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Novel 7-Aryliden-3,3a,4,5,6,7-(hexahydro-5-(2-ethoxyethyl)-2-phenyl-3-aryl-2*H*-pyrazolo[4,3-*c*]pyridine Hydrochloride: Synthesis and Structure

Zh.A. Koshetova[1,2], V.K. Yu[1*], T.K. Iskakova[1], N.A. Zhumanova[1,2], K.M. Beketov[1], A.E. Malmakova[1], K.D. Praliyev[1], T.M. Seilkhanov[3] and K.D. Berlin[4]

[1]A.B. Bekturov Institute of Chemical Sciences, 106, Ualikhanov str., Almaty, Kazakhstan
[2]Kazakh National Women's Teacher Training University, 99, Ayteke bi str., Almaty, Kazakhstan
[3]Sh. Ualikhanov State University, 76, Abai str., Kokshetau, Kazakhstan
[4]Oklahoma State University, Stillwater, 74078, USA

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Abstract

A Claisen-Schmidt type reaction of 1-(2-ethoxyethyl)piperidin-4-one with different aromatic aldehydes led to corresponding dienones with a yield of 65–71%. 7-Arylidene-3,3a,4,5,6,7-(hexahydro-5-(2-ethoxyethyl)-2-phenyl-3-aryl-2*H*-pyrazolo[4,3-*c*]pyridines were synthesized by heterocyclization of 3,5-diarylidene-piperidin-4-ones with phenylhydrazine hydrochloride in methanol at 70 °C over 4–6 h. The X-ray crystal structure determination of 7-(*p*-methoxybenzyliden)-3,3a,4,5,6,7-(hexahydro-5-(2-ethoxyethyl)-2-phenyl-3-(*p*-methoxyphenyl)-2*H*-pyrazolo[4,3-*c*]pyridine hydrochloride (the deposition number is CCDC 862410) was completed. The piperidine and pyrazoline rings are close to a chair and envelope conformations, respectively.

1. Introduction

Pyrazolopiperidines have shown high central nervous system depressant activity with certain examples comparing favorably with phenylbutazone with anti-inflammatory properties [1]. Studies of selected derivatives of hydrazine to form pyrazolines have revealed an important class of medicinal agents [2]. Such derivatives can be made in a simple manner and have found wide use in medicine and veterinary science [3]. Low toxicity in some piperidine-pyrazoline derivatives, along with a wide spectrum of high pharmacological activity, has prompted further research. The 1-(2-ethoxyethyl)piperidine units led to several pharmacologically active substances [4–6]. One of the most useful procedures for generating pyrazolines involves the interaction of hydrazine, or its mono-substituted derivatives with α,β-unsaturated aldehydes or ketones, especially chalcones. Chalcones can usually be prepared by the treatment of cyclic ketones with aromatic aldehydes [7–8]. Moreover, the molecular structures, supramolecular interactions and vibrational properties of several pyrazolopiperidine derivatives have been recently determined [9–11].

Targeted pyrazoline-piperidines and intermediated bis-arylidenpiperidin-4-one are of interest as having a potential for broad-spectrum bioactivity. The key starting compound was 1-(2-ethoxyethyl)piperidin-4-one. Under the conditions of the Claisen-Schmitt reaction, novel substituted dienones were obtained, and subsequent cyclization with phenylhydrazine hydrochloride led to 7-(*p*-methoxybenzyliden)-3,3a,4,5,6,7-(hexahydro-5-(2-ethoxyethyl)-2-phenyl-3-aryl-2*H*-pyrazolo[4,3-*c*]pyridine. The structure of the synthesized compounds was identified by IR and NMR spectroscopy, and X-ray diffraction.

*Corresponding author. E-mail: yu_vk@mail.ru

2. Experimental section

2.1. General procedures

All NMR spectra were recorded on Mercury 3300 spectrometer (300 MHz) using $CDCl_3$ as a solvent. IR spectra were recorded on Specord-M80 spectrophotometer in KBr pellets. Single crystals of **VI** were obtained by crystallization from chloroform at room temperature. A yellow needle crystal (0.8 × 0.3 × 0.07 mm) was used for the diffraction experiments on a KUMA/OXFORD KM4 diffractometer (MoK_α, radiation, graphite monochromator) at 100 K. Crystal data and experimental data are given in Tables 1–3. The structure was solved by direct methods and refined by full-matrix least-squares procedure with anisotropic temperature factors for non-hydrogen atoms [12]. Hydrogen atoms were located from different Fourier maps. Estimated sin(theta_max)/wavelength = 0.6859, crystal quality was not optimal. The absolute structure could not be determined. The water molecule was located with 0.13 (1) site occupancy.

