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A COMPARATIVE ANALYSIS OF THE CRYSTAL STRUCTURE OF R,S-RACEMATE AND R-ENANTIOMER OF 7-BROMO-3-(2-METHOXY)ETHOXY-5-PHENYL-1,2-DIHYDRO-3*H*-1,4-BENZODIAZEPINE-2-ONE EXHIBITING A HIGH ANALGESIC ACTIVITY

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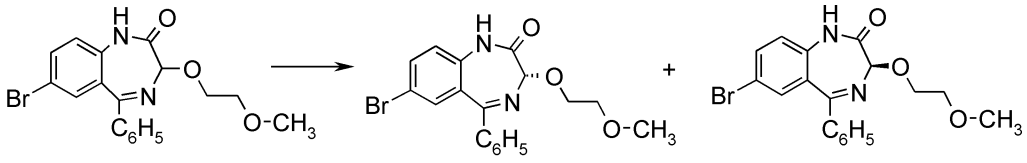
The crystal structure of racemate R,S-7-bromo-3-(2-methoxy)ethoxy-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine-2-one (1) has been compared to the structure of R-enantiomer. It has been determined that crystals of R-enantiomer and R,S-racemate are formed by the similar H-bonded chains. In the crystal of racemate there are two types of chains each built up exclusively from the molecules of the same configuration whereas the crystal of R-enantiomer is formed by identical parallel chains. All the compounds studied have been found to possess a high analgesic activity, which exceeds the activity of the reference medicine.

СРАВНИТЕЛЬНЫЙ АНАЛИЗ КРИСТАЛЛИЧЕСКОЙ СТРУКТУРЫ R,S-РАЦЕМАТА И R-ЭНАНТИОМЕРА 7-БРОМ-5-(2-МЕТОКСИ)ЭТОКСИ-5-ФЕНИЛ-1,2-ДИГИДРО-3H-1,4-БЕНЗДИАЗЕПИН-2-ОНА, ПРОЯВЛЯЮЩИХ ВЫСОКУЮ АНАЛЬГЕТИЧЕСКУЮ АКТИВНОСТЬ
Ю.Симонов, П.Боурош, В.Кравцов, М.Гданец, Е.Семенишина, В.Павловский, Т.Кабанова, Е.Халимова, С.Андронати
Проведено сравнение кристаллической структуры R,S-7-бром-5-(2-метокси)этокси-5-фенил-1,2-дигидро-3H-1,4-бенздиазепин-2-она со структурой R-энантиомера. Установлено, что кристаллы R-энантиомера и R,S-рацемата сформированы цепями, связанными за счет водородных связей. В кристалле рацемата образуются цепи, состоящие из молекул только R- либо S-энантиомеров, которые формируют противоположно направленные спирали, а кристалл R-энантиомера образован идентичными параллельными цепями. Обнаружено, что все исследуемые соединения обладают высокой анальгетической активностью, превосходящей активность препарата сравнения.

ПОРІВНЯЛЬНИЙ АНАЛІЗ КРИСТАЛІЧНОЇ СТРУКТУРИ R,S-РАЦЕМАТУ ТА R-ЕНАНТІОМЕРА 7-БРОМ-5-(2-МЕТОКСИ)ЕТОКСИ-5-ФЕНІЛ-1,2-ДИГІДРО-3H-1,4-БЕНЗДІАЗЕПІН-2-ОНУ, ЯКІ МАЮТЬ ВИСОКУ АНАЛГЕТИЧНУ АКТИВНІСТЬ
Ю.Симонов, П.Боурош, В.Кравцов, М.Гданець, К.Семенішина, В.Павловський, Т.Кабанова, О.Халімова, С.Андронаті
Проведено порівняння кристалічної структури R,S-7-бром-5-(2-метокси)етокси-5-феніл-1,2-дигідро-3H-1,4-бенздіазепін-2-ону зі структурою R-енантіомера. Встановлено, що кристали R-енантіомера і R,S-рацемату сформовані ланцюгами, зв'язаними за рахунок воднев их зв'язків. У кристалі рацемату утворюються ланцюги, що складаються з молекул тільки R- або S-енантіомера, які формують протилежно спрямовані спіралі, а кристал R-енантіомера утворений ідентичними паралельними ланцюгами. Виявлено, що всі досліджені сполуки мають високу аналгетичну активність, яка перевершує активність препарату порівняння.

