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Some fluoroaryl substituted 2-amino-3-cyanopyrroles **2** were synthesized from the reaction between (2-bromo-1-arylalkylidene)propanedinitriles **1** and fluoroaryl substituted aromatic amines under Gewald reaction condition, which on reaction with formamide and formic acid gave 4-aminopyrrolo[2,3-*d*]pyrimidines **3** and pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-ones **4** respectively. 4-Chloropyrrolo[2,3-*d*]pyrimidines **5** were prepared by chlorination of **4** with phosphorus oxychloride, which on hydrazinolysis provided 4-hydrazinopyrrolo[2,3-*d*]pyrimidines **6**.

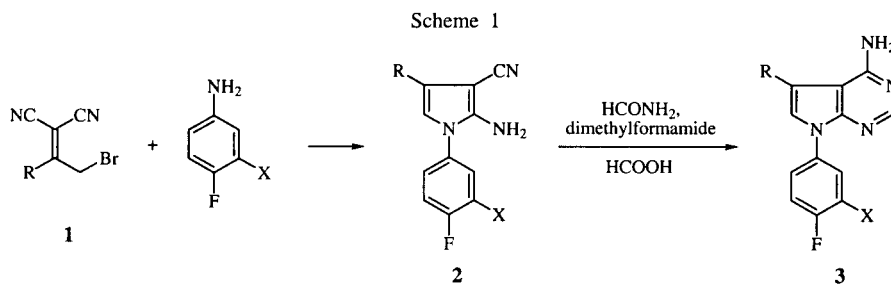
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Aromatic and heterocyclic *o*-aminonitriles have widely been used as building blocks for the construction of several heterocycles [1]. For long time now the 2-amino-3-cyanopyrrole system has been our preferential basis for the synthesis of pyrrolo[2,3-*d*]pyrimidines [2-4], pyrroloquinazolines [5] and pyrrolo[1,2-*a*]pyrimidines [6]. Due to the presence of pyrrolo[2,3-*d*]pyrimidine moiety in important antibiotics tubercidin [7], toyocamycin [7] and sangivamycin [8,9] the interest has aroused in the construction of such molecules. 4-Amino or 4-hydroxypyrrolo[2,3-*d*]pyrimidines were known to possess antiinflammatory, anticonvulsant and sedative activities [10,11] and hypoxanthin isosters pyrrolo[2,3-*d*]pyrimidine-4-ones have been found to occur as heterocyclic bases in a number of antibiotics [12,13]. Further, it has been a recent interest in utilizing fluorine to alter the physical and chemical properties of organic compounds and as a result a number of fluoro substituted heterocycles have been synthesized for various applications [14]. In view of these findings, we wish to report herein the synthesis and reactions of some new pyrrolo[2,3-*d*]pyrimidines of pharmacological importance.

For the purpose, novel fluoroaryl substituted 2-amino-3-cyanopyrroles have been synthesized as building blocks.