2.2. General procedure for preparation of 1-(2-ethoxyethyl)-3,5-diarylidenepiperidin-4-ones (II-V)

A mixture of 0.1 mol of 1-(2-ethoxyethyl) piperidin-4-one and 0.2 mol of benzaldehyde were added to a water-ethanol solution (5:4) containing 0.5 mol NaOH. The reaction mixture was stirred at room temperature for 4 h. A precipitate formed which was filtered and washed with neutral water. After drying, the precipitate was recrystallized (propanol-2).

1-(2-Ethoxyethyl)-3,5-bis(benzyliden)piperidin-4-one, II

Yield 70.6%, m.p. 102-103 °C; ^{13}C NMR δ, ppm: 54.9 (t, $C_{2,6}$); 132.9 (d, $C_{3,5}$); 186.9 (s, C_4); 136.2 (s, C_7); 128.1-134.9 (C_{Ar}); 56.0; 68.7; 66.0; 14.6 ($\underline{C}H_2\underline{C}H_2O\underline{C}H_2\underline{C}H_3$). Anal. Calc. for $C_{23}H_{25}NO_2$., %: C, 79.53; H, 7.20; N, 4.70.

Found., %: C, 79.58; H, 7.03; N 4.79.

1-(2-Ethoxyethyl)-3,5-bis(*p*-methoxybenzylidene)piperidin-4-one, III

Yield 70%, m.p. 122-124 °C; ^{13}C NMR, δ, ppm: 55.3 (t, $C_{2,6}$); 132.3 (d, $C_{3,5}$); 187.1 (s, C_4); 136.0 (s, C_7); 131.5; 132.3; 114.0; 128.1 (C_{Ar}); 56.5; 69.0; 66.3; 13.5 ($\underline{C}H_2\underline{C}H_2O\underline{C}H_2\underline{C}H_3$). Anal. Calc. for $C_{25}H_{29}NO_4$., %: C, 73.7; H, 7.12; N, 3.40.

Found: C, 73.60; H, 7.17; N 3.58.

1-(2-Ethoxyethyl)-3,5-bis(*m*-,*p*-dimethoxybenzylidene)piperidin-4-one, IV

Yield 65.3%, m.p. 135-136 °C; ^{13}C NMR δ, ppm: 54.8 (t, $C_{2,6}$); 131.1 (d, $C_{3,5}$); 186.4 (s, C_4); 136.1 (s, C_7); 110.4-149.4 (C_{Ar}); 56.5; 69.0; 66.0; 14.7 ($\underline{C}H_2\underline{C}H_2O\underline{C}H_2\underline{C}H_3$). Anal. Calc. for $C_{27}H_{33}NO_6$., %: C, 69.37; H, 7.06; N, 3.00.

Found., %: C, 68.92; H, 7.06; N 3.14.

1-(2-Ethoxyethyl)-3,5-bis(*p*-fluorobenzylidene) piperidin-4-one, V

Yield 71.4%, m.p. 119-122 °C; ^{13}C NMR δ, ppm 55.3 (t, $C_{2,6}$); 132.9 (d, $C_{3,5}$); 187.2 (s, C_4); 135.6 (s, C_7); 161.7-164.2 (C-F); 115.2-132.9 (C_{Ar}); 56.6; 69.2; 66.5; 15.1 ($\underline{C}H_2\underline{C}H_2O\underline{C}H_2\underline{C}H_3$). Anal. Calc. for $C_{23}H_{23}F_2NO_2$, %: C, 72.05; H, 6.05; F, 9.91; N, 3.65.

Found., %: C, 71.93; H, 6.25; F, 9.68; N, 3.76.

General procedure for preparation of 7-arylidene-3,3a,4,5,6,7-hexahydro-2-phenyl-5-(2-ethoxyethyl)-3-aryl-2*H*-pyrazolo[4,3-*c*]pyridines (VI-IX)

One mole of phenylhydrazine hydrochloride was added to a suspension of 1 mol 3.5-diarylidenpiperidone-4 in methanol. The reaction mixture was stirred at 70 °C over 4–6 h. The precipitate was filtered.

7-Benzylidene-3,3a,4,5,6,7-hexahydro-2,3-diphenyl-5-(2-ethoxyethyl)-2*H*-pyrazolo[4,3-*c*] pyridine hydrochloride, VI

Yield 65,2%, m.p. 142-143 °C; ^{13}C NMR δ, ppm 72.1 (d, C_3); 56.9 (t, C_4); 53.7 (s, C_6); 138.8 (s, C_7); 152.7 (s, C_8), 52.3 (d, C_9), 138.8 (d, C_{10}); 113.2-132.2 (C_{Ar}); 67.2; 69.7; 66.8; 14.5 ($\underline{C}H_2\underline{C}H_2O\underline{C}H_2\underline{C}H_3$). Anal. Calc. for $C_{29}H_{32}N_3OCl$, %: C, 73.50; H, 6.76; N, 8.87, Cl, 7.50.

Found., %: C, 73.66; H, 6.41; N 8.70; Cl, 7.45.

