Biologically Active 1-Arylpiperazines. Synthesis of *N*-[3-(4-Aryl-1-piperazinyl)propyl] Derivatives of Benzoxazinone and Benzoxazolinone

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The synthesis of new *N*-[3-(4-aryl-1-piperazinyl)propyl] derivatives of 1*H*-2,4-benzoxazin-3(4*H*)-one (**1a-b**), 2*H*-1,4-benzoxazin-3(4*H*)-one (**2a-b**, **3a-b** and **4b**), and benzoxazolin-2-one (**5a-b**), as biologically active agents, is described.

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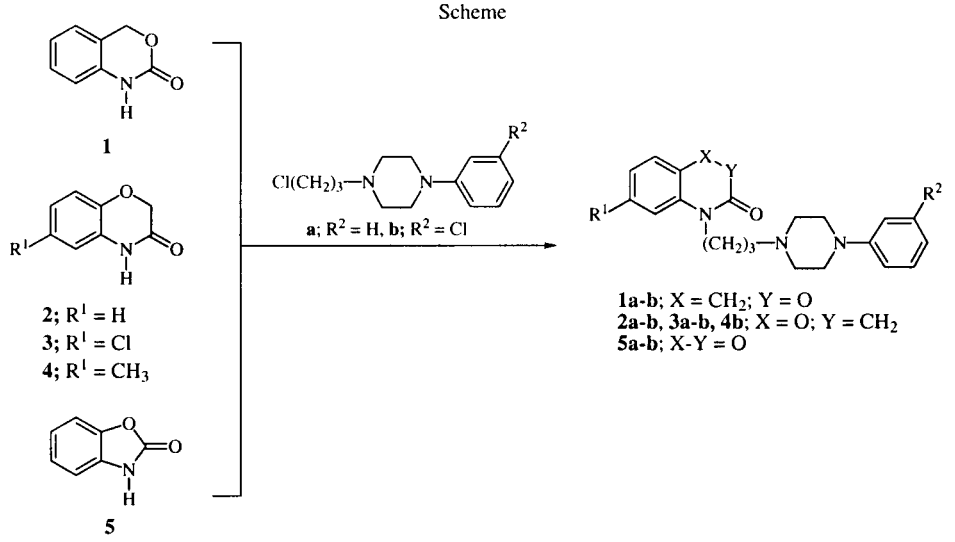
1-Arylpiperazines are a common fragment of structure of second generation anxiolytics, such as buspirone - {4-[4-(2-pyrimidyl)-1-piperazinyl]butyl}-8-azaspiro-[4.5]decane-7,9-dione - which binds with high affinity and selectivity at 5-HT serotonin receptor sites [1-4]. Relatively small structure modification of the arylpiperazine fragment, the side chain length or terminal amide system, result in significant changes in biological activity of the agents [5-8]. The association of arylpiperazine derivatives with biological activity led us to synthesise a new series of *N*-[3-(4-aryl-1-piperazinyl)propyl] derivatives of 1*H*-2,4-benzoxazin-3(4*H*)-one (**1a** and **b**), 2*H*-1,4-benzoxazin-3(4*H*)-one (**2a**, **2b**, **3a**, **3b** and **4b**), and benzoxazolin-2-one (**5a** and **5b**), in which we set the length of a spacer constant (a 3-member chain), while both arylpiperazine and amide (lactam) terminal group were systematically modified.

Starting 1*H*-2,4-benzoxazin-3(4*H*)-one (**1**) was obtained from phthalide [9], while 2*H*-1,4-benzoxazin-3(4*H*)-one (**2-4**) [10] and 2-benzoxazolinone (**5**) [11] from *o*-aminophenol or its chloro or methyl derivatives, as described previously. 3-(1-Aryl-4-piperazinyl)propyl chlorides (**a** and **b**) were obtained by reaction of the appropriate 1-arylpiperazines with 1-bromo-3-chloropropane according to procedure described by Bourdais [12]. Final products (**1a, 1b, 2a, 2b, 3a, 3b, 4b** and **5a-b**) were obtained by alkylation of lactams **1-5** with 1-aryl-4-(3-chloropropyl) piperazines (**a** and **b**) (Scheme).

