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SYNTHESIS AND STRUCTURE OF 3-ARYLIDENE AND 3-HETARYLIDENE-1,2-DIHYDRO-3H-1,4-BENZO-DIAZEPIN-2-ONES AND THEIR AFFINITY TOWARD CNS BENZODIAZEPINE RECEPTORS

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The condensation of 5-aryl-7-bromo-1,2-dihydro-3H-1,4-benzodiazepin-2-ones with aromatic aldehydes gives 5-aryl-3-arylidene- and 5-aryl-7-bromo-3-hetarylidene-1,2-dihydro–3H-1,4–benzodiazepin–2–ones. X-ray diffraction structural analysis yielded the molecular and crystal structures of 7-bromo-3-(4'-methoxybenzylidene)-5-phenyl-1,2-dihydro-3H-1,4-diazepin-2-one and showed that this compound has cis configuration. Radioligand analysis was used to study the affinity of these products toward central nervous system and peripheral benzodiazepine receptors.

Keywords: 3-arylidene- and 3-hetarylidene-1,2-dihydro-3H-1,4-benzodiazepin-2-ones, affinity, central and peripheral benzodiazepine receptors.

1,4-Benzodiazepin-2-one derivatives bind to two types of benzodiazepine receptors: central (CBDR) and peripheral (PBDR). The CBDR are found exclusively in the central nervous system (CNS). Ligands of these receptors are commonly used in medicine as anticonvulsants, anxiolytics, hypnotics, myorelaxants, and sedatives [1, 2].

PBDR are found predominantly in tissues such as kidney, adrenal gland, placenta, and heart but are also observed in the CNS (glial cells) [3].

These relatively small proteins with molecular mass 18 kDa hold interest due to their biological effects such as cell proliferation regulation, immunomodulation (chemotaxis, apoptosis), cholesterol and porphyrin transport, the biosynthesis of heme, steroids, and neurosteroids, and mitochondrial oxidative phosphorylation [4, 5].

Recent studies to determine the density of PBDR in neurodegenerative and oncological diseases stress the importance of developing new strategies for the diagnosis and therapy of these diseases using PBDR ligands.

In a search for potentially selective ligands for central and peripheral benzodiazepine receptors of the CNS, we synthesized a series of new 3-arylidene- and 3-hetarylidene-1,2-dihydro-3H-1,4-benzodiazepin-2-one derivatives and studied the capacity of these products to competitively replace [^{3}H]PK 11195 and [^{3}H]flunitrazepam radioligands from the sites of their specific binding to PBDR and CBDR, respectively.

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TABLE 1. Characteristics of 3-Arylidene- and 3-Hetarylidene-1,2-dihydro-1,4-diazepin-2-ones **1-17** and Their Affinity Toward CNS BDR