7-(*p*-Methoxybenzylidene-3,3a,4,5,6,7-hexahydro-2-phenyl-3-(*p*-methoxyphenyl)-5-(2-ethoxyethyl)-2*H*-pyrazolo[4,3-*c*]pyridine hydrochloride, VII

Yield 45.1%, m.p. 135-136 °C; ^{13}C NMR δ, ppm 72.2 (d, C_3); 57.0 (t, C_4); 54.0 (s, C_6); 130.7 (s, C_7); 145.4 (s, C_8), 52.5 (d, C_9), 134.0 (d, C_{10}); 110.4-149.4 (C_{Ar}); 68.0; 69.1; 66.9; 13.7 ($\underline{C}H_2\underline{C}H_2O\underline{C}H_2\underline{C}H_3$). Anal. Calc. for $C_{31}H_{36}N_3O_3Cl$, %: C, 69.73; H, 6.75; N, 7.87; Cl, 6.65.

Found, %: C, 68.08; H, 6.80; N 7.57; Cl, 6.57. The deposition number CCDC 862410.

7-(*m*-,*p*-Dimethoxybenzylidene-3,3a,4,5,6,7-hexahydro-2-phenyl-3-(m,*p*-dimethoxyphenyl)-(2-ethoxyethyl)-2*H*-pyrazolo[4,3-*c*]pyridine hydrochloride, VIII

Yield 76.1%, m.p. 135-136 °C; δ ^{13}C NMR ppm 76.7 (d, C_3); 55.7 (t, C_4); 52.3 (s, C_6); 126.1 (s, C_7); 143.0 (s, C_8); 51.9 (d, C_9); 126.0 (d, C_{10}); 114.4-149.8 (C_{Ar}); 67.9; 69.5; 66.4; 14.8 ($\underline{C}H_2\underline{C}H_2O\underline{C}H_2\underline{C}H_3$). Anal. Calc. for $C_{33}H_{40}N_3O_5Cl$, %: C, 66.72; H, 6.74; N, 7.08; Cl, 5.98.

Found., %: C, 66.52; H, 6.70; N 7.14, Cl, 5.81.

7-(*p*-Fluorobenzylidene-3,3a,4,5,6,7-hexahydro-2-phenyl-3-(*p*-fluorophenyl)-5-(2-ethoxyethyl)-2*H*-pyrazolo[4,3-*c*]pyridine hydrochloride, IX

Yield 59.4%, m.p. 135-136 °C; δ ^{13}C NMR ppm 71.2 (d, C_3); 55.7 (t, C_4); 54.9 (s, C_6); 146.7 (s, C_7); 152.5 (s, C_8); 54.6 (d, C_9); 131.6 (d, C_{10}); 163.6-161.3; 163.3-160.9 (d, C-F); 115-2-134.5 (C_{Ar}); 57.0; 69.0; 66.5; 15.3 ($\underline{C}H_2\underline{C}H_2O\underline{C}H_2\underline{C}H_3$). Anal. Calc. for $C_{29}H_{30}F_2N_3OCl$, %: C, 68.29; H, 5.93; N, 8.24; Cl, 6.95; F, 7.45.

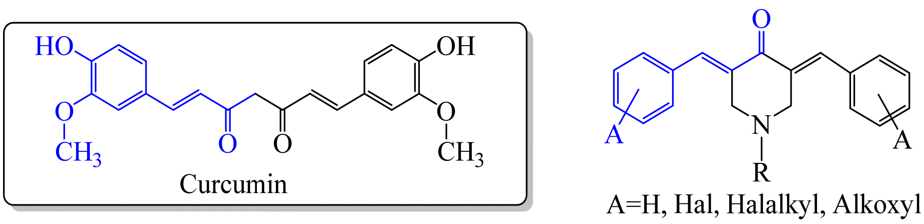
Found., %: C, 68.59; H, 6.01; N, 8.19; Cl, 7.00; F, 7.28.

To obtain an inclusion complex, solutions of 0.92 g (1.80 mmol) of 5-(2-ethoxyethyl)-7-(*p*-fluorobenzylidene)-3-(*p*-fluorophenyl)-2-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*] pyridine hydrochloride are mixed in 20 ml of ethyl alcohol and 2.04 g (1.80 mmol) of β-cyclodextrin in 30 ml of distilled water. The mixture is placed in an oven, ethanol and water are evaporated at 50–55 °C. The inclusion complex of 5-(2-ethoxyethyl)-7-(*p*-fluorobenzylidene)-3-(*p*-fluorophenyl)-2-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]pyridine hydrochloride with β-cyclodextrin are obtained in a yield of 92.5% (2.7 g) as a white powder, melting with decomposition above 240 °C. Anal. Calc. for $C_{71}H_{100}N_3O_{36}ClF_2$, %: C 51.84; H 6.08; N 2.55.

Found, %: C 51.79; H 6.12; N 2.51.