Scheme



N-Alkylation of lactams take place in the presence of sodium hydride [13], potassium amide [7,14] or alkoxides [15,16], however they are rather hazardous reaction conditions. As a result, we did not try to use these bases for the synthesis of derivatives **1-5**. Lactams also undergo *N*-alkylation under mild reaction conditions, such as, in the presence of potassium hydroxide or potassium carbonate [5-7,11,17]. However, this procedure failed in the cases of lactams **1-4**, where starting materials were recovered in 80-90% yield from the reaction mixtures. Only **5** was converted into **5a** and **5b** in the presence of potassium carbonate in good yields.

Transformation of **1-4** into final products **1a, 1b, 2a, 2b, 3a, 3b** and **4b** occurred, when the reaction was carried

out in the presence of alumina-supported potassium fluoride (KF/Al_2O_3), catalyst for *N*-arylation reaction of indoles [18] and *N*-alkylation reaction of lactams [5-7]. Yields of the obtained products, under these reaction conditions, carried out in boiling acetonitrile, were from 57% for **1a** to 89% for **3a**.

Biological Activity.

The affinity of the investigated compounds for 5-HT_{1A} and 5-HT_{2A} receptors was assessed *in vitro* on the basis of their ability to displace [^{3}H]-8-OH-DPAT 8-hydroxy-2-(propylamino)tetraline and [^{3}H]-ketanserin, respectively. Radioligand binding experiments were conducted in the rat hippocampus for 5-HT_{1A} receptors and in the cortex for 5-HT_{2A} receptors according to published procedures [19].

The majority of the newly synthesised compounds show a distinct affinity for 5-HT_{1A} and/or 5-HT_{2A} receptor binding sites. Radioligands binding studies show that compounds **1b, 2a, 2b** and **4b** have good affinities (K_i = 5.2 -40 nM) and compounds **1a, 3a, 3b, 5a** and **5b** have moderate affinities (K_i = 72-110 nM) for 5-HT_{1A} receptor. The 5-HT_{2A} affinities of these compounds are within a range of 24 to 240 nM. Detailed biological *in vitro* and *in vivo* data of the obtained compounds were presented previously [8].

EXPERIMENTAL

Elemental analyses were performed on a Perkin-Elmer 2400 analyser, mass spectra were carried out with a Varian MAT 112 spectrometer at 70 eV. The ^{1}H-nmr spectra were recorded in deuteriochloroform with a Tesla 487C (80 MHz) spectrometer and tetramethylsilane (TMS) as an internal standard; the chemical shifts are reported in ppm (δ); coupling constants were taken from the expanded spectrum. Melting points, measured in a Boetius apparatus, are uncorrected. Catalyst KF/Al_2O_3 was obtained according to the published procedure [20].

For biological experiments, free bases **1a, 1b, 2a, 2b, 3a, 3b, 4b, 5a** and **5b** were converted into hydrochloride salts with ethanol saturated with HCl and their molecular formulae and molecular weights were established on the basis of elemental analysis.

General Procedure for Preparation Derivatives **1-4**.

A mixture of the lactam (2 mmoles), an appropriate 4-(3-chloropropyl)-1-arylpiperazine (2.1 mmoles), KF/Al_2O_3 catalyst (5 g) in acetonitrile (50 ml) was stirred and refluxed for 5 hours. An inorganic precipitate was filtered off and the solvent was evaporated. The residue was purified by column chromatography ($SiO_2/CHCl_3$:MeOH = 9:1) (**2b, 4b**) or crystallized from the appropriate solvent.

4-[3-(4-Phenyl-1-piperazinyl)propyl]-1*H*-2,4-benzoxazin-3-one (**1a**).

Base **1a** was obtained in 57% yield, mp 139-144° (acetonitrile); ^{1}H-nmr: δ 1.84-2.06 (m, 2H, CH_2), δ 2.52 (t, 2H, CH_2, J = 7 Hz), δ 2.56-2.70 (m, 4H, 2 x CH_2), δ 3.17-3.31 (m, 4H, 2 x CH_2), δ 4.02 (t, 2H, CH_2, J = 7 Hz), δ 5.22 (s, 2H, CH_2), δ 6.77-7.41 (m, 9H_{Ar}); ms: m/z (I%); M 351 (8.8), 175 (100); hydrochloride mp 184-185° (chloroform:acetone 1:3).

