Synthesis of 8-Cyano-1,4-dihydro-4-oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylic Acids as Potential Antimicrobial Agents

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The preparation of a variety of 8-cyano-1,4-dihydro-7-phenyl-4-oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylic acids and 8-cyano-1,4-dihydro-7-*p*-fluorophenyl-4-oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylic acids is described.

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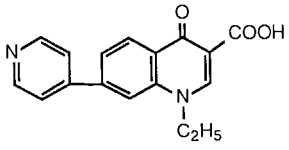
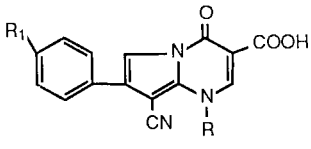
Rosoxacin (**I**), 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic acid, is a new quinolone antibacterial agent, which has good *in vitro* activity against common urinary pathogens with less activity against gram-positive cocci [1,2]. The synthesis of rosoxacin and derivatives with differing substitutions in the pyridine ring and at position-1 has been reported [3].



I

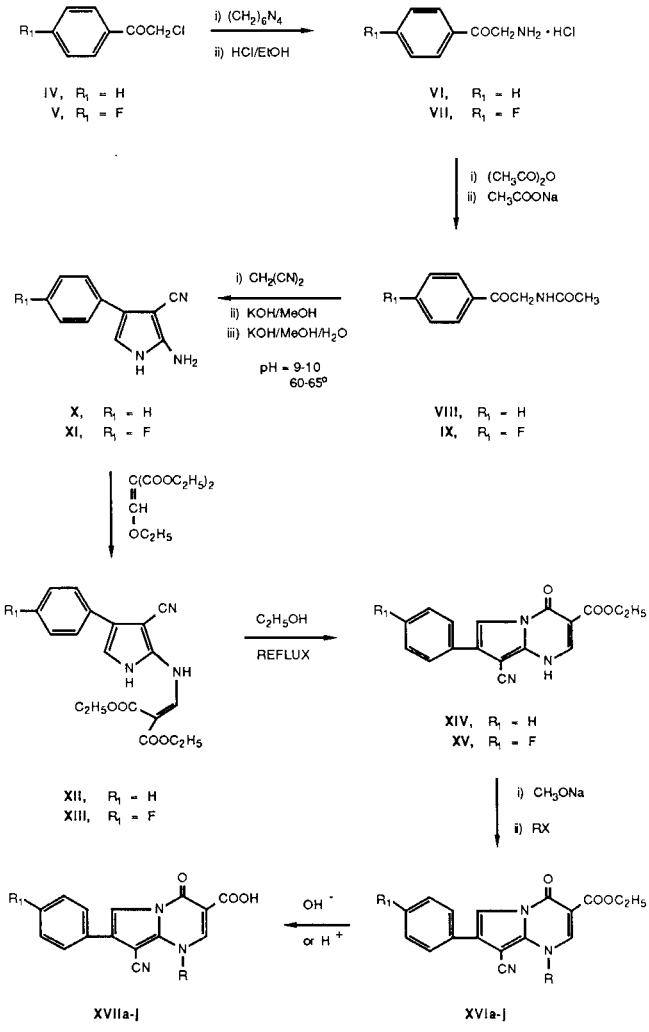


II, R_1 = H
III, R_1 = F

In this report, we describe the synthesis of a series of 8-cyano-1,4-dihydro-7-phenyl-4-oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylic acids (**II**) and 8-cyano-1,4-dihydro-7-*p*-fluorophenyl-4-oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylic acids (**III**), as potential antimicrobial agents.

Scheme 1 outlines the synthetic path used to prepare the desired 4-oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylic acids **XVIIa-j**. In the initial step of the synthesis, hexamethylenetetramine salts of α-chloroacetophenone (**IV**) and *p*-fluoro-α-chloracetophenone (**V**) formed in absolute ethanol, were hydrolyzed with concentrated hydrochloric acid in ethanol [4] to yield α-aminoacetophenone hydrochloride (**VI**), and *p*-fluoro-α-aminoacetophenone hydrochloride (**VII**), respectively. Acetylation of **VI** and **VII** was accomplished with acetic anhydride in the presence of sodium acetate [5] to give α-acetamidoacetophenone (**VIII**) and *p*-fluoro-α-acetamidoacetophenone (**IX**) in good yields. Pyrroles **X** and **XI** were prepared by a modified Gewald procedure [6]. In this procedure, compounds **VIII** and **IX** were condensed with malononitrile in methanol using potassium hydroxide as the base catalyst, followed by *in situ* deacylation of the corresponding 1-acetylpyrroles by alkaline hydrolysis at 60-65°. The aminomethylenemalonates **XII** and **XIII** were obtained by the treatment of the pyrroles (**X**) and (**XI**) with diethyl ethoxymethylenemalonate in absolute ethanol. The acrylates **XII** and

