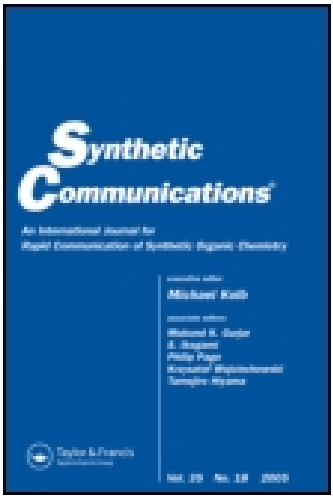

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Facile Synthesis of 2-Amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols

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Facile Synthesis of 2-Amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols

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Abstract: 2-Amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols were synthesized from various ethyl 2,6-diaryl-4-oxopiperidin-3-carboxylates with guanidine hydrochloride in presence of sodium ethoxide.

Keywords: Aminopyrimidines, hydroxypyrimidines

INTRODUCTION

Pyrimidine is a widespread heterocyclic moiety present in numerous natural products. Pyrimidines are important not only because they are an integral part of genetic materials (viz., DNA and RNA as nucleotides and nucleosides), but also they have important biodynamic properties and biological activities such as antibacterial, antifungal, antitubercular, antiviral, antimicrobial, dopaminergic, VEGF-RZ kinase inhibitory, and central nervous system depressant activity.[1–6] Substituted pyrimidines, particularly with an amino group at 2 or 4 positions, are known pharmacophores in several structure-based drug-design approaches in medicinal chemistry.[7,8] For example, aryl-2-aminopyrimidines have been reported for the treatment of diseases modulated by the adenosine receptor. The anti-HIV/HBV drugs abacavir and anti-atherosclerotic drug arnoxil are examples of aminopyrimidine drugs available on the market.[9,10] Drugs

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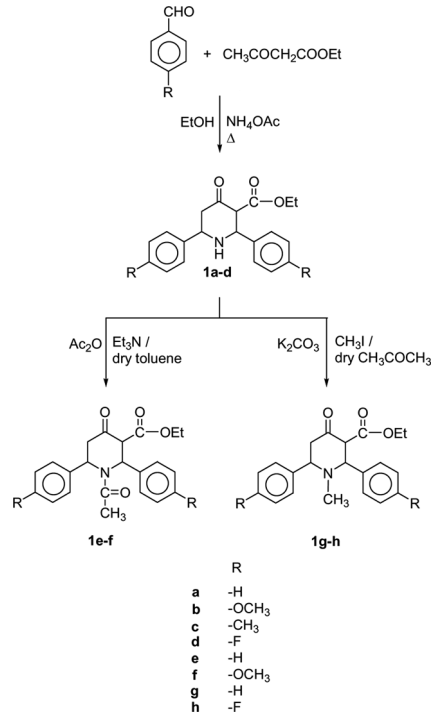
containing a pyrimidine with a hydroxy group such as tetrahydrofolate and 5-methyltetrahydrofolate possess high antioxidant activity.[11]

The unique structure and great potential of these compounds inspired us to report the synthesis and antibacterial activity of naphthyl and thienyl substituted 2-aminopyrimidines.[12,13] In continuation of our interest in the synthesis of the biologically active heterocyclic compounds, here we address the synthesis of 2-amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols.

RESULTS AND DISCUSSION

The synthetic strategy adopted in this work to obtain the ethyl 2,6-diaryl-4-oxopiperidin-3-carboxylates is presented in Scheme 1 and uses the condensation of aromatic aldehyde with keto ester in the presence of ammonium acetate to furnish ethyl 2,6-diaryl-4-oxopiperidin-3-carboxylate **1a–h**.[14] Refluxing **1a–h** with guanidine hydrochloride in sodium



Scheme 1. Synthesis of ethyl 4-oxopiperidin-3-carboxylate.

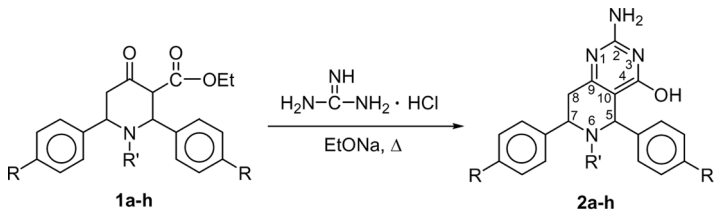
ethanolate for about 16 h yielded the desired 2-amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols **2a–h** (Scheme 2).