3. Results and discussion

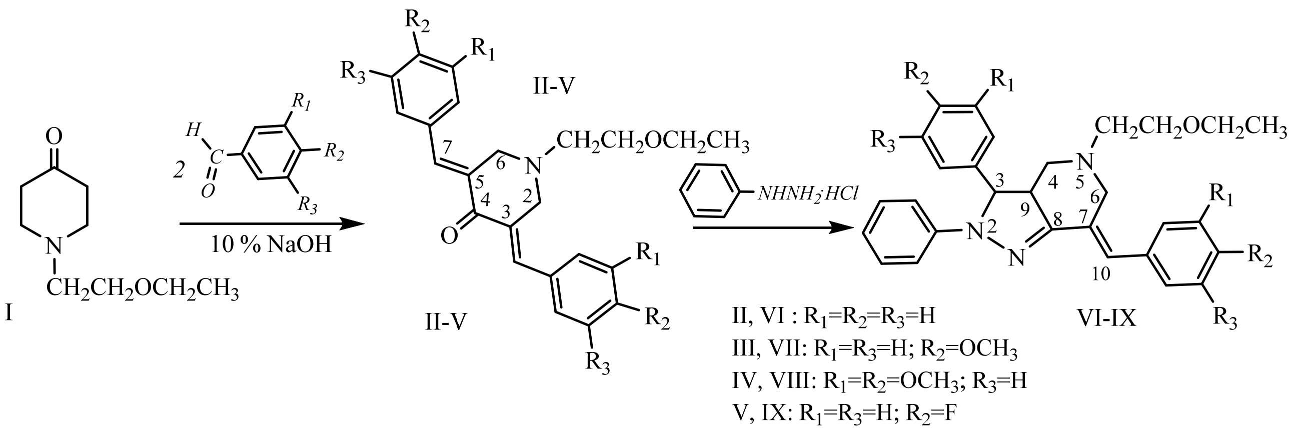
Structural similarity of 3,5-bis(arylidene)piperidin-4-one with natural curcumin [13], the main curcuminoid in turmeric root, known for its biological activity (antioxidant, antidiabetic, anti-inflammatory and anticancer, etc.) had been found.



The appending fluorine to the molecule of biologically active substances favorably affects bioefficiency [14]. Therefore, a directed search for novel derivatives in a series of synthetic analogs of curcumins as models/targets for compounds with a variational structure is justified.

A novel series of 3,5-diarylidene-4-piperidones **II-V** as chalcone analogs carrying a variety of aryl groups were synthesized by a Claisen-Schmidt type reaction of 1-(2-ethoxyethyl)piperidin-4-one (**I**) with different aromatic aldehydes including benzaldehyde and the corresponding 4-methoxy and 3,5-dimethoxy derivatives. The procedure was most efficient if ethanol containing sodium hydroxide was employed and generated products in isolated yields 65–70%.

The 3,5-diarylidenpiperidin-4-ones **II-V** are yellow crystalline substances. The identification of **II-V** was established by IR, ^1H and ^{13}C NMR analyses. Members of **II-V** displayed IR bands in ranges of 2855–3100 cm^{-1} [Ar-H], 1671–1685 cm^{-1} [C=O], 1610–1620 cm^{-1} [C=C]. Interestingly, the band for the double bond was more intense than that for the carbonyl group. This suggests a planar piperidine ring in the dienones and a *sym-cis* conformation present [15]. Due to the high symmetry of such molecules, the ^1H-NMR and ^{13}C-NMR spectra were simple. Proton spectra of **II-V** contain singlet for the four $C_{2,6}$ β-methylene protons at δ 3.93–3.96, a singlet for H-7 protons at δ 7.7–7.8, and signals for the protons on the alkyl chain attached to the nitrogen. The ^{13}C-NMR spectra had



double intensities for equivalent carbons except for the carbonyl group [186.4-187.1 ppm] and the alkyl carbons attached to the nitrogen. Alkenyl carbon signals were observed downfield [$C_{3,5}$ - s, 131.1–132.9; C_7 – d, 136.0–136.2 ppm] in the ^{13}C-NMR spectra. 7-Arylidene-3,3a,4,5,6,7-hexahydro-2-phenyl-5-R-3-aryl-2*H*-pyrazolo[4,3-*c*] pyridines **VI-IX** were obtained in moderate yields from the reaction of 3,5-diarylidenpiperidin-4-ones **II-V** with phenylhydrazine hydrochloride in methanol. IR spectral analysis of **VI-IX** revealed the absence of a carbonyl signal and the appearance of a band at 1620–1612 cm^{-1} for the C=N bond. Confirmation of the structures of **VI-IX** was realized from ^{13}C-NMR analyses where a singlet and a doublet occurred for C_7 and C_{10} for the double bond carbons, respectively and a broad singlet for the carbon in the C=N double bond downfield [135.7–138.7 ppm]. The presence of doublets for C_3 and C_9 at 72.1–76.7 and 51.9–52.5 ppm, respectively, along with the signals for C_7 and C_{10}, was taken as evidence that cyclization had resulted from the reaction. As confirmation of the structures, an X-ray diffraction study was undertaken with **VII**. The diagram below (Fig. 1) illustrates the orientation of groups in the molecule. Tables 1 and 2 contain selected bond lengths/bond angles and H-bond geometry.