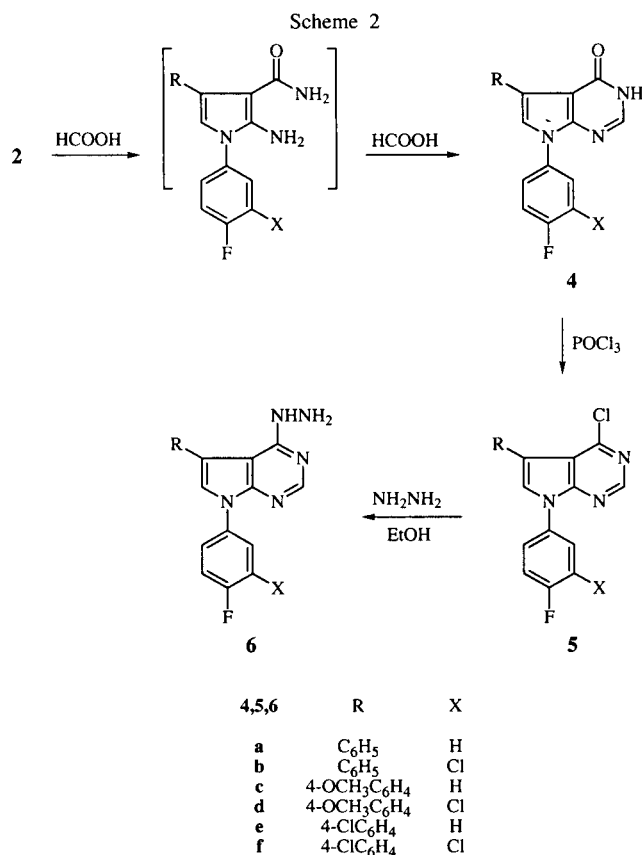
(2-Bromo-1-arylalkylidene)propanedinitriles **1** when condensed with various fluorinated aromatic amines under mild Gewald reaction conditions [15], 1,4-disubstituted 2-amino-3-cyanopyrroles **2** were obtained which on cyclcondensation with formamide in *N,N*-dimethylformamide, 5,7-disubstituted 4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidines **3** were formed. It was found during these reactions that a little amount of formic acid plays an important roll to increase the yields (Scheme 1).

When 2-amino-3-cyanopyrroles **2** were refluxed in formic acid, 5,7-disubstituted 7*H*-pyrrolo[2,3-*d*]pyrimidine-4(3*H*)ones **4** were obtained in good yields. This reaction is supposed to proceed *via* intermediate amide formation, resulted from the partial hydrolysis of cyano functionality present at position-2 of **2**, followed by intramolecular cyclization. The chlorination at position-4 was achieved by refluxing **4** with phosphorus oxychloride to give 5,7-disubstituted 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidines **5** which in turn were subjected to nucleophilic



1,2,3	R	X
a	C <sub>6</sub> H <sub>5</sub>	H
b	C <sub>6</sub> H <sub>5</sub>	Cl
c	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H
d	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Cl
e	4-ClC <sub>6</sub> H <sub>4</sub>	H
f	4-ClC <sub>6</sub> H <sub>4</sub>	Cl

substitution reaction with hydrazine hydrate in ethanol to afford 5,7-disubstituted 4-hydrazino-7*H*-pyrrolo[2,3-*d*]-pyrimidines **6** (Scheme 2), which are the building blocks for the design of triheterocycles such as triazolopyrrolopyrimidines and tetrazolopyrrolopyrimidines [16,17].



The ir (potassium bromide) spectra of 2-amino-3-cyanopyrroles **2** exhibited stretching vibrations in the region 3480-3320 cm<sup>-1</sup> (NH<sub>2</sub>), 2200 cm<sup>-1</sup> (C≡N), 1600-1512 cm<sup>-1</sup> (C=C, C=N ring) together with a bending vibrations near 1640-1628 cm<sup>-1</sup> (NH<sub>2</sub>). The stretching vibrations were found to be present near 3470, 3300 and 3100 cm<sup>-1</sup> (NH) and 1590-1480 cm<sup>-1</sup> (C=C, C=N ring) whereas bending vibration due to amino functionality was found around 1640 cm<sup>-1</sup> in the case of **3**. The absence of a signal in the region 2210-2200 cm<sup>-1</sup> (CN) established the formation of **3**. The <sup>1</sup>H nmr (deuteriochloroform) spectra of **2** displayed a broad singlet because of amino protons at δ 5.40-5.50 (2H), while aromatic protons resonated at δ 7.10-8.40 giving a multiplet. 5,7-Disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-ones **4** showed a strong stretching vibration for cyclic ketone at 1682-1672 cm<sup>-1</sup> along with other characteristic stretching bands in the region 3300-3200 cm<sup>-1</sup> (NH) and 1596-1484 cm<sup>-1</sup> (C=C, C=N ring), which confirmed the formation of **4** via the formation of the intermediate 2-amino-3-carboxamidopyrroles followed by the cyclization (Scheme 2). A