Scheme 1

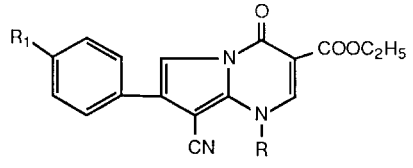


XIII were cyclized either thermally using Dowtherm® A or ethanol, or by the treatment with potassium *t*-butoxide in dry dimethylformamide at room temperature to yield the corresponding 3-carbethoxy-8-cyano-4-hydroxypyrrolo-[1,2-*a*]pyrimidines **XIV** and **XV**. Selective alkylation of

compounds **XIV** and **XV** was achieved through anion generation using sodium methoxide in dry dimethylformamide, followed by alkylation with methyl iodide, ethyl iodide, allyl bromide, propargyl bromide and benzyl bromide to yield compounds **XVIa-j** in generally good yields (Table 1). Hydrolysis of the esters **XVIa-j** gave the desired 1-alkyl-8-cyano-1,4-dihydro-4-oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylic acids **XVIIa-j** (Table 2). The infrared and ^{1}H-nmr spectra of the final carboxylic acids **XVIIa-j** were consistent with the assigned structures. These compounds showed typical amide and carbonyl absorptions in the region from 1645-1740 cm^{-1}. In the ^{1}H-nmr spectra, the aro-

Table I

1-Alkyl-3-carbethoxy-8-cyano-1,4-dihydro-4-oxopyrrolo[1,2-**a**]pyrimidine



Compound Number	R	R_1	Mp (°C) [a]	Yield %
XV1a	$-CH_3$	-H	244-245	82
XV1b	$-C_2H_5$	-H	185-187	69
XV1c	$-CH_2CH{=}CH_2$	-H	232-234	63
XV1d	$-CH_2C{\equiv}CH$	-H	235-236	75
XV1e	$-CH_2C_6H_5$	-H	172-174	86
XV1f	$-CH_3$	-F	268-270	81
XV1g	$-C_2H_5$	-F	187-189	66
XV1h	$-CH_2CH{=}CH_2$	-F	170-172	64
XV1i	$-CH_2C{\equiv}CH$	-F	208-209	57
XV1j	$-CH_2C_6H_5$	-F	228-229	88

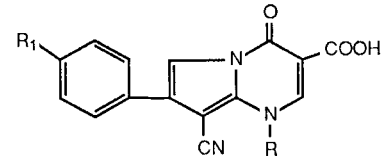
(a) The compounds have been purified by recrystallization from absolute methanol.

Table 1a

Compound Number	Molecular Formula	Analysis % Calcd./(Found) C	H	N
XVIa	$C_{18}H_{15}N_3O_3{\cdot}0.4H_2O$	65.80 (65.64)	4.60 (4.82)	12.79 (12.54)
XVIb	$C_{19}H_{17}N_3O_3{\cdot}0.5H_2O$	66.27 (66.20)	4.98 (5.01)	12.20 (12.32)
XVIc	$C_{20}H_{17}N_3O_3{\cdot}0.7H_2O$	66.73 (66.66)	4.76 (4.89)	11.67 (11.61)
XVId	$C_{20}H_{15}N_3O_3{\cdot}0.5H_2O$	67.81 (67.82)	4.27 (4.55)	11.86 (11.86)
XVIe	$C_{24}H_{19}N_3O_3{\cdot}0.2H_2O$	71.88 (71.87)	4.78 (4.87)	10.57 (10.79)
XVIf	$C_{18}H_{14}FN_3O_3$	63.71 (63.60)	4.16 (4.17)	12.38 (12.36)
XVIg	$C_{19}H_{16}FN_3O_3$	64.59 (64.63)	4.56 (4.83)	11.89 (11.62)
XVIh	$C_{20}H_{16}FN_3O_3{\cdot}0.55H_2O$	64.01 (64.27)	4.41 (4.38)	11.19 (10.87)
XVIi	$C_{20}H_{14}FN_3O_3$	66.12 (66.04)	3.88 (3.94)	11.57 (11.51)
XVIj	$C_{24}H_{18}FN_3O_3{\cdot}0.3H_2O$	68.50 (68.52)	4.31 (4.42)	9.99 (10.08)

Table 2

1-Alkyl-8-cyano-1,4-dihydro-4-oxopyrrolo[1,2-**a**] pyrimidine-3-Carboxylic Acids



Compound Number	R	R_1	Mp (°C) [a]	Yield %
XVIIa	$-CH_3$	-H	285-287	73
XVIIb	$-C_2H_5$	-H	245-246	69
XVIIc	$-CH_2CH{=}CH_2$	-H	223-225	77
XVIId	$-CH_2C{\equiv}CH$	-H	263-265	66
XVIIe	$-CH_2C_6H_5$	-H	251-252	71
XVIIf	$-CH_3$	-F	321-322	79
XVIIg	$-C_2H_5$	-F	249-251	57
XVIIh	$-CH_2CH{=}CH_2$	-F	217-219	71
XVIIi	$-CH_2C{\equiv}CH$	-F	265-266	80
XVIIj	$-CH_2C_6H_5$	-F	265-266	70

(a) The compounds have been purified by recrystallization from absolute methanol.