The packing diagram is shown in Fig. 2 below. The average bond lengths agree reasonably well with standard dimensions [16] with the exception that the π conjugation altered some bond lengths. For example, the single bonds of single C(7)-C(8) [1.464(4) Å] and C(10)-C(11) [1.467(5) Å] bonds were slightly shorter, than normal while the double bond of C(8)-N(1) [1.279(4) Å] was slightly longer than expected.

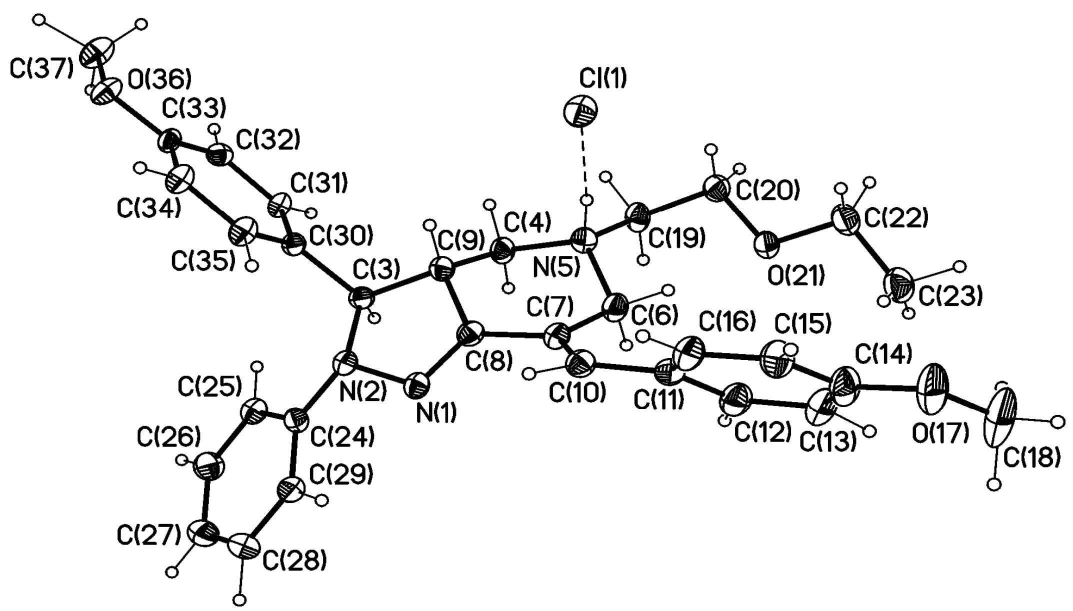


Fig. 1. Perspective view of **VII** showing the atom numbering system with ellipsoid at the 50% probability level.

Table 1
Selected bond lengths (Å) and angles (°)

Atoms	Distance	Atoms	Distance
N(1)-C(8)	1.279(4)	C(6)-C(7)	1.518(4)
N(1)-N(2)	1.398(4)	C(7)-C(10)	1.350(4)
N(2)-C(24)	1.411(4)	C(7)-C(8)	1.464(4)
N(2)-C(3)	1.499(4)	C(8)-C(9)	1.508(4)
C(3)-C(30)	1.505(4)	C(10)-C(11)	1.467(5)
C(3)-C(9)	1.546(4)	C(19)-C(20)	1.516(5)
C(4)-N(5)	1.505(4)	C(20)-O(21)	1.409(4)
C(4)-C(9)	1.517(4)	O(21)-C(22)	1.427(4)
N(5)-C(19)	1.503(4)	C(22)-C(23)	1.502(6)
N(5)-C(6)	1.505(4)		
C(8)-N(1)-N(2)	108.5(2)	C(8)-C(7)-C(6)	113.4(3)
N(1)-N(2)-C(24)	115.2(2)	N(1)-C(8)-C(7)	125.6(3)
N(1)-N(2)-C(3)	110.9(2)	N(1)-C(8)-C(9)	114.8(3)
C(24)-N(2)-C(3)	119.9(3)	C(7)-C(8)-C(9)	119.5(3)
N(2)-C(3)-C(30)	112.0(2)	C(8)-C(9)-C(4)	111.1(2)
N(2)-C(3)-C(9)	101.3(2)	C(8)-C(9)-C(3)	101.4(2)
C(30)-C(3)-C(9)	114.9(3)	C(4)-C(9)-C(3)	115.1(3)
N(5)-C(4)-C(9)	109.9(3)	C(7)-C(10)-C(11)	127.4(3)
C(19)-N(5)-C(6)	112.2(2)	N(5)-C(19)-C(20)	113.7(3)
C(19)-N(5)-C(4)	109.0(2)	O(21)-C(20)-C(19)	109.8(3)
C(6)-N(5)-C(4)	112.9(2)	C(20)-O(21)-C(22)	111.7(3)
N(5)-C(6)-C(7)	112.4(3)	O(21)-C(22)-C(23)	108.6(3)
C(10)-C(7)-C(8)	122.0(3)	C(25)-C(24)-N(2)	121.2(3)
C(10)-C(7)-C(6)	124.6(3)	C(29)-C(24)-N(2)	119.7(3)

