ELSEVIER

Il Farmaco 57 (2002) 897–908

IL FARMACO

www.elsevier.com/locate/farmac

Investigations on the synthesis and pharmacological properties of 4-alkoxy-2-[2-hydroxy-3-(4-aryl-1-piperazinyl)propyl]-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-diones

Helena Śladowska [a,*], Barbara Filipek [b], Dominika Szkatuła [a], Aleksandra Sabiniarz [a], Małgorzata Kardasz [b], Joanna Potoczek [a], Maria Sieklucka-Dziuba [c], Grażyna Rajtar [d], Zdzisław Kleinrok [d], Tadeusz Lis [e]

[a] *Department of Chemistry of Drugs, Wrocław University of Medicine, Tamka 1, 50-137 Wrocław, Poland*
[b] *Laboratory of Pharmacological Screening, Faculty of Pharmacy, Jagiellonian University, Collegium Medicum, Medyczna 9, 30-688 Kraków, Poland*
[c] *Department of Hygiene, Medical School, Radziwiłłowska 11, 20-085 Lublin, Poland*
[d] *Department of Pharmacology, Medical School, Jaczewskiego 8, 20-090 Lublin, Poland*
[e] *Faculty of Chemistry, University of Wrocław, Joliot-Curie 14, 50-383 Wrocław, Poland*

Received 3 May 2002; accepted 29 June 2002

Abstract

Synthesis of 2-[2-hydroxy-3-(4-aryl-1-piperazinyl)propyl] derivatives of 4-alkoxy-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-diones (**8**–**12**) is described. The chlorides used in the above synthesis can exist in two isomeric forms: chain (**18**–**20**) and cyclic (**19a**, **20a**). The compounds **8**–**12** exhibited potent analgesic activity which was superior than that of acetylsalicylic acid in two different tests. Most of the investigated imides suppressed significantly spontaneous locomotor activity in mice.

Keywords: 4-Alkoxy-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-diones; *N*-[2-hydroxy-3-(4-aryl-1-piperazinyl)propyl] derivatives; Synthesis; Analgesic and sedative activities; Derivatives of 7-aza-4-azoniaspiro[3.5]nonane chloride

1. Introduction

It has been reported previously [1,2] that *N*-[2-hydroxy-3-(4-phenyl(2-pyrimidinyl)-1-piperazinyl)propyl] derivatives of the suitable 1H-pyrrolo[3,4-c]pyridine-1,3(2H)-diones (3,4-pyridinedicarboximides) (**1**–**5**) significantly suppressed spontaneous locomotor activity in mice. Compounds **1** and **2** decreased significantly their amphetamine induced hyperactivity (Fig. 1). Compound **1** caused hypothermia in normothermic mice. Most of the investigated imides did not display analgesic activity in 'writhing syndrome' and 'hot-plate' tests. Only the compounds **1** and **4** substituted at the position 2 of the pyridine ring by the piperidino group were active in one of these tests. The imide **1** showed a weak analgesic effect in the 'writhing syndrome' test at the dose of 200 mg/kg whereas compound **4** increased the time of appearance of the pain reaction at the dose of 68.09 mg/kg in the 'hot-plate' test. Among the studied substances only imide **5** increased the number of head twitches, induced by 5-HTP in mice, at the dose of 126.6 mg/kg. All the investigated compounds did not affect the pulse rate and arterial blood pressure in rats.

From our earlier published findings [3] it follows that the replacement of the piperidino group in compound **6** [4] by a methoxy one (imide **7**) caused appearance of strong analgesic activity (Fig. 2). Compound **7** was effective in the 'writhing syndrome' test up to the dose of 6.25 mg/kg. In the 'hot-plate' test it showed analgesic action in doses 200 and 100 mg/kg whereas compound **6** was inactive as an analgesic agent in both tests. At the same time the above mentioned modification resulted in a non-toxic substance (LD_{50} for **6** = 1750 mg/kg, for **7** > 2000 mg/kg).

* Corresponding author
E-mail address: helena@bf.uni.wroc.pl (H. Śladowska).

0014-827X/02/$ - see front matter
PII: S0014-827X(02)01302-2

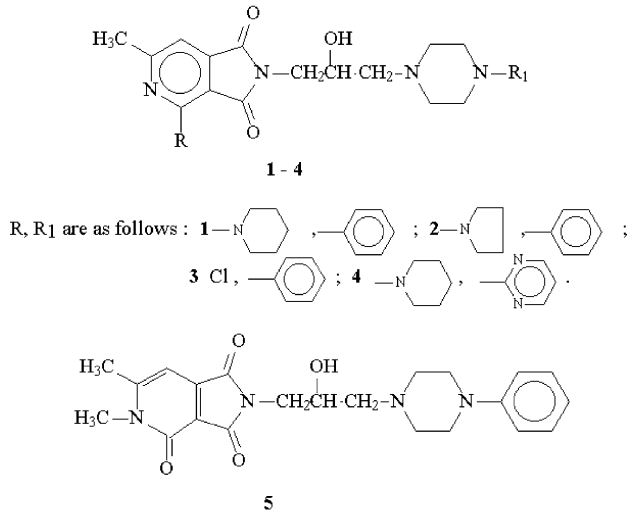


Fig. 1.

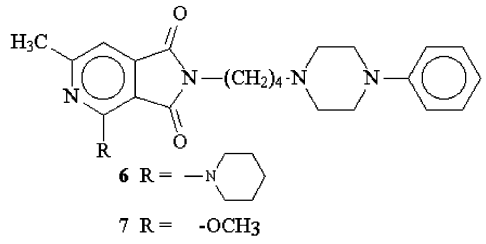


Fig. 2.

In order to obtain further information concerning structure–activity relationships (SAR) in this group of compounds we modified the structure of 1H-pyrrolo[3,4-c]pyridine-1,3(2H)-diones (**1**–**3**). The modification consisted mainly in introduction of alkoxy groups in the position 2 of the pyridine ring.

In the further investigations we also introduced pharmacophoric groups: OCH_3 and CF_3 into the phenyl substituent at N-4 of the piperazine ring and investigated the influence of this modification on the pharmacological action. According to the above we performed the synthesis of the derivatives of 1H-pyrrolo[3,4-c]pyridine-1,3(2H)-diones reported in Fig. 3 with the expectation that the compounds obtained (**8**–**12**) would exhibit analgesic activity. Furthermore, the 2-hydroxy-3-(4-aryl-1-piperazinyl)propyl substituent has similar structure to that of the side chains of β-blockers. Therefore, we also evaluated the influence of imides **8**–**12** on the arterial blood pressure in rats.

2. Chemistry

The starting materials for the synthesis of compounds **8**–**12** were 4-methoxy- and 4-ethoxy-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-diones (**13**, **14**) synthesized previously [3]. They were transformed into the imides **8**–**12** according to the reactions presented in Scheme 1 (methods 'a', 'b_1' and 'b_2', 'c'). In the method 'a' compounds **13** and **14** were condensed with epichlorohydrin in the presence of anhydrous potassium carbonate obtaining suitable *N*-2,3-epoxypropyl derivatives **15**, **16** which in the reaction with *N*-arylpiperazines were transformed into compounds **8**–**11**.

In the method 'b' 4-methoxy- and 4-ethoxy-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-diones (**13**, **14**) were condensed with appropriate 2-hydroxy-3-(4-aryl-1-piperazinyl)propyl chlorides (**18**–**20**) or their cyclic isomers (**19a**, **20a**) in anhydrous ethanol in the presence of C_2H_5ONa ('b_1') or C_2H_5OK ('b_2'). In this way all compounds (**8**–**12**) were synthesized.

