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THERMODYNAMICS OF 3-HYDROXY-7-BROMO-5-(2'-CHLORO) PHENYL-1,2-DIHYDRO-3H-1,4-BENZODIAZEPINE-2-ONES ESTERS COMPLEXATION WITH THE CENTRAL BENZODIAZEPINE RECEPTORS

S.P.Smulsky, N.O.Burenkova, S.A.Andronati, V.I.Pavlovsky, P.G.Polishchuk, K.S.Andronati

A.V.Bogatsky Physico-Chemical Institute of the NAS of Ukraine
65080, Odessa, Lustdorfskaya doroga 86. E-mail: andronati_s@ukr.net

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The complexation of 3-alkylcarbonyloxy-7-bromo-5-(2'-chloro)phenyl-1,2-dihydro-3H-1,4-benzodiazepine-2-ones (R=Me (1), R=t-Bu (2)) with the central benzodiazepine receptors (CBDR) at six temperatures within the range of 0-35°C has been studied by the radioligand analysis method. It has been found that formation of the supramolecular complex of compound 1 with CBDR is endothermic with a rather great and unfavourable change of enthalpy (∆H1° = +32,3 kJ/mol), which is compensated by significant change in entropy (∆S1° = +266,7 J/(mol×K)). On the contrary, the binding of compound 2 to CBDR is exothermic (∆H2° = -20,7 kJ/mol) and with a favourable entropy change (∆S2° = +90,4 J/(mol×K)). The ester carbonyl groups in compounds 1 and 2 are also supposed to form different hydrogen bonds with the receptor.

ТЕРМОДИНАМІКА КОМПЛЕКСОУТВОРЕННЯ ЕСТЕРІВ 3-ГІДРОКСИ-7-БРОМ-5-(2'-ХЛОР)ФЕНІЛ-1,2-ДИГІДРО-3Н-1,4-БЕНЗОДІАЗЕПІН-2-ОНІВ З ЦЕНТРАЛЬНИМИ БЕНЗДІАЗЕПІНОВИМИ РЕЦЕПТОРАМИ

С.П.Смульський, Н.О.Буренкова, С.А.Андронаті, В.І.Павловський, П.Г.Поліщук, К.С.Андронаті

Методом радіолігандного аналізу вивчено комплексоутворення 3-алкілкарбонілокси-7-бром-5-(2'-хлор)феніл-1,2-дигідро-3Н-1,4-бенздіазепін-2-онів (R=алкіл R=Me (1), R=t-Bu (2)) з центральними бенздіазепіновими рецепторами (ЦБДР) при шести температурах у інтервалі 0-35°С. Встановлено, що утворення супрамолекулярного комплексу сполуки 1 з ЦБДР ендотермічне з доволі великою та несприятливою зміною ентальпії (∆H1°=32,3 кДж/моль), яка компенсується значною зміною ентропії (∆S1°=266,7 Дж/(моль×К)). Зв'язування сполуки 2 з ЦБДР екзотермічне (∆H2°=-20,7 кДж/моль) зі сприятливою зміною ентропії (∆S2°=90,4 Дж/(моль×К)). Передбачається також, що естерні карбонільні групи у сполуках 1 і 2 утворюють різні водневі зв'язки з рецептором.

ТЕРМОДИНАМИКА КОМПЛЕКСООБРАЗОВАНИЯ ЭФИРОВ 3-ГИДРОКСИ-7-БРОМ-5-(2'-ХЛОР) ФЕНИЛ-1,2-ДИГИДРО-3Н-1,4-БЕНЗОДИАЗЕПИН-2-ОНОВ С ЦЕНТРАЛЬНЫМИ БЕНЗДИАЗЕПИНОВЫМИ РЕЦЕПТОРАМИ

С.П.Смульский, Н.А.Буренкова, С.А.Андронати, В.И.Павловский, П.Г.Полищук, К.С.Андронати

Методом радиолигандного анализа изучено комплексообразование 3-алкилкарбонилокси-7-бром-5-(2'-хлор)фенил-1,2-дигидро-3Н-1,4-бенздиазепин-2-онов R=Me (1), R=t-Bu (2)) с центральными бенздиазепиновыми рецепторами (ЦБДР) при шести температурах в интервале 0-35°С. Обнаружено, что образование супрамолекулярного комплекса соединения 1 с ЦБДР эндотермическое с довольно большим и неблагоприятным изменением энтальпии (∆H1°=32,3 кДж/моль), которое компенсировано значительным изменением энтропии (∆S1°=266,7 Дж/(моль×К)). Связывание соединения 2 с ЦБДР экзотермическое (∆H2°=-20,7 кДж/моль) и с благоприятным изменением энтропии (∆S2°=90,4 Дж/(моль×К)). Предполагается также, что сложноэфирные карбонильные группы в соединениях 1 и 2 образуют различные водородные связи с рецептором.