Table 2
Hydrogen bong geometry (Å, °) [D – donor, A – acceptor]

Interactions	D-H	H…A	D…A	<D-H…A	Symm. codes
N(5)-H(5N)…Cl(1)	0.92(4)	2.09(4)	3.001(3)	172(3)	x,y,z
C(4)-H(4A)…Cl(1)	0.95(5)	2.93(5)	3.455(3)	116(3)	x,-1+y,z
C(3)-H(3)…Cl(1)	1.08(4)	2.84(4)	3.752(3)	142(3)	x,-1+y,z
C(31)-H(31)…Cl(1)	0.98(3)	2.78(3)	3.693(3)	156(2)	x,-1+y,z
C(19)-H(19A)…Cl(1)	1.03(4)	2.76(4)	3.693(3)	148(3)	-1-x,-.5+y,1-z
C(37)-H(37B)…Cl(1)	1.14(4)	2.63(4)	3.703(4)	155(3)	-x,-.5+y,1-z
C(34)-H(34)…O(21)	0.98(4)	2.39(4)	3.324(4)	158(3)	1+x,y,z
C(32)-H(32)…O(36)	0.98(3)1.05(4)	2.57(3) 2.40(5)	3.349(4)	135(2)	-x,-.5+y,1-z
C(4)-H(4B)…O(1W)	1.05(4)	2.55(4)	3.23(2)	135(3)	-1-x,-.5+y,1-z
C(19)-H(19A)…O(1W)	0.97(4)	2.29(5)	3.39(2)	137(3)	-1-x,-.5+y,1-z
C(20)-H(20A)…O(1W)	1.14(4)	2.33(4)	3.22(2)	159(3)	x,y,z
C(37)-H(37B)…O(1W)			3.11(2)	123(3)	1+x,-1+y,z
O(1W)…Cl(1)			2.96(2)		x,y,z
O(1W)…Cl(1)			3.09(2)		-1-x,.5+y,1-z

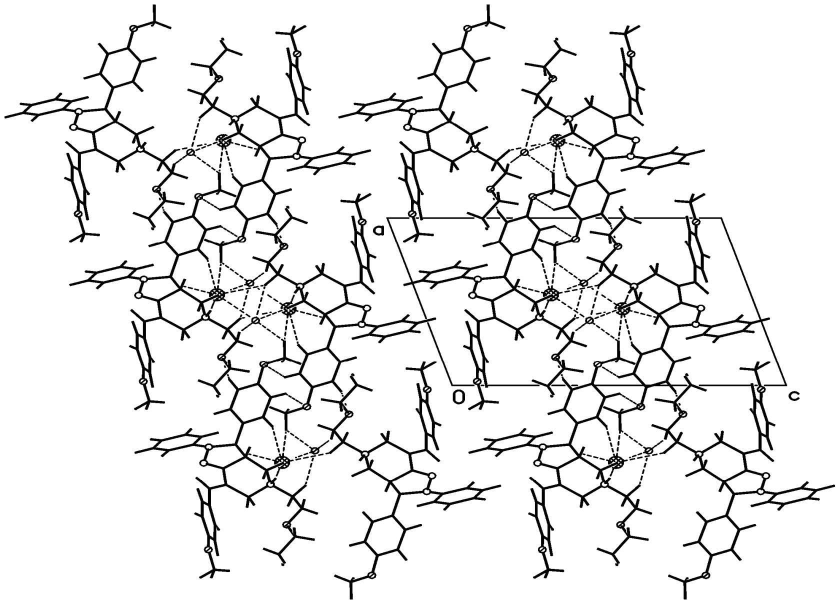


Fig. 2. Packing diagram viewed down ***b***-axes.

There is no common conjugation along with the system C(10)-C(7)-C(8)-N(1). The piperidine ring is close to a chair conformation, but N(5) and C(8) atoms are displaced by 0.649(4) Å and -0.461(4) Å, respectively, from the common plane formed by the remaining four atoms. Whereas, in other pyrazolo-piperidine derivatives [9], less close to ideal chair conformations can be observed, in which the N(5) atoms of the piperidine ring leave the plane of 4 carbon atoms in the range from 0.288 (5) to 0.409 (5) Å, and the C(8) atom is in the range of 0.373 (6) and 0.463 (4) Å. In general, the geometric parameters (Table 1) of the compounds are in good agreement with related compounds described in the literature [9–11].