The compounds **8** and **9** were also obtained as a result of condensation of 4-chloro-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (**17**) [5] with 2-hydroxy-3-(4-phenyl-1-piperazinyl)propyl chloride (method 'c'). This reaction was performed in anhydrous methanol or ethanol in the presence of 2 mol of sodium methoxide or ethoxide for 1 mol of starting imide **17**.

According to the literature data [6,7] 2-hydroxy-3-(4-aryl-1-piperazinyl)propyl chlorides were obtained in the reaction of epichlorohydrin with suitable *N*-arylpiperazines. Often non-isolated products of this reaction were

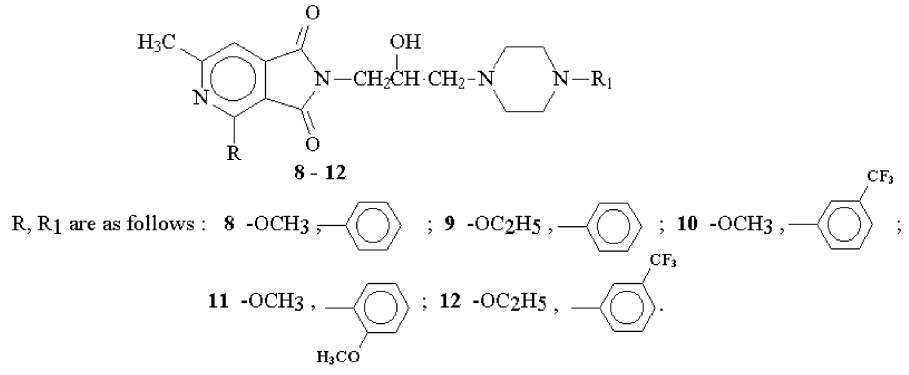
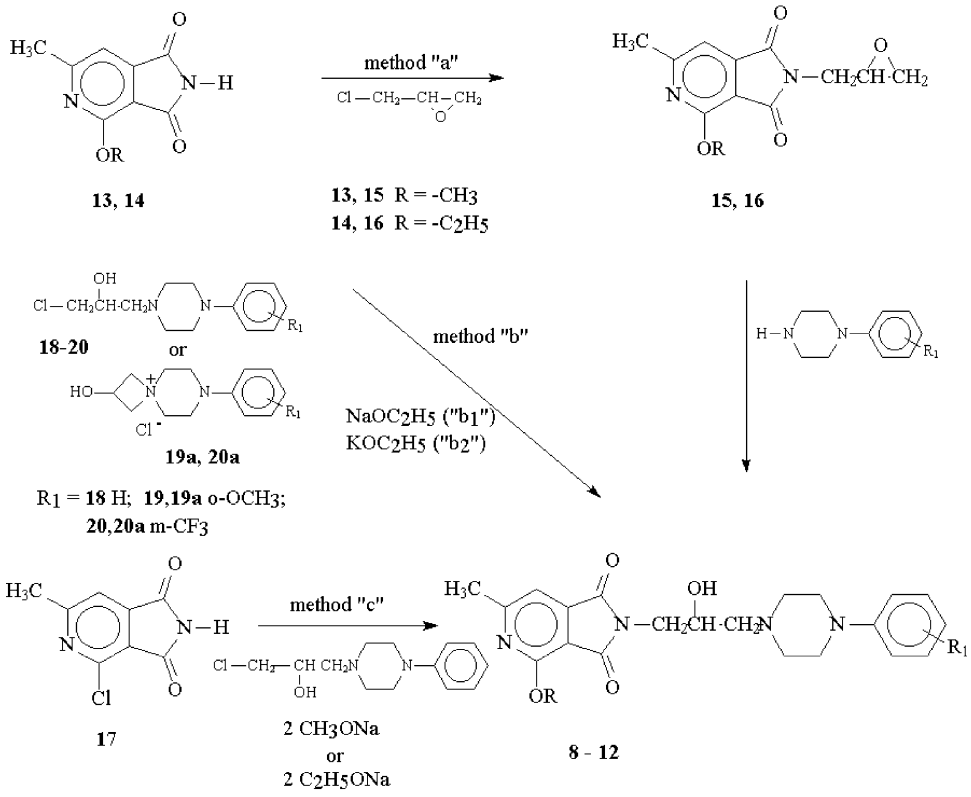


Fig. 3.



R, R_1 are as follows : **8** -CH_3, -H ; **9** -C_2H_5, -H ; **10** - CH_3, m-CF_3 ; **11** CH_3, o-OCH_3 ; **12** -C_2H_5, m-CF_3 .

Scheme 1.

used as intermediates in the synthesis of other compounds.

Carrying out the above reaction with *N*-(*o*-methoxyphenyl)- and *N*-(*m*-trifluoromethylphenyl)piperazines we observed that the structure of the formed products was dependent on temperature. At room temperature they reacted with epichlorohydrin affording water nonsoluble substances which elemental composition corresponded to 2-hydroxy-3-[4-(*o*-methoxyphenyl)- and 2-hydroxy-3-[(4-*m*-trifluoromethylphenyl)-1-piperazinyl]propyl chlorides, respectively. In the case of *N*-(*m*-trifluoromethylphenyl)piperazine a small amount of isomeric water-soluble by-product was formed. The same reaction performed at first at 40 °C for 0.5 h and then at room temperature led to the isomeric compounds which were soluble in water and gave positive reaction for chloride ions with silver nitrate. *N*-Phenylpiperazine reacted with epichlorohydrin giving in both the cases the same water insoluble substance having elemental composition corresponding to the known [6] 2-hydroxy-3-(4-phenyl-1-piperazinyl)propyl chloride.

In order to establish and dispel our doubts concerning structures of the obtained compounds appropriate investigations were performed. Based on the results of the elemental, spectral and X-ray analyses we ascribed to the water-insoluble products the structures of the suitable 2-hydroxy-3-(4-aryl-1-piperazinyl)propyl chlorides (**18**–**20**). Isomeric compounds (soluble in water) were appropriate derivatives of 7-aza-4-azoniaspiro[3,5]nonane chloride (**19a**, **20a**) (Scheme 1).

According to our knowledge the possibility of formation of cyclic structures (type **19a**, **20a**) in the reaction of *N*-arylpiperazines with epichlorohydrin was not hitherto taken into consideration.

2.1. Crystal structures of *18* and *20a*

The perspective view of the structures **18** and **20a** is shown in Fig. 4a and b. Compound **18** is racemic and one of enantiomers (with C2 atom in *R* absolute configuration) was chosen to presentation. Atomic coordinates and equivalent isotropic displacement parameters are listed in Table 1 and principal bond distances, bond angles and torsion angles in Table 2.

Compound **18** is a molecular structure, whereas **20a** is a salt where cation is represented by 2-hydroxy-7-(3-trifluoromethyl)phenyl-7-aza-4-azoniaspiro[3,5]nonane and positive charge is located on the quaternary nitrogen atom in position 4 of piperazine ring. The anion is chloride ion.