After our initial success in the cyclization of ethyl 2,6-diaryl-4-oxopiperidin-3-carboxylate **1a–d** to 2-amino-5,6,7,8-tetrahydro-5,7-diarylpyrido [4,3-d]pyrimidin-4-ols, we extended the same protocol to the N-substituted ethyl 2,6-diaryl-4-oxopiperidin-3-carboxylate **1e–h** with guanidine hydrochloride in sodium ethanolate.

Ethyl-1-acetyl-2,6-diaryl-4-oxopiperidin-3-carboxylates **1e** and **1f** were synthesized by treatment of **1a** or **1b** with acetic anhydride and triethylamine (1:3:3 ratio) in dry toluene. Similarly, ethyl-1-methyl-2,6-diaryl-4-oxopiperidin-3-carboxylates **1g** and **1h** were obtained by refluxing **1a** and **1d** with methyl iodide and anhydrous potassium carbonate in dry acetone (Scheme 1). Soldatenkov et al. reported that the acylation of ethyl 4-oxopiperidin-3-carboxylate gave enol-form and acylation took place at both nitrogen and hydroxyl groups, but we were not able to isolate the diacetylated product under our experimental conditions.

2-Amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols **2a–h** were obtained in moderate to good yields (Table 1). All the new compounds were characterized on the basis of their analytical, one- and two-dimensional NMR spectral data, which are in agreement with their proposed structure.

To conclude, we have proposed an efficient method for the preparation of 2-amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols by reaction of guanidine hydrochloride with ethyl 4-oxopiperidin-3-carboxylate. These compounds are known pharmacophores in several structure-based drug-design approaches.



	R	R'
a	-H	-H
b	$-OCH_3$	-H
c	$-CH_3$	-H
d	-F	-H
e	-H	$-COCH_3$
f	$-OCH_3$	$-COCH_3$
g	-H	$-CH_3$
h	-F	$-CH_3$

Scheme 2. Synthesis of 2-aminopyrimidin-4-ols.

Table 1. Physical and analytical data of 2-amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols (**2a–h**)

Compound **2**	Molecular formula	Melting point (°C)	Yield (%)	Elemental analysis[a]		
				C	H	N
a	$C_{19}H_{18}N_4O$	251.8–253.6	61.5	70.82 (71.68)	5.21 (5.70)	16.50 (17.60)
b	$C_{21}H_{22}N_4O_3$	166.0–167.2	59.9	64.93 (66.65)	5.11 (5.86)	14.97 (14.81)
c	$C_{21}H_{22}N_4O$	225.8–228	65.2	71.72 (72.81)	6.69 (6.40)	16.02 (16.17)
d	$C_{19}H_{16}F_2N_4O$	209.6–211.0	63.1	63.14 (64.40)	4.82 (4.55)	15.87 (15.81)
e	$C_{21}H_{20}N_4O_2$	281.4–282.8	50.7	68.39 (69.98)	5.17 (5.59)	15.51 (15.55)
f	$C_{23}H_{24}N_4O_4$	191.6–193.4	48.4	64.66 (65.70)	5.03 (5.75)	13.42 (13.33)
g	$C_{20}H_{20}N_4O$	201.2–203.4	70.1	71.29 (72.27)	6.34 (6.06)	15.22 (16.86)
h	$C_{20}H_{18}F_2N_4O$	242.0–242.8	67.3	64.38 (65.21)	4.87 (4.93)	14.82 (15.21)

[a]Values within the parantheses are calculated.