singlet at δ 5.20-5.30 (2H) was responsible for amino protons where as a multiplet at δ 7.00-8.40 was assigned to aromatic protons in the <sup>1</sup>H nmr (deuteriochloroform) spectra of **3**. The aromatic protons were resonated at δ 7.00-8.20 producing a multiplet together with a broad singlet at δ 11.40-11.65 (1H) due to ring NH proton in the <sup>1</sup>H nmr (deuteriodimethyl sulfoxide) spectra of 5-7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-ones **4**. As no absorption was found in the region 3300-3208 cm<sup>-1</sup> and 1700 cm<sup>-1</sup> responsible for cyclic -NHCO- functionality in the case of **5**, the chlorination at position-4 of 5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-ones **4** was supported. The <sup>1</sup>H nmr spectra(deuteriochloroform) of **5** also provided the satisfactory results showing a multiplet due to aromatic protons in the region δ 7.10-8.20. The ir (potassium bromide) spectra of **6** exhibited the stretching vibrations near 3450, 3330 and 3200 cm<sup>-1</sup> (NH), 1612-1496 cm<sup>-1</sup> (C=N ring) and bending vibration at 1650 cm<sup>-1</sup> (NH<sub>2</sub>). Signals at δ 4.10-4.20 (2H) and 6.10-6.20 (1H) were assigned to hydrazino protons in the <sup>1</sup>H nmr (deuteriochloroform) spectra of **6**, where as a multiplet near δ 7.20-8.40 was found to be present because of aromatic protons.

## EXPERIMENTAL

Melting points are uncorrected and were determined in open capillaries. The infrared spectra were recorded in cm<sup>-1</sup> on Buck-500 spectrophotometer using the potassium bromide technique. The <sup>1</sup>H nmr spectra were recorded on Varian 400 MHz spectrometer using deuteriochloroform and deuteriodimethyl sulfoxide as solvents using tetramethylsilane as the internal standard and the chemical shifts are expressed in δ ppm. The purity of the compounds was checked by tlc using silica gel G and spots were visualized by exposing the dried plates to iodine vapour.

**General Procedure for the Synthesis of 1,4-Disubstituted 2-Amino-3-cyanopyrroles 2a-f.**

To the solution of (2-bromo-1-arylalkylidene)propanedinitriles [14] (0.02 mole) in propan-2-ol (50 ml) was added a solution of the aromatic amine (0.02 mole) in propan-2-ol (10 ml) portionwise over a period of 0.5 hour with constant stirring at 60-65°. After the completion of addition, the reaction mixture was further stirred for 1 hour at the same temperature and for 1 hour at room temperature. The solid separated was filtered, dried and crystallized (Table 1).

**General Procedure for the Synthesis of 5,7-Disubstituted 4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidines 3a-f.**

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

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

1,4-Disubstituted 2-amino-3-cyanopyrrole (**2**, 0.01 mole) and formic acid (25 ml) were refluxed for 6-8 hours. The reaction