Anal. Calcd. for $C_{21}H_{25}N_3O_2$•HCl (387.91): C, 65.02; H, 6.76; N, 10.83. Found: C, 65.00; H, 6.73; N, 10.72.

4-{3-[4-(3-Chlorophenyl)-1-piperazinyl)}propyl]-1*H*-2,4-benzoxazin-3-one (**1b**).

Base **1b** was obtained in 66% yield, mp 98-100° (acetone-water 10:1); ^{1}H-nmr: δ 1.84-2.06 (m, 2H, CH_2), δ 2.52 (t, 2H, CH_2, J = 7 Hz), δ 2.58-2.69 (m, 4H, 2 x CH_2), δ 3.17-3.30 (m, 4H, 2 x CH_2), δ 4.02 (t, 2H, CH_2, J = 7 Hz), δ 5.20 (s, 2H, CH_2), δ 6.72-7.33 (m, 8H_{Ar}); ms: m/z (I%); M 385 (21.3), 209 (100); hydrochloride mp 194-197° (2-propanol).

Anal. Calcd. for $C_{21}H_{24}N_3O_2Cl$•HCl•H_2O (440.37): C, 57.28; H, 6.18; N, 9.54. Found: C, 56.94; H, 6.12; N, 9.65.

4-[3-(4-Phenyl-1-piperazinyl)propyl]-2*H*-1,4-benzoxazin-3-one (**2a**).

Base **2a** was prepared according to literature procedures [7].

4-{3-[4-(3-Chlorophenyl)-1-piperazinyl)}propyl]-2*H*-1,4-benzoxazin-3-one (**2b**).

Base **2b** was obtained as an oil in 87% yield; ^{1}H-nmr: δ 1.63-1.91 (m, 2H, CH_2), δ 2.47 (t, 2H, CH_2, J = 7 Hz), δ 2.50-2.66 (m, 4H, 2 x CH_2), δ 3.16-3.30 (m, 4H, 2 x CH_2), δ 4.03 (t, 2H, CH_2, J = 7 Hz), δ 4.61 (s, 2H, CH_2), δ 6.73-7.20 (m, 8H_{Ar}); ms: m/z (I%); M 385 (29.0), 209 (100); hydrochloride mp 201-205° (2-propanol).

Anal. Calcd. for $C_{21}H_{24}N_3O_2Cl$•HCl (422.35): C, 59.72; H, 5.97; N, 9.95. Found: C, 59.68; H, 6.01; N, 9.73.

6-Chloro-4-[3-(4-phenyl-1-piperazinyl)propyl]-2*H*-1,4-benzoxazin-3-one (**3a**).

Base **3a** was obtained in 89% yield, mp 92-95° (ethanol); ^{1}H-nmr: δ 1.81-2.00 (m, 2H, CH_2), δ 2.45 (t, 2H, CH_2, J = 7 Hz), δ 2.53-2.69 (m, 4H, 2 x CH_2), δ 3.19-3.33 (m, 4H, 2 x CH_2), δ 4.01 (t, 2H, CH_2, J = 7 Hz), δ 4.59 (s, 2H, CH_2), δ 6.77-7.38 (m, 8H_{Ar}); ms: m/z (I%); M 385 (23.2), 175 (100); hydrochloride mp 203-205° (acetone-ethanol 10:1).

Anal. Calcd. for $C_{21}H_{24}N_3O_2Cl$•2HCl (458.82): C, 54.97; H, 5.71; N, 9.16. Found: C, 54.98; H, 5.61; N, 9.00.

6-Chloro-4-{3-[4-(3-chlorophenyl)-1-piperazinyl)}propyl]-2*H*-1,4-benzoxazin-3-one (**3b**).