Table 2a

Compound Number	Molecular Formula	Analysis % Calcd./(Found) C	H	N
XVIIa	$C_{16}H_{11}N_3O_3$	65.52 (65.66)	3.78 (3.90)	14.33 (14.43)
XVIIb	$C_{17}H_{13}N_3O_3{\cdot}0.2H_2O$	65.67 (65.57)	4.21 (4.32)	13.52 (13.45)
XVIIc	$C_{18}H_{13}N_3O_3$	67.70 (67.64)	4.10 (4.13)	13.16 (13.09)
XVIId	$C_{18}H_{11}N_3O_3$	68.13 (68.10)	3.50 (3.53)	13.24 (13.21)
XVIIe	$C_{22}H_{15}N_3O_3{\cdot}0.4H_2O$	70.17 (70.18)	4.02 (4.36)	11.15 (10.90)
XVIIf	$C_{16}H_{10}FN_3O_3$	61.74 (61.85)	3.24 (3.28)	13.50 (13.49)
XVIIg	$C_{17}H_{12}FN_3O_3{\cdot}0.2H_2O$	62.08 (62.17)	3.68 (3.79)	12.78 (12.80)
XVIIh	$C_{18}H_{12}FN_3O_3$	64.09 (64.04)	3.59 (3.61)	12.46 (12.41)
XVIIi	$C_{18}H_{10}FN_3O_3$	61.19 (61.17)	2.85 (3.12)	11.89 (11.88)
XVIIj	$C_{22}H_{14}FN_3O_3$	68.21 (68.06)	3.64 (3.67)	10.85 (10.82)

matic proton at 6-position appeared as a sharp singlet from 7.60-7.85 ppm. The aromatic proton at 2- position appeared as a sharp singlet from 8.20-8.85 ppm. The remaining protons in the obtained compounds were observed in the expected region of the spectra.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Varian EM360A or EM390 spectrometer using tetramethylsilane as an internal standard and deuteriochloroform, DMSO-d_6 or trifluoroacetic acid as the solvent. Infrared spectra were determined on a Beckman Acculab 4 spectrophotometer using the potassium bromide technique. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

α-Aminoacetophenone Hydrochloride (VI).

Hexamethylenetetramine (10.8 g, 0.077 mole) was dissolved in absolute ethanol (850 ml). α-Chloroacetophenone (**IV**) (10.82 g, 0.07 mole) in chloroform (25 ml) was added and stirred at room temperature for 10 minutes. Sodium iodide (10.5 g, 0.07 mole) was added and the mixture was stirred at room temperature for 20 hours. A white suspension was obtained, which was cooled to 5°, filtered, washed with cold ethanol (30 ml) and air dried. The white solid was heated at 50-52° in a mixture of absolute ethanol (150 ml) and concentrated hydrochloric acid (40 ml) for 3 hours. A light brown suspension was obtained, which was cooled to 10° and filtered. The filtrate was evaporated to dryness. The residue was recrystallized from isopropyl alcohol/concentrated hydrochloric acid (100:1), washed with anhydrous ether and air dried. Light brown crystals were obtained (9.65 g, 80%), mp 185° (lit [7] mp 186.5°); ir (potassium bromide): 3460-3375, 3010-2860, 2805, 1980, 1685, 1595, 1580, 1545, 1496, 1445, 1420, 1375, 1235, 1130, 955, 750, 680 cm^{-1}; nmr (DMSO-d_6): δ 4.45 (s, 2H, methylene). 7.40-8.05 (m, 5H, aromatic protons), 8.30-8.70 (br s, 3H, ammonium group) ppm.

p-Fluoro-α-aminoacetophenone Hydrochloride (VII).

A solution of hexamethylenetetramine (16.8 g, 0.12 mole) in absolute ethanol (1300 ml) was treated with *p*-fluoro-α-chloroacetophenone (**V**) (17.3 g, 0.1 mole) in chloroform (50 ml) and the resulting mixture was stirred at room temperature for 10 minutes. Sodium iodide (14.99 g, 0.1 mole) was added and the mixture was stirred at room temperature for 24 hours. The white suspension was cooled to 5°, filtered, washed with cold ethanol (60 ml) and air dried. The white solid was heated at 50-55° in a mixture of absolute ethanol (250 ml) and concentrated hydrochloric acid (40 ml) for 4 hours. A yellow suspension was obtained, which was cooled to 5°, filtered, washed with cold ethanol (30 ml) and air dried. The yellow crystalline product, which consists of the amine hydrochloride and ammonium chloride was stirred for 15 minutes with distilled water (25 ml), cooled to 10°, filtered and air dried. Light brown crystals were obtained (12.2 g, 64%), mp > 310°; ir (potassium bromide): 3120-2810, 2740, 2475, 1990, 1675, 1597, 1575, 1505, 1455, 1380, 1315, 1298, 1247, 1230, 1160, 1110, 1095, 965, 825, 747 cm^{-1}; nmr (DMSO-d_6): δ 4.52 (s, 2H, methylene group), 7.02-7.45 (t, 2H, aromatic protons), 7.85-8.30 (two d, 2H, aromatic protons), 8.32-8.95 (br s, 3H, ammonium group) ppm.

