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Synthesis and selectivity of 1-methoxycarbonylmethyl-3-arylamino-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones binding for CNS benzodiazepine receptors

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Summary. Earlier, the methoxycarbonylmethyl fragment at the 1-position and the nitrophenylamine fragment at the 3-position of the 1,4-benzodiazepine ring, on the base of the QSAR analysis of series of 1,4-benzodiazepin-2-one derivatives [1], have been shown to gave compounds with increased affinity for peripheral benzodiazepine receptors (PBR). The 3-arylamine derivatives of 1-methoxycarbonylmethyl-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one were proposed for the directed synthesis as a promising high selective ligands of PBR. The target compounds were synthesized through the condensation of 1-methoxycarbonylmethyl-3-chloro-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one with substituted anilines. Affinities of synthesized compounds for the CNS benzodiazepine receptors of peripheral (PBR) and central (CBR) types were determined by the radioligand method *in vitro*. Selective PBR ligand with a high affinity — 1-methoxycarbonylmethyl-3-(2'-nitro)phenylamino-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one, **7** (**MX-1785**, K_i(PBR)=19.1 nM, K_i(CBR)>10000 nM) was found among the studied compounds.

Keywords: 1,3-substituted 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones, affinity, benzodiazepine receptors, selectivity, QSAR analysis.

Introduction. There are central (CBR) [2], and peripheral (PBR) [3] benzodiazepine receptors. CBR are presented exclusively in the central nervous system. They are located at pre- and postsynaptic membranes of neurons and mediate the classic effects of benzodiazepines [4]. PBR were initially discovered in the kidney [5], then in many organs and tissues, including the CNS [3]. Originally PBR were considered as one of the CBR subtypes, but later they were identified as an individual class of receptors due to their unique structure, cell localization and performance of physiological functions mediated by them [3, 6, 7]. Peripheral benzodiazepine receptors are 5-transmembrane 169-amino acid polypeptides with a molecular weight of 18 kDa, which are localized mainly on the mitochondrial outer membrane of peripheral tissues and glial cells of the CNS [3, 6].

Recent years the results of studies have shown that PBR are an important component of the so-called mitochondrial permeability transition pore (MPTP) involved in regulation of ions concentration, pH, and the volume of mitochondria as well as in Ca^{2+} ions transfer [6, 8].

The exact physiological function of PBR is not yet fully understood, but a wide range of pharmacological activities, such as anticonvulsant, anxiolytic, immunomodulating, and cardiovascular, has been related to its activation [3, 7, 9].

In particular, there is growing number of

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experimental evidence that high affinity PBR ligands stimulate the synthesis of neurosteroids in glial cells. PBR mediate the delivery of cholesterol to the inner mitochondrial membrane where it is oxidized by cytochrome $P450_{scc}$ (scc — side chain cleavage) to pregnenolone — parent compound of endogenous steroids [6-11]. Some neurosteroids [pregnenolone sulfate, 3α,21-dihydroxy-5α-pregnan-20-one (3α,5α-THDOC), 3α-hydroxy-5α-pregnan-20-one (3α,5α-THPROG), and dehydroepiandrosterone] are known to modulate GABAergic and glutamatergic neurotransmission [8, 11-13]. Numerous studies show that such neuropatologic states as multiple sclerosis, Wernicke's encephalopathy, Alzheimer's disease, Huntington's disease, epilepsy, stroke and stress are associated with the PBR expression [3, 7, 11, 14-16]. The highest PBR density is observed in many tumor types such as brain, hepatic, liver glial, and mammary tumors, adenocarcinoma, breast carcinoma, and ovarian, and colorectal cancers — all of them have showed a selective increase in PBR density compared with non-transformed tissue [17, 18]. In some cases the grade of PBR over-expression appears to be correlated with the malignancy of the tumor and mortality of patients [18, 19].

PBR-specific ligands are considered both as new intracellular targets of action [20] of radiological diagnostic imaging agents [21] and receptor-mediated drug carriers [22, 23], which can selectively deliver anticancer agents into tumors [24, 25]. The development of new strategies for molecular design and synthesis of high affinity and selective PBR ligands with a given pharmacological properties is the top issue for medical and bioorganic chemistry, experimental and clinical medicine.