1,2-Dihydro-3*H*-1,4-benzodiazepine-2-ones have gained wide popularity in medical practice due to their characteristic types of pharmacological activity — high anxiolytic, hypnotic and anticonvulsive actions. Some of representatives of given class are antagonists of cholecystokinin [1, 2] and bradykinin receptors [3, 4]. Such typical representatives of 3-substituted derivatives of 3*H*-1,4-benzodiazepine-2-ones as oxazepam, lorazepam, lormetazepam and temazepam are widely applied for the therapy of CNS disorders, convulsions,



1 **2** **3**

(±) R, S **(+) S** **(-) R**

Scheme

anxiety state, various sleep disturbances [5-10]. Main pharmacological effects of 1,4-benzodiazepine derivatives mediated by GABA-receptor ensemble, strongly depends on stereo center configuration [11-13]. To study the intermolecular mechanism of action of biologically active compounds, crystal structure of compounds may be used as a convenient model. Ligand-receptor interaction is realized owing to week bonds such as hydrogen, π-π and C—H...π ones, which are presented in crystal grid as well, determining supposed routes of intermolecular association.

Herein, we compare the crystal structure of racemate R,S-7-bromo-3-(2-methoxy)ethoxy-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine-2-one (**1**) to the structure of R-enantiomer (**3**), described earlier [14]. The separation of enantiomers has been carried out by semi-preparative HPLC method [14]. Crystals of the compounds **1** and **3** were grown from ethanol (Scheme).

In the crystal, molecules of R-enantiomer **3** related by two-fold screw axis are linked into a chain by N(1)-H · · · O(2) = 2.958(2)A° (N—H = 0.82(2) A°, O · · · H = 2.21(2) A°, N—H · · · O angle 153(2)°) and C(9)—H...O(2) = 3.165(2) A° (C—H = 0.93(2) A°, O · · · H = 2.47(2) A°, N—H · · · O angle 132(2) A°) intermolecular hydrogen bonds (Fig. 1).

Molecules of racemate (**1**) form in crystal (space group $P2_1$) the similar to **3** infinite chains owing to the formation of classical N-H · · · O and weak C-H · · · O hydrogen bonds between amide groups of adjacent molecules related again by two-fold screw axis, N(1)-H · · · O(2) = 2.926(2) A° (N-H = 0.82(2) A°, O · · · H = 2.15(2) A°, N-H · · · O angle 159(2) °) and C(9)-H · · · O(2) = 3.171(2) A° (C-H = 0.93(2) A°, O · · · H = 2.48(2) A°, C-H · · · O angle 131(2)°) (Fig. 2). The structure does not reveal the dimeric associates which may be expected in centrosymmetric crystal of 1,4-benzodiazepine-2-ones derivatives non-substituted at the position 1. The survey of CSD [15] reveals 17 hits for H-bonded dimers among 29 structures of such derivatives (see for examples [16-20]).

Thus, crystals of R-enantiomer and R,S-racemate are built up from the similar H-bonded chains. In the structure of R-enantiomer these chains are parallel. In the crystal of racemate there are two types of chains each built up exclusively from the molecules of the same configuration. The chains with opposite configuration of the molecules alternate in the structure and run in anti-parallel directions, Figs. 3 and 4. The unit cell parameter *b* along two-fold screw axis are comparable in **1** (*b* = 8.1926(2)), and **3** (*b* = 8.2524(3)A°) due to affinity of chains.