Compound*	R^2	Empirical formula	Found, % / Calculated, %			mp, °C	Color	Yield, %	Affinity (*I*, %)	
			C	N	H				CBDR	PBDR
1	Ph	$C_{22}H_{15}BrN_2O$	65.74 / 65.63	6.87 / 6.98	3.69 / 3.74	250-252	Yellow	40	61.9±5.1	37.2±3.4
2	*p*-$MeOC_6H_4$	$C_{23}H_{17}BrN_2O_2$	63.85 / 63.74	6.56 / 6.47	3.89 / 3.92	234-236	Orange	75	13.8±1.5	42.7±3.8
3	*o*-BrC_6H_4	$C_{22}H_{14}Br_2N_2O$	54.76 / 54.88	5.89 / 5.82	2.98 / 2.91	260-263	Yellow	71	57.9±5.9	39.8±4.0
4	*m*-BrC_6H_4	$C_{22}H_{14}Br_2N_2O$	54.76 / 54.88	5.75 / 5.82	2.97 / 2.91	191-194	Yellow	70	16.0±1.5	32.9±3.0
5	*p*-BrC_6H_4	$C_{22}H_{14}Br_2N_2O$	54.94 / 54.88	5.79 / 5.82	2.87 / 2.91	256-260	Yellow	67	17.0±1.8	67.6±6.2
6	*Ph*	$C_{22}H_{14}BrClN_2O$	60.32 / 60.41	6.58 / 6.64	2.65 / 2.72	242-245	Yellow	46	79.9±7.4	60.9±5.9
7	*o*-BrC_6H_4	$C_{22}H_{13}Br_2ClN_2O$	51.34 / 51.26	5.39 / 5.44	2.43 / 2.52	249-252	Yellow	74	67.7±6.3	66.8±6.2
8	*m*-BrC_6H_4	$C_{22}H_{13}Br_2ClN_2O$	51.32 / 51.26	5.51 / 5.44	2.49 / 2.52	218-220	Yellow	75	27.3±2.6	44.0±4.2
9	*p*-BrC_6H_4	$C_{22}H_{13}Br_2ClN_2O$	51.39 / 51.26	5.48 / 5.44	2.47 / 2.52	274-276	Yellow	72	6.0±0.5	73.1±7.1
10	*p*-ClC_6H_4	$C_{22}H_{13}BrCl_2N_2O$	56.12 / 56.05	5.85 / 5.94	2.68 / 2.76	265-267	Yellow	73	2.1±0.3	74.5±8.0
11	*p*-FC_6H_4	$C_{22}H_{13}BrClFN_2O$	58.16 / 58.02	6.19 / 6.15	2.77 / 2.86	268-270	Yellow	71	1.2±0.1	12.5±1.1
12	4-C_5H_4N	$C_{21}H_{13}BrClN_3O$	57.48 / 57.53	9.51 / 9.59	2.85 / 2.97	240-242	Yellow	70	96.4±9.1	43.3±4.0
13	*p*-$O_2NC_6H_4$	$C_{22}H_{13}BrClN_3O_3$	54.68 / 54.77	8.65 / 8.71	2.65 / 2.70	310-314	Orange	70	0.0	30.0±2.9
14	*p*-$O_2NC_6H_4$	$C_{22}H_{14}BrN_3O_3$	58.87 / 58.93	9.31 / 9.37	3.21 / 3.12	290-292	Orange	75	20.9±2.0	65.2±6.3
15	*p*-$NMe_2C_6H_4$	$C_{24}H_{19}BrClN_3O$	59.65 / 59.75	8.78 / 8.71	3.87 / 3.94	205-212	Red	70	74.4±7.3	36.6±3.5
16	*p*-$OCHF_2$, *m*-$MeOC_6H_3$	$C_{24}H_{17}BrF_2N_2O_3$	57.65 / 57.71	5.56 / 5.61	2.75 / 2.80	193-196	Yellow	68	22.0±2.1	39.9±3.8
17	3,4,5-$(MeO)_3C_6H_2$	$C_{25}H_{20}BrClN_2O_4$	56.73 / 56.81	5.25 / 5.30	3.61 / 3.78	165-170	Orange	73	86.9±8.4	40.0±3.8

* **1-5**, **14, 16** R^1 = H; **6-13**, **15**, **17** R^1 = Cl.

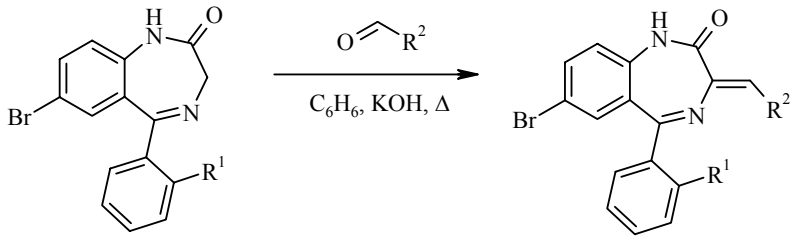
TABLE 2. Spectral Characteristics for compounds **1-17**