The ethoxyethyl substituent attached to N(5) occupies a pseudo equatorial position, assuming *gauche-trans-trans* orientation with the torsion angles of N(5)C(19)-C(20)-O(21)-C(22)C(23) being 74.6(4)°, 178.7(3)° and –176.4(3)°, respectively. The *p*-methoxybenzyliden group in **VI** is planar (to within 0.016 Å) and is inclined to the mean-square plane of the piperidine ring at an angle of 60.0(1)°. The conformation of the five-membered pyrazoline ring is close to an envelope with the vertex at the C(3) atom displaced by -0.281(5) Å from the plane of the remaining four atoms. The dihedral angle between the piperidine and pyrazoline cycles is 25.8(2)°.

The planar (to within 0.007 Å) *p*-methoxyphenyl group attached to C(3) has a pseudo-equatorial position and is twisted with respect to the pyrazoline ring. The twisting is described by the torsion angle C(9)-C(3)-C(30)-C(31) of 95.3(3)°. The N(2) atom is in a pyramidal arrangement, and the planar aryl ring makes an angle of 26.9(1)° with the best plane of the pyrazoline ring. The nitrogen N(5) of the piperidine ring is protonated and culminating with the cation and anion forming an ion pair *via* a hydrogen bond involving N(5)–H…Cl(1). Interestingly, in crystalline of **VII** (data not included) the ion pairs arising from C–H…Cl bonds create infinite columns directed in the *b*-axis, which are aligned in layers parallel to the *ab*-plane by means of C–H…O hydrogen bonds (data not shown). Small cavities exist in the crystal structure of **VII** with water molecules containing traces of chloroform occupying the cavities. The water molecules are part of the system *via* hydrogen bonds. Details of the geometry concerning hydrogen bonding are found in Table 2. Interactions through van der Waals forces maintain the layers within the crystalline structure with other interactions being evident in the packing diagram (Fig. 2).

Table 3 possesses crystal and experimental data for **VII**.

Proprietary results [17–19] in pending patents indicate that members of **VI-VIII** possess the good analgesic activity and have low toxicity. Moreover, hydrochloride members of **VI** and **VII** displayed both analgesic and antiarrythmic activities. It turned out that 7-(*p*-fluorobenzyliden)-3,3a,4,5,6,7-(hexahydro-5-(2-ethoxyethyl)-2-phenyl-3-(*p*-fluorophenyl)-2*H*-pyrazolo[4,3-*c*]pyridine hydrochloride as a complex with β-cyclodextrin stimulates erythropoiesis, thrombocytosis, and leukopoiesis at the level of the reference drug methyluracil, almost to the level of the blood of intact animals [20].

Table 3
Crystal and experimental data

Chemical formula	$C_{31}H_{36}ClN_3O_3 \cdot 0.13\ H_2O$
Molecular weight	534.08
Crystal system	Monoclinic
Space group	$P2_1$
a, (Å)	11.9618(9)
b, (Å)	6.9347(5)
c, (Å)	18.4040(10)
β, (°)	107.44(1)
V, (Å^3)	1456.5(2)
Z	2
D_x, (g.cm^{-3})	1.218
μ, cm^{-1}	1.67
F(000)	568
θ range for data collection, (°)	3.41 to 29.18
Index ranges	-16<=h<=16, -9<=k<=4, -24<=l<=24
Reflections collected	9640
Independent reflections	4428 [R(int) = 0.0502]
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.050
Final R indices [I>2σ(I)]	R1 = 0.0532, wR2 = 0.1258
R indices (all data)	R1 = 0.0634, wR2 = 0.1345
Largest diff. peak and hole, (eA^{-3})	0.272 and -0.297

4. Conclusion

In summary, we have prepared a novel series of 7-aryliden-3,3a,4,5,6,7-hexahydro-5-(2-ethoxyethyl)-2-phenyl-3-aryl-2*H*-pyrazolo[4,3-*c*] pyridine hydrochloride systems, in the IR spectra of which C=N absorption bands (1580–1620 cm^{-1}) are observed. In the ^{13}C NMR spectra of piperidine-pyrazolines, along with C_7 and C_{7a} singlets and a C_{12} doublet of double bond carbons, a broad C=N group singlet (143.0–159.5 ppm) and C_3 and C_{3a} doublets at 70.0–73.5 and 52.5–56.4 ppm.

Single crystal X-ray analysis confirmed the basic structural unit in 7-(*p*-methoxybenzylidene-3,3a,4,5,6,7-hexahydro-2-phenyl-3-(*p*-methoxyphenyl)-5-(2-ethoxyethyl)-2*H*-pyrazolo[4,3-*c*] pyridine hydrochloride. It has been shown that the piperidine ring adopts a distorted "armchair" conformation, where the N_5 and C_{7a} atoms move out of the plane of the other four ring atoms, while the methoxyphenyl and phenyl substituents are in the dipseudo-equatorial position. Piperidinopyrazoline molecules interact with each other by van der Waals contacts.