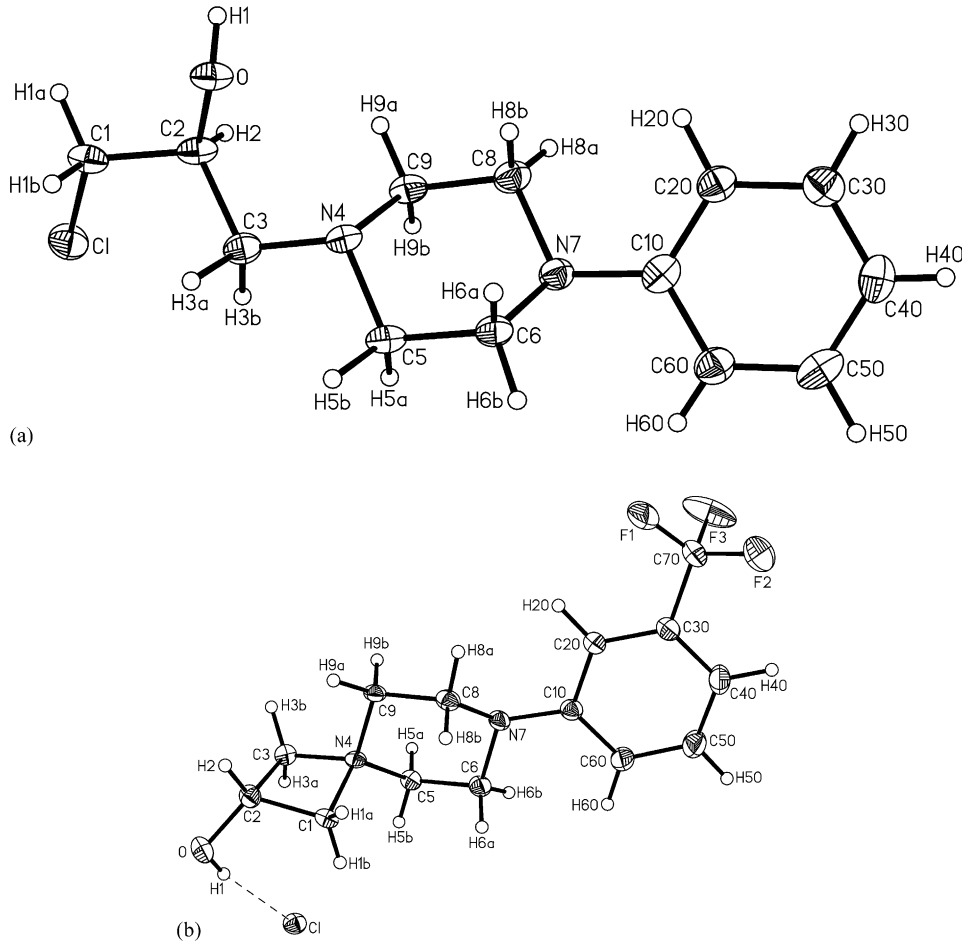


Fig. 4. (a) A wiev of the molecule **18** (in the picture molecule exists in *R* conformation). (b) A view of cation and anion of 2-hydroxy-7-(3-trifluoromethyl)phenyl-7-aza-4-azoniaspiro[3.5]nonane chloride (**20a**).

The structure of both compounds is extended with the piperazine ring in chair conformation. The mutual position of the phenyl and piperazine rings is different in both cases and may be described by C6–N7–C10–C60 torsion angle (59.7(3)° for **18** and 2.1(3)° for **20a**). The orientation of the phenyl with respect to the piperazine ring is dependent on presence, location and nature of substituents in the phenyl ring, which was described earlier in the literature, i.e. Ref. [8].

In **18** the propyl group is staggered. Chlorine and C3 atoms are in synclinar conformation and simultaneously Cl atom is in antiperiplanar position in relation to O atom. The position of O atom with respect to N4 is synperiplanar.

The four-membered ring in **20a** is not flat and the angles within this ring are close to 90° similarly to structure of diphenylmethyl-3-hydroxyazetidinium chloride (DPHA) [9]. The OH-group is located in the equatorial position. The N4–C5 and N4–C9 lengths are close to an average of C_{sp3}–N^+ bond length and similar values were found in derivative of morpholine [10].

3. Experimental

3.1. Chemistry

All the results of the C, H, N determinations (carried out by a Carlo Erba elemental analyzer model NA-1500) were within ±0.4% of the theoretical values. All the melting points are uncorrected. The IR spectra, in KBr pellets, were measured with a Zeiss Jena specord model IR 75 and specord M 80 (Jena). ^{1}H NMR spectra were determined in $CDCl_3$ on a Tesla 587A spectrometer (80 MHz), when not otherwise indicated, using TMS as an internal standard.

3.1.1. General method for synthesis 2-(2,3-epoxypropyl) derivatives of 4-methoxy- and 4-ethoxy-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-diones (**15**, **16**)

4-Methoxy- or 4-ethoxy-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (13, 14) (0.005 mol) and 0.006 mol of anhydrous potassium carbonate in 15 ml of epichlorohydrin were refluxed for 14 h. Then inorganic substances were collected on a filter. From the filtrate an excess of epichlorohydrin was distilled off under dimi-

Table 1
Fractional atomic coordinates and equivalent isotropic displacement parameters with the e.s.d.'s in parentheses for **18** and **20a**

