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SYNTHESIS AND NMR SPECTRAL CHARACTERIZATION OF NOVEL 2,3-POLYMETHYLENEPYRIDO[2,3-d]PYRIMIDIN-4-ONES

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Abstract.

We have synthesized of novel 2,3-polymethylenepyrido[2,3-d]pyrimidine-4-ones via condensation of the 2-aminonicotinic acid together with lactams in the presence of phosphorus oxychloride. The structures of the newly synthesized pyrido[2,3-d]pyrimidines were confirmed by ^{1}H and ^{13}C NMR spectral data.

Keywords

2,3-Polymethylenepyrido[2,3-d]pyrimidines, synthesis, NMR spectra.

Academic Discipline and Sub-Disciplines

Chemistry

Subject classification

Heterocyclic compounds synthesis

Type (method/approach)

Organic synthesis, NMR spectroscopy.

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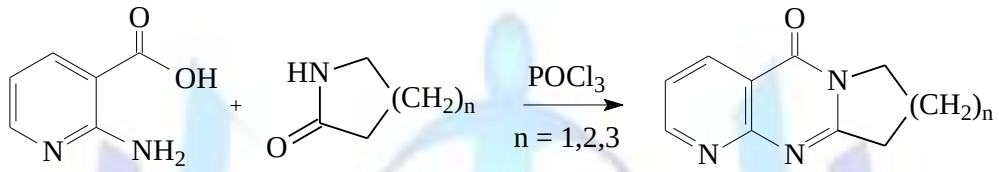
Introduction

It is well known that the pyrido[2,3-d]pyrimidine derivatives are of great interest due to diverse biological activity including anticancer or antiproliferative activities [1-4] . This structural motif is present in Palbociclib (PD 0322991) which is an oral inhibitor of CDK4/6. Moreover, single-agent palbociclib is well tolerated and active in patients with endocrine-resistant, HR^+, Rb-positive breast cancer [3]. There are many encouraging the representatives of high biological and pharmacological activities together with many other applications. On the other hand, the chemical structure of pyrido[2,3-d]pyrimidines is attractive of chemists due to presenting many of reaction centers. That is why the synthetic methods for preparing of the new representatives of pyrido[2,3-d]pyrimidine series of compounds are increased [5]. Our group has been actively working on the development of synthetic strategies for the preparation of 2,3-polymethylene derivatives of condensed with thiophene and benzene cycles pyrimidines, i.e. thieno[2,3-d]- and benz[2,3-d]pyrimidin-4(1H)-ones (quinazolin-4-ones) and non-condensed pyrimidin-4-ones also [6-8]. As a continuation of our efforts to find new pyrido[2,3-d]pyrimidines with further transformations we have synthesized novel 2,3-polymethylene-pyrido[2,3-d]-pyrimidin-4-ones.

Results and Discussion.

The following scheme outline the synthetic pathway used to obtain compounds described in this paper:



Thus, heating of the 6-aminonicotinic acid with lactams (γ-butyrolactam, δ-valerolactam, and ε-caprolactam) in the presence of phosphorus oxychloride afforded to 2,3-polymethylene (tri-, tetra, and pentamethylene) pyrido[2,3-d]pyrimidin-4(1H)-ones with satisfactory yields. Structures of the newly synthesized 2,3-tri(tetra-, and penta-)methylenepyrido[2,3-d]pyrimidin-4(1H)-ones were evidenced on the basis of ^{1}H NMR and ^{13}C-NMR spectral data.

The ^{1}H-NMR ($CDCl_3$) spectrum of 2,3-polymethylene pyrido[2,3-d]pyrimidin-4(1H)-ones showed aromatic proton signals at 7.29-7.35 (1H, q, H-6), 7.47-7.54 (1H, dd, J=2.8Hz, H-5), and 8.85-8.89 (1H, dd, J=2-6Hz, H-7), which are characteristic for pyridine part of the molecules.

It was observed shifting of β-methylene proton signals to more strong field of the ^{1}H NMR spectrum at increasing of carbon atoms in polymethylene chain. If for 2,3-trimethylene derivative the β-methylene proton signals appeared at 2.2-2.3 ppm as a multiplet, and in 2,3-tetramethylene derivative it appeared at 1.91-1.92 ppm, while for 2,3-pentamethylene the signal is overlapped with γ-methylene protons and appeared at 1.809-1.821 ppm. Similarly, chemical shifts of α-methylene proton signals appeared at 3.2 (trimethylene-derivative), 3.03 (tetramethylene-derivative), and 3.076-3.102 ppm (pentamethylene-derivative), respectively.

Methylene protons' signals of neighboring to N3 nitrogen atom in all cases are appeared in weakly field and observed at 4.16 (γ-CH_2 of trimethylene), 4.00 (δ-CH_2 of tetramethylene), and 4.298-4.322

(ε-CH_2 of pentamethylene-derivative), respectively.