The seven membered heterocycle in **1** and **3** have the same pseudo boat conformation. The deviation of atoms N(1), C(2), N(4) and C(5) from the common mean plane is less than 0.012A° in **1**, and 0.001A° in **3**, while atoms C(3), C(10) and C(11) are displaced from this plane in the same direction on 0.781, 0.702 and 0.703A° in **1** and 0.782, 0.664 and 0.693A° in **3**. The bond length and angles as well as torsion angles are very similar in **1** and **3** (Table). Dihedral angle between aromatic cycles equals 41.1 and 37.1° in **1** and **3**, respectively.

Bioassays *in vivo* for testing of analgesic activity of 7-bromo-3-(2-methoxy)ethoxy-5-phenyl-1,2-dihydro-3*H*-1,4-benzodizepine-2-one as racemic mixture, as well as its R- and S-enantiomers, revealed their potency to increase the resistance to pain stimulus. All the tested compounds after intraperitoneal administration exhibited analgesic activity in a bioassay with abdominal irritation by 0.75% solution of acetic acid.

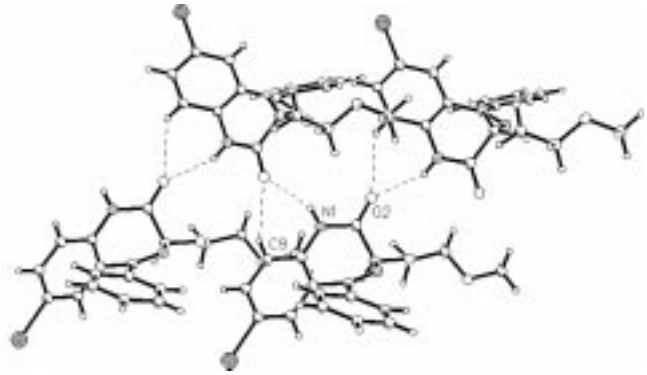


Fig. 1. Chain of R-3-(2-methoxy)ethoxy-7-bromo-5-phenyl-1,2-dihydro-3 H-1,4-benzodiazepine-2-one (**3**).

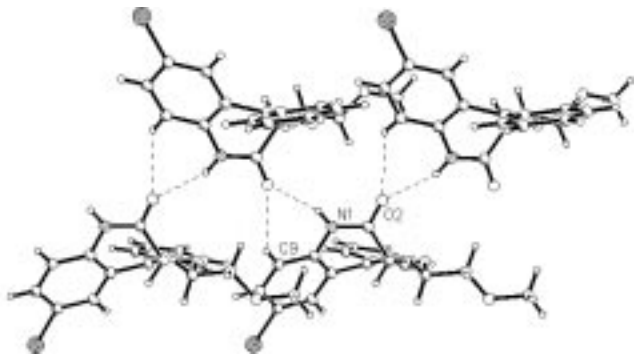


Fig. 2. Chain of R,S-7-bromo-3-(2-methoxy)ethoxy-5-phenyl-1,2-dihydro-3 H-1,4-benzodiazepine-2-one (**1**).

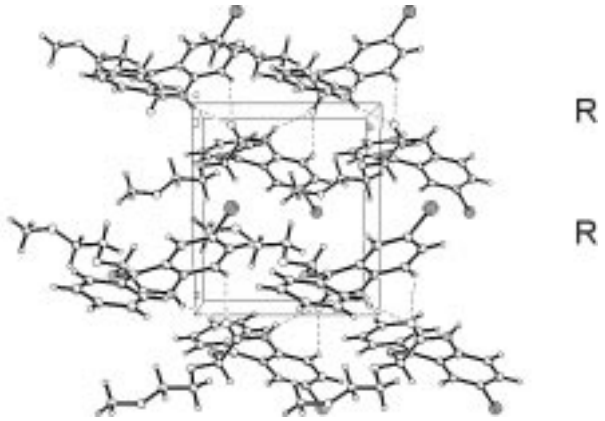


Fig. 3. Packing of chains in the structure of R-3-(2-methoxy)ethoxy-7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine-2-one (**3**).