Com-pound	IR spectrum ($CHCl_3$), ν, cm^{-1}			UV spectrum (ethanol), λ_{max}, nm (log ε)				^{1}H NMR spectrum ($CDCl_3$)*, δ, ppm			Mass spectrum, *m/z* (I_{real}, %)
	N-H as. N-H noas.	C=O	C=C, C=N					NH (1H, s)	C=CH (1H, s)	H arom.	
1	3180, 3360	1660	1600	208 (4.45)	233 (4.47)	289 (4.26)	366 (3.72)	9.18	6.67	7.09-7.84	402 (100), 373 (23), 325 (32), 286 (40), 207 (21)
2	3170, 3360	1650	1590	206 (4.44)	230 (4.39)	297 (4.17)	383 (3.76)	9.17	6.67	7.47-7.60	432 (100), 403 (5), 389 (11), 355 (8), 286 (7), 207 (12)
3	3170, 3350	1650	1600	211 (4.67)	229 (4.66)	290 (4.40)	364 (3.92)	9.06	6.99	7.07-7.85	480 (18), 401 (100), 373 (5), 293 (25)
4	3170, 3350	1650	1600	214 (4.80)	233 (4.84)	291 (4.60)	371 (4.12)	9.18	6.58	7.09-7.94	480 (100), 451 (7), 401 (26), 373 (11), 293 (12), 286 (20), 207 (21)
5	3170, 3360	1660	1600		234 (4.77)	292 (4.43)	369 (3.93)	9.2	6.59	7.08-7.81	480 (100), 453 (6), 401 (15), 373 (8), 293 (11), 286 (19), 207 (18)
6	3170, 3350	1640	1600	209(4.53)		282 (4.08)	355 (3.66)	9.15	6.81	7.06-7.77	436 (100), 407 (28), 401 (15), 325 (33), 293 (13), 285 (10)
7	3170, 3340	1650	1600	209 (4.60)		282 (4.15)	355 (3.73)	8.98	6.72	7.06-7.62	514 (8), 435 (100), 292 (11)
8	3180, 3350	1650	1600	209 (4.72)		284 (4.31)	357 (3.88)	8.12	6.72	7.12-7.85	514 (100), 435 (9), 405 (10), 322 (8), 292 (7), 285 (12)
9	3170, 3350	1650	1600	208 (4.69)		290 (4.42)	360 (3.00)	8.87	6.72	7.02-7.68	514 (100), 489 (4), 435 (12), 405 (12), 322 (11), 292 (12), 287 (9)
10	3180, 3350	1650	1600	208 (4.74)		288 (4.42)	359 (3.98)	9.08	6.75	7.04-7.70	470 (100), 441 (8), 435 (20), 407 (5), 359 (12), 322 (6), 285 (12)
11	3170, 3350	1650	1590	208 (4.70)		283 (4.36)	359 (3.98)	8.92	6.78	7.03-7.76	454 (100), 425 (20), 419 (6), 343 (13), 322 (14), 285 (11)
12	3170, 3340	1650	1580	211 (4.63)		289 (4.26)	356 (3.77)	9.13	6.62	7.06-7.70	437 (100), 408 (15), 402 (15), 373 (5), 326 (28), 322 (4), 285 (7)
13	3160, 3360	1670	1580	205 (4.52)		329 (4.06)	368 (4.06)	11.07	6.71	7.12-8.34	481 (100), 407 (5), 372 (16), 322 (8), 292 (15), 285 (14)
14	3180, 3370	1670	1600	203 (4.66)		329 (4.16)	372 (4.15)	9.02	6.65	7.50-7.83	447 (100), 373 (18), 368 (15), 293 (18), 286 (13), 207 (19)
15	3170, 3360	1650	1600	203 (4.71)		334 (4.24)	415 (4.20)	8.01	6.70	7.42-7.50	481 (100)
16	3190, 3370	1670	1600	204 (4.67)		291 (4.28)	369 (3.84)	9.02	6.83	7.45-7.59	498 (100), 469 (5), 431 (7), 421 (13), 349 (4), 286 (12), 213 (10)
17	3180, 3350	1650	1600		233 (4.47)	301 (4.25)	372 (3.94)	8.84	6.74	7.00-7.76	526 (100), 511 (32)

*^{1}H NMR spectrum, δ, ppm: **2** -3.85 (3H, s); **15** - 302 (6H, s); **16** - 390 (3H, s); **17** - 3.87-3.88 (9H, s).