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References

[1]. J. Krapcho, C.F. Turk. *J. Med. Chem.* 22 (1979) 207–210. DOI: 10.1021/jm00188a018

[2]. B. Insuasty, A. Montoya, D. Becerra, J. Quiroga, R. Abonia, S. Robledo, I.D. Vélez, Y. Upegui, M. Nogueras, J. Cobo, *European J. Med. Chem.* 67 (2013) 252–262. DOI: 10.1016/j.ejmech.2013.06.049

[3]. B. Sharifzadeh, N.O. Mahmoodi, M. Mamaghani, K. Tabatabaeian, A.S. Chirani, I. Nikokar, *Bioorg. Med. Chem. Lett.* 23 (2013) 548–551. DOI: 10.1016/j.bmcl.2012.11.024

[4]. V.K. Yu, A.Zh. Kabdraissova, K.D. Praliyev, S.N. Shin, K.D. Berlin, *J. Saudi Chem. Soc.* 13 (2009) 209–217. DOI: 10.1016/j.jscs.2009.04.001

[5]. V. Yu, K. Praliyev, A. Nagimova, A. Zazybin, *Tetrahedron Lett.* 56 (2015) 1631–1634. DOI: /10.1016/j.tetlet.2015.02.001

[6]. S.S. Zhumakova, A.E. Malmakova, V.K. Yu, K.D. Praliev, T.K. Iskakova, A.Yu. Ten, M.K. Amirkulova, D.M. Kadyrova, E.M. Satpaeva, T.M. Seilkhanov, *Pharm. Chem. J.* 54 (2021) 1209–1214. DOI: 10.1007/s11094-021-02345-9

[7]. V. Nair, S. Vellalath, B.P. Babu, V. Varghese, R.R. Paula, E. Suresh, *Org. Biomol. Chem.* 8 (2010) 4861. DOI: 10.1039/c0ob00180e

[8]. A.G. Golikov, A.P. Kriven'ko, A.A. Bugaev, S. F. Solodovnikov, *J. Struct. Chem*. 47 (2006) 102–105. DOI: 10.1007/s10947-006-0273-0

[9]. B.K. Sagar, K.B. Harsha, H.S. Yathirajan, K.S. Rangappa, R.S. Rathore, C. Glidewell, *Acta Cryst.* 73 (2017) 298–304. DOI: 10.1107/S205322961700273X

[10]. C. Pang, C. Sun, J. Wang, D. Xiao, L. Ding, H. Bu, *Sci. China Chem*. 56 (2013) 702–715. DOI: 10.1007/s11426-013-4840-x

[11]. E. McDonald, P.N. Horton, M.B. Hursthouse (2007) University of Southampton, Crystal Structure Report Archive. DOI: 10.5258/ecrystals/353

[12]. F.H. Allen, O. Kennard, D.G. Warson, L. Brammer, A.G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans.* 2 (1987) S1-S18. DOI: 10.1039/P298700000S1

[13]. Y. Eryanti, R. Hendra, T. Herlina, A. Zamri, U. Supratman, *Procedia Chem.* 17 (2015) 224–229. DOI: 10.1016/j.proche.2015.12.136

[14]. R.S. Rathore, S. Karthikeyan, Y. Alekhyak, K. Sathiyanarayanan, P.G. Aravindan, *J. Chem. Sci.* 123 (2011) 403–409. DOI: 10.1007/s12039-011-0091-6

[15]. B.N. Tarasevich, Moskva: Izd. MGU (2012) 55. [in Russian]. https://studizba.com/files/show/pdf/54167-1-b-n-tarasevich--ik-spektry-osnovnyh.html

[16]. G.M. Sheldrick, *Acta Cryst.* A 64 (2008) 112–122. DOI: 10.1107/S0108767307043930

[17]. Patent KZ 10436. K.D. Praliyev, V.K. Yu, T.K. Iskakova, N.A. Ismagulova et al. Bull. #12, 2004.

[18]. Preliminary patent KZ 10435. K.D. Praliyev, T.K. Iskakova, V.K. Yu, S.N. Shin, N.A. Ismagulova et al. Bull. #7, 2001.

[19]. Preliminary patent KZ 11197. T.K. Iskakova, K.D. Praliyev, N.A. Ismagulova, V.K. Yu, S.N. Shin et al. Bull. #2, 2002.

[20]. V.K. Yu, L.K. Bahtybayeva, A.Yu. Ten, A.E. Malmakova, Proceedings of XXI Int. Conf. Sci. Techn. – Russia-Korea-CIS, (2021), Moscow, 242.