There are several classes of PBR ligands available including 1,4-benzodiazepines (Ro 5-4864 [26]; gidazepam, MX-633 [27]), isoquinoline carboxamides (PK 11195) [28], 2-aryl-3-indolacetamides (FGIN-1-27) [29], N-phenoxyphenyl-N-isopropoxybenzylacetamides (DAA1097) [30], pyrrolobenzoxazepines (OXA-17f) [31], 1,3,4-benzotriazepines (MX-1189) [32] and some others (Fig. 1).

We have conducted the search for selective highly active PBR ligands among 1- and 3-substituted derivatives of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-one. Earlier [27], we studied affinity of gidazepam (MX-633) for CBR and PBR. Gidazepam has an original range of pharmacological activity and demonstrated a prominent anxiolytic effect with poor myorelaxant and hypnotic side effects [33]. The results of the radioligand binding analysis showed [27] that gidazepam has a 3-fold higher affinity for PBR than for CBR; IC_{50} values are of 710 nM and 2200 nM, respectively.

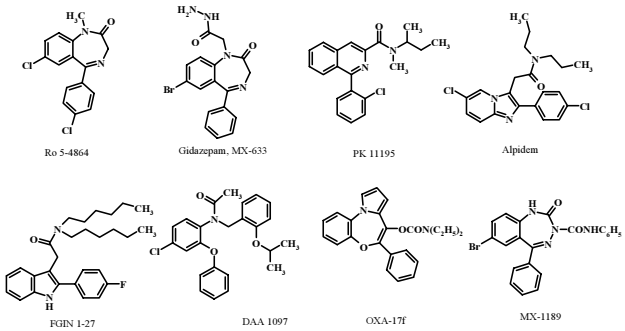


Fig. 1. The structures of some PBR ligands.

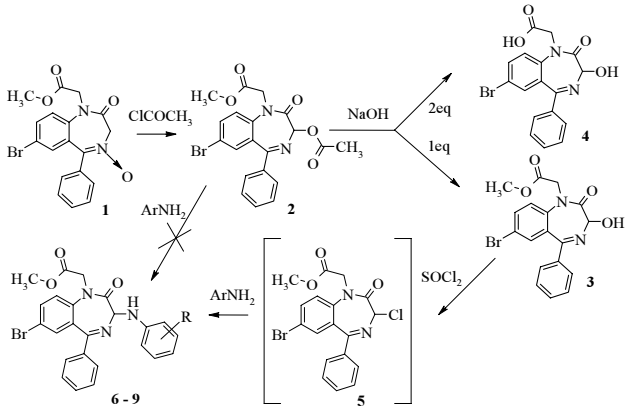
Our data demonstrate that substitutions of bromine atom at the 7-position of the gidazepam template either with a chlorine atom or a methyl group led to the decrease in affinity for PBR. The substitution of the hydrazine fragment with methoxy group and the presence of (2'-chloro)phenyl substituent at the 5-position of the benzodiazepine ring contributed to an unexpected increase in affinity for PBR [27].

We have reported earlier [34], that some of 3-arylidene-7-bromo-5-(2'-chloro)phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones are selective PBR ligands. A selective PBR ligand 3-(4'-chloro)benzylidene-7-bromo-5-(2'-chloro)phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (MX-1735) is especially interesting among these ligands. We have shown that the presence of either chlorine or bromine atom in a *para*-position of the 3-benzylidene fragment plays a crucial role in the manifestation of selectivity and affinity for PBR versus CBR.