α-Acetamidoacetophenone (VIII).

α-Aminoacetophenone Hydrochloride (**VI**) (11.16 g, 0.065 mole) was mixed with water (50 ml) and chipped ice (75 g) in 250 ml flask fitted with a stirrer, a thermometer, and a dropping funnel. Acetic anhydride (13.26 g, 0.13 mole) was added to the mixture, which was then stirred while a solution of sodium acetate (10.66 g, 0.13 mole) in water (40 ml) was added rapidly. The temperature of the mixture was kept below 10°, ice being added if necessary. After the addition of sodium acetate was complete, the mixture was stirred until the temperature increased to 20°. It was then made strongly acidic with concentrated hydrochloric acid. The mixture was extracted with methylene chloride (150 ml), the organic layer was separated and the aqueous layer was extracted three times with methylene chloride (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and filtered. The solvent was removed *in vacuo* to yield a light brown oil, which solidified upon standing at room temperature overnight. The product was purified by recrystallization from toluene (12 ml) to yield light yellow crystals (8.6 g, 75%), mp 85-87° (lit [8] mp 85.5-86.5°); ir (potassium bromide); 3320, 3065, 2940, 1635, 1597, 1545, 1440, 1360, 1220, 1000, 970, 740, 675 cm^{-1}; nmr (deuteriochloroform): δ 2.10 (s, 3H, methyl group), 4.60-4.80 (d, 2H, methylene group), 6.40-6.80 (br s, 1H, NH), 7.20-7.95 (m, 5H, aromatic protons) ppm.

p-Fluoro-α-acetamidoacetophenone (IX).

p-Fluoro-α-aminoacetophenone Hydrochloride (**VII**) (7.70 g, 0.041 mole) was mixed with water (20 ml) and chipped ice (50 g) in 250 ml flask fitted with a stirrer, a thermometer and a dropping funnel. Acetic anhydride (10.2 g, 0.1 mole) was added to the mixture, which was then stirred while sodium acetate (8.2 g, 0.1 mole) in water (25 ml) was added rapidly. The temperature of the mixture was kept below 10°, ice being added if necessary. After the addition of the sodium acetate was complete, the mixture was stirred until the temperature increased to 20°. It was then made acidic with concentrated hydrochloric acid, filtered, washed with distilled water and air dried. White colored crystals were obtained (2.3 g). The filtrate was extracted with methylene chloride (100 ml), the organic layer was separated and the aqueous layer was extracted three times with methylene chloride (40 ml). The organic layers were combined, dried over anhydrous sodium sulfate and filtered. The solvent was removed *in vacuo* to yield white crystals (3.17 g). The total yield of *p*-fluoro-α-acetamidoacetophenone was 5.47 g (68%), mp 145-146°; ir (potassium bromide): 3300, 3075, 2945, 1655, 1590, 1540, 1420, 1400, 1365, 1295, 1220, 1150, 1090, 1000, 980, 830, 810, 755, 675 cm^{-1}; nmr (deuteriochloroform): δ 2.10 (s, 3H, methyl group), 4.55-4.75 (d, 2H, methylene group), 6.40-6.80 (br s, 1H, NH), 6.85-7.20 (t, 2H, aromatic protons), 7.70-8.05 (two d, 2H, aromatic protons) ppm.

Anal. Calcd. for $C_{10}H_{10}FNO_2$: C, 61.53; H, 5.16; H, 7.18. Found: C, 61.37; H, 5.18; N, 7.12.

2-Amino-3-cyano-4-phenylpyrrole (X).

A solution of α-acetamidoacetophenone (**VIII**) (1.42 g, 0.008 mole) and malononitrile (0.79 g, 0.012 mole) in absolute methanol (10 ml) was stirred in an ice bath while the *p*H of the solution was adjusted to 10 by the addition of 50% aqueous potassium hydroxide solution. The solution was stirred for 15 minutes in the ice bath, then heated at 60-65° for 35 minutes as the *p*H was maintained between 9 and 10. The dark orange colored solution was poured over crushed ice (50 g). After the ice had melted, the precipitate was collected, washed with distilled water and air dried. The crude product was recrystallized from absolute methanol (15 ml) to yield a silver colored solid (0.97 g, 66%), mp 172-173° (lit [6] mp 173°); ir (potassium bromide): 3450, 3390, 3380, 3360, 3260, 3070, 2197, 1635, 1590, 1548, 1485, 1350, 1120, 1070, 1030, 945, 725, 685 cm^{-1}; nmr (DMSO-d_6): δ 5.60 (s, 2H, amino group at 2-position), 6.40 (s, 1H, aromatic proton at 5-position), 6.98-7.45 (m, 5H, aromatic protons), 9.95-10.30 (br s, 1H, NH) ppm.

2-Amino-3-cyano-4-*p*-fluorophenylpyrrole (XI).