Table 1  
Physical and Analytical Data of Compounds 2, 3, 4, 5 and 6

Compound No.	Yield% %	mp°C\crystallization solvent	Molecular Formula\ Molecular weight	Analysis %		
				Calcd.	Found	
				C	H	N
2a	45	145-147	C <sub>17</sub> H <sub>12</sub> FN <sub>3</sub>	73.63	4.36	15.15
		E	277.29	73.42	4.19	15.31
2b	50	175-176	C <sub>17</sub> H <sub>11</sub> ClFN <sub>3</sub>	65.50	3.58	13.48
		P	311.73	65.13	3.28	13.29
2c	40	120-122	C <sub>18</sub> H <sub>14</sub> FN <sub>3</sub> O	70.35	4.59	13.67
		E	307.31	70.50	4.63	13.48
2d	55	138-140	C <sub>18</sub> H <sub>13</sub> ClFN <sub>3</sub> O	63.28	3.84	12.30
		E	341.75	63.50	3.69	12.48
2e	50	250-252	C <sub>17</sub> H <sub>11</sub> ClFN <sub>3</sub>	65.50	3.58	13.48
		P	311.73	65.68	3.37	13.71
2f	54	230-232	C <sub>17</sub> H <sub>10</sub> Cl <sub>2</sub> FN <sub>3</sub>	58.99	2.91	12.14
		P	346.18	58.74	2.68	12.49
3a	48	183-185	C <sub>18</sub> H <sub>13</sub> FN <sub>4</sub>	71.04	4.31	18.41
		E-D	304.31	71.33	4.10	18.40
3b	65	238-240	C <sub>18</sub> H <sub>12</sub> ClFN <sub>4</sub>	63.81	3.57	16.54
		D	338.78	63.54	3.38	16.81
3c	55	153-154	C <sub>19</sub> H <sub>15</sub> FN <sub>4</sub> O	68.25	4.52	16.76
		E-D	334.34	68.02	4.22	16.38
3d	72	220-222	C <sub>19</sub> H <sub>14</sub> ClFN <sub>4</sub> O	61.88	3.83	15.20
		E-D	368.78	61.43	3.92	15.50
3e	77	276-278	C <sub>18</sub> H <sub>12</sub> ClFN <sub>4</sub>	63.82	3.58	16.54
		D	338.76	63.51	3.44	16.71
3f	66	308-310	C <sub>18</sub> H <sub>11</sub> Cl <sub>2</sub> FN <sub>4</sub>	57.93	2.97	15.01
		D	373.21	57.60	3.12	15.34
4a	66	238-240	C <sub>18</sub> H <sub>12</sub> FN <sub>3</sub> O	70.81	3.96	13.76
		C	305.3	71.10	4.26	13.50
4b	68	288-290	C <sub>18</sub> H <sub>11</sub> ClFN <sub>3</sub> O	63.63	3.26	12.37
		D	339.74	63.42	3.47	12.30
4c	60	291-293	C <sub>19</sub> H <sub>14</sub> FN <sub>3</sub> O <sub>2</sub>	68.05	4.21	12.53
		E-D	335.32	68.32	4.25	12.42
4d	50	228-230	C <sub>19</sub> H <sub>13</sub> ClFN <sub>4</sub> O <sub>2</sub>	61.72	3.54	11.36
		C	369.76	61.79	3.73	11.09
4e	70	301-303	C <sub>18</sub> H <sub>11</sub> ClFN <sub>3</sub> O	63.63	3.26	12.37
		D	339.74	63.78	3.40	12.50
4f	67	345-347	C <sub>18</sub> H <sub>10</sub> Cl <sub>2</sub> FN <sub>3</sub> O	57.77	2.69	11.23
		D	374.19	57.42	2.80	11.42
5a	62	139-140	C <sub>18</sub> H <sub>11</sub> ClFN <sub>3</sub>	66.78	3.43	12.98
		E	323.74	66.50	3.48	12.71
5b	79	146-147	C <sub>18</sub> H <sub>10</sub> Cl <sub>2</sub> FN <sub>3</sub>	60.35	2.81	11.73
		C	358.19	60.32	2.79	11.65
5c	60	178-179	C <sub>19</sub> H <sub>13</sub> ClFN <sub>3</sub> O	64.50	3.71	11.88
		E	353.77	64.34	4.10	12.13
5d	75	135-136	C <sub>19</sub> H <sub>12</sub> Cl <sub>2</sub> FN <sub>3</sub> O	58.78	3.12	10.82
		C	388.22	58.72	3.24	10.71
5e	85	220-222	C <sub>18</sub> H <sub>10</sub> Cl <sub>2</sub> FN <sub>3</sub>	60.35	2.81	11.73
		E-D	358.19	60.11	3.19	12.03
5f	86	228-230	C <sub>18</sub> H <sub>9</sub> Cl <sub>3</sub> FN <sub>3</sub>	55.06	2.31	10.70
		D	392.64	55.23	2.53	10.51
6a	69	198-200	C <sub>18</sub> H <sub>14</sub> FN <sub>5</sub>	67.70	4.42	21.93
		C	319.33	67.58	4.13	21.71
6b	78	240-242	C <sub>18</sub> H <sub>13</sub> ClFN <sub>5</sub>	61.11	3.70	19.80
		D	353.77	60.82	3.89	19.62
6c	63	172-173	C <sub>19</sub> H <sub>16</sub> FN <sub>5</sub> O	65.31	4.62	20.05
		E-D	349.36	65.23	4.58	20.34
6d	72	202-204	C <sub>19</sub> H <sub>15</sub> ClFN <sub>5</sub> O	59.46	3.94	18.25
		D	383.80	59.30	3.55	18.03
6e	79	210-212	C <sub>18</sub> H <sub>13</sub> ClFN <sub>5</sub>	61.11	3.70	19.80
		C	353.77	61.38	3.65	19.90
6f	77	243-245	C <sub>18</sub> H <sub>12</sub> Cl <sub>2</sub> FN <sub>5</sub>	55.68	3.12	18.04
			388.23	55.41	3.40	18.20