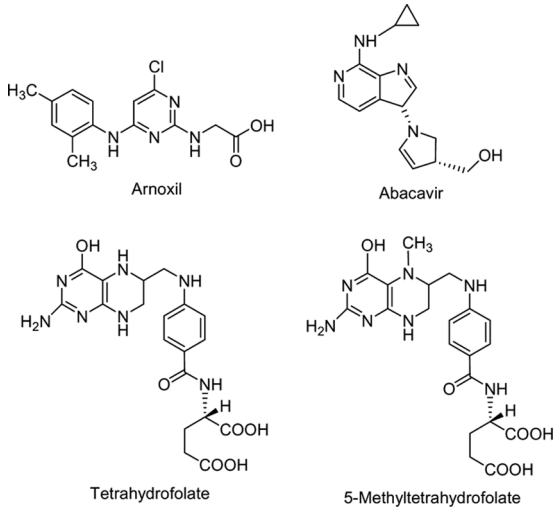


Figure 1. Biologically active aminopyrimidines.

EXPERIMENTAL

Melting points are determined in open capillaries and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AMX-500 spectometer operating at 400 MHz using dimethylsulfoxide (DMSO) as solvent. The (FT-IR) spectra were recorded on a Nicolet Avatar 360-FT-IR instrument Fourier transform–infrared using KBr pellets. Elemental analyses were done on a Vario EL CHNOS elemental analyzer.

General Procedure for the Synthesis of Ethyl 2,6-Diaryl-4-oxopiperidin-3-carboxylates 1a–d

Ammonium acetate (0.1 mol), bezaldehyde (0.2 mol), and ketoester (0.1 mol) were dissolved in 95% ethanol (40 ml). The ether insoluble matters were filtered off, and concentrated hydrochloric acid (14 ml) was added to the filtrate. The precipitated piperidone hydrochloride was collected by filtration. The hydrochloride was dispersed in acetone (50 ml), and concentrated aqueous ammonia was added dropwise until a clear solution was obtained. The clear solution was poured into cold water (500 ml), and the precipitated solid was collected and crystallized from hot ethanol.

General Procedure for Synthesis of Ethyl-1-acetyl-2,6-diaryl-4-oxopiperidin-3-carboxylates 1e–f

A mixture of appropriate piperidin-4-one (0.01 mol), acetic anhydride (0.03 mol), and triethylamine (0.03 mol) in dry benzene was refluxed for 6–8 h to afford the N-acetyl piperidin-4-ones. The reaction mixture was washed with sodium bicarbonate (10%) and water, and then the solvents were removed at low pressure. The residue was recrystallized from distilled ethanol.

General Procedure for Synthesis of Ethyl-1-methyl-2,6-diaryl-4-oxopiperidin-3-carboxylate 1g–h

A mixture of piperidin-4-one (10 g), anhydrous potassium carbonate (10 g), and methyl iodide (5 ml) in acetone (100 ml) was refluxed for 3 h. Removal of acetone by distillation, dilution with water, and treatment with aqueous ammonia yielded the compound.

General Procedure for Synthesis of 2-amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols 2a–h

A mixture of ethyl 4-oxopiperidine-3-carboxylate (0.01 mol, 1.0 eq.) and guanidine hydrochloride (0.012 mol, 1.2 eq.) was added to the sodium ethanolate solution (dry sodium 0.25 g in 30 ml of anhydrous ethanol) and refluxed for 16 h. After cooling to room temperature, the slurry was evaporated. The residue was taken up in a minimum of 95% ethanol, and water was added until precipitation. The white solid was collected and purified using column chromatography (silica gel): eluent $CHCl_3$–CH_3OH (9:1).

Data

Compound **2a**

^{1}H NMR ($CDCl_3$): $\delta = 10.79$ (s, 1H, OH), 6.42 (s, 2H, NH_2), 4.92 (s, 1H, H-5), 3.72 (dd, 1H, H-7), 2.58 (dd, 1H, H-8_{ax}), 2.49 (dd, 1H, H-8_{eq}), 7.1–7.4 (Ar-H); ^{13}C NMR (DMSO): $\delta = 161.08$ (C-2), 162.04 (C-4), 53.81 (C-5), 50.49 (C-7), 126.39–128.15 (Ar-C).

Compound **2b**

^{1}H NMR ($CDCl_3$): δ = 10.82 (s, 1H, OH), 6.43 (s, 2H, NH_2), 4.88 (s, 1H, H-5), 2.54 (dd, 1H, H-8_{ax}), 2.38 (dd, 1H, H-8_{eq}), 6.8–7.3 (Ar-H), 3.69 (d, 6H, -OCH_3); ^{13}C NMR (DMSO): δ = 160.86 (C-2), 161.76 (C-4), 53.25 (C-5), 49.77 (C-7), 113.04–128.99 (Ar-C), 54.95 (-OCH_3).

