ISSN 1070-3632, Russian Journal of General Chemistry, 2008, Vol. 78, No. 5, pp. 949–953. © Pleiades Publishing, Ltd., 2008.
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# Preparation and Biological Properties of Inclusion Compounds of Calix[4]arene and 1,4-Benzodiazepinone Derivatives

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Received October 8, 2007

**Abstract**—The possibility of enhancing the oral bioavailability of certain 1,4-benzodiazepinones by using them as complexes with a series of calix[4]arene derivatives was examined. All the inclusion compounds prepared exhibit anticonvulsant activity by antagonism with Corazol spasmodic agent. Complexes with 25,27-bis[(hydrazinocarbonyl)methoxy]-26,28-dihydroxy-*p*-*tert*-butylcalix[4]arene exhibit higher pharmacological activity compared to the starting 7-bromo-5-(*o*-chloro)phenyl- and 1-hydrazinocarbonylmethyl-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones.

**DOI:** 10.1134/S1070363208050204

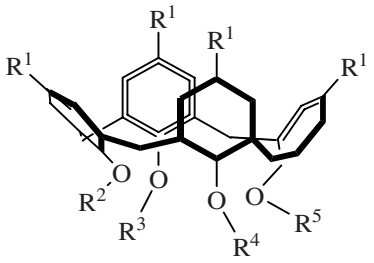
Benzodiazepine derivatives are still the most extensively used drugs of the anxiolytic group. The majority of anxiolytics of the benzodiazepine series are derivatives of 1,4-benzodiazepin-2-one [1, 2]. A promising way to enhance the bioavailability of many drugs, in particular, of benzodiazepinones, is their complexation with such natural complexones as β-cyclodextrin [3] and amylose.

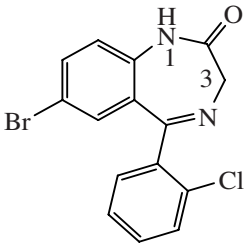
In view of the capability of calixarenes for transfer of biologically active substances through cell membranes [4, 5], it was interesting to prepare complexes of 7-bromo-5-(*o*-chloro)phenyl-1,2-dihydro-3*H*-1,3-benzodiazepin-2-one **I** and 1-hydrazinocarbonylmethyl-7-bromo-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one **II** with derivatives of *p*-*tert*-butylcalix[4]arene **III** and to study their biological properties at oral introduction.

As the presence of lipophilic fragments in the host molecule should enhance the capability of the forming complexes to penetrate through the lipid shell and the presence of donor atoms favors binding of a guest molecule through hydrogen bonds, we chose calixarenes derived from *p*-*tert*-butylcalix[4]arene **III** and occurring in the cone conformation: 25,27-bis[(methoxycarbonyl)methoxy]-26,28-dihydroxy (**IV**), 25,27-bis[(hydrazinocarbonyl)methoxy]-26,28-dihydroxy (**V**), 25,27-diheptyloxy-26,28-dihydroxy (**VI**), and 25,27-diheptyloxy-26,28-bis[(methoxycarbonyl)meth-oxy] (**VII**) derivatives. For comparison, we also included a macrocycle containing no *tert*-butyl groups in the *p*-position of the phenolic fragment but substituted at the lower rim with propyl groups and acetohydrazide fragment, 25,26,27-tripropoxy-28-[(hydrazinocarbonyl)methoxy]calix[4]arene **VIII**.

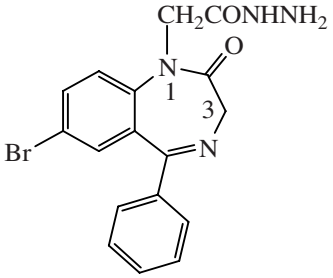
When evaluating the pharmacological activity of the complexes obtained, we determined the minimal effective doses of Corazol spasmodic agent that induce clonicotonic convulsions and tonic extension, DCTC and DTE, in experimental animals (mice weighing 20 ± 2 g). As control we used a group of intact animals and the starting benzodiazepin-2-ones **I** and **II**. The use of the intravenous infusion of Corazol allowed quantitative estimation of the concentration of the anticonvulsants in the biophase of their action: The recorded effects are reversible and concentration-dependent [6, 7] (Tables 1, 2).