C = chloroform, D = *N,N*-dimethylformamide, E = ethanol, P = petroleum ether (40-60°).

Table 2  
IR and <sup>1</sup>H nmr Spectral Data of Compounds 2, 3, 4, 5 and 6

Compound No	ir (potassium bromide) cm <sup>-1</sup>	<sup>1</sup> H nmr (δ ppm)
2a	3480, 3360, 2210, 1628, 1600, 1500	5.40 (s, 2H, NH), 7.20-8.20 (m, 10H, Ar-H)
2b	3480, 3360, 2220, 1636, 1596, 1512	5.50 (s, 2H, NH), 7.10-8.30 (m, 9H, Ar-H)
2c	3460, 3330, 2220, 1640, 1598, 1516	3.90 (s, 3H, OCH <sub>3</sub> ), 5.40 (s, 2H, NH <sub>2</sub> ), 7.10-8.30 (m, 9H, ArH)
2d	3450, 3330, 2210, 1644, 1600, 1508	3.88 (s, 3H, OCH <sub>3</sub> ), 5.40 (s, 2H, NH <sub>2</sub> ), 7.00-8.40 (m, 8H, ArH)
2e	3440, 3320, 2210, 1640, 1596, 1510	5.40 (s, 2H, NH <sub>2</sub> ), 7.10-8.30 (m, 9H, Ar-H)
2f	3460, 3360, 2210, 1640, 1600, 1512	5.50 (s, 2H, NH <sub>2</sub> ), 7.20-8.40 (m, 8H, Ar-H)
3a	3510, 3300, 1628, 1590, 1492	5.20 (s, 2H, NH <sub>2</sub> ), 7.10-8.30 (m, 11H, Ar-H)
3b	3510, 3300, 1644, 1588, 1486	5.30 (s, 2H, NH <sub>2</sub> ), 7.20-8.40 (m, 10H, Ar-H)
3c	3500, 3330, 1648, 1586, 1488	3.90 (s, 3H, OCH <sub>3</sub> ), 5.20 (s, 2H, NH <sub>2</sub> ), 7.10-8.40 (m, 10H, ArH)
3d	3510, 3310, 1644, 1584, 1480	3.85 (s, 3H, OCH <sub>3</sub> ), 5.20 (s, 2H, NH <sub>2</sub> ), 7.00-8.20 (m, 9H, ArH)
3e	3510, 3320, 1648, 1590, 1496	5.20 (s, 2H, NH <sub>2</sub> ), 7.10-8.30 (m, 10H, Ar-H)
3f	3510, 3310, 1648, 1586, 1488	5.30 (s, 2H, NH <sub>2</sub> ), 7.20-8.40 (m, 9H, Ar-H)
4a	3270, 1680, 1586, 1508	7.10-8.00 (m, 11H, Ar-H), 11.65 (s, 1H, NH)
4b	3300, 1682, 1588, 1500	7.10-8.00 (m, 10H, Ar-H), 11.40 (s, 1H, NH)
4c	3260, 1680, 1588, 1498	3.80 (s, 3H, OCH <sub>3</sub> ), 7.00-8.00 (m, 10H, Ar-H), 11.45 (s, 1H, NH)
4d	3280, 1672, 1584, 1484	3.90 (s, 3H, OCH <sub>3</sub> ), 7.20-8.10 (m, 9H, Ar-H), 11.40 (s, 1H, NH)
4e	3210, 1672, 1590, 1500	7.20-8.10 (m, 10H, Ar-H), 11.55 (s, 1H, NH)
4f	3210, 1680, 1586, 1496	7.20-8.20 (m, 9H, Ar-H), 11.45 (s, 1H, NH)
5a	1604, 1524, 1504	7.20-8.00 (m, 11H, Ar-H)
5b	1600, 1524, 1504	7.30-8.00 (m, 10H, Ar-H)
5c	1616, 1580, 1500	3.90 (s, 3H, OCH <sub>3</sub> ), 7.10-8.10 (m, 10H, Ar-H)