Atom	*x*	*y*	*z*	U_{eq}/U_{iso}
18				
Cl	0.38388(7)	0.20909(9)	0.521742(13)	0.0296(2)
O	0.7458(2)	0.4366(2)	0.56594(4)	0.0235(4)
C1	0.5772(3)	0.2919(4)	0.52963(5)	0.0230(5)
C2	0.5899(3)	0.3819(3)	0.56123(5)	0.0206(5)
C3	0.4899(3)	0.5692(3)	0.56455(5)	0.0218(5)
N4	0.5281(2)	0.6885(3)	0.59146(4)	0.0195(4)
C5	0.4220(3)	0.8585(3)	0.59389(5)	0.0222(5)
C6	0.4681(3)	0.9919(4)	0.62044(5)	0.0222(5)
N7	0.4680(2)	0.8814(3)	0.64939(4)	0.0215(4)
C8	0.5696(3)	0.7067(4)	0.64694(5)	0.0242(5)
C9	0.5221(3)	0.5758(4)	0.62012(5)	0.0224(5)
C10	0.4925(3)	1.0047(3)	0.67542(5)	0.0236(5)
C20	0.6141(3)	0.9743(4)	0.69574(5)	0.0245(5)
C30	0.6309(3)	1.0963(4)	0.72135(6)	0.0277(6)
C40	0.5288(3)	1.2485(4)	0.72721(6)	0.0300(6)
C50	0.4077(3)	1.2796(4)	0.70708(6)	0.0324(6)
C60	0.3896(3)	1.1606(4)	0.68166(6)	0.0274(6)
H1	0.803(4)	0.341(5)	0.5737(7)	0.059(10)
H1A	0.648(3)	0.165(4)	0.5274(6)	0.046(8)
H1B	0.602(2)	0.393(3)	0.5146(4)	0.012(5)
H2	0.556(3)	0.279(3)	0.5751(5)	0.020(6)
H3A	0.504(2)	0.650(3)	0.5443(5)	0.014(6)
H3B	0.372(3)	0.527(3)	0.5649(5)	0.022(6)
H5A	0.314(3)	0.814(3)	0.5971(5)	0.018(6)
H5B	0.429(3)	0.934(3)	0.5721(5)	0.019(6)
H6A	0.576(3)	1.043(4)	0.6166(6)	0.033(7)
H6B	0.400(3)	1.102(4)	0.6200(5)	0.028(7)
H8A	0.563(3)	0.633(4)	0.6652(5)	0.023(6)
H8B	0.677(3)	0.744(3)	0.6432(5)	0.017(6)
H9A	0.595(2)	0.464(3)	0.6181(4)	0.004(5)
H9B	0.415(3)	0.520(3)	0.6245(5)	0.016(6)
H20	0.688(4)	0.864(5)	0.6924(6)	0.062(10)
H30	0.710(3)	1.065(4)	0.7350(5)	0.033(7)
H40	0.540(3)	1.315(4)	0.7441(6)	0.037(8)
H50	0.340(3)	1.387(4)	0.7107(6)	0.036(7)
H60	0.309(3)	1.175(3)	0.6685(5)	0.023(6)
20a				
Cl	0.185294(11)	0.76808(7)	0 (fixed)	0.02025(9)
F1	0.09121(4)	−0.3256(3)	1.1859(2)	0.0426(4)
F2	0.03353(4)	−0.3782(4)	1.1764(3)	0.0503(5)
F3	0.06877(7)	−0.6062(3)	1.0305(3)	0.0621(6)
O	0.22977(4)	0.8561(2)	0.3693(2)	0.0220(3)
C1	0.17610(5)	0.6345(3)	0.5015(3)	0.0165(3)
C2	0.21800(5)	0.6747(3)	0.4818(3)	0.0182(3)
C3	0.22126(5)	0.4379(3)	0.3943(3)	0.0175(3)
N4	0.18287(4)	0.3836(2)	0.4681(2)	0.0135(3)
C5	0.15839(5)	0.2716(3)	0.3224(3)	0.0160(3)
C6	0.12032(5)	0.2303(3)	0.4063(3)	0.0197(3)
N7	0.12300(4)	0.0976(3)	0.5851(2)	0.0176(3)
C8	0.14502(5)	0.2159(3)	0.7313(3)	0.0183(3)
C9	0.18369(5)	0.2551(3)	0.6554(3)	0.0164(3)
C10	0.09058(5)	−0.0073(3)	0.6513(3)	0.0180(3)
C20	0.09222(5)	−0.1382(3)	0.8225(3)	0.0191(3)
C30	0.06126(5)	−0.2496(3)	0.8863(3)	0.0216(4)
C40	0.02804(6)	−0.2422(4)	0.7853(3)	0.0266(4)
C50	0.02650(6)	−0.1150(4)	0.6159(4)	0.0296(4)
C60	0.05707(6)	0.0049(4)	0.5514(3)	0.0251(4)
C70	0.06372(6)	−0.3900(4)	1.0672(4)	0.0282(4)
H1	0.2193(8)	0.847(5)	0.265(5)	0.036(8)
H1A	0.1642(8)	0.664(5)	0.629(5)	0.032(8)
H1B	0.1628(7)	0.692(4)	0.394(4)	0.015(6)
H2	0.2300(6)	0.686(3)	0.605(3)	0.007(5)
H3A	0.2224(7)	0.446(4)	0.250(4)	0.022(6)
H3B	0.2404(7)	0.333(4)	0.446(4)	0.020(6)
H5A	0.1697(6)	0.137(4)	0.286(3)	0.009(5)
H5B	0.1565(7)	0.367(4)	0.210(4)	0.023(6)
H6A	0.1073(7)	0.373(5)	0.424(4)	0.024(7)
H6B	0.1081(7)	0.148(4)	0.319(4)	0.022(6)
H8A	0.1484(8)	0.127(5)	0.848(5)	0.032(7)
H8B	0.1335(7)	0.367(5)	0.771(4)	0.035(8)
H9A	0.2002(8)	0.339(5)	0.744(5)	0.032(7)
H9B	0.1957(7)	0.112(4)	0.615(4)	0.016(6)
H20	0.1157(6)	−0.152(4)	0.892(3)	0.006(5)
H40	0.0064(6)	−0.321(4)	0.831(4)	0.014(5)
H50	0.0041(8)	−0.106(5)	0.540(5)	0.037(8)
H60	0.0550(7)	0.100(5)	0.433(4)	0.032(8)

nished pressure. The residue was crystallized from ethanol with simultaneous decolorization with charcoal in the case of the compound **15**.

The properties of compounds **15** and **16** are given in Table 3 but the assignments in their ^{1}H NMR spectra are presented below.

^{1}H NMR of **15**: $\delta = 2.63–2.84$ (m-5H, $\mathbf{CH_3}+\mathbf{CH_2}\gamma$); 3.05–3.40 (m-1H, C**H**); 3.58–4.13 (m-5H, $\mathrm{OCH_3}+\mathbf{CH_2}\alpha$); 7.19 (s-1H, H in pyridine ring).

^{1}H NMR of **16**: $\delta = 1.39–1.56$ (t-3H, $\mathbf{CH_3}–\mathrm{CH_2}–$); 2.62–2.79 (m-5H, $\mathbf{CH_3}+\mathbf{CH_2}\gamma$); 3.05–3.38 (m–1H, CH); 3.76–3.91 (m-2H, $\mathbf{CH_2}\alpha$); 4.48–4.75 (q-2H, $–\mathbf{CH_2}–\mathrm{CH_3}$); 7.18 (s-1H, H in pyridine ring).

*3.1.2. General methods for synthesis 2-[2-hydroxy-3-(4-aryl-1-piperazinyl)propyl] derivatives of 4-methoxy- and 4-ethoxy-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-diones (**8**–**12**)*

3.1.2.1. Method 'a'. 2-(2,3-Epoxypropyl)-4-methoxy- or 2-(2,3-epoxypropyl)-4-ethoxy-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (**15** or **16**) (0.001 mol) and 0.002 mol of *N*-phenylpiperazine (**8**, **9**), 0.0011 mol of *N*-(*m*-trifluoromethylphenyl)piperazine (**10**), 0.0013 mol of *N*-(*o*-methoxyphenyl)piperazine (**11**) in 30 ml (**8**, **9**) or 15 ml (**10**, **11**) of anhydrous ethanol were refluxed for 1 h (**8**, **9**), 15 min (**10**, **11**). The crystals separated after cooling of the reaction mixture were collected on a filter and purified by crystallization from ethanol.

3.1.2.2. Methods 'b_1' and 'b_2'. Sodium (method 'b_1') (0.01 mol) or 0.01 mol of potassium (method 'b_2') was dissolved in 100 ml of anhydrous ethanol and to this solution 0.01 mol of 4-methoxy- or 4-ethoxy-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (**13** or **14**) was added. The reaction mixture was refluxed for 15 min in case of the imide **13** and to the obtained suspension or

Table 2
Principal bond distances (Å), bond angles (°) and torsion angles (°) with ESD's in parentheses for **18** and **20a**