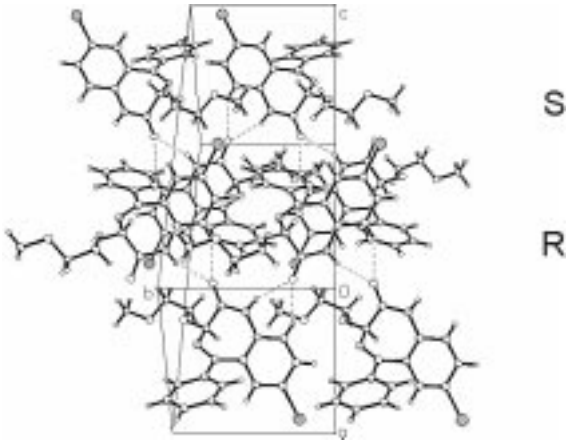


Fig. 4. Packing of chains in the structure R,S-7-bromo-3-(2-methoxy)ethoxy-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine-2-one (**1**).

This standard test was realized in mice with body weight of 22-24 g, namely the protection against acetic acid-induced abdominal constrictions according to [21] in comparison to Diclofenac as reference drug. The results obtained in mentioned test revealed that the studied compounds posses a remarkable analgesic activity exceeding the activity or reference drug. According to the obtained data, 7-bromo-3-(2-methoxy) ethoxy-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine-2-one racemate, R-enantiomer, and S-enantiomer have demonstrated analgesic activity with values ED_{50} of 0.100±0.013; 1.600±0.160; 0.060±0.007 mg/kg, correspondingly (ED_{50} for standard analgesic agent Diclofenac is of 10±0.9 mg/kg).

Crystal structure determination of compound **1**

X-ray diffraction data for **1** (colorless, 0.4×0.3×0.3 mm) was collected at 293K with a KM4 CCD diffractometer using graphite-monochromated Mo- *K*α radiation. Intensity data was corrected for the Lorentz and polarization effects and for absorption. Crystal **1** is monoclinic, space group $P2_1/c$, a = 9.7462(2), b = 8.1926(2), c = 21.5606(6)A°, β = 96.160(2)°, V = 1711.60(7)A°^{3}, Z = 4, ρ_{calc} = 1.511 gcm^{-3}. The structure was solved by direct methods (2755 reflections with F(hkl)>2σ (F), R (int) = 0.0218, final $R1$ = 0.0246, $wR2$ = 0.0563) and was refined by full-matrix least-squares techniques based on F^2 with anisotropic displacement parameters for the non-hydrogen atoms, using the program SHELXL-97 [22]. In structure **1** hydrogen atoms linked with carbon atoms were placed

Table

Bond lengths (A°), valence and torsion angles (deg) in 7-membered heterocycles of compounds **1** and **3**