In previous work [6-9], we described the preparation of 3-arylidene- and 3-hetarylidene-1,2-dihydro-3H-1,4-benzodiazepin-2-ones under conditions of the Perkin reaction using acetic anhydride and sodium acetate. Methods have been described for the formation of a C=C bond in the reaction of 1,4-benzodiazepin-2-ones with aldehydes in the presence of sodium butylate in tetrahydrofuran [10] or in the presence of potassium hydroxide in ethanol [11].

In the present work, we synthesized 3-arylidene- and 3-hetarylidene-1,2-dihydro-3H-1,4-benzodiazepin-2-ones **1-17** (Table 1) by the condensation of dihydrobenzodiazepines **I** with aromatic aldehydes upon heating in benzene at reflux in the presence of potassium hydroxide.



I **1–17**

The structure of **1-17** was supported by IR, UV, and ^{1}H NMR spectroscopy, mass spectrometry (Table 2), and X-ray diffraction structural analysis for **2**.

The IR spectra of **1-17** contain narrow bands corresponding to vibrations of nonassociated (3370-3340 cm^{-1}) and associated N-H groups (3190-3160 cm^{-1}), strong carbonyl group bands at 1670-1640 cm^{-1}, and bands at 1600-1580 cm^{-1} corresponding to the azomethine group and benzene ring C=C bonds.

The UV spectra for **1-17** show bands characteristic for 1,2-dihydro-3H-1,4-benzodiazepin-2-ones, corresponding to $\pi\rightarrow\pi^*$ transitions of the benzene ring electrons and $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions of the azomethine bond conjugated with aromatic substituents and the hetarylidene fragment [12].

The ^{1}H NMR spectra of **1-17** (Table 2) show signals for all the proton types: a singlet for the NH group proton at 8.01-11.07 ppm, aromatic proton multiplet at 7.02-7.94 ppm, and a singlet for the C-H proton at the C=C bond at 6.58-6.99 ppm.

The mass spectra of **1-17** (with the exception of **3** and **7**) have a molecular ion peak with 100% intensity. The molecular ion peak intensity for **3** and **7**, containing an *o*-bromophenyl substituent, is only ~8%, while the major peak is found for the $[M\text{-}Br]^+$ cation. The subsequent fragmentation is similar to the fragmentation characteristic for 1,2-dihydro-3H-1,4-benzodiazepin-2-ones [12].

The molecular and crystal structure of **2** was studied by X-ray diffraction analysis (Figs. 1 and 2, Tables 3 and 4).

The molecules of **2** in the crystal are arranged in dimers due to the N(1)-H···O(2) hydrogen bonds (N(1)···O(2), 2.824 Å; H···O(2), 2.044 Å; N(1)-H···O(2), 178.17º). This bond is similar in its parameters to the hydrogen bond characteristic for benzodiazepines unsubstituted at N(1) [13-15].

The major lengths in the seven-membered heterocycle are similar to those found for other benzodiazepines. The heterocycle has *pseudoboat* conformation with dihedral angles between the C(2)C(3)N(4) plane and the N(1)C(2)N(4)C(5) and C(10)N(1)C(5)C(11) planes equal to 135.6º and 98.2º, respectively.

Substituent R^2 is in the *cis* position relative to the C=C bond.

The bromophenyl group forms an angle of 56.6º with the methoxyphenyl substituent.

We should note that there are deviations from the standard bond lengths in the C(5)–N(4)–C(3)–C(31)–C(32) chain (Table 3), indicating strain in this molecular fragment.