Analysis of equilibrium formation of supramolecular complexes of drugs with membrane receptors within range from 0 to 35°C temperature led to certain generalizations. For the majority of membrane receptors, it was found ability for thermodynamic discrimination of ligands as agonists and antagonists. For 184 independent experiments and 10 receptor systems the phenomenon of enthalpy-entropy compensation was described [1]. The majority of membrane receptors form supramolecular complexes with drugs and endogenous

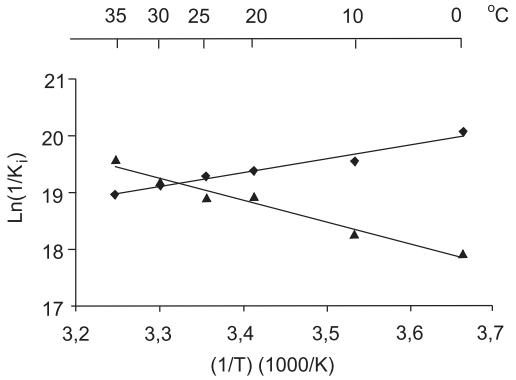


Fig. 1. The van't Hoff plots showing the affect of temperature on the association constants ($1/K_i$) of compounds **1**, **2** in the experiment on the displacement of [^{3}H] flumazenil. Values $1/K_i$ are mean of four independent determinations, each performed in triplicate. Linear interpolation over the points connected by the continuous line (0≤t≤35 C) gives correlation coefficients, r, in the range of 0.98-0.99.

ligands (neurotransmitters) with the temperature independent enthalpies (ΔH) and entropies (ΔS) [2].

Information obtained on the basis of thermodynamic analysis of ligand receptors binding is unique and is not available if equilibrium constants are measured at one temperature. Cautious interpretation of thermodynamic analysis results allows concluding on the mechanism of complexation and the nature of intermolecular interactions between a ligand and a receptor in supramolecular complexes, as well as on the causes of intrinsic activity [2, 3].

Analysis of the binding in dependence of temperature allows determining free energies and, consequently, the equilibrium constants at different temperatures within a given range (typically from 0 to 35°C), including the constant at body temperature, what is the closest approximation to the conditions of pharmacological tests in experimental animals.

The van't Hoff equation is used in the thermodynamic analysis

$$\ln K_A = -\Delta H°/RT + \Delta S°/R,$$

where R – gas constant; T – temperature in Kelvin; K_A – equilibrium association constant of ligand-receptor complex; ΔH° and ΔS° are standard enthalpy and entropy of complexation, respectively. The temperature of 298,15 K (25°C) and atmospheric pressure are the standard conditions as a rule.

$GABA_A$ receptor-ionophoric complex belongs to the superfamily of ionotropic receptors and provides the Cl^- and HCO_3^- ion transport into the cell. In addition to the GABA binding sites, $GABA_A$ ionophoric complex includes binding sites of benzodiazepines, picrotoksinin, β-carbolines, barbiturates, and other ligands [4]. 1,4-Benzodiazepine derivatives are the most common and known ligands of the central benzodiazepine receptors and are widely used as medicine neurotropic drugs [4, 5]. Thermodynamic analysis of binding of drugs of benzodiazepine series (diazepam, clonazepam, alprazolam and others) with CBDR is described in [6-13], and results of studies [6-12], are summarized in the review [3]. The van't Hoff plots of the $\ln(1/K_i)$ versus the $(1/T)\times(1000/K)$ for all benzodiazepines described in the literature are linear within the temperature range from 0 to 35°C, with the exception of certain cases, when broken lines of plots for clonazepam at 21°C [8] and flunitrazepam at 10°C were observed [9]. All 1,4 benzodiazepines described in the literature [6-13], with the exception for triazolam and dezmethylmedazepam, form exothermic complexes with CBDR. It is known from the literature that changes in the benzodiazepine chemical structure ambiguously affect the free energy (ΔH° and ΔS°) of the complexation with CBDR. For example, molecules of alprazolam and triazolam differ by a chlorine atom in 2 position of 5-phenyl radical, while the thermodynamic profiles of their interaction with CBDR are diametrically opposed. Alprazolam, containing no chlorine atom in the 5-phenyl radical, forms an exothermic complex with CBDR, and triazolam, which contains a chlorine atom in this position, forms an endothermic complex with the CBDR [10]. At the same time, flunitrazenpam, diazepam and nordiazepam not only have close values of free binding energies at 37°C (ΔG°= -48±6, -45±5, -41±4 kJ/mol), but also relatively close values of enthalpy (ΔH°=-53±3, -41±2, -44±7 kJ/mol) and entropy (TΔS°=-5±7, +5±5, -3±8 kJ/mol) members of free energies [9].