Later, in [1] we have reported the results of QSAR analysis of 1- and 3-substituted 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones with the use of the method of simplex representation of molecular structure [35, 36] and the «Dragon» program [37, 38]. Based on the interpretation of obtained highly adequate models, it was found that the presence of methoxycarbonylalkyl group at the 1-

Scheme 1

Synthesis of 1-methoxycarbonylmethyl-3-arylamino-1,2-dihydro-3H-1,4-benzodiazepin-2-ones



*R=H (**6**), R=2-NO_2 (**7**, **MX-1785**); R=3-NO_2 (**8**); R=4-NO_2 (**9**)*

position of the benzodiazepine cycle, is an important descriptor to ensure recognition of the studied 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones by PBR. In the series of 3-amino-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones, compounds containing nitroaniline substituent at the 3-position of the benzodiazepine cycle have the higher affinity for PBR. By the results of the QSAR analysis [1], molecular design and computer screening were conducted for new selective PBR ligands, 1,4-benzodiazepin-2-one derivatives, which are recommended for directed synthesis.

Thus, the aim of our study was the synthesis of new 1,3-substituted derivatives of 1,4-benzodiazepin-2-one and the estimation of their affinity and selectivity for CBR and PBR in CNS.

Results and discussion. Synthesis of 1-methoxycarbonylmethyl-3-arylamino-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (**6-9**) (Table 1) has been carried out as follows.

1-Methoxycarbonylmethyl-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one-4-oxide (**1**) obtained according to [39] was used as an initial compound. 3-Acetoxy derivative **2** was obtained through the acylation of the compound **1** with acetyl chloride.

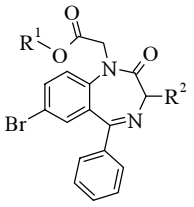
An attempt to obtain the final compounds **6-9** from the 3-acetoxy derivative **2** through the coupling with the corresponding arylamines was unsuccessful.

Saponification of the compound **2** was carried out with sodium hydroxide in methanol. At equimolar ratio of the base and substrate, selective saponification of 3-acetoxy group with the formation of **3** was occurred, and at the double excess of the base — saponification of two ether groups with the formation of **4**.

Through the coupling of the 3-hydroxy derivative **3** with thionyl chloride, 3-chloro derivative **5** has been obtained, followed by its conden-

Table 1

*Properties of 1,3-substituted 1,2-dihydro-3H-1,4-benzodiazepin-2-ones (**2-9**) and their affinity for CNS benzodiazepine receptors*



№	R^1	R^2	mp, °C	Yield, %	Colour	Formula	Found % / Calculated %			Affinity (K_i, nM)	
							C	N	H	CBR	PBR
2	CH_3	$OCOCH_3$	188-192	80	White	$C_{20}H_{17}BrN_2O_5$	53.95 / 53.90	6.29 / 6.33	3.85 / 3.79	-	-
3	CH_3	OH	168-172	65	White	$C_{18}H_{15}BrN_2O_4$	53.62 / 53.68	6.95 / 6.93	3.75 / 3.77	-	-
4	H	OH	265-269 (destr.)	60	White	$C_{17}H_{13}BrN_2O_4$	52.46 / 52.41	7.20 / 7.24	3.37 / 3.28	-	-
6	CH_3	NHC_6H_5	178-182	85	White	$C_{24}H_{20}BrN_3O_3$	60.26 / 60.22	8.78 / 8.83	4.21 / 4.19	>10000	740.0±180.0
7, MX-1785	CH_3	NH-(2-$NO_2C_6H_4$)	242-244	65	Yellow	$C_{24}H_{19}BrN_4O_5$	55.08 / 55.13	10.71 / 10.66	3.66 / 3.73	>10000	19.1±3.0
8	CH_3	NH-(3-$NO_2C_6H_4$)	186-190	75	Yellow	$C_{24}H_{19}BrN_4O_5$	55.08 / 55.03	10.71 / 10.68	3.66 / 3.70	>10000	360.4±41.0
9	CH_3	NH-(4-$NO_2C_6H_4$)	240-244	70	Yellow	$C_{24}H_{19}BrN_4O_5$	55.08 / 55.04	10.71 / 10.77	3.66 / 3.61	>10000	87.3±10.1

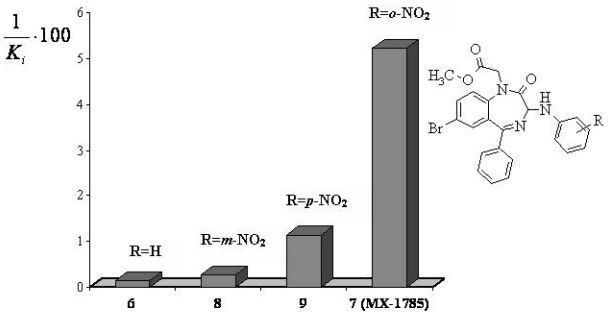


Fig. 2. Affinity of 1-methoxycarbonylmethyl-3-arylamino-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones for CNS PBR.