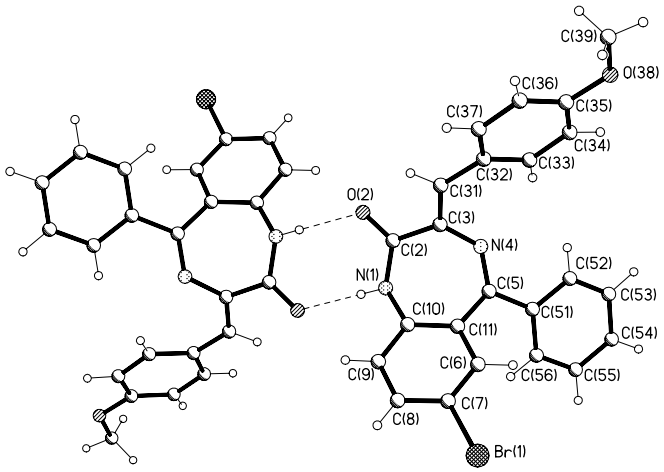


Fig. 1. General view of **2** in the crystal with numbering of the independent atoms. Formation of the dimer is shown.

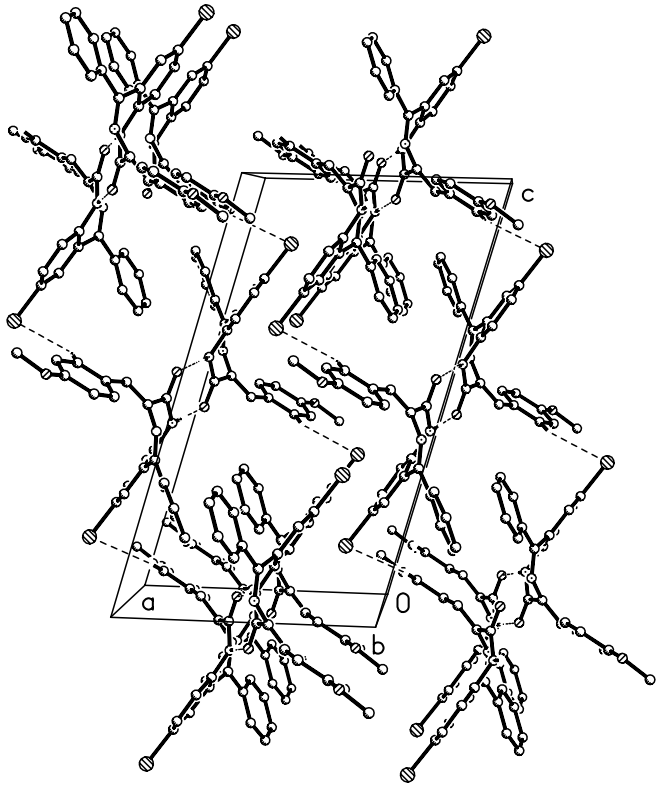


Fig. 2. Crystal packing of **2** (the intermolecular N(1)-H···O(2) hydrogen bonds are shown by dashed lines).

Figure 2 shows a fragment of the crystal packing for **2**. In addition to the N(1)-H···O(2) hydrogen bond in the crystal, there is also a weak C-H···Br interaction (C···Br, 3.777 Å; H···Br, 2.996 Å) and a dipole-dipole interaction between the O(38)-C(39) fragments (O···C, 3.216 Å). The other contacts conform to van der Waals forces.

TABLE 3. Some Bond Lengths (*d*) and Bond Angles (ω) in **2**

Bond	*d*, Å	Angle	ω, deg
N(1)–C(2)	1.360(2)	N(1)–C(2)–C(3)	117.6(2)
C(2)–C(3)	1.496(2)	C(2)–N(1)–C(10)	125.8(2)
C(2)–O(2)	1.235(2)	O(2)–C(2)–N(1)	120.8(2)
C(3)–N(4)	1.407(2)	O(2)–C(2)–C(3)	121.6(2)
N(4)–C(5)	1.286(2)	N(4)–C(3)–C(2)	117.4(2)
C(5)–C(11)	1.488(2)	N(4)–C(3)–C(31)	124.5(2)
C(10)–C(11)	1.398(2)	C(31)–C(3)–C(2)	117.6(2)
N(1)–C(10)	1.409(2)	C(3)–N(4)–C(5)	122.7(2)
C(3)–C(31)	1.344(3)	N(4)–C(5)–C(11)	124.1(2)
C(31)–C(32)	1.469(2)	N(4)–C(5)–C(51)	117.5(2)
		C(10)–C(11)–C(5)	121.3(2)
		C(11)–C(10)–N(1)	122.4(2)