Base **3b** was obtained in 74% yield, mp 88-92° (2-propanol); ^{1}H-nmr: δ 1.83-2.05 (m, 2H, CH_2), δ 2.47 (t, 2H, CH_2, J = 7 Hz), δ 2.52-2.67 (m, 4H, 2 x CH_2), δ 3.20-3.34 (m, 4H, 2 x CH_2), δ 4.03 (t, 2H, CH_2, J = 7 Hz), δ 4.61 (s, 2H, CH_2), δ 6.73-7.30 (m, 7H_{Ar}); ms: m/z (I%); M 419 (17.0), 209 (100); hydrochloride mp 200-203° (acetone-methanol 10:1).

Anal. Calcd. for $C_{21}H_{23}N_3O_2Cl_2$•HCl (456.80): C, 55.22; H, 5.30; N, 9.20. Found: C, 55.00; H, 5.12; N, 9.23.

6-Methyl-4-{3-[4-(3-chlorophenyl)-1-piperazinyl)}propyl]-2*H*-1,4-benzoxazin-3-one (**4b**).

Base **4b** was obtained as an oil in 60% yield; ^{1}H-nmr: δ 1.79-2.03 (m, 2H, CH_2), δ 2.34 (s, 3H, CH_3), δ 2.38-2.67 (m, 6H, 3 x CH_2), δ 3.12-3.30 (m, 4H, 2 x CH_2), δ 4.03 (t, 2H, CH_2, J = 7 Hz), δ 4.59 (s, 2H, CH_2), δ 6.70-7.31 (m, 7H_{Ar}); ms: m/z (I%); M 399 (33.0), 209 (100); hydrochloride mp 200-202° (1-propanol).

Anal. Calcd. for $C_{22}H_{26}N_3O_2Cl$•HCl (436.38): C, 60.55; H, 6.24; N, 9.63. Found: C, 60.05; H, 6.20; N, 9.24.

General Procedure for Preparation Derivatives **5**.

A mixture 2.4 g of **5** (2 mmoles), an appropriate 4-(3-chloropropyl)-1-arylpiperazine (2.1 mmoles), 8.3 g of potassium carbonate (6 mmoles) in acetone (50 ml) was refluxed with stirring for 12 hours. An inorganic precipitate was filtered off and the solvent was evaporated. The residue was purified by crystallisation from the appropriate solvent.

3-[3-(4-Phenyl-1-piperazinyl)propyl]benzoxazolin-2-one (**5a**).

Base **5a** was obtained in 57% yield, mp 78-81° (acetone); ^{1}H-nmr: δ 1.94-2.19 (m, 2H, CH_2), δ 2.53 (t, 2H, CH_2, J = 7 Hz), δ 2.53-2.66 (m, 4H, 2 x CH_2), δ 3.12-3.25 (m, 4H, 2 x CH_2), δ 3.98 (t, 2H, CH_2, J = 7 Hz), δ 6.78-7.37 (m, 9H_{Ar}); ms: m/z (I%); M 337 (33.3), 175 (100); hydrochloride mp 190-193° (acetone-ethanol 10:1).

Anal. Calcd. for $C_{20}H_{23}N_3O_2$•HCl (373.88): C, 64.25; H, 6.47; N, 11.24. Found: C, 64.08; H, 5.18; N, 11.37.

3-{3-[4-(3-Chlorophenyl)-1-piperazinyl)]propyl}benzoxazolin-2-one (**5b**).

Base **5b** was obtained in 64% yield, mp 107-109° (acetone-water 10:1); ^{1}H-nmr: δ 1.91-2.14 (m, 2H, CH_2), δ 2.48 (t, 2H, CH_2, J = 7 Hz), δ 2.47-2.60 (m, 4H, 2 x CH_2), δ 3.06-3.22 (m, 4H, 2 x CH_2), δ 3.95 (t, 2H, CH_2, J = 7 Hz), δ 6.72-7.30 (m, 8H_{Ar}); ms: m/z (I%); M 371 (49.1), 209 (100); hydrochloride mp 213-215° (ethanol).

Anal. Calcd. for $C_{20}H_{22}N_3O_2Cl$•HCl (408.33): C, 58.83; H, 5.68; N, 10.29. Found: C, 58.96; H, 5.96; N, 10.19.

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