Currently, there are no systematic data of studies on the relationship between the chemical structure of the 1,4-benzodiazepines, the degree of activation of $GABA_A$ receptor complex and the structures of free energies (ΔH°, ΔS°) of their complexation with CBDR. There are no works on the thermodynamic analysis of complexation of substituted in the third position 1,4-benzodiazepines with CBDR, despite the fact that this series of derivatives is very promising concerning the search for new neurotrophic drugs. There are well known drugs among the representatives of this series of compounds: lorazepam, oxazepam, temazepam, and others. For a long period of time we carry out research in molecular design, synthesis and study of relationship of structure – properties, mode of action and pharmacology of 1,4-benzodiazepine-2-one derivatives [14-19]. Affinity and selectivity for central and peripheral benzodiazepine CNS receptors at the 0°C was examined for many compounds by radioligand analysis [17, 20-26]. However, information obtained at the same temperature is insufficient and doesn't allow making a decision about driving forces of complexation and nature of interactions with CBDR of the investigated 1,4-benzodiazepines. Thereby (and in continuation of our ongoing research), it was interesting to investigate thermodynamics of complexation of 3-substituted 1,4-benzodiazepin-2-ones (com-

Table

Equilibrium inhibition constants (K_i), dissociation constants (K_D) at various temperatures, standard enthalpies ($\Delta H°$) and entropies ($\Delta S°$) for complexation of the compounds 1-4 and [^{3}H]flumazenil with CBDR

Compounds	K_i±SEM [nM]						ΔH°±SEM (kJ/mol)	ΔS°±SEM (J/(mol×K))
	0°C	10°C	20°C	25°C	30°C	35°C		
1	16,50 (1,2)	11,80 (1,1)	6,05 (0,4)	6,21 (0,3)	4,56 (0,2)	3,13 (0,1)	+32,3 (3,0)	+266,7 (10)
2	1,91 (0,04)	3,19 (0,15)	3,91 (0,1)	4,19 (0,3)	5,00 (0,2)	5,83 (0,4)	-20,7 (2)	+90,4 (6)
3*							+35,1	+305,0
4*							+23,4	+191,6
[^{3}H]Flu-mazenil**	K_D±SEM [nM]							
	1,23 (0,05)	2,3 (0,1)	3,2 (0,1)	4,00 (0,2)	4,90 (0,2)	6,30 (0,5)		

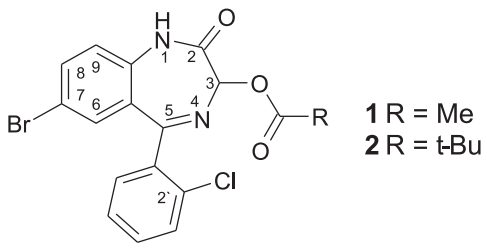
* Data taken from ref. [10]; ** Data taken from ref. [33]

pounds 1 and 2, Fig. 1, Scheme 1) with CBDR. The compounds for which the thermodynamics of binding to the $GABA_A$ receptor complex have been studied in this paper have highly anxiolytic, anticonvulsant and sedative activity and high affinity for CBDR [24]. In this paper, compounds 1 and 2 as research objects were used.