	18	**20a**
Bond distances		
F1–C70		1.346(3)
F2–C70		1.331(3)
F3–C70		1.329(3)
O–C2	1.421(3)	1.397(2)
C1–N4		1.536(2)
C1–C2	1.512(3)	1.551(2)
C2–C3	1.536(3)	1.541(3)
C3–N4	1.462(3)	1.522(2)
N4–C9	1.465(3)	1.494(2)
N4–C5	1.472(3)	1.495(2)
C5–C6	1.520(3)	1.521(3)
C6–N7	1.467(3)	1.461(2)
N7–C10	1.423(3)	1.411(2)
N7–C8	1.472(3)	1.464(2)
C8–C9	1.523(3)	1.520(3)
C10–C60	1.404(3)	1.401(3)
C10–C20	1.397(3)	1.410(2)
C20–C30	1.395(3)	1.380(3)
C30–C40	1.378(4)	1.394(3)
C30–C70		1.497(3)
C40–C50	1.389(4)	1.388(3)
C50–C60	1.378(4)	1.396(3)
C1–Cl	1.805(2)	
Bond angles		
N4–C1–C2		88.89(12)
O–C2–C3	108.4(2)	118.4(2)
O–C2–C1	107.8(2)	118.07(15)
C3–C2–C1	111.8(2)	88.12(13)
N4–C3–C2	113.3(2)	89.78(13)
C9–N4–C5	108.4(2)	110.76(13)
C9–N4–C3	113.5(2)	112.07(13)
C5–N4–C3	109.8(2)	114.94(14)
C9–N4–C1		112.15(14)
C5–N4–C1		116.09(13)
C3–N4–C1		89.34(12)
N4–C5–C6	110.2(2)	111.35(14)
N7–C6–C5	111.2(2)	110.08(15)
C10–N7–C6	113.4(2)	116.97(15)
C10–N7–C8	115.5(2)	116.97(15)
C6–N7–C8	109.8(2)	110.27(14)
N7–C8–C9	110.6(2)	110.40(15)
N4–C9–C8	110.6(2)	110.73(14)
C60–C10–C20	117.9(2)	118.1(2)
C60–C10–N7	119.5(2)	123.3(2)
C20–C10–N7	122.5(2)	118.5(2)
C30–C20–C10	120.3(2)	119.7(2)
C20–C30–C40	121.1(3)	122.5(2)
C20–C30–C70		118.9(2)
C40–C30–C70		118.6(2)
C50–C40–C30	118.8(3)	117.8(2)
C40–C50–C60	120.8(3)	120.9(2)
C50–C60–C10	121.0(2)	120.9(2)
F3–C70–F2		105.8(2)
F3–C70–F1		106.8(2)
F2–C70–F1		105.1(2)
F3–C70–C30		113.4(2)
F2–C70–C30		112.6(2)
F1–C70–C30		112.5(2)
Cl–C1–C2	111.5(2)	
Torsion angles		
N4–C1–C2–O		136.1(2)
N4–C1–C2–C3		14.7(2)
O–C2–C3–N4	−46.4(3)	−135.9(2)
C1–C2–C3–N4	−165.2(2)	−14.8(2)
C2–C3–N4–C9	−55.4(3)	−98.8(2)
C2–C3–N4–C5	−176.9(2)	133.6(2)
C2–C3–N4–C1		14.9(2)
C2–C1–N4–C9		98.8(2)
C2–C1–N4–C5		−132.5(2)
C2–C1–N4–C3		−14.8(2)
C9–N4–C5–C6	59.7(2)	53.5(2)
C3–N4–C5–C6	−175.8(2)	−178.2(2)
C1–N4–C5–C6		−75.9(2)
N4–C5–C6–N7	−58.7(3)	−56.7(2)
C5–C6–N7–C10	−173.0(2)	−162.9(2)
C5–C6–N7–C8	56.2(3)	60.1(2)
C10–N7–C8–C9	174.3(2)	−162.3(2)
C6–N7–C8–C9	−56.0(3)	−60.8(2)
C5–N4–C9–C8	−60.1(2)	−53.6(2)
C3–N4–C9–C8	177.6(2)	176.6(2)
C1–N4–C9–C8		77.9(2)
N7–C8–C9–N4	59.0(3)	57.4(2)
C6–N7–C10–C60	59.7(3)	2.1(3)
C8–N7–C10–C60	−172.4(2)	136.1(2)
C6–N7–C10–C20	−121.9(2)	179.5(2)
C8–N7–C10–C20	6.1(3)	−46.5(2)
C20–C30–C70–F3		−97.5(3)
C20–C30–C70–F2		142.4(2)
C20–C30–C70–F1		23.9(3)
Cl–C1–C2–O	178.06(15)	
Cl–C1–C2–C3	−62.8(2)	

clear solution (imide **14**) 0.012 mol of the appropriate chloride was added. The mixture was refluxed until the alkaline reaction disappeared. The crystals separated after cooling were collected on a filter, washed with distilled water and dried. Then they were purified by crystallization from ethanol.

3.1.2.3. Method 'c'. Sodium (0.01 mol) was dissolved in 50 ml of anhydrous methanol or ethanol and to this solution 0.005 mol of 4-chloro-6-methyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (**17**) was added. The mixture was refluxed for 15 min and after cooling 0.006 mol of 2-hydroxy-3-(4-phenyl-1-piperazinyl)propyl chloride was introduced. The mixture was refluxed for 10 h. Then the substance separated after cooling was collected on a filter, washed with distilled water and purified by crystallization from ethanol.

The properties of the obtained compounds **8**–**12** are listed in Table 3 but the assignments of their ^{1}H NMR spectra are shown below.

^{1}H NMR of **8**: $\delta = 2.47$–2.82 (m-9H, C**H**$_3$ + –C**H**$_2$–N(C**H**$_2$)$_2$–); 3.13–3.25 (distorted t-4H, –(C**H**$_2$)$_2$N–C$_6$H$_5$); 3.73–3.80 (d-2H, Hα of propyl); 3.80–4.30 (m-5H, OC**H**$_3$ + Hβ of propyl + O**H**); 6.85–7.26 (m-6H, arom. H).

Table 3
Properties of the investigated compounds

Comp.	Formula (molecular weight)	M.p. (°C) (solvent)	Yield (%)	IR absorptions in KBr (cm^{-1})		
				CO	OH	Mono- and disubstituted benzene
15	$C_{12}H_{12}N_2O_4$ (248.23)	126–128 (ethanol)	60–65	1720, 1780		
16	$C_{13}H_{14}N_2O_4$ (262.26)	78–81 (ethanol)	50	1720, 1780		
8	$C_{22}H_{26}N_4O_4$ (410.46)	190–192 (ethanol)	51 method 'a'; 54 method 'b_1'; 65 method 'b_2'; 61 method 'c'	1730, 1780	3380–3420	700, 770
9	$C_{23}H_{28}N_4O_4$ (424.49)	188–190 (ethanol)	55 method 'a'; 71 method 'b_1'; 75 method 'b_2'; 48 method 'c'	1725, 1770	3370–3410	690, 760
10	$C_{23}H_{25}F_3N_4O_4$ (478.46)	165–167 (ethanol)	42 method 'a'; 82 method 'b_2'	1724, 1772	3088	692, 756
11	$C_{23}H_{28}N_4O_5$ (440.49)	175–177 (ethanol)	46 method 'a'; 67 method 'b_2'	1726, 1772	3060	752
12	$C_{24}H_{27}F_3N_4O_4$ (492.49)	167–168 (ethanol)	80 method 'b_2'	1720, 1770	3080–3120	690, 750

^{1}H NMR of **9**: $\delta = 1.37$–1.55 (t-3H, CH_3–CH_2–); 2.46–2.72 (m-9H, CH_3 + –H_2C–N–(CH_2)$_2$–); 3.12–3.24 (distorted t-4H, –(H_2C)$_2$–N–C_6H_5); 3.73–3.91 (distorted d-3H, Hα of propyl + OH); 3.92–4.37 (m–1H, Hβ of propyl); 4.48–4.83 (q-2H, CH_3–CH_2–); 6.83–7.25 (m-6H, arom. H).

^{1}H NMR of **10**: $\delta = 2.45$–2.70 (m-9H, CH_3 + –H_2C–N–(CH_2)$_2$–); 3.15–3.20 (distorted t-4H, –(H_2C)$_2$–N–C_6H_4–*m*-CF_3); 3.73–3.80 (distorted d-2H, Hα of propyl); 3.85–4.12 (m-5H, Hβ of propyl + OH + OCH_3); 7.08–7.43 (m-5H, arom. H).

^{1}H NMR of **11**: $\delta = 2.45$–2.80 (m-9H, CH_3 + –H_2C–N–(CH_2)$_2$–); 3.00–3.10 (m-4H, –(H_2C)$_2$–N–C_6H_4–*o*-OCH_3); 3.72–4.13 (m-10H, Hα and Hβ of propyl + OH + 2 × OCH_3); 6.91–7.20 (m-5H, arom. H).