5d	1612, 1560, 1504	3.80 (s, 3H, OCH <sub>3</sub> ), 7.20-8.10 (m, 9H, Ar-H)
5e	1600, 1544, 1524	7.10-8.10 (m, 10H, Ar-H)
5f	1584, 1620, 1500	7.20-8.20 (m, 9H, Ar-H)
6a	3420, 3320, 3260, 1656, 1612, 1508	4.12 (s, 2H, NH <sub>2</sub> ), 6.15 (s, 1H, NH), 7.30-8.30 (m, 11H, Ar-H)
6b	3450, 3330, 3260, 1632, 1604, 1500	4.10 (s, 2H, NH <sub>2</sub> ), 6.10 (s, 1H, NH), 7.20-8.40 (m, 10H, Ar-H)
6c	3440, 3340, 3240, 1660, 1600, 1698	3.85 (s, 3H, OCH <sub>3</sub> ), 4.14 (s, 2H, NH <sub>2</sub> ), 6.16 (s, 1H, NH), 7.10-8.30 (m, 10H, Ar-H)
6d	3450, 3330, 3200, 1652, 1608, 1504	3.89 (s, 3H, OCH <sub>3</sub> ), 4.15 (s, 2H, NH <sub>2</sub> ), 6.20 (s, 1H, NH), 7.30-8.40 (m, 9H, Ar-H)
6e	3460, 3330, 3210, 1632, 1604, 1496	4.10 (s, 2H, NH <sub>2</sub> ), 6.20 (s, 1H, NH), 7.20-8.50 (m, 10H, Ar-H)
6f	3480, 3300, 3200, 1630, 1608, 1508	4.10 (s, 2H, NH <sub>2</sub> ), 6.17 (s, 1H, NH), 7.20-8.40 (m, 9H, Ar-H)

mixture was cooled and the separated solid was filtered, washed with cold water (pH 7), followed by aqueous methanol, dried and crystallized (Table 2)

General Procedure for the Synthesis of 5,7-Disubstituted 4-Chloro-7H-pyrrolo[2,3-d]pyrimidines 5a-f.

A mixture of 5,7-disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one 4 and phosphorus oxychloride (25 ml) was refluxed for 15-17 hours. Excess phosphorus oxychloride was removed under vacuum. The reaction mixture was cooled to room temperature and poured onto the crushed ice. The solid thus separated was filtered, washed with water, dried and crystallized from ethanol (Table 2).

General Procedure for the Synthesis of 5,7-Disubstituted 4-Hydrazino-7H-pyrrolo[2,3-d]pyrimidines 6a-f.

To a mixture of hydrazine hydrate (99 %, 15 ml) and absolute ethanol (30 ml) was added 5,7-disubstituted 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (5, 0.01 mole) and heated under reflux condition for 3-4 hours. Then the reaction mixture was allowed to attain the room temperature, poured onto the crushed ice,

neutralized with acetic acid (pH 7) to obtain the solid, which was filtered, washed with water, dried and crystallized (Table 2).

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