Results and Discussion

The table contains inhibition constants (K_i) for the compounds **1** and **2** at six temperatures 0, 10, 20, 25, 30 and 35°C, as well as, calculated on the base of van't Hoff plots standard enthalpies ($\Delta H°$) and entropies ($\Delta S°$) for equilibrium displacement of [^{3}H]flumazenil from specific binding sites of CBDR. The table shows also dissociation constants for [^{3}H] flumazenil complex with CBDR, which were used by us for the calculation of K_i for compounds **1** and **2** by the Cheng-Prusoff equation. The van't Hoff plots for compounds **1** and **2**, in the studied temperature range, were strictly linear (Fig. 1).

The binding of compound 1 to the CBDR of the rats cerebral cortex was accompanied by heat absorption ($\Delta H°_1$ = +32,3 kJ/mol) and relatively large increase in entropy ($\Delta S°_1$ = +266,7 J/(mol×K)). While the compound **2** complexation with CBDR was exothermic ($\Delta H°_2$ = -20,7 kJ/mol and $\Delta S°_2$ = +90,4 J/(mol×K)),



1 R = Me
2 R = t-Bu

Scheme 1

and was accompanied with temperature increase which was two-fold lesser. Thus, complexation of compounds 1 and 2 with CBDR are driven by different forces. Thus, the compound 1 complexation with the receptor is exclusively driven by entropy, while the compound 2 binding to the receptor is driven by both enthalpy and entropy.

A well-known generalized model of the receptor complex with benzodiazepines of Huang Q. et al. [27] suggests the following features of the molecular interaction of 1,4-benzodiazepine-2-ones with CBDR. Carbonyl oxygen of the amide group and nitrogen atom N4 of diazepine ring form hydrogen bonds with the receptor site. Benzene ring in position 5 and the ring condensed with 1,4-diazepine cycle, as well as substituents in position 7, interact with the hydrophobic centers of the receptor site. Taking into account the given model, and keeping in mind the acceptor properties of the ester carbonyl groups (the substituents in position 3 of compounds **1** and **2**), one can assume the formation of different hydrogen bonds with donor regions of CBDR sites (Fig. 2), weak hydrogen bond with the receptor for the compound **1**, and stronger one in the case of compound **2**. It is

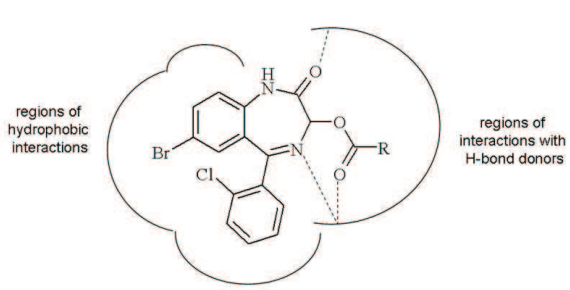


Fig. 2. Hypothetical scheme of interactions of compounds **1** and **2** with hydrophobic sites and donor sites of hydrogen bonds (indicated by dotted lines) of CBDR site (based on Huang Q model) [30].

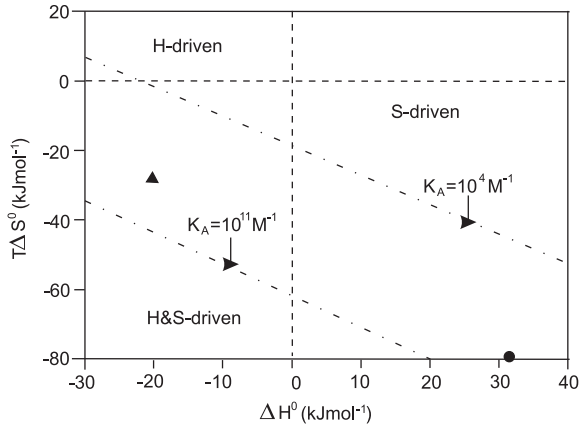
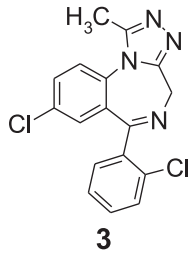


Fig. 3. Represent the thermodynamic data of the interaction of compound 1 (●) and 2 (▲) with CBDR in the coordinated -TDS° versus ΔH° (were $K_A=10^4 M^{-1}$ and $K_A=10^{11} M^{-1}$ are lower and upper limits of values of association constants of the drugs, respectively, with bioreceptors, see ref. 1).