^{1}H NMR of **12**: $\delta = 1.38$–1.56 (t-3H, CH_3–CH_2–); 2.51–2.92 (m-9H, CH_3 + –H_2C–N–(CH_2)$_2$–); 3.20-3.31 (distorted t-4H, –(H_2C)$_2$–N–C_6H_4–*m*-CF_3); 3.52 (s-1H, OH); 3.73–3.80 (distorted d-2H, Hα of propyl); 4.05–4.24 (m-1H, –CH–); 4.47–4.74 (q-2H, –CH_2–CH_3); 7.09–7.36 (m-5H, arom. H).

3.1.3. 2-Hydroxy-3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl chloride (*19*)

Epichlorohydrin (0.012 mol) was added to a solution containing 0.012 mol of *N*-(2-methoxyphenyl)piperazine in 30 ml of anhydrous ethanol. The reaction mixture was vigorously stirred at room temperature (r.t.) for 2 h. The separated solid substance was collected on a filter and washed with ethanol. It melted at 103–104 °C, yield 80%.

The compound **19** was not soluble in water and gave no chloride ions test with silver nitrate.

$C_{14}H_{21}ClN_2O_2$, M_W 284.78 (C, H, N determinations).

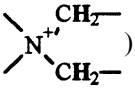
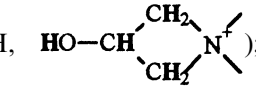
^{1}H NMR of **19**: $\delta = 2.52$–2.95 (m-6H, –H_2C–N–(CH_2)$_2$–); 2.95–3.25 (m–4H, –(H_2C)$_2$–*N*-Aryl); 3.50–3.68 (m-3H, –CH_2–Cl + OH); 3.86–4.16 (m-4H, OCH_3 + –CH–); 6.93 (m-4H, H of phenyl).

3.1.4. Chloride of 2-hydroxy-7-(2-methoxy)phenyl-7-aza-4-azoniaspiro[3.5]nonane (*19a*)

In this case the same amount of reagents was used as described in Section 3.1.3. The reaction mixture was stirred at 40 °C for 0.5 h, then at r.t. for 8 h. A few mililiters of diethyl ether were added to a cold solution and the mixture was left overnight. The resulting solid substance was collected on a filter and washed with ethanol. The analytical sample was obtained after crystallization from ethanol. It melted at 125–127 °C, 67% of yield.

The compound **19a** was water-soluble and gave positive reaction for chloride ions with silver nitrate.

$C_{14}H_{21}ClN_2O_2$, M_W 284.78 (C, H, N determinations).

^{1}H NMR of **19a**: $\delta = 3.15$–3.42 (m-4H, –(H_2C)$_2$–*N*-Aryl); 3.72–4.12 (m-7H, –OCH_3 + ); 4.39–4.93 (m-6H, ); 6.69–7.20 (m-4H, arom. H).

3.1.5. 2-Hydroxy-3-[4-(3-trifluoromethylphenyl)-1-piperazinyl]propyl chloride (*20*)

Epichlorohydrin (0.01 mol) was added to a vigorously stirred solution of *N*-(3-trifluoromethylphenyl)piperazine (0.01 mol) in 40 ml of anhydrous ethanol. The mixture was stirred at room temperature, monitoring

the reaction through TLC on silica gel (ethyl acetate as eluant). Then ethanol was evaporated at r.t. A residue was a crude colorless oily product which was purified by column chromatography on silica gel (70–230 mesh) using ethyl acetate as eluant. The obtained in this way compound **20** melted at 67–69 °C after crystallization from *n*-hexane. Yield 85%. $R_f = 0.71$.

$C_{14}H_{18}ClF_3N_2O$, M_W 322.75 (C, H, N determinations).

^{1}H NMR of **20**: $\delta = 2.51$–3.01 (m-6H, –**H**$_2$C–N–(CH$_2$)$_2$–); 3.01–3.42 (t-4H, –(H$_2$C)$_2$–*N*-Aryl); 3.47–3.67 (distorted d-3H, –C**H**$_2$–Cl+O**H**); 3.77–4.17 (m-1H, –C**H**–); 6.86–7.53 (m-4H, H of phenyl).

3.1.6. Chloride of 2-hydroxy-7-(3-trifluoromethyl)-phenyl-7-aza-4-azoniaspiro[3.5]nonane (*20a*)

Epichlorohydrin (0.025 mol) was added to a solution of 0.025 mol of *N*-(3-trifluoromethylphenyl)piperazine in 30 ml of anhydrous ethanol. The mixture was stirred at first at 40 °C for 0.5 h, then at r.t. for 24 h. The separated white solid substance was collected on a filter and washed with ethanol. It melted at 147–149 °C, 55% of the yield.

The substance was water-soluble and gave positive reaction for chloride ions with silver nitrate.

$C_{14}H_{18}ClF_3N_2O$, M_W 322.75 (C, H, N determinations).

^{1}H NMR of **20a** in DMSO-d_6 (300 MHz): $\delta = 3.49$–3.56 (m-4H, –(**H**$_2$C)$_2$–*N*-Aryl); 3.63–3.70 and 3.74–3.82 (2 distorted t-4H, 2 × C**H**$_2$ of piperazine fragment); 4.22–4.33 (dd-2H, C**H**$_2$–); 4.55–4.64 (m-3H, –CH$_2$–+O**H**); 4.64–4.74 (m-1H, –C**H**–); 6.73–6.78 and 7.15–7.55 (4H, arom. H).

3.1.7. X-ray analysis of *18* and *20a*

The crystals of **18** and **20a** suitable for X-ray analysis were grown from chloroform (**18**) or ethanol (**20a**). Both structures were solved by direct methods using the SHELXS-97 program [11] and refined using SHELXL-97 [12]. The molecular graphics were prepared using XP [13] and ORTEP3 [14]. The experimental and crystal data are listed in Table 4.

Table 4
Data referring to the crystal structure analysis of **18** and **20a**

	18	**20a**
Formula	$C_{13}H_{19}ClN_2O$	$C_{14}H_{18}ClF_3N_2O$
Molecular weight	254.75	322.75
Crystal system	orthorhombic	orthorhombic
Space group	*Pbca*	$Pna2_1$
Unit cell dimensions		
a (Å)	8.703(3)	36.421(6)
b (Å)	6.709(3)	5.975(2)
c (Å)	43.737(9)	6.842(2)
V (Å^3)	2553.7(15)	1488.9(7)
Z	8	4
T (K)	100(2)	100(2)
D_{calc} (g/cm^3)	1.325	1.440
μ (mm^{-1})	0.285	0.289
Measured reflections	15560 (2975 unique)	16981 (4485 unique)
Reflections with $I > 2\sigma(I)$	2031	4236
Reflections used in refinement	2975	4485
Flack parameter		0.01(6)
Parameters refined	230	262
Max./min. height in final *F* map (e/Å^3)	−0.31, 0.37	−0.37, +0.70
R	0.0561	0.0429
R_w	0.0986	0.0916

3.2. Pharmacology

3.2.1. Materials and methods

3.2.1.1. Substances. Acetylsalicylic acid (ZF-Starogard Gdaski, PL), morphine (Morphinum hydrochloricum, Polfa-Kutno, PL).