A solution of *p*-fluoro-α-acetamidoacetophenone (**IX**) (2.73 g, 0.014 mole) and malononitrile (1.11 g, 0.017 mole) in absolute methanol (25 ml) was stirred in an ice bath while the *p*H of the solution was adjusted to 10 by dropwise addition of 50% aqueous potassium hydroxide solution. The solution was stirred for 15 minutes in the ice bath, then heated at 60-65° for 35 minutes as the *p*H was maintained between 9 and 10. The dark orange colored solution was poured over crushed ice (100 g). After the ice had melted, the precipitate was collected, washed with distilled water and air dried. The product was further purified by recrystallization from absolute methanol (20 ml) to yield a silver colored solid (2.13 g, 76%), mp 174-176°; ir (potassium bromide): 3395, 3255, 2940, 2197, 1635, 1580,

1550, 1485, 1390, 1345, 1235, 1155, 1115, 1090, 1030, 945, 830, 800, 740, 675 cm^{-1}; nmr (DMSO-d_6): δ 5.30 (s, 2H, amino group at 2-position), 6.25 (s, 1H, aromatic proton at 5-position), 6.75-7.05 (t, 2H, aromatic protons), 7.30-7.60 (two d, 2H, aromatic protons), 9.75-10.45 (br s, 1H, NH) ppm.

Anal. Calcd. for $C_{11}H_8FN_3 \cdot 0.2H_2O$: C, 64.51; H, 3.94; N, 20.52. Found: C, 64.24; H, 4.15; N, 20.43.

Diethyl *N*-[3-Cyano-4-phenylpyrrol-2-yl]aminomethylenemalonate (**XII**).

A suspension of 2-amino-3-cyano-4-phenylpyrrole (**X**) (0.82 g, 0.0045 mole) in absolute ethanol (10 ml) was treated with diethyl ethoxymethylenemalonate (0.97 g, 0.0045 mole) and the mixture was stirred at room temperature for 20 hours. A light green suspension was obtained, which was kept in the freezer overnight. The precipitate was collected, washed with cold ethanol (5 ml) and air dried. The crude product was further purified by recrystallization from absolute methanol (20 ml) to yield light green powder (1.16 g, 73%), mp 152-153°; ir (potassium bromide): 3440, 3220, 3140, 3075, 2995, 2205, 1710, 1680, 1615, 1585, 1475, 1440, 1400, 1380, 1345, 1285, 1270, 1235, 1180, 1120, 1070, 1020, 940, 790, 740, 680 cm^{-1}; nmr (DMSO-d_6): δ 2.10-2.40 (two t, 6H, methyl of ethyl ester), 3.90-4.30 (two q, 4H, methylene of ethyl ester), 6.40 (d, 1H, aromatic proton at 5-position), 6.95-7.60 (m, 5H, aromatic protons), 8.25-8.50 (d, 1H, vinyl proton), 10.80-11.15 (d, 1H, NH at 2-position), 12.15 (br s, 1H, NH at 1-position) ppm.

Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.48; H, 5.43; N, 11.86.

Diethyl *N*-[3-Cyano-4-*p*-fluorophenylpyrrol-2-yl]aminomethylenemalonate (**XIII**).

A suspension of 2-amino-3-cyano-4-*p*-fluorophenylpyrrole (**XI**) (1.31 g, 0.0065 mole) in absolute ethanol (10 ml) was treated with diethyl ethoxymethylenemalonate (1.41 g, 0.0065 mole) and the mixture was stirred at room temperature overnight and kept in the freezer for 2 hours. A light green precipitate was obtained, which was collected, washed with cold ethanol (5 ml) and air dried. The product was purified by recrystallization from absolute methanol (35 ml) to yield a light green solid (1.78 g, 74%), mp 226-227°; ir (potassium bromide): 3445, 3210, 3150, 3090, 2990, 2197, 1720, 1675, 1637, 1608, 1575, 1540, 1475, 1435, 1370, 1340, 1285, 1260, 1230, 1155, 1120, 1080, 1015, 940, 830, 785, 680 cm^{-1}; nmr (DMSO-d_6): δ 1.20-1.55 (two t, 6H, methyl of ethyl ester), 4.20-4.65 (two q, 4H, methylenes of ethyl ester), 6.60 (d, 1H, aromatic proton at 5-position), 6.80-7.10 (t, 2H, aromatic protons), 7.22-7.60 (two d, 2H, aromatic protons), 8.60-8.80 (d, 1H, vinyl proton), 10.90-11.20 (d, 1H, NH at 2-position), 12.25 (br s, 1H, NH at 1-position) ppm.

Anal. Calcd. for $C_{19}H_{18}FN_3O_4$: C, 61.45; H, 4.89; N, 11.32. Found: C, 61.31; H, 4.96; N, 11.30.

3-Carbethoxy-8-cyano-4-hydroxy-7-phenylpyrrolo[1,2-*a*]pyrimidine (**XIV**).

Method A.