Bond	d, A°	
	1 racemate	**3** R-enantiomer
O(2)-C(2)	1.217(2)	1.224(2)
O(3)-C(3)	1.402(2)	1.403(2)
N(1)-C(2)	1.356(2)	1.362(3)
N(1)-C(10)	1.417(2)	1.413(2)
N(1)-H(1)	0.82(2)	0.82(2)
N(4)-C(3)	1.439(2)	1.446(3)
N(4)-C(5)	1.284(2)	1.293(3)
C(2)-C(3)	1.531(2)	1.530(3)
C(5)-C(11)	1.487(2)	1.478(3)
C(10)-C(11)	1.399(2)	1.405(3)
Angle	ω, deg	
	1	**3**
O(2)-C(2)-N(1)	122.6(2)	122.2(2)
O(2)-C(2)-C(3)	123.3(2)	123.6(2)
C(2)-N(1)-C(10)	125.7(2)	126.1(2)
N(1)-C(10)-C(11)	121.9(2)	122.2(2)
N(1)-C(2)-C(3)	114.1(2)	114.3(2)
C(2)-N(1)-H(1N1)	118(2)	114(2)
C(10)-N(1)-H(1N1)	116(2)	119(2)
N(4)-C(3)-C(2)	107.0(1)	107.4(1)
N(4)-C(5)-C(11)	123.7(2)	124.4(2)
C(5)-C(11)-C(10)	122.1(2)	122.3(2)
C(5)-N(4)-C(3)	118.2(2)	117.0(2)
O(3)-C(3)-N(4)	107.0(1)	106.7(2)
O(3)-C(3)-C(2)	111.1(2)	111.0(2)
Angle	ω, deg	
	1	**3**
N(1)-C(2)-C(3)-N(4)	-73.7(2)	-73.4(2)
N(1)-C(2)-C(3)-O(3)	169.8(2)	170.3(2)
C(5)-N(4)-C(3)-C(2)	74.9(2)	76.0(2)
C(5)-N(4)-C(3)-O(3)	-165.9(2)	-164.9(2)
O(2)-C(2)-C(3)-N(4)	105.3(2)	106.1(2)
O(2)-C(2)-C(3)-O(3)	-11.2(2)	-10.2(2)
C(3)-N(4)-C(5)-C(11)	-0.8(2)	-2.6(2)
N(4)-C(5)-C(11)-C(10)	-42.8(2)	-42.7(2)
N(1)-C(10)-C(11)-C(5)	-0.7(3)	1.8(3)
C(2)-N(1)-C(10)-C(11)	42.9(3)	40.7(3)
C(10)-N(1)-C(2)-O(2)	179.6(2)	179.1(2)
C(10)-N(1)-C(2)-C(3)	-1.4(3)	-1.3(3)

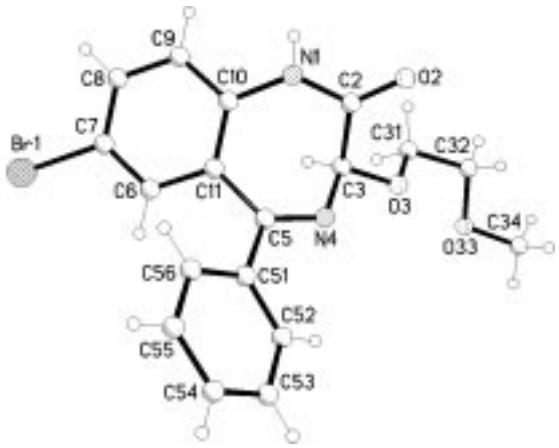


Fig. 5. Molecular structure of **1** with numbering scheme, R-enantiomer is shown.

in the calculated positions with the isotropic displacement parameters equal to $1.2 \times U_{eq}$ (C), the hydrogen atom on N(1) was found from difference Fourier maps and refined isotropically.

Supplementary material

Crystallographic data for 1 have been deposited with the Cambridge Crystallographic Data Center, CCDC 781177. Copies of this information may be obtained from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK(fax: +44-1233-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Summary

In our investigation it was found that crystals of R-enantiomer and R,S-racemate are built up from the similar H-bonded chains. In the structure of R-enantiomer these chains are parallel and formed only by one type of enantiomer. In the crystal of racemate there are two types of chains each built up exclusively from the molecules of the same configuration. The chains with opposite configuration of the molecules alternate in the structure and run in anti-parallel directions. It was found that the studied compounds posses a remarkable analgesic activity, which exceeds the activity of reference drug. Racemate, R-enantiomer, and S-enantiomer have demonstrated analgesic activity with the values ED_{50} of 0.100±0.013; 1.600±0.160; 0.060±0.007 mg/kg, correspondingly. The data of this work may be used for further search of novel analgesic compounds among 1,2-dihydro-3*H*-1,4-benzodiazepine-2-ones.

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