3.2.1.2. Animals. The experiments were carried out on male and female Albino–Swiss mice (body weight 18–26 g) and male Wistar rats (body weight 180–250 g). The animals were housed in constant temperature facilities exposed to 12:12 h light-dark cycle and maintained on a standard pellet diet, tap water was given *ad libitum*. Control and experimental groups consisted of six to eight animals each. The investigated compounds were administered intraperitoneally as a suspension in 3% Tween 80 or 0.5% methylcellulose at a constant volume of 10 ml/kg (mice) and 5 ml/kg (rats).

3.2.1.3. Statistical analysis. The statistical significance was calculated using a one-way ANOVA or Student's *t*-test. The ED_{50} values and their confidence limits were calculated according to the method of Litchfield and Wilcoxon [15].

Acute toxicity was assessed by the methods of Litchfield and Wilcoxon [15] and presented as LD_{50} calculated from the mortality of mice after 24 h.

Pain reactivity was measured in the 'hot-plate' test according to the method of Eddy and Leimbach [16]. The animals were placed individually on a metal plate heated to 56 °C. The time (s) of appearance of the pain reaction (licking of the forepaws or jumping) was recorded by a stop-watch. The experiments were performed 30 min after administration of the investigated compounds.

Pain reactivity was also measured by the 'writhing syndrome' test of Koster et al. [17]. The test was performed in mice by the i.p. injection of a 0.6% solution of acetic acid, in a volume of 10 ml/kg 60 min after the administration of investigated compounds. The number of writhing episodes was counted for 30 min after the injection of 0.6% acetic acid.

Spontaneous locomotor activity in mice was measured in circular photoresistor actometers (32 cm in diameter). The investigated compounds were injected intraperitoneally in doses 200–12.5 mg/kg. Thirty min after the injection of the investigated compounds mice were placed in the actometers for 30 min. Each crossing of the light beam was recorded automatically. The amount of impulses was noted after 30 min.

Arterial blood pressure was determined according to the method of Gerold and Tschirky [18] using UGO-BASILE equipment (blood pressure recorder, cat. no. 80006). Systolic blood pressure on the tail artery was measured 30 min after administration of investigated compounds.

4. Results and discussion

4.1. Acute toxicity

All investigated compounds were not toxic ($LD_{50} >$ 2000 mg/kg).

4.2. Pain reactivity

In order to screen the compounds for analgesic activity two methods were chosen: the 'hot-plate' and 'writhing' tests. All investigated compounds possessed analgesic action in both tests (Tables 5 and 6).

In the 'hot-plate' test the imides **8** and **12** produced a significant effect up to the dose of 12.5 mg/kg, whereas the compounds **9** and **10** had analgesic activity in doses up to 25 mg/kg. Also **11** increased significantly the times of appearance of the pain reaction but only in doses up to 100 mg/kg. All the investigated compounds showed more potent analgesic activity than acetylsalicylic acid (Table 5).

The compounds **8**–**11** possessed very strong activity in the 'writhing' method. The most potent effect was produced by the imide **8** which was effective up to a dose of 0.39 mg/kg. The compound **10** was active up to the dose of 0.78 mg/kg, while **9** and **11** decreased the pain sensitivity in mice in this test up to the dose of 1.56 mg/kg. Also the compound **12** showed strong analgesic activity in the 'writhing syndrome' test up to the dose of 3.125 mg/kg. The summarized data are shown in Table 6. It was interesting to observe that in the 'writhing' test all the investigated compounds displayed activity superior to that of acetylsalicylic acid. What more, the results reported in Table 6 indicate that the compounds **8**, **10**, **11** and **9** were about 6 to 1.7 times more potent than morphine, but the anti-writhing activity of **12** was comparable to that reported for morphine.

Table 5
The influence of the investigated compounds on the pain reactivity in 'hot-plate' test in mice

Comp.	Dose (mg/kg) i.p.	% Prolongation of the time reaction	ED_{50} (mg/kg)
8	25	85.8***	11.9 (6.6–13.1)
	12.5	75.5***	
	6.25	6.8	
9	50	101.7****	17.6 (12.6–23.8)
	25	59.9****	
	12.5	28.8	
10	75	79.3**	53.6 (42.1–64.0)
	50	43.3*	
	25	41.6*	
	12.5		
11	150	85.0*	96.8 (72–121)
	100	49.1*	
	50	7.5	
12	25	87.5**	10.6 (5.9–18.8)
	12.5	62.5*	
	6.25	21.8	
Acetylsalicylic acid	400	116.0**	266.7 (148.2–533.4)
	200	35.0	
	100	9.45	
Morphine	6	66.0**	2.55 (1.59–4.08)
	3	61.0*	
	1	5.4	

Results are expressed as a mean ± SEM, $n = 6$–8.
* $p < 0.05$.
** $p < 0.02$.
*** $p < 001$.
**** $p < 0.001$.

Table 6
Effects of investigated compounds on the 'writhing syndrome' induced by acetic acid on mice

Comp.	Dose (mg/kg) i.p.	% inhibition of writhing	ED_{50} (mg/kg)
8	6.25	97.8****	0.40 (0.27–0.69)
	3.125	94.0****	
	1.56	88.7****	
	0.78	88.7****	
	0.39	45.45*	
	0.195		
9	25	96.7****	1.4 (0.79–1.8)
	12.5	90.0****	
	6.25	86.7****	
	3.125	80.0****	
	1.56	65.3****	
	0.78	11.7	
10	12.5	96.7****	1.04 (0.4–2.7)
	6.25	93.8***	
	3.125	62.1***	
	1.56	59.7***	
	0.78	45.3*	
	0.39	23.0	
11	50	89.7****	1.35 (0.33–5.57)
	25	80.6****	
	12.5	72.8***	
	6.25	72.0***	
	3.125	60.0***	
	1.56	56.8**	
	0.78	37.4	
12	50	91.3****	2.49 (1.7–5.6)
	25	85.0****	
	12.5	76.3***	
	6.25	62.8**	
	3.125	54.5**	
	1.56	41.9	
Acetylsalicylic acid	100	83.5****	39.15 (29.1–48.4)
	50	56.0**	
	30	41.6	
Morphine	10	93.7****	2.44 (1.18–5.02)
	3	61.0**	
	1	15.6	

Results are expressed as a mean ± SEM, $n = 6–8$.
* $p < 0.05$.
** $p < 0.02$.
*** $p < 0.01$.
**** $p < 0.001$.

4.3. Locomotor activity

The compounds **10**, **11** and **12** suppressed significantly the spontaneous locomotor activity of mice during a 30 min observation period up to the dose of 12.5 mg/kg. The imide **9** was active at the dose of 200 mg/kg while **8** also inhibited spontaneous locomotor activity in mice by *ca*. 37–23%, but this effect was not significant (Table 7).

4.4. Arterial blood pressure

All the tested compounds administered at the dose of 200 mg/kg did not affect the pulse rate and arterial blood pressure in rats.

From the data presented above it can be seen that all the studied compounds **8**–**12** displayed strong analgesic properties and were non-toxic. In the 'writhing' test the most active substance was the imide **8**, containing methoxy group in position 2 of the pyridine ring and unsubstituted phenyl at N-4 of piperazine. The replacement of methoxy group by ethoxy one (imide **9**) caused almost fourfold decrease of the analgesic activity in this test. Similarly the imide **10** with methoxy group in the pyridine ring was more active than its ethoxy analog **12**.