Compound **XII** (1.77 g, 0.005 mole) in warm Dowtherm® A (20 ml), was added to boiling Dowtherm® A (30 ml), under an argon atmosphere. After the addition was complete, the solution was refluxed for 2 minutes and the Dowtherm® A was removed under reduced pressure. The residue was triturated with *n*-hexane (150 ml) and the brown solid was collected, washed with *n*-hexane and air dried. The crude product was purified by recrystallization from absolute methanol (80 ml) to yield a light yellow-white solid (1.16 g, 76%), mp 296-298°; ir (potassium bromide): 3460-3390, 3140, 3060, 2935, 2205, 1705, 1650, 1620, 1580, 1470, 1450, 1370, 1335, 1285, 1170, 1095, 1030, 945, 890, 735, 680 cm^{-1}; nmr (DMSO-d_6): δ 1.10-1.40 (t, 3H, methyl of ethyl ester), 3.98-4.35 (q, 2H, methylene of ethyl ester), 7.25-7.65 (m, 5H, aromatic protons), 7.70 (s, 1H, aromatic proton at 6-position), 8.25 (s, 1H, aromatic proton at 2-positions) ppm.

Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.24; H, 4.31; N, 13.60.

Method B.

2-Amino-3-cyano-4-phenylpyrrole (**X**) (7.33 g, 0.04 mole) in absolute ethanol (50 ml) was treated with diethyl ethoxymethylenemalonate (8.65 g, 0.04 mole) and the mixture was refluxed for 30 hours. A dark blue colored suspension was obtained, which was cooled to 5°, filtered, washed with cold ethanol (25 ml) and air dried. The product was purified by recrystallization from absolute methanol (175 ml) to yield a white solid (8.6 g, 70%). The ir, nmr spectra and melting point were identical to the product obtained under method A.

Method C.

Compound **XII** (0.8 g, 0.002 mole) in dry dimethylformamide (8 ml) was treated with potassium *t*-butoxide (0.76 g, 0.006 mole) and the mixture was stirred at room temperature overnight. A light yellow solid was formed, which was mixed with ice-water (50 ml). The obtained suspension was neutralized with concentrated hydrochloric acid. The precipitate was collected, washed with distilled water and air dried. The product was purified by recrystallization from absolute methanol (30 ml) to yield a white solid (0.42 g, 68%). The ir, nmr spectra and melting point were identical to the product obtained under method A.

3-Carbethoxy-8-cyano-4-hydroxy-7-*p*-fluorophenylpyrrolo[1,2-*a*]pyrimidine (**XV**).

Method A.

2-Amino-3-cyano-4-*p*-fluorophenylpyrrole (**XI**) (4.0 g, 0.02 mole) in absolute ethanol (40 ml) was treated with diethyl ethoxymethylenemalonate (4.32 g, 0.02 mole) and the mixture was refluxed for 36 hours. A dark blue suspension was obtained, which was cooled to 5°, filtered, washed with cold ethanol (15 ml) and air dried. The product was further purified by recrystallization from absolute methanol (80 ml) to yield a white solid (4.40 g, 68%), mp 318-320°; ir (potassium bromide): 3420, 3260, 3150, 3080, 2985, 2910, 2207, 1720, 1620, 1575, 1495, 1455, 1380, 1340, 1270, 1225, 1175, 1150, 1100, 1030, 950, 830, 765, 660 cm^{-1}; nmr (trifluoroacetic acid): δ 1.20-1.55 (t, 3H, methyl of ethyl ester), 4.15-4.55 (q, 2H, methylene of ethyl ester), 6.85-7.20 (t, 2H, aromatic protons), 7.40-7.65 (two d, 2H, aromatic protons), 7.68 (s, 1H, aromatic proton at 6-position), 8.55 (s, 1H, aromatic proton at 2-position) ppm.

Anal. Calcd. for $C_{17}H_{12}FN_3O_3$: C, 62.77; H, 3.72; N, 12.92. Found: C, 62.68; H, 3.75; N, 12.90.

Method B.

Compound **XIII** (1.10 g, 0.003 mole) in dry dimethylformamide (12 ml) was treated with potassium *t*-butoxide (1.0 g, 0.009 mole) and the mixture was stirred at room temperature for 18 hours. A yellow solid was formed, which was mixed with ice water (50 ml) and the suspension was neutralized with 6*N* hydrochloric acid. The precipitate was collected, washed with distilled water and air dried. The product was purified by recrystallization from absolute methanol (40 ml) to yield white solid (0.72 g, 74%). The ir, nmr spectra and melting point were identical to the product obtained under method A.

3-Carbethoxy-8-cyano-1,4-dihydro-1-ethyl-7-phenyl-4-oxopyrrolo[1,2-*a*]-pyrimidine (**XVIb**).

The procedure given for the synthesis of **XVIb** was utilized in the preparation of **XVIa** and **XVIc-e**. A solution of compound **XIV** (1.38 g, 0.0045 mole) in dry dimethylformamide (6 ml) was treated with sodium methoxide (0.29 g, 0.0054 mole) and stirred at room temperature for 15 minutes. Ethyl iodide (1.05 g, 0.0068 mole) was added and the mixture was stirred at room temperature for 15 hours. A dark brown suspension was obtained, which was poured into ice-water (50 ml). The precipitate was collected, washed with distilled water and air dried. The crude product was further purified by recrystallization from absolute methanol (70 ml) to yield light yellow solid (1.04 g, 69%), mp 185-187°; ir (potassium bromide): 3460-3375, 3135, 3040, 2975, 2205, 1740, 1685, 1560, 1550, 1440, 1360, 1305, 1270, 1220, 1195, 1090, 1015, 775, 680 cm^{-1}; nmr (deuteriochloroform): δ 1.15-1.80 (two t, 6H, methyl groups), 4.15-4.65 (two q, 4H, methylene groups), 7.30-7.60 (m, 5H, aromatic protons), 7.65 (s, 1H, aromatic proton at 6-position), 8.20 (s, 1H, aromatic proton at 2-position), ppm.

