute ethanol (30 ml) and heated under reflux conditions for 3–4 h. Then the reaction mixture was allowed to attain the room temperature, poured onto the crushed ice, and neutralized with acetic acid (pH 7) to obtain the solid, which was filtered, washed with water, dried, and crystallized from chlorofrorm.

Data

4-Hydrazino-5-(4-fluorophenyl)-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4a**): Yield, 76%, mp 196–198°C; IR (KBr): $\nu = 3420$, 3320, 3260 (NH), 1612, 1504 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 4.12$ (s, 2H, NH_2), 6.15 (s, 1H, NH), 7.28–8.46 (m, 11H, Ar-H); anal. calcd. for $C_{18}H_{14}FN_5$ (319.34): C, 67.70; H, 4.42; N, 21.93%. Found: C, 67.53; H, 4.55; N, 21.89%.

4-Hydrazino-5-(4-fluorophenyl)-7-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4b**): Yield, 65%, mp 178–180°C; IR (KBr): $\nu = 3440$, 3330, 3250 (NH), 1608, 1508 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 3.89$ (s, 3H, OCH_3), 4.14 (s, 2H, NH_2), 6.17 (s, 1H, NH), 7.30–8.48 (m, 10H, Ar-H); anal. calcd. for $C_{19}H_{16}FN_5O$ (349.36): C, 65.32; H, 4.62; N, 20.05%. Found: C, 65.22; H, 4.73; N, 19.99%.

4-Hydrazino-5-(4-fluorophenyl)-7-(4-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4c**): Yield, 79%, mp 203–205°C; IR (KBr): $\nu = 3440$, 3340, 3240 (NH), 1604, 1500 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 4.10$ (s, 2H, NH_2), 6.19 (S, 1H, NH) 7.32–8.44 (m, 10H, Ar-H); anal. calcd. for $C_{18}H_{13}ClFN_5$ (353.78): C, 61.11; H, 3.70; N, 19.80%. Found: C, 61.23; H, 3.58; N, 19.89%.

4-Hydrazino-5,7-bis(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4d**): Yield, 61%, mp 157–159°C; IR (KBr): $\nu = 3420, 3320, 3260$ (NH), 1616, 1508 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 4.12$ (s, 2H, NH_2), 6.13 (s, 1H, NH), 7.30–8.50 (m, 10H, Ar-H); anal. calcd. for $C_{18}H_{13}F_2N_5$ (337.33): C, 64.09; H, 3.88; N, 20.76%. Found: C, 64.28; H, 3.78; N, 20.90%.

4-Hydrazino-5-(4-fluorophenyl)-7-(3-chloro-4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4e**): Yield 72%, mp 212–214°C; IR (KBr): $\nu = 3440, 3310, 3250$ (NH), 1604, 1512 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 4.15$ (s, 2H, NH_2), 6.13 (s, 1H, NH), 7.32–8.46 (m, 9H, Ar-H); anal. calcd. for $C_{18}H_{12}ClF_2N_5$ (371.17): C, 58.15; H, 3.25; N, 18.84%. Found: C, 58.24; H, 3.20; N, 18.96%.

General Procedure for the Synthesis of 7,9-Disubstituted-7*H*-1,2,3,4-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines 5a–e

Method A

4-Hydrazino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4**, 0.01 mol) was dissolved in glacial acetic acid (40 ml), and an aqueous solution of sodium nitrite (20% w/v, 4.2 ml) was added in small portions with cooling (0–5°C) and constant stirring. The reaction mixture was further stirred for 1–1.5 h at this temperature and poured onto crushed ice (25 g). The solid obtained was filtered, washed with sodium bicarbonate (20% w/v) followed by water, dried, and crystallized from 1,4-dioxane.The physical and analytical data are represented in (Table 1).

Method B

4-Chloro-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3**, 0.01 mol) was added in portions with constant stirring to the well-stirred solution of ammonium chloride (0.011 mol, 0.059 g.) and sodium azide (0.011 mol, 0.072 g) in dimethyl sulfoxide (25 ml). The reaction mixture was stirred for 2 h at 90°C and 1 h at room temperature. The cold solution was poured on to crushed ice (25 g), and the obtained solid was filtered, washed with water, dried, and crystallized (Table 1).

Data

5-(4-Fluorophenyl)-7-phenyl-7*H*-1,2,3,4-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines (**5a**). IR (KBr): $\nu = 1604, 1508$ cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 7.18–8.10$ (m, 11H, Ar-H); MS: $m/z = 330$ (M^+).

Table 1. Physical and analytical data of 7,9-disubstituted-7*H*-1,2,3,4-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines **5a**–**e**

Compound no.	Reaction time (h)		Yield[a] (%)		Mp (°C)	Molecular formula (molecular wt.)	Analysis calcd. (found)		
	Method A	Method B	Method A	Method B			C	H	N
5a	2	3	65	55	218–220	$C_{18}H_{11}FN_6$ (330.32)	65.45(65.64)	3.36(3.33)	25.44(25.64)
5b	2	3	68	63	245–247	$C_{19}H_{13}FN_6O$ (360.34)	63.33(63.17)	3.64(3.85)	23.32(23.06)
5c	2	3	58	55	226–228	$C_{18}H_{10}ClFN_6$ (364.76)	59.27(59.09)	2.76(2.90)	23.04(22.85)
5d	2	3	66	60	201–202	$C_{18}H_{10}F_2N_6$ (348.31)	62.07(62.20)	2.89(3.08)	24.13(24.40)
5e	2	3	70	64	234–236	$C_{18}H_9ClF_2N_6$ (382.75)	56.48(56.33)	2.37(2.08)	21.96(21.99)

[a]Overall yields for method A from compound **4** and for method B from compound **3**.