possible that formation of the hydrogen bonds can occur either competing for the donor centers of the receptor with nitrogen atoms N4 or amide carbonyl groups of the 1,4-benzodiazepine ring or by the formation of new additional hydrogen bonds with donor sites of CBDR. In any case, thermodynamic profiles of these compounds complexation with the receptor give indirect evidence in favour of the offered assumption (Table and Fig. 3). It is generally accepted, that hydrogen bonds formation is accompanied by decrease of enthalpy and entropy. Therefore, in whole energetic balance (change in free energy), strong hydrogen bonds may exceed energy of non-specific (hydrophobic) interactions, and that often leads to decrease of the process enthalpy and minor positive changes in entropy, and in some cases, to its decrease. Weak hydrogen bonds, which are accompanied with insignificant decrease of enthalpy, in many cases, aren't able to exceed positive change of enthalpy of non-specific hydrophobic interaction of ligand with its receptor. As a result, change of complexation enthalpy may turn out to be a positive one. However, it is arise of question how to explain the fact that hydrogen bond in the case of compound 1 (R = Me) is weaker then hydrogen bond of compound 2 (R = t-Bu) when they interact with their receptors.

Unfortunately, the involvement of a methyl group (compound **1**) and *tert*-butyl group (compound **2**) in interaction with CBDR can not be described within the model of Huang Q. et al. [27], because substituted in the 3 position of 1,4-benzodiazepines are not taken into account at creation of this model.



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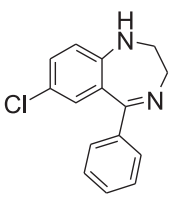

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Scheme 2

According to the results of our long-term research [28], pharmacological activity of 3-alkyl-substituted (alkyl = Me, Et, *i*-Pr and *t*-Bu) 1,4-benzodiazepines is inversely related to lipophilicity. Taking into account these indirect facts and thermodynamic analysis conducted by us on the binding of the compounds **1** and **2** with CBDR, it could be assumed that the *t*-Bu radical of the compound **2** does not enter into hydrophobic interactions with the receptor. The thermodynamic profiles of the interaction of compounds **1** and **2** with benzodiazepine receptor ($\Delta H°_1$ = +32,3 kJ/mol, $\Delta S°_1$ = +266,7 J/(mol×K), $\Delta H°_2$ = -20,7 kJ/mol, $\Delta S°_2$ = +90,4 J/(mol×K)) prove this fact. It is seen in the coordinates -TΔS° versus ΔH° (Fig. 3) that the driving forces for the complexation of compound **2** with CBDR are changes in enthalpy (ΔH°) and entropy (ΔS°). Compound **1**, in contrast to compound **2**, binds to the receptor due to the entropy change only.

There are at least two examples in the literature where the driving force of benzodiazepine complexation with CBDR is the change in entropy. These compounds are triazolam (**3**) and dezmethylmedazepam (**4**), the thermodynamic analysis of the binding of which was carried out under conditions similar to conditions of our experiments (on the twice washed membranes in the presence of 0,2 M NaCl in the incubation medium) [10]. Thus, the compounds **1**, **3** and **4** form a ligand group, which binding with CBDR differs significantly from those described in the literature and benzodiazepines studied by us (compound **2**) (Scheme 2).

Thermodynamic analysis of complexation of compounds **1**, **3** and **4** with CBDR has demonstrated that:

1) compounds **1**, **3** and **4** bind to CBDR with the heat absorption and a large favorable change in entropy (see Table). This means that their interaction with the receptor is mainly caused by the rearrangement of solvent molecules near the receptor site and near the interacting ligand molecules. It is generally accepted that such complexation thermodynamic profile mainly is a result of hydrophobic ligand-receptor interactions [29]:

2) unlike the compound **1**, the compound **2** (just as benzodiazepines described in literature [6-13], with the exception of the compounds **3** and **4**) forms exotermic complex with CBDR.

It is known not only numerous multi-center relationships and interactions, but also the reorganization of a solvent contribute to the free energy of ligand-protein (receptor) complexation. It is considered that the only theoretical calculation is able to differentiate these contributions and to correlate them with structural fragments of molecules of ligands and receptors [30, 31].Our results on the thermodynamics of binding of the esters (compounds **1** and **2**) to CBDR, as well as literature data, for example [10], on

the binding of alprazolam, triazolam and dezmethylmedazepam to benzodiazepine receptors demonstrate that the thermodynamics of the formation of supramolecular ligand-CBDR complexes can be extremely sensitive to changes in the ligand chemical structure.