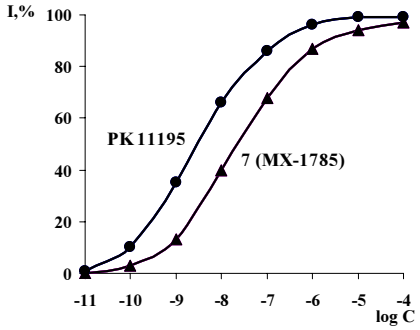


*Fig. 3. The dependence of inhibition (I, %) of the specific binding of the [³H]PK 11195 radioligand to PBR on the concentrations of PK 11195 and compound **7** (**MX-1785**), respectively. According to the abscissa axis — logarithms of the concentrations of PK 11195 and compound **7** (**MX-1785**), to the ordinate axis — % of inhibition of specific binding of the [³H]PK 11195 radioligand to CNS PBR.*

sation either with aniline (at room temperature) or with *ortho*-, *meta*-, *para*-nitroaniline (refluxed in chloroform for 5-6 hours) and obtaining of final 3-arylamino derivatives **6-9**.

The structures of synthesized compounds have been proved by the methods of mass spectrometry, infrared spectroscopy and ^{1}H NMR spectroscopy. Properties of compounds and their affinities for the central and peripheral benzodiazepine CNS receptors are shown in the Table 1.

In the IR spectra of compounds **6-9** the absorption bands corresponding to the vibration of carbonyl group bonds (C=O) within the region 1660-1690 cm^{-1}, and vibrations of C=O bonds in methoxycarbonylmethyl fragment within the region 1690-1730 cm^{-1}, are observed.

The absorption bands corresponding to the vibrations of NH-group for the compounds **6**, **8-9** are within the region 3360-3380 cm^{-1}, and for the compound **7** (**MX-1785**) it is shifted to the long-wave region and can be observed at 3320 cm^{-1} resulting from the formation of intramolecular hydrogen bonds between the hydrogen atoms of NH-group and oxygen atoms of nitro group.

The bands corresponding to vibrations of C=C and C=N bonds are in the 1580-1600 cm^{-1} region.

In the ^{1}H NMR spectra of compounds **6-9**, the signals of aromatic protons are within the region 7.26-8.11 ppm, and the signals of protons of methoxycarbonyl group are within the region 3.62-3.72 ppm. A proton signal at the C (3) atom is observed at 4.26-6.04 ppm. The NH proton signal is in the aromatic protons region.

Affinity of compounds **6-9** for benzodiazepine CNS receptor was determined by the radioligand method *in vitro*. Affinity was evaluated by the values of inhibition constants (K_i) which were estimated by the ability of the investigated compounds to displace competitively radioligands (CBR antagonist [³H]flumazenil and PBR antagonist [³H]PK 11195) from their specific binding sites in benzodiazepine receptors of central and peripheral types of sinaptosomal and mitochondrial membrane fractions of rats brain, respectively.

It was found that the 3-aniline substituent containing compound **6** is characterized by low affinity for PBR with a value of K_i=740.0 nm. Changing the position of the nitro group in the 3-aniline fragment of molecule 1-methoxycarbonylmethyl-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one resulted in the preparation of high-affinity compounds and revealed the following trends in changes of affinity of compounds for PBR (Fig. 2): the compound containing *ortho*-nitroaniline substituent (**7**, **MX-1785**, K_i=19.1 nM) at the 3-position of benzodiazepine cycle is bind to the PBR of CNS better that the *para*- and *meta*-nitroaniline derivatives (**9**, K_i=87.3 nM, and **8**, K_i=360.4 nM, respectively).

This group of compounds has high selectivity of binding to PBR (values K_i of binding of these substances to CBR>10000 nM).