TABLE 4. Some Torsion Angles (τ) in **2**

Angle	τ, deg	Angle	τ, deg
N(1)C(2)C(3)N(4)	46.0	N(4)C(5)C(11)C(10)	44.4
C(10)N(1)C(2)C(3)	25.8	C(3)N(4)C(5)C(11)	-0.7
C(11)N(1)C(10)C(2)	-48.5	C(2)C(3)N(4)C(5)	-62.0
C(5)C(11)C(10)N(1)	-6.0		

The radioligand data given in Table 1 indicate that these compounds are competitive with commercial radioligands for sites with specific binding both with rat brain CBDR and PBDR but display different affinities.

3-Benzylidene-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (**1**) shows low affinity to both types of receptors. This compound in concentration 1 μM inhibits the specific binding of radioligands [^{3}H]PK 11195 and [^{3}H]flunitrazepam with PBDR and CBDR by 37.2 and 61.9%, respectively (Table 1).

Variation of the position of the bromine atom in the 3-benzylidene fragment in 3-(bromo)benzylidene-7-bromo-5-(2'-chloro)phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones yielded the following trend for the affinity of these compounds toward CNS BDR. The compounds with a *p*-bromobenzylidene substituent at C(3) in the benzodiazepine system bind more actively to CNS PBDR than the *o*- and *m*-bromobenzylidene derivatives.

Different behavior is observed in the case of CBDR: higher affinity is found for compounds containing an *o*-bromobenzylidene substituent at C(3) in the 7-bromo-5-(2'-chloro)phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one molecule.

Thus, we should note the following trend for the influence of the position of the bromine atom in the benzylidene moiety on the affinity toward BRD found in the series of 7-bromo-5-phenyl- and 7-bromo-5-(2'-chloro)phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones:

p-Br > > *o*-Br > *m*-Br (affinity toward PBDR)
p-Br > > *o*-Br ≥ *p*-Br (affinity toward CBDR)

The greatest capacity to form the ligand-PBDR molecular complex is found for **12, 17**, and **6**. These compounds in concentration 1 μM inhibit the specific binding of [^{3}H]flunitrazepam with PBDR by 96.4, 86.9, and 79.9%, respectively.

Linearization of the curves for inhibition of specific binding of [^{3}H]flunitrazepam with CNS PBDR by **12** and **6** (Fig. 3) gave IC_{50} values of 45.7 and 575.4 nM, respectively.