Moreover, the ^{13}C-NMR spectrum showed characteristic signals at strong field for polymethylene part of the molecules. The carbonyl group's carbon atom and C-9 atoms of 2,3-polymethylenepyrido[2,3-d]pyrimidin-4(1H)-ones are observed at more weakly fields of the ^{13}C-NMR spectrum.

Experimental

IR spectra of samples were taken in pressed KBr pellets on a PerkinElmer model 2000 IR-Fourier spectrometer. The NMR spectrums of 2,3-polymethylenepyrido[2,3-d]pyrimidin-4-ones were recorded in $CDCl_3$ on a Varian 400-MR spectrometer at operating frequency 400MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts are given on the δ scale. HMDSO is used as internal standard. Melting points were determined on Boethius apparatus and are uncorrected.

Synthesis of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one. General method. To the mixture of 2-aminonicotinic acid (3.335 g, 0.024 mol) and γ-butyrolactam (3.6 ml, 0.048 mol) was treated $POCl_3$ (5.0ml, 0.54 mol). The obtained mixture was refluxed (about 160-170^{0}C) during 2 hours. Water was added. Extracted by chloroform (3 times, 30mL). The solvent evaporated, re-crystallized from appropriate solvent.

2,3-Trimethylenepyrido[2,3-d]pyrimidin-4-one. Yield: 38% of light-yellowish solid. M.p. 139-140^{0}C. IR-spectrum (KBr, ν, cm^{-1}): 3409 (weak), 3221, 2921, 2862, 1718, 1625, 1491, 1457, 1400, 1307, 1257. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.2-2.3 (2H, m, β-CH_2), 3.2 (2H, t, J=8, α-CH_2), 4.16 (2H, t, J=7, γ-CH_2), 7.3-7.35 (1H, q, H-6), 8.52-8.54 (1H, dd, J=2, 8, H-5), 8.87-8.89 (1H, dd, J=2, 6, H-7). ^{13}C NMR spectrum of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one (100 MHz, $CDCl_3$, δ, ppm): 19.483 (β-C), 32.962 (α-C), 46.883 (γ-C), 115.711 (C-10), 121.853 (C-6), 136.144 (C-5), 155.994 (C-7), 159.428 (C-2), 161.226 (C-4), 163.351(C-9). LC-MS: 188 $[M+H]^+$, (R_t = 3.794).

2,3-Tetramethylenepyrido[2,3-d]pyrimidin-4-one. Yield: 45% of yellow solid. M.p. 161-162^{0}C. IR spectrum (KBr, v, cm^{-1}): 2948, 2875, 1683, 1594, 1579, 1567, 1463, 1436, 1397. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.91-1.92 (2H, m, β-CH_2), 1.98 (2H, m, γ-CH_2), 3.03 (2H, t, J=7.3, α-CH_2), 4.00 (2H, t, J=6.2, δ-CH_2), 7.29-7.32 (1H, q, H-6), 8.49-8.51 (1H, dd, J=2, 8, H-5), 8.86-8.87 (1H, dd, J=2, 4.6, H-7). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm, J/Hz): 19.225 (β-C), 22.001 (γ-C), 32.294 (α-C), 42.809 (δ-C), 115.353 (C-10), 121.702 (C-6), 136.217 (C-5), 156.190 (C-7), 157.427 (C-2), 158.748 (C-4), 162.617 (C-9). DEPT spectrum shows seven protonated carbon atoms.

2,3-Pentamethylenepyrido[2,3-d]pyrimidin-4(1H)-one. Yield: 30% of brown solid. M.p. 119-120^{0}C. IR spectrum (KBr, v, cm^{-1}): 3442, 2934, 2859, 1722, 1681, 1596, 1586, 1568, 1438, 1395, 1350. ^{1}H NMR spectrum of 2,3-pentamethylenepyrido[2,3-d]pyrimidin-4-one (400MHz, $CDCl_3$, δ, ppm, J/Hz): 1.809-1.821 (6H, m, β, γ, δ-CH_2), 3.076-3.102 (2H, t, α-CH_2), 4.298-4.322 (2H, t, ε-CH_2), 7.295-7.326 (1H, q, H-6), 8.469-8.494 (1H, dd, J=2, 8, H-5), 8.850-8.861 (1H, dd, J=2, 6, H-7). ^{13}C NMR spectrum of 2,3-pentamethylenepyrido[2,3-d]pyrimidin-4-one (100MHz, $CDCl_3$, δ, ppm): 25.129, 27.945, and 29.564 (carbon atoms of three methylenes at β, γ, δ-positions), 37.928 (α-C), 43.235 (ε-C), 121.979 (C-6), 136.575 (C-5), 156.061 (C-7), 115.233 (C-10), 157.445 (C-2), 162.290 (C-4), 163.480 (C-9).

DEPT shows 8 protonated C atoms.

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