Changes of standard entropies of complexation of compounds **1**, **3**, **4** allow supposing that the rearrangement of solvent molecules is the main reason for the change of the free energies of complexation of these compounds with CBDR and it demonstrates that the thermodynamics of the formation of supramolecular ligand-CBDR complexes can be extremely sensitive to changes in the ligand chemical structure. There is no yet satisfactory explanation of the fact concerning the dominant participation of nonspecific interactions of the studied compound **1** as compared to compound **2**, at the formation of complex with benzodiazepine receptors. These differences are difficult to explain without pharmacophore-receptor models for 3-substituted 1,4-benzodiazepines. We hope that further investigation of thermodynamics of complexation in the series of 3-substituted 1,4-benzodiazepines with CBDR will contribute to the clarification of this interesting fact and may be used in the further development of models of the complex 1,4-benzodiazepin – CBDR.

Experimental part

Compounds **1-2** were synthesized using literature procedures [32].

***In vitro* receptor binding assays. [^{3}H]Flumazenil binding**

Adult male Wistar rats with a body weight of 180-220 g were maintained under an artificial 12-h-light/dark cycle (light on 08.00 to 20.00 h). Food and water were freely available until the time of the experiment. Animal care and handling throughout the experimental procedures were in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). The experimental protocols were approved by the Animal Ethical Committee of the University of Cagliari. Affinity of compounds **1, 2** for CBDR of rat brain was determined by modified method and values of IC_{50} were evaluated.

Animals were anesthetized and decapitated, the cerebral cortex was quickly extracted and homogenized in 30 ml of 0,05 M ice-cold citrate buffer (pH 7,1 at 4°C) with a Dounce homogenizer. The homogenate was centrifuged at 20 000 g for 15 min at 4°C. The pellet was resuspended in initial volume of the same buffer and centrifuged again under the same conditions. The process of homogenization and centrifugation was repeated for 2 times. Supernatant was decanted, the residue was resuspended in 0,05 M of ice-cold incubation citrate buffer containing 200 mM NaCl to obtain the suspension with wet membrane concentration of 50 mg/ml and adjusted for each temperature.

Thermodynamic analysis of the formation of complexes of compounds **1**, **2** with CBDR was carried out at temperatures of 0, 10, 20, 25, 30 and 35°C. Determination of equilibrium binding constants ($K_A = 1/K_i$) for the binding of compounds **1**, **2** to membrane complex of the rats cerebral cortex was carried out in 0,5 cm^3 of tris-citrate incubation buffer pH 7,1, adjusted for each temperature. The incubation time ranged from 75 min at 0°C to 20 min at 35°C [33]. Nonspecific binding (which was no more than 10%) of the radioligand [^{3}H] flumazenil ([^{3}H]Ro15-1788) was determined in the presence of 1×10^{-6}mol/dm^3 cold flumazenil. To determine the semi-inhibitory concentrations (IC_{50}) for the compounds **1**, **2** eight concentrations were used for each compound, ranging from $0{,}1\times10^{-9}$ to $1\times10^{-6}\times$mol/dm^3. Inhibition constant K_i was calculated using the Cheng-Prusoff formula ($K_i = IC_{50}/(1+[L]/K_D)$) [34], where IC_{50} – concentration of test ligand at which is observed 50% radioligand displacement from specific binding sites of the receptor, [L] – total concentration of radioligand, K_D – dissociation constant of the radioligand complex with the CBDR for each of the experimental temperatures, taken from [33]. The standard free energies ($\Delta G°$) of compounds **1**, **2** complexation were calculated by the equation of van't Hoff ($\Delta G° = -RT\ln(1/K_i)$). The standard enthalpy ($\Delta H°$) and entropy ($\Delta S°$) of complexation were obtained by regression analysis from the slope of the van't Hoff plots ($-\Delta H°/RT$) and the intersection plots ($-\Delta S°/R$) with the ordinate axis, where T = 298,15 K, R = 8,314 J/(mol×K).

Conclusion

1. Enthalpy and entropy of the compounds 1 and 2 complaxetion are more sensitive to changes in their chemical structure, than free energy.

2. Driving forces of complexation of the compounds 1 and 2 with CBDR are different. The compound 1 binds to receptor solely due to the changes in both enthalpy and entropy.

3. It is suggested that the compounds 1 and 2 form different in respect to energy hydrogen bonds with the receptor.

Acknowledgments

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