An NMR, UV, and IR study of the complex of calixarene diether **IV** with benzodiazepinone **I** allows a conclusion that the formation of the inclusion compound involves interaction of the acetic acid ester fragments of the calixarene molecule with the diazepinone ring fragment of the gidazepam molecule,





**I**



**II**

**IV**: $R^1$ = *t*-Bu, $R^2 = R^5 = CH_2COOCH_3$, $R^3 = R^4$ = H; **V**: $R^1$ = *t*-Bu, $R^2 = R^5 = CH_2CONHNH_2$, $R^3 = R^4$ = H; VI: $R^1$ = *t*-Bu, $R^2 = R^5 = C_7H_{15}$, $R^3 = R^4$ = H; **VII**: $R^1$ = *t*-Bu, $R^2 = R^5 = C_7H_{15}$, $R^3 = R^4 = CH_2COOCH_3$; **VIII**: $R^1$ = H, $R^2 = R^3 = R^4 = C_3H_7$, $R^5 = CH_2COOCH_3$.

bearing the hydrazide substituent. This complex, in contrast to the adduct of calixarene **IV** with benzodiazepinone **I**, enhanced the oral bioavailability of **II**. On the other hand, calixarene V containing two acetohydrazide fragments forms complexes with molecules of both benzodiazepinones owing to intermolecular hydrogen bonding between the hydrazide groups of the macroring and heteroatoms of the diazepinone core. The protons of the $NH_2$ group of the hydrazide moiety of **II** in the $^1$H NMR spectrum of the free benzodiazepinone give rise to a pair of doublets, which is due to nonequivalence of these protons, caused by hindered rotation around the N–N bond owing to intramolecular hydrogen bonding of these protons with the carbonyl oxygen atom of the ring [1]. In the $^1$H NMR spectra of the complexes, the amino group protons are manifested as singlets shifted downfield (3.87 and 4.63 ppm in the spectrum of the "free" compound and >8 ppm in the spectrum of the complex). The use of these complexes at oral administration allows the bioavailability of the benzodiazepinones in question to be considerably enhanced.

**Table 1.** Anticonvulsant effect of complexes of **I** by antagonism with Corazol 1 and 24 h after oral introduction

| Compound | 1 h | | 24 h | |
|---|---|---|---|---|
| | DCTC, % | DTE, % | DCTC, % | DTE, % |
| Control (intact animals) | 100 | 100 | 100 | 100 |
| **I** | 289.7±32.1 | 278.4±28.2 | 295±69.3 | 263±53.8 |
| **I + IV** | 228.5±22.5 | 235.2±22.2 | 254.6±49.5 | 230.3±34 |
| **I + V** | 324±54.2 | 325.2±69.1 | 264.8±20.8 | 253.5±19.9 |
| **I + VI** | 355.6±37.5 | 333.6±37.2 | 255.8±17.3 | 242.6±15.4 |
| **I + VII** | 219.5±23.4 | 213.6±18.2 | 173.7±11.9 | 169.9±11.9 |
| **I + VIII** | 312.8±34.4 | 286.6±33.2 | 217.2±15.6 | 217.4±13.8 |

**Table 2.** Anticonvulsant effect of complexes of **II** by antagonism with Corazol 1 and 24 h after oral introduction

| Соединение | 1 h | | 24 h | |
|---|---|---|---|---|
| | DCTC, % | DTE, % | DCTC, % | DTE, % |
| Control (intact animals) | 100 | 100 | 100 | 100 |
| **II** | 198.3±15.5 | 191±12.6 | 228.2±39.4 | 205.2±23.5 |
| **II + IV** | 244.0±30.5 | 258.1±39 | 212.9±38 | 184.3±22.8 |
| **II + V** | 243.6±11.8 | 233.8±8.8 | 183.7±23.3 | 178.6±19.5 |
| **II + VI** | 169.7±12.1 | 157.4±9 | 196.7±19.5 | 199.3±20.4 |
| **II + VII** | 128.1±14.6 | 122.7±14.3 | 161.7±15 | 159.3±16.1 |
| **II + VIII** | 202.2±9.8 | 197.9±7 | 235.7±43.7 | 227.9±41.7 |

Comparison of the DCTC and DTE values for the complexes of calixarene **VI** with benzodiazepinones **I** and **II**, and also of data on their stability in digestive juices suggests that the interaction of **VI** with the guest molecule of **I** leads to the formation of a stable complex, mainly due to interaction of the aromatic moiety of the benzodiazepinone and lipophilic groups of the calixarene. The compound administrated as the complex becomes more bioavailable (Table 1). In the interaction of calixarene **VI** with compound **II**, formation of intermolecular hydrogen bonds makes a large contribution to the stability of the complex, as indicated by the downfield shift of the signals of hydrazide protons of gidazepam and OH groups of calixarene, manifestation of the methylene protons of the substituent in the benzodiazepine ring as doublets, and changes in the coupling constants of protons at the $C^3$ atom of the diazepinone core. However, this complex is broken down in the acidic medium of digestive juices, which eliminates its advantages (the DCTC and DTE values remain high 1 h after introduction but decrease in 24 h, which is also characteristic of free compound **II**).