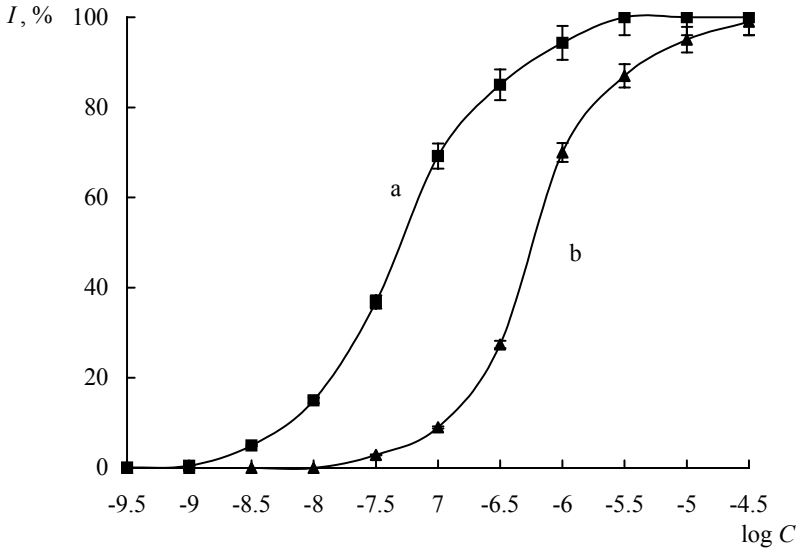


Fig. 3. Dependence of the inhibition (*I*, %) of the specific binding of the [^{3}H]flunitrazepam radioligand with CBDR of the synaptic fraction of rat brain cortex membranes on the concentrations of **12** (*a*) and **6** (*b*), respectively. log *C* – logarithm of the concentration of **12** (*a*) and **6** (*b*), *I*, % – inhibition of specific binding of the [^{3}H]flunitrazepam radioligand with CNS CBDR.

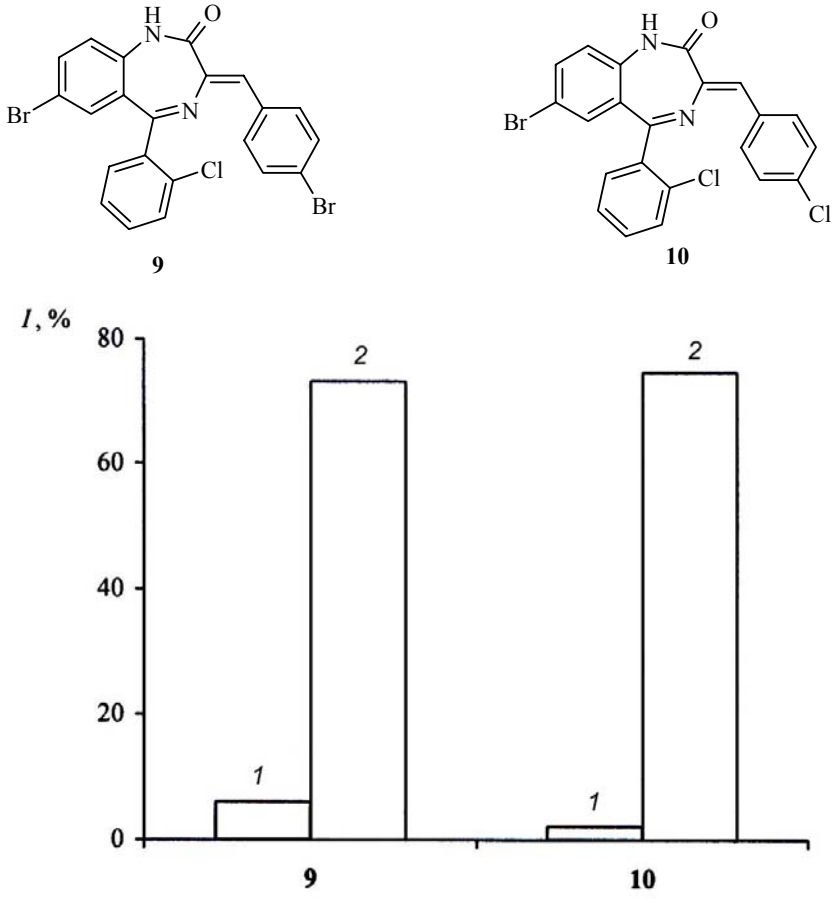


Fig. 4. Inhibition of specific binding of [^{3}H]flunitrazepam with CBDR (*1*) and of [^{3}H]PK 11195 with rat brain cortex PBDR (*2*) by compounds **9** and **10** (*C* = 1 μM).

Selective PBDR ligands were found in the series of 7-bromo-5-(2'-chloro)phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one derivatives containing different substituents in the *para* position in the 3-benzylidene fragment. The affinity of these ligands (**9** and **10**) is two orders of magnitude greater toward PBDR than toward CBDR (Fig. 4).

In the series of compounds studied, **12** and **17** bind predominantly with CBDR, **9, 5**, and **10** bind predominantly with PBDR, while **3** and **6** show equal affinity toward the two types of receptors.