In the series of studied 1-methoxycarbonylmethyl-3-arylamino-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones, the high affinity compound **7** (**MX-1785**) was found. This compound has affinity for PBR comparable to that of radioligand [³H]PK 11195 (Fig. 3). The

above-mentioned compound is of interest for pharmacological research.

Experimental section. ***Materials and methods.*** The IR spectra were recorded on a Specord 75-IR (solutions in $CHCl_3$). Mass spectra were obtained using the method of electron ionization on mass spectrometer MX-1321 (ionization voltage 70 eV, temperature of the ionization chamber is 200 ˚C).

^1H NMR spectra were recorded on a Bruker spectrometer at 300 MHz frequency, in $CDCl_3$, internal standard TMS, at 25 ˚C. Thin layer chromatography was performed on plates Silufol UV-254, in benzene : chloroform : hexane (1 : 1 : 3) system, development with UV-light at λ=254 nm.

Methods for the synthesis of 1,2-dihydro-3H-1,4-benzodiazepin-2-one derivatives.

1-Methoxycarbonylmethyl-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one-4-oxide ***(1)***. The compound was obtained according to the procedure described in [39].

1-Methoxycarbonylmethyl-3-acetoxy-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one ***(2)***. To a solution of compound **1** (30 g, 0.075 mol) in benzene (100 ml), the acetyl chloride (10.6 ml, 0.15 mol) was added. The mixture was heated at 40 ˚C for 40 minutes. Residue was filtered and crystallized from methanol. Yield 26 g (78 %), mp 142-144 ˚C. Mass spectrum, m/z (%): 444 (10) $[+H]^+$. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.62 s (3H, $CH_2COO\underline{CH_3}$), 6.04 s (1H, C^3-H), 7.42-7.72 m (8H, H_{arom}). IR spectrum, ν, cm^{-1} ($CHCl_3$): 1720 ($COOCH_3$), 1690 (C=O).

1-Methoxycarbonylmethyl-3-hydroxy-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one ***(3)***. To a mixture of compound **2** (1.0 g, 1.9 mmol) in methanol (20 ml), the solution of NaOH (75 mg, 1.9 mmol) in H_2O (6 ml) was added. The reaction mixture was stirred for 3 minutes, and then chloroform (30 ml) and water (30 ml) were added. Chloroform layer was separated, washed with water to pH 7, dried over magnesium sulphate, and then chloroform was evaporated. The resulting oil was triturated with ethanol (5 ml) to give white solid. Yield 0.66 g (78 %), mp 138-142 ˚C. Mass spectrum m/z (%): 403 (43) $[+H]^+$. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.69 s (3H, $CH_2COO\underline{CH_3}$), 5.09 d (J=9.65 Hz, 1H, C^3-H), 7.41-7.70 m (8H, H_{arom}). IR spectrum, ν, cm^{-1} ($CHCl_3$): 1720 ($COOCH_3$), 1680 (C=O).

1-Carboxymethyl-3-hydroxy-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one ***(4)***. To a solution of compound **2** (1.0 g, 1.9 mmol) in methanol, the solution of NaOH (0.15 g, 3.8 mmol) in H_2O (6 ml) was added. The reaction mixture was stirred for 10 minutes, and product precipitated with water. Then it was crystallized from ethanol. Yield 0.5 g (68 %), mp 232-235 ˚C. Mass spectrum m/z (%): 389 (27) $[+H]^+$. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 5.10 d (J=9.65 Hz, 1H, C^3-H), 7.42-7.73 m (8H, H_{arom}), IR spectrum, ν, cm^{-1} ($CHCl_3$): 1680 (C=O).

1-Methoxycarbonylmethyl-3-chloro-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one ***(5)***. The mixture of compound **3** (1.0 g, 2.4 mmol) and thionyl chloride (10 ml) were placed into a flask and left for 10 hours. Excess of thionyl chloride was evaporated under reduced pressure. Then absolute chloroform (20 ml) was added, and solvent was evaporated, process was repeated three times to remove thionyl chloride completely. The compound **5** was used in further synthesis without isolation.