Introduction into the calixarene molecule of two heptyl groups and two ester fragments (compound **VII**) enhances the strength of binding of **II** in the complex owing to interaction both with the hydrocarbon substituents and with the groups containing donor centers. As a result, the lifetime of the complex increases, and the pharmacological response time increases from 1 h, which is typical of the free benzodiazepinone and rapidly degrading complexes, to 24 h after the introduction (Table 2).

Close DCTC values obtained for the *tert*-butyl-substituted and de-*tert*-butylated analogs are difficult to interpret because of the lack of the experimental data, but certain conclusions can be made even now. The complexation of calixarenes with a molecule of compound **I** in which the hydrogen bonding sites are few in number depends on whether the host molecule contains fragments capable of interaction with the aromatic moiety of the benzodiazepinone. The properties of complexes with **II** are determined by the presence in the host molecule of sites capable of hydrogen bonding, but the number and nature of such substituents in the calixarene molecule should not result in too strong host–guest bonding at which the breakdown of the complex will become hindered.

## EXPERIMENTAL

The $^1$H NMR spectra of the complexes were recorded on a Varian VXR-300 NMR spectrometer (300 MHz) from ~10% solutions in $CDCl_3$, internal reference TMS. The IR spectra were taken on a Specord IR-75 spectrophotometer from $CHCl_3$ solutions. The UV spectra were measured on Perkin–Elmer Lambda 9UV/VIS/NIR spectrophotometer from $CH_3CN$ solutions. The TLC analysis was performed on Silufol UV-254 plates.

**Complexes of 1,4-benzodiazepin-2-one derivatives with calixarenes.** A mixture of 0.5 mmol of appropriate calixarene derivatives and 0.5 mmol of benzoidiazepinone **I** or **II** was ground in a mortar with intermittent addition of 2–4 ml of ethanol. The precipitates obtained were dried and recrystallized from aqueous alcohol. Yield 78–89%.

**Evaluation of anticonvulsant activity.** The complexes were administrated orally to experimental animals in a concentration corresponding to 1 mg/kg of **I** and **II** as Tween emulsions. After 1- and 24-h intervals, intravenous infusion of Corazol (1% solution) was made. The minimal effective doses of the spasmodic agent, inducing clonicotonic convulsions and tonic extension, were determined by the formula $D = (V/m) \times 100$, where $D$ is the Corazol dose inducing clonicotonic convulsions (tonic extension); $V$, volume of Corazol solution ($cm^3$); and $m$, animal weight (g).

**25,27-Bis[(methoxycarbonyl)methoxy]-26,28-dihydroxy-p-tert-butylcalix[4]arene IV**. $^1$H NMR spectrum, δ, ppm: 0.97 s [18H, $(CH_3)_3C$], 1.25 s [18H, $(CH_3)_3C$], 3.32 d (4H, $ArCH_2Ar$, $J$ 13.37 Hz), 3.4 s (6H, $OCH_3$), 4.43 d (4H, $ArCH_2Ar$), 4.73 s (4H, $OCH_2$), 5.12 s (2H, OH), 6.8 s (4H, ArH), 7.01 s (4H, ArH).

**Complex of calixarene IV with benzodiazepinone II**. $^1$H NMR spectrum, δ, ppm: 1.13 s [18H, $(CH_3)_3C$], 1.21 s [18H, $(CH_3)_3C$], 3.35 d (4H, $ArCH_2Ar$, $J$ 13.08 Hz), 3.83 d (1H, $CH_{2benzod}$, $J$ 10.5 Hz), 3.87 s (6H, $OCH_3$), 4.43 d (4H, $ArCH_2Ar$), 4.58 d (1H, $CH_{2benzod}$, $J$ 15.56 Hz), 4.74 d (1H, $CH_{2benzod}$), 5.02 s (4H, $OCH_2$), 5.05 d (1H, $CH_{2benzod}$, $J$ 15.56 Hz), 7.03 s (4H, ArH), 7.04 s (4H, ArH), 7.42–7.62 m, 7.66 d, 7.7 d (7H, $ArH_{benzod}$), 7.75 s (2H, OH), 9.1 br.s (2H, $NH_2$).