Compound **2c**

^{1}H NMR ($CDCl_3$): δ = 10.53 (s, 1H, OH), 6.35 (s, 2H, NH_2), 4.86 (s, 1H, H-5), 3.96 (dd, 1H, H-7), 2.61 (dd, 1H, H-8_{ax}), 2.44 (dd, 1H, H-8_{eq}), 6.98–7.45 (Ar-H), 1.24 (s, 6H, -CH_3); ^{13}C NMR (DMSO): δ = 161.18 (C-2), 162.26 (C-4), 57.47 (C-5), 56.26 (C-7), 114.28–130.43 (Ar-C), 27.1 (CH_3).

Compound **2d**

^{1}H NMR ($CDCl_3$): δ = 10.56 (s, 1H, OH), 6.36 (s, 2H, NH_2), 4.86 (s, 1H, H-5), 3.97 (dd, 1H, H-7), 2.62 (dd, 1H, H-8_{ax}), 2.42 (dd, 1H, H-8_{eq}), 6.98–7.47 (Ar-H); ^{13}C NMR (DMSO): δ = 161.22 (C-2), 162.28 (C-4), 57.47 (C-5), 56.25 (C-7), 115.21–130.42 (Ar-C).

Compound **2e**

^{1}H NMR ($CDCl_3$): δ = 11.05 (s, 1H, OH), 6.70 (s, 2H, NH_2), 5.21 (s, 1H, H-5), 2.74 (dd, 1H, H-8_{ax}), 2.66 (dd, 1H, H-8_{eq}), 6.88–7.36 (Ar-H), 1.89 (s, 3H, -CO CH_3); ^{13}C NMR (DMSO): δ = 160.33 (C-2), 161.33 (C-4), 57.35 (C-5), 48.85 (C-7), 126.25–128.72 (Ar-C), 22.89 (CH_3), 170.76 (-CO CH_3).

Compound **2f**

^{1}H NMR ($CDCl_3$): δ = 10.94 (s, 1H, OH), NH_2-protons merged in aromatic region, 5.12 (s, 1H, H-5), 2.71 (dd, 1H, H-8_{ax}), 2.6 (dd, 1H, H-8_{eq}), 6.98–6.65 (Ar-H), 1.88 (s, 3H, -CO CH_3), 3.63 (d, 6H, OCH_3); ^{13}C NMR (DMSO): δ = 160.23 (C-2), 161.87 (C-4), 56.63 (C-5), 48.32 (C-7), 113.36–134.53 (Ar-C), 22.86 (CH_3), 54.97 (OCH_3), 170.59 (-CO CH_3).

Compound **2g**

^{1}H NMR ($CDCl_3$): δ = 10.50 (s, 1H, OH), 6.36 (s, 2H, NH_2), 4.15 (s, 1H, H-5), 3.53 (dd, 1H, H-7), 2.94 (dd, 1H, H-8_{ax}), 2.36 (dd, 1H, H-8_{eq}),

7.12–7.40 (Ar-H), 1.82 (s, 3H, CH_3); ^{13}C NMR (DMSO): $\delta = 160.41$ (C-2), 160.82 (C-4), 66.54 (C-5), 64.55 (C-7), 127.67–129.69 (Ar-C), CH_3–merged with DMSO.

Compound **2h**

^1H NMR ($CDCl_3$): $\delta = 10.52$ (s, 1H, OH), 6.37 (s, 2H, NH_2), 4.15 (s, 1H, H-5), 3.54 (dd, 1H, H-7), 2.92 (dd, 1H, H-8_{ax}), 2.48 (dd, 1H, H-8_{eq}), 6.99–7.44 (Ar-H), 1.78 (s, 3H, CH_3); ^{13}C NMR (DMSO): $\delta = 161.94$ (C-2), 162.49 (C-4), 65.18 (C-5), 63.02 (C-7), 41.47 (C-8), 113.60–130.46 (Ar-C), CH_3–merged with DMSO.

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