1-Methoxycarbonylmethyl-3-phenylamino-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one ***(6)***. The mixture of compound **5** (1.0 g, 2.3 mmol), aniline (0.42 g, 4.6 mmol) and chloroform (20 ml) were placed into a flask. The mixture was left for 10 hours. Precipitate of aniline hydrochloride was filtered, chloroform layer was washed with water (5x20 ml), dried over magnesium sulphate. Solution was evaporated under reduced pressure, the residue was crystallized from benzene. Yield 0.8 g (73 %), mp 144-146 ˚C. Mass spectrum m/z (%): 479 (25) $[+H]^+$. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.69 s (3H, $CH_2COO\underline{CH_3}$), 5.16 d (J=7.47 Hz, 1H, C^3-H), 7.26-7.73 m (8H, H_{arom}). IR spectrum, ν, cm^{-1} ($CHCl_3$): 1690 ($COOCH_3$), 1660 (C=O), 3360 (N-H).

1-Methoxycarbonylmethyl-3-(2'-nitro)phenylamino-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one ***(7, MX-1785)***. A mixture of compound **5** (1.0 g, 2.3 mmol) and *o*-nitroaniline (0.63 g, 4.6 mmol) in anhydrous chloroform (20 ml) was refluxed for 4 hours, then cooled to room temperature and washed with water (4x20 ml). The organic layer was dried over magnesium sulphate. The solvent was evaporated and the residue was crystallized from benzene. Yield 0.7 g (58 %), mp 223-226 ˚C. Mass spectrum m/z (%): 524 (11) $[+H]^+$. ^1H NMR spec-

trum ($CDCl_3$), δ, ppm: 3.71 s (3H, $CH_2COO\underline{CH_3}$), 5.29 d (*J*=6.23 Hz, 1H, C^3-H), 7.35-7.75 m (8H, H_{arom}). IR spectrum, ν, cm^{-1} ($CHCl_3$): 1720 ($COOCH_3$), 1680 (C=O), 3320 (N-H).

*1-Methoxycarbonylmethyl-3-(3'-nitro)phenylamino-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (**8**).* The compound was obtained according to the procedure described for **7**. Yield 0.6 g (51 %), mp 223-226 ˚C. Mass spectrum m/z (%): 524 (43) $[+H]^+$. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.72 s (3H, $CH_2COO\underline{CH_3}$), 5.22 d (*J*=7.47 Hz, 1H, C^3-H), 7.30-7.76 m (8H, H_{arom}). IR spectrum, ν, cm^{-1} ($CHCl_3$): 1730 ($COOCH_3$), 1680 (C=O), 3380 (N-H).

*1-Methoxycarbonylmethyl-3-(4'-nitro)phenylamino-7-bromo-5-phenyl-1,4-benzodiazepin-2-one (**9**).* The compound was obtained according to the procedure described for **7**. Yield 0.68 g (67 %), mp 214-216 ˚C. Mass spectrum m/z (%): 524 (100) $[+H]^+$. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.72 s (3H, $CH_2COO\underline{CH_3}$), 5.21 d (*J*=7.16 Hz, 1H, C^3-H), 7.35-8.11 m (8H, H_{arom}). IR spectrum, ν, cm^{-1} ($CHCl_3$): 1720 ($COOCH_3$), 1680 (C=O), 3360 (N-H).

All experiments on animals were carried out in accordance with the experimental protocol for humane treatment for animals European Communities Council Directive of 24 November 1986 (86/609/EEC).

Study of affinity of synthesized compounds for CBR and PBR CNS.

The experiments were conducted in white nonpedigreed male rats (180-220 g) from the vivarium at Odessa State Medical University, with free access to water and food. The anesthetized animals were decapitated, then the cortex was quickly isolated on a cold. Experiment on radioligand binding was conducted with the use of the membranes synaptic fraction of rats brain, that was obtained similar to [40] and mitochondrial membranes fraction of rats brain obtained similar to [41]. Affinities of synthesized compounds for both central and peripheral benzodiazepine CNS receptors were determined by the radioligand method *in vitro*. Antagonist CBR [^{3}H] flumazenil (3219 TBq/mol, «Du Pont NEN») and antagonist PBR [^{3}H]PK 11195 (2775 TBq/mol, «Du Pont NEN») were used as radioligands.