EXPERIMENTAL

The course of the reactions and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using 1:10 methanol-chloroform as the eluent and detection with UV light ($\lambda = 254$ nm). The IR spectra were taken on a Specord IR-75 spectrometer for solutions in $CHCl_3$. The UV spectra were taken on an SF-56 spectrometer for solutions in ethanol. The ^1H NMR spectra were taken for ~2% solutions of the compounds in $CDCl_3$ on a Bruker spectrometer at 300 MHz using TMS as the internal standard. The mass spectra were taken on an MKh-1321 mass spectrometer. The ionizing voltage was 70 eV and the temperature of the ionization chamber was 220°C.

X-Ray Diffraction Structural Analysis. A monocrystal of 7-bromo-3-(4'-methoxybenzyidene)-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (**2**) was obtained by crystallization from ethanol. The unit cell parameters of the monoclinic crystal were as follows: $a = 11.0595(5)$, $b = 9.4768(8)$, $c = 19.2114(9)$ Å, $\gamma = 105.33(1)°$, space group $P2_1/n$, $V = 1941.8(4)$ Å^3, $M = 433.3$, $Z = 4$, $d_{calc} = 1.482$ g/cm^3.

The X-ray diffraction study was carried out on a monocrystal (0.4×0.3×0.1 mm) on a KUMA-4CCD diffractometer using MoKα radiation with ω-scanning at 123 K. A total of 11,214 reflections were measured, of which 3938 were symmetrically independent ($R_{int} = 0.0211$). No correction for absorption was introduced ($\mu = 1.666$ mm^{-1}). The structure was solved by the direct method using the SHELX-97 program [16] and refined by the method of least squares in the full-matrix anisotropic approximation for the non-hydrogen atoms. All the hydrogen atoms were found from the electron density difference map and refined isotropically. The final R factor for reflections with $I > 2\sigma(I)$ was 0.0264 and for all reflections was 0.349. The residual electron density from the Fourier difference map was in the range from +0.435 to -0.302 eÅ^3. The atomic coordinates were deposited at the Cambridge Crystal Data Center, CCDC 643684.

***cis*-7-Bromo-3-(4'-methoxybenzylidene)-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (2).** A mixture of 7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (2 g, 6.4 mmol), *p*-methoxybenzaldehyde (1.3 ml, 10.7 mmol), and potassium hydroxide (0.2 g, 3.6 mmol) in benzene (15 ml) was heated at reflux for 24 h with monitoring of the reaction course by thin-layer chromatography. The hot reaction mixture was filtered and evaporated in vacuum to dryness. The solid residue was crystallized from ethanol. Recrystallization from ethanol gave 1.92 g (70%) **2**, $R_f = 0.43$.

Products **1-17** were obtained analogously. Tar formation was noted in the preparation of **1** and **6**.

Affinity to Central and Peripheral Benzodiazepine CNS Receptors was determined by the *in vitro* radioligand method. Amersham flunitrazepam (2960 TBq/mol) was used for CBDR and Du Pont NEN [^{3}H]PK 11195 (2775 TBq/mol) was used for PBDR.

All the experiments were carried out on white nonpedigreed male rats with mass 180-220 g maintained in a vivarium under standard conditions with free access to food and water. The anesthetized animals were decapitated and the brain cortex, characterized by high BDR content, was rapidly removed in the cold. The analysis of the interaction of **1-17** with CBDR and PBDR was carried out according to previous procedures [17, 18]. The affinity was found relative to the compounds at 1 μM to remove radioligands from sites of their specific binding with receptors. IC_{50} values (concentrations at which the tested compound gives 50% inhibition of specific binding of the radioligand with the receptor) were determined for the most active compounds.

A total of eight concentrations in the range from 10^{-9} to 10^{-5} M were used to determine the IC_{50} values. Each experimental point was obtained in sextets. The data are given at $M \pm m$, where M is the mean value of three independent experiments and *m* is the standard mean error.

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