Anal. Calcd. $C_{19}H_{17}N_3O_3 \cdot 0.5H_2O$: C, 66.27; H, 4.98; N, 12.20. Found: C, 66.20; H, 5.01; N, 12.32. (See Table 1 for Analogs).

3-Carbethoxy-8-cyano-1,4-dihydro-1-methyl-7-*p*-fluorophenyl-4-oxopyrrolo[1,2-*a*]pyrimidine (**XVIf**).

The procedure given for the synthesis of (**XVIf**) was utilized in the preparation of (**XVIg-j**). A solution of compound (**XV**) (0.98 g, 0.003 mole) in dry dimethylformamide (8 ml) was treated with sodium methoxide (0.25 g, 0.0046 mole) and stirred at room temperature for 10 minutes. Methyl iodide (0.86 g, 0.006 mole) was added and the mixture was stirred at room temperature for 12 hours. A white solid was formed, which was mixed with ice-water (50 ml). The solid was collected, washed with distilled water and air dried. The product was further purified by recrystallization from absolute methanol (70 ml) to yield white solid (0.82 g, 81%), mp 268-270°; ir (potassium bromide): 3480-3360, 3140, 3060, 2995, 2945, 2205, 1740, 1675, 1580, 1535, 1490, 1430, 1380, 1355, 1305, 1265, 1215, 1155, 1130, 1080, 1020, 1000, 960, 910, 830, 775, 750, 680 cm^{-1}; nmr (trifluoroacetic acid): δ 1.20-1.60 (t, 3H, methyl of ethyl ester), 4.20 (s, 3H, methyl at 1-position), 4.20-4.55 (q, 2H, methylene of ethyl ester), 6.85-7.20 (t, 2H, aromatic protons), 7.40-7.60 (two d, 2H, aromatic protons), 7.65 (s, 1H, aromatic proton at 6-position), 8.60 (s, 1H, aromatic proton at 2-position) ppm.

Anal. Calcd. for $C_{18}H_{14}FN_3O_3$: C, 63.71; H, 4.16; N, 12.38. Found: C, 63.60; H, 4.17; N, 12.36. (See Table 1 for Analogs).

8-Cyano-1,4-dihydro-1-methyl-7-phenyl-4-oxopyrrolo-[1,2-*a*]pyrimidine-3-carboxylic Acid (**XVIIa**).

The procedure described for the synthesis of **XVIIa** was utilized in the preparation of **XVIIb** and **XVIId**. Compound **XVIa** (0.84 g, 0.0026 mole), in concentrated hydrochloric acid (10 ml), was heated at 60° for 15 hours. After cooling, a light brown solid was formed, which was mixed with ice-water (20 ml). The solid was collected, washed with distilled water and air dried. The crude product was purified by recrystallization from absolute methanol (120 ml) to yield light brown powder (0.56 g, 73%), mp 285-287°; ir (potassium bromide): 3460-3380, 3135, 3070, 2995, 2207, 1737, 1645, 1595, 1555, 1430, 1385, 1340, 1205, 1090, 780, 745, 680 cm^{-1}; nmr (DMSO-d_6): δ 4.05 (s, 3H, methyl at 1-position), 7.25-7.65 (m, 5H, aromatic protons), 7.70 (s, 1H, aromatic proton at 6-position), 8.60 (s, 1H, aromatic proton at 2-position) ppm.

Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.52; H, 3.78; N, 14.33. Found: C, 65.66; H, 3.90; N, 14.43. (See Table 2 for Analogs).

1-Allyl-8-cyano-1,4-dihydro-7-phenyl-4-oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylic Acid (**XVIIc**).

The procedure given for the synthesis of **XVIIc** was utilized in the preparation of **XVIIe**. Compound **XVIc** (0.76 g, 0.0022 mole), in hot methanol (250 ml), was treated with 5% sodium hydroxide (30 ml). The mixture was heated on a boiling water bath for 40 minutes. After cooling, the white suspension was filtered. The filtrate was acidified with 6*N* hydrochloric acid and kept in the freezer for 1 hour. White crystals, were formed, which were collected, washed with distilled water and air dried. The product was purified by recrystallization from absolute methanol (125 ml) to yield white needles (0.54 g, 77%), mp 223-225°; ir (potassium bromide): 3480-3400, 3145, 3070, 2995, 2205, 1745, 1645, 1595, 1560, 1495, 1435, 1385, 1350, 1295, 1215, 1190, 1155, 1095, 1045, 950, 835, 770, 680 cm^{-1}; nmr (trifluoroacetic acid): δ 5.05-6.25 (m, 5H, allyl group at 1-position), 7.15-7.65 (m, 5H, aromatic protons), 7.70 (s, 1H, aromatic proton at 6-position), 8.60 (s, 1H, aromatic proton at 2-position) ppm.