The analysis of the interaction of compounds **6-9** with CBR and PBR was conducted according to the previously described methods [42, 43]. The affinity was evaluated on the ability of the compounds (1 μM) to displace radioligands from sites of their specific binding to the receptors. For the most active compounds IC_{50} values (concentration, when tested compound inhibits the receptor — radioligand specific binding by 50 %) were determined.

A total of eight concentrations within the range of 0.1 nM — 10 μM were used to determine the value of IC_{50}. Each experimental point was obtained in sextets. The data are given as $M \pm m$, where M is mean value of three independent experiments, m is the standard mean error.

Calculation of IC_{50} was conducted through the linearization of S-like curve. The calculation of inhibition constant K_i was determined using the Cheng-Prusoff equation [44]:

$$K_i = \frac{IC_{50}}{1 + \frac{[L]}{K_d}}$$

IC_{50} — concentration of the tested ligand for the displacement of 50 % of the radioligand from the sites of its specific binding to receptor; [L] — the initial radioligand concentration; K_d — radioligand dissociation constant.

Conclusions. Ability of 1-methoxycarbonylmethyl-3-arylamino-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (**6-9**) for selective binding to CNS PBR was shown. A high affinity compound 1-methoxycarbonylmethyl-3-(2'-nitro)phenylamino-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-on, **7** (**MX-1785**, K_i(PBR)=19.1 nM, K_i(CBR)>10000 nM) was revealed in series of investigated substances. Given compound is prospective for the pharmacological research. Among the investigated 1-methoxycarbonylmethyl-3-arylamino-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones it was found the following trend concerning the influence of nitrogen group position in 3-aniline moiety on affinity for PBR:

$o\text{-}NO_2 > p\text{-}NO_2 > m\text{-}NO_2$.

The high affinity and selectivity of compound **MX-1785** designed by QSAR analysis indicate a possibility of further QSAR research for identification of selective and highly active PBR ligands in the series of 1,3-substituted 1,4-benzodiazepin-2-ones.

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Синтез і селективність зв'язування з бенздіазепіновими рецепторами ЦНС 1-метоксикарбонілметил-3-ариламіно-7-бром-5-феніл-1,2-дигідро-3*H*-1,4-бенздіазепін-2-онів

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Резюме. Раніше на підставі результатів QSAR-аналізу ряду похідних 1,4-бенздіазепін-2-ону [1] було показано, що наявність метоксикарбонілметильного фрагменту в положенні 1 і нітрофеніламінного фрагменту в положенні 3 1,4-бенздіазепінового циклу сприяють прояву високого афінітету до периферичних бенздіазепінових рецепторів (ПБДР). Для цілеспрямованого синтезу були запропоновані 3-ариламінопохідні 1-метоксикарбонілметил-7-бром-5-феніл-1,2-дигідро-3*H*-1,4-бенздіазепін-2-ону як перспективні високоафінні ліганди ПБДР. Конденсацією 1-метоксикарбонілметил-7-бром-3-хлор-5-феніл-1,2-дигідро-3*H*-1,4-бенздіазепін-2-ону із заміщеними анілінами синтезовано цільові сполуки. Методом радіолігандного аналізу в експериментах *in vitro* вивчено афінітет синтезованих сполук до бенздіазепінових рецепторів ЦНС периферичного (ПБДР) і центрального (ЦБДР) типів. У ряді досліджених сполук виявлено високоафінний і селективний ліганд ПБДР — 1-метоксикарбонілметил-3-(2'-нітро)феніламіно-7-бром-5-феніл-1,2-дигідро-3*H*-1,4-бенздіазепін-2-он, **7** (**МХ-1785**, K_i(ПБДР)=19,1 нМ, K_i(ЦБДР)>10000 нМ).

Ключові слова: 1,3-заміщені 1,2-дигідро-3*H*-1,4-бенздіазепін-2-они, афінітет, бенздіазепінові рецептори, селективність, QSAR-аналіз.

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