5-(4-Fluorophenyl)-7-(4-methoxyphenyl)-7*H*-1,2,3,4-tetrazolo[1,5-*c*]pyrrolo-[3,2-*e*]pyrimidine (**5b**): IR (KBr): $\nu = 1600$, $1500\,cm^{-1}$ (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 3.88$ (s, 3H, OCH_3), 7.16–8.20 (m, 10H, Ar-H); MS: $m/z = 360(M^+)$.

5-(4-Fluorophenyl)-7-(4-chlorophenyl)-7*H*-1,2,3,4-tetrazolo[1,5-*c*]pyrrolo-[3,2-*e*]pyrimidine (**5c**): IR (KBr): $\nu = 1608$, $1496\,cm^{-1}$ (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 7.24$–8.30 (m, 10H, Ar-H); MS: $m/z = 364$ (M^+).

5,7-Bis(4-fluorophenyl)-7*H*-1,2,3,4-tetrazolo[1,5-*c*]pyrrolo-[3,2-*e*]pyrimidine (**5d**): IR (KBr): $\nu = 1600$, $1504\,cm^{-1}$/(C═C, C═N ring); ^1H NMR ($CDCl_3$): δ = 7.10–8.14 (m, 10H, Ar-H); MS: $m/z = 348$ (M^+).

5-(4-Fluorophenyl)-7-(3-chloro-4-fluorophenyl)-7*H*-pyrrolo-1,2,3,4-tetrazolo-[1,5-*c*]pyrrolo[3,2-*e*]pyrimidine (**5e**): IR (KBr): $\nu = 1608$, $1504\,cm^{-1}$ (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 7.16$–8.24 (m, 9H, Ar-H); MS: $m/z = 382$ (M^+).

General Procedure for the Synthesis of 4-Amino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines 6a–e

Method C

Powdered zinc (0.5 g) was added cautiously to the mixture of 7,9-disubstituted-7*H*-1,2,3,4-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidine (**5**, 0.002 mol) in glacial acetic acid (10 ml) over a period of 30 min. (An exothermic reaction was observed.) The reaction mixture was then refluxed for 1–1.5 h, cooled, and poured onto crushed ice (25 g). The resulting mixture was neutralized to (pH 7) with ammonia solution (6*N*) and extracted with chloroform (2×30 ml). The total chloroform layer was dried over anhydrous magnesium sulfate, concentrated in vacuo, and crystallized from a mixture of ethanol and chloroform (8 : 2 v/v). The physical and analytical data are given in Table 2.

Method D

A mixture of 1,4-disubstituted 2-amino-3-cyanopyrrole (**1**, 0.01 mol), formamide (15 ml), *N*,*N*-dimethylformamide (5 ml), and formic acid (2 ml) was heated under reflux for 6–8 h. The reaction mixture was allowed to stand overnight at room temperature. The solid thus obtained was filtered, washed with cold methanol, dried, and crystallized (Table 2).

Table 2. Physical and analytical data of 4-amino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **6a**–**e**

Compound no.	Reaction time (h)		Yield[a] (%)		Mp (°C)	Molecular formula (molecular wt.)	Analysis calcd. (found)		
	Method C	Method D	Method C	Method D			C	H	N
6a	2	6	65	55	185–187	$C_{18}H_{13}FN_4$ (304.32)	71.04(71.12)	4.31(4.33)	18.41(18.64)
6b	2.5	7	68	63	153–154	$C_{19}H_{15}FN_4O$ (334.35)	68.25(68.37)	4.52(4.65)	16.76(16.96)
6c	3	6.5	58	55	276–278	$C_{18}H_{12}ClFN_4$ (338.77)	63.82(63.90)	3.57(3.48)	16.54(16.65)
6d	2	8	66	60	163–165	$C_{18}H_{12}F_2N_4$ (322.31)	67.08(67.28)	3.75(3.95)	17.38(17.40)
6e	2	7	70	64	241–243	$C_{18}H_{11}ClF_2N_4$ (355.75)	60.77(60.83)	2.83(2.86)	15.75(15.99)

[a]Overall yields for method C from compound **5** and for method D from compound **1**.

Data

4-Amino-5-(4-fluorophenyl)-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**6a**). IR (KBr): $\nu = 3470$, 3290 (NH), 1585, 1500 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 5.30$ (s, 2H, NH_2), 7.10–8.38 (m, 11H, Ar-H).

4-Amino-5-(4-fluorophenyl)-7-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**6b**): IR (KBr): $\nu = 3480$, 3270 (NH), 1580, 1510 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 3.91$ (s, 3H, OCH_3), 5.20 (s, 2H, NH_2), 7.20–8.40 (m, 10H, Ar-H).

4-Amino-5-(4-fluorophenyl)-7-(4-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**6c**): IR (KBr): $\nu = 3465$, 3280 (NH), 1580, 1510 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 5.24$ (s, 2H, NH_2), 7.12–8.36 (m, 10H, Ar-H).

4-Amino-5,7-bis(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine change (**6d**): IR (KBr): $\nu = 3480$, 3300 (NH), 1580, 1485 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 5.28$ (s, 2H, NH_2), 7.20–8.38 (m, 10H, Ar-H).

4-Amino-5-(4-fluorophenyl)-7-(3-chloro-4-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**6e**): IR (KBr): $\nu = 3460$, 3280 (NH), 1580, 1500 cm^{-1} (C═C, C═N ring); ^1H NMR ($CDCl_3$): $\delta = 5.30$ (s, 2H, NH_2), 7.18–8.34 (m, 9H, Ar-H).

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