Anal. Calcd. for $C_{18}H_{13}N_3O_3$: C, 67.70; H, 4.10; N, 13.16. Found: C, 67.64; H, 4.13; N, 13.09. (See Table 2 for Analogs).

8-Cyano-1,4-dihydro-1-methyl-7-*p*-fluorophenyl-4-oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylic Acid (**XVIIf**).

The procedure given for the synthesis of **XVIIf** was utilized in the preparation of **XVIIg**. Compound (**XVIf**) (1.0 g, 0.003 mole) in concentrated hydrochloric acid (12 ml) was heated at 55° for 15 hours. After cooling, the white suspension was poured into ice-water (100 ml). The precipitate was collected, washed with distilled water and air dried. The crude product was purified by recrystallization from absolute methanol (25 ml) to yield white solid (0.74 g, 79%), mp 321-322°; ir (potassium bromide): 3445-3390, 3130, 3075, 2997, 2207, 1735, 1630, 1590, 1535, 1490, 1420, 1370, 1320, 1220, 1155, 1130, 1085, 1040, 1000, 930, 895, 835, 765, 720, 680 cm^{-1}; nmr (trifluoroacetic acid): δ 4.05 (s, 3H, methyl at 1-position), 6.85-7.35 (t, 2H, aromatic protons), 7.40-7.75 (two d, 2H, aromatic protons), 7.80 (s, 1H, aromatic proton at 6-position), 8.65 (s, 1H, aromatic proton at 2-position) ppm.

Anal. Calcd. for $C_{16}H_{10}FN_3O_3$: C, 61.74; H, 3.24; N, 13.50. Found: C, 61.85; H, 3.28; N, 13.49. (See Table 2 for Analogs).

1-Benzyl-8-cyano-1,4-dihydro-7-*p*-fluorophenyl-4-oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylic Acid **XVIIj**.

The procedure described for the synthesis of **XVIIj** was utilized in the preparation of **XVIIh**. Compound **XVIj** (0.83 g, 0.002 mole) in hot methanol (150 ml) was treated with 5% sodium hydroxide (30 ml) and the mixture was heated on a boiling water bath for 45 minutes. After cooling, the white suspension was filtered. The filtrate was acidified with 6*N* hydrochloric acid and kept in the freezer for 30 minutes. A white precipitate was formed which was collected, washed with distilled water and air dried. The product was purified by recrystallization from absolute methanol (40 ml) to yield white solid (0.54 g, 70%), mp 265-266°; ir (potassium bromide): 3460-3400, 3140, 3055, 2995, 2207, 1735, 1650, 1590, 1565, 1495, 1445, 1415, 1380, 1360, 1335, 1297, 1235, 1160, 1055, 940, 830, 765, 747, 705, 680 cm^{-1}; nmr (trifluoroacetic acid): δ 5.65 (s, 2H, benzylic protons), 6.80-7.45 (m, 9H, aromatic protons), 7.55 (s, 1H, aromatic proton at 6-position), 8.55 (s, 1H, aromatic proton at 2-position) ppm.

Anal. Calcd. for $C_{22}H_{14}FN_3O_3$: C, 68.21; H, 3.64; N, 10.85. Found: C, 68.06; H, 3.67; N, 10.82. (See Table 2 for Analogs).

8-Cyano-1,4-dihydro-7-*p*-fluorophenyl-1-propargyl-4-oxopyrrolo-[1,2-*a*]pyrimidine-3-carboxylic Acid (**XVIIi**).

A solution of compound **XVIi** (0.56 g, 0.0016 mole) in a mixture of 95% formic acid (4 ml) and methanesulfonic acid (0.15 g, 0.0016 mole) was heated at 70° for 14 hours [9]. After cooling, the white suspension was poured into ice-water (40 ml). The precipitate was collected, washed with distilled water and air dried. The product was purified by recrystallization from absolute methanol (50 ml) to yield a white powder (0.43 g, 80%), mp 265-266°; ir (potassium bromide): 3470-3395, 3260, 3145, 3085, 2995, 2207, 1725, 1650, 1590, 1565, 1495, 1450, 1405, 1360, 1290, 1225, 1155, 1100, 1055, 945, 830, 785, 760, 720, 665 cm^{-1}; nmr (DMSO-d_6): δ 3.90 (t, 1H, propargyl proton), 5.35-5.45 (d, 2H, propargyl group at 1-position), 6.85-7.25 (t, 2H, aromatic protons), 7.30-7.75 (two d, 2H, aromatic protons), 7.80 (s, 1H, aromatic proton at 6-position), 8.80 (s, 1H, aromatic proton at 2-position) ppm.

Anal. Calcd. for $C_{18}H_{10}FN_3O_3 \cdot 1.0H_2O$: C, 61.19; H, 2.85; N, 11.89. Found: C, 61.17; H, 3.12; N, 11.88.

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