It indicates that the kind of the alkoxy group in position 4 of 1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione derivatives has influence on the strength of the analgesic action in the 'writhing' test. Introduction of trifluoromethyl or methoxy groups into the phenyl substituent at

Table 7
Influence of the investigated compounds on the spontaneous locomotor activity in mice

Comp.	Dose (mg/kg)	% inhibition of locomotor activity	ED_{50} (mg/kg)
8	200	36.9	
	100	23.5	
9	200	84.4***	107.9 (91–121)
	100	45.8	
	50	38.6	
	25	38.4	
10	50	84.9***	6.15 (3.8–8.2)
	25	73.3**	
	12.5	64.3*	
11	50	82.9***	7.2 (5.1–10.4)
	25	76.0**	
	12.5	68.7*	
12	50	64.5***	19.7 (15.2–23.3)
	25	58.3***	
	12.5	39.9*	
	6.25	34.1	

Each group consisted of 6–8 animals.
* $p < 0.05$.
** $p < 0.02$.
*** $p > 0.01$.

N-4 of piperazine in the compound **8** (imides **10** and **11**) also weakens the analgesic properties, more in case of **11**. Similar relationship was observed in the case of the compounds **9** and **12**.

Among the five studied substances the compound **12** (with OC_2H_5 group in 4 and CF_3 one in the *meta* position of phenyl) proved to be the least active analgesic agent in the 'writhing test' although its activity was comparable with that of morphine. Contrary to this, imide **12** was (apart from **8**) the most active substance in the 'hot-plate' test. Compound **11** containing in its structure two methoxy groups was endowed with the weakest analgesic properties in this test.

Except for **8**, in all the cases analgesic action was associated with the significant suppression of the spontaneous locomotor activity in mice. It was interesting to observe that the introduction of the substituent (*m*-CF_3 or *o*-OCH_3) into the phenyl in **8** (imides **10** and **11**) caused a considerable increase of the activity in this test in comparison with that of the parent substance **8**. The similar relationship took place in the case of the compounds **9** and **12**.

The data presented above indicate that substitution of the piperidino group in position 4 in compound **1** by one alkoxy (OCH_3 and OC_2H_5) proved to be very profitable because it caused marked increase of the analgesic activity. Compound **1** was active only in the 'writhing syndrome' test at a dose of 200 mg/kg while the imides **8** and **9** showed analgesic effects at doses as low as dose of 0.40 and 1.40 mg/kg (ED_{50}), respectively. This modification did not influence the toxicity of the mentioned compounds. All had $LD_{50} > 2000$ mg/kg.

5. Conclusion

The analgesic action of new derivatives of 1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione was investigated on mice, using the 'hot-plate' and 'writhing' tests. All of the compounds studied exhibited analgesic activity which was superior to that of acetylsalicylic acid in the both tests. Furthermore they caused significant suppression of the spontaneous locomotor activity in mice.

It is accepted that analgesics are generally considered to act centrally, peripherally or both centrally and peripherally. Narcotic analgesics such as morphine produce their analgesic actions by a central mechanism, but non-steroidal antiinflammatory agents, such as aspirin-by a peripheral mechanism [19]. However, it is supposed that salicylates produce their analgesic effects partly by a central mechanism [20].

Our results suggest that the investigated compounds can show analgesic activity across central and peripheral mechanism. The explanation of the exact mechanism of action will demand of the further pharmacological investigations.

References

[1] H. Śladowska, J. Potoczek, M. Sieklucka-Dziuba, A. Semczuk, Z. Kleinrok, Synthesis, chemical and pharmacological properties of some *N*-aminoalkyl derivatives of 3,4-pyridinedicarboximides, Farmaco 50 (11) (1995) 761–768.
[2] H. Śladowska, J. Potoczek, G. Rajtar, M. Sieklucka-Dziuba, D. Żółkowska, Z. Kleinrok, Investigations on the synthesis and properties of some *N*-[4-phenyl(2-pyrimidinyl)-1-piperazinyl]alkyl(hydroxyalkyl)-3,4-pyridinedicarboximides, Acta Polon. Pharm. Drug Res. 33 (6) (1996) 417–424.
[3] H. Śladowska, D. Szkatuła, B. Filipek, D. Maciag, J. Sapa, M. Zygmunt, Synthesis and properties of 2-(4-substituted)butyl derivatives of some 2,3-dihydro-1,3-dioxo-1H-pyrrolo[3,4-c]pyridines, Pharmazie 56 (2001) 133–138.
[4] H. Śladowska, M. Sieklucka-Dziuba, M. Misztal, Z. Kleinrok, Investigations on the synthesis and properties of *N*-aryl(heteroaryl)piperazinylalkyl derivatives of imide of 6-methyl-2-(1-piperidino)-3,4-pyridinedicarboxylic acid, Farmaco 49 (7,8) (1994) 493–498.
[5] H. Dobeneck, B. Hansen, Aza-isoindole, I. Aza-phthalimidine, Chem. Ber. 105 (1972) 3611–3621.
[6] J.J. Bosc, C. Jarry, A. Carpy, E. Panconi, P. Descas, Synthesis and antidepressant activity of 5-(1-aryl-4-piperazino)methyl-2-amino-2-oxazolines, Eur. J. Med. Chem. 27 (1992) 437–442.
[7] C. Jarry, R. Golse, E. Panconi, M.H. Creuzet, Synthesis and pharmacological properties of some 5-dialkylaminomethyl 2-amino-2-oxazolines, Eur. J. Med. Chem. Chim. Ther. 21 (1986) 138–142.
[8] M.L. Verdonk, J.W. Voogd, J.A. Kanters, J. Kroon, R. den Besten, L. Brandsma, D. Leysen, J. Kelder, Structure and

serotonin 5-HT_{2C} receptor activity of ortho- and meta-substitued phenylpiperazines, Acta Crystallogr., Sect. B 53 (1997) 976–983.
[9] K.R. Acharya, S.S. Tavale, T.N. Guru Row, K. Venkatesan, Structure of 1-diphenylmethyl-3-hydroxyazetidinium chloride, Acta Crystallogr., Sect. C 40 (1984) 846–848.
[10] W.N. Kniazev, O.A. Borbulewicz, O.W. Siskin, Spirocykliceskie kompleksy miejzengeimiera, Zh. Org. Khim. (Russ.) 36 (2000) 733–738.
[11] G.M. Sheldrick, Acta Crystallogr., Sect. A 46 (1990) 467.
[12] G.M. Sheldrick, SHELXL-97, Program for Refinement of Crystal Structure, University of Göttingen, Germany, 1993.
[13] XP, Interactive Molecular Graphics, ver. 5.1, Copyright © 1998 Brucker AXS.
[14] L.J. Farrugia, ORTEP-3 for Windows, ver. 1.05, Department of Chemistry, University of Glasgow, Scotland, UK, 1999.
[15] J.T. Litchfield, F. Wilcoxon, A simplified method of evaluating dose-effect experiments, J. Pharmacol. Exp. Ther. 96 (1949) 99–113.
[16] N.B. Eddy, D. Leimbach, Synthetic analgesics: II dithienylbutenyl- and dithienylbutylamines, J. Pharmacol. Exp. Ther. 107 (1953) 385–393.
[17] R. Koster, M. Anderson, E.J. de Bear, Acetic acid for analgesic screening, Fed. Proc. 18 (1959) 412.
[18] M. Gerold, H. Tschirky, Measurement of blood pressure in unanesthetized rats, Arzneim. Forsch. 18 (1968) 1285–1287.
[19] H. Nakamura, A. Shimoda, K. Ishii, T. Kadokawa, Central and peripheral analgesic action of non-acidic non-steroidal antiinflammatory drugs in mice and rats, Arch. Int. Pharmacodyn. 282 (1986) 16–25.
[20] T.C. Dubas, J.M. Parker, A central component in the analgesic action of sodium salicylate, Arch. Int. Pharmacodyn. 194 (1971) 117–122.