**25,27-Bis[(hydrazinocarbonyl)methoxy]-26,28-dihydroxy-*p-tert*-butylcalix[4]arene V**. $^1$H NMR spectrum, δ, ppm: 1.05 s [18H, $(CH_3)_3C$], 1.27 s [18H,

$(CH_3)_3C$], 3.44 d (4H, $ArCH_2Ar$, *J* 13.39 Hz), 4.12 d (4H, $ArCH_2Ar$, *J* 13.07 Hz), 4.64 s (4H, $OCH_2$), 6.94 s (4H, ArH), 7.08 s (4H, ArH), 7.79 s (2H, OH), 8.64 s (4H, $NH_2$), 9.69 s (2H, NH).

**Complex of calixarene V with benzodiazepinone I.** $^1$H NMR spectrum, δ, ppm: 1.12 s [9H, $(CH_3)_3C$], 1.16 s [9H, $(CH_3)_3C$], 1.23 s [9H, $(CH_3)_3C$], 1.24 s [9H, $(CH_3)_3C$], 3.49 d (1H, $CH_{2benzod}$, *J* 9.6 Hz), 3.55 d (1H, $CH_{2benzod}$), 4.07 d (2H, $ArCH_2Ar$, *J* 13.07 Hz), 4.14 d (2H, $ArCH_2Ar$, *J* 12.76 Hz), 4.2 d (2H, $ArCH_2Ar$, *J* 12.76 Hz), 4.23 d (2H, $ArCH_2Ar$, *J* 13.38 Hz), 4.32 s (4H, $OCH_2$), 7.05 s (2H, ArH), 7.06 s (2H, ArH), 7.08 s (2H, ArH), 7.1 s (2H, ArH), 7.11, 7.19 d.d (1H, $ArH_{benzod}$), 7.4 m (2H, $ArH_{benzod}$), 7.52 m (4H, $ArH_{benzod}$), 7.91 s (2H, OH), 8.28 br.s (1H, NH), 8.31 br.s (4H, $NH_2$), 9.7 s (2H, NH).

**Complex of calixarene V with benzodiazepinone II**. $^1$H NMR spectrum, δ, ppm: 1.15 s [9H, $(CH_3)_3C$], 1.16 s [9H, $(CH_3)_3C$], 1.22 s [9H, $(CH_3)_3C$], 1.23 s [9H, $(CH_3)_3C$], 3.5 d (2H, $ArCH_2Ar$, *J* 13.7 Hz), 3.58 d (2H, $ArCH_2Ar$, *J* 13.7 Hz), 3.85 d (1H, $CH_{2benzod}$, *J* 10.8 Hz), 4.07 d (2H, $ArCH_2Ar$, *J* 13.07 Hz), 4.23 d (2H, $ArCH_2Ar$, *J* 13.7 Hz), 4.58 s (4H, $OCH_2$), 4.63 d (1H, $CH_{2benzod}$, *J* 15.26 Hz), 4.73 d (1H, $CH_{2benzod}$, *J* 10.8 Hz), 5.02 d (1H, $CH_{2benzod}$, *J* 15.26 Hz), 7.04 s (2H, ArH), 7.08 s (2H, ArH), 7.09 s (2H, ArH), 7.11 s (2H, ArH), 7.23, 7.26 d.d (1H, $ArH_{benzod}$), 7.46–7.58 m (7H, $ArH_{benzod}$), 8.31 s (2H, OH), 8.4 br.s (1H, NH), 8.51 br.s (2H, $NH_2$), 8.7 br.s (4H, $NH_2$), 9.9 br.s (2H, NH).

**25,27-Diheptyloxy-26,28-dihydroxy-*p*-*tert*-butylcalix[4]arene VI**. $^1$H NMR spectrum, δ, ppm: 0.92 m (6H, $CH_3$), 1.19–1.22 m (20H, $CH_2$), 1.21 s [18H, $(CH_3)_3C$], 1.25 s [18H, $(CH_3)_3C$], 3.42 d (2H, $ArCH_2Ar$, *J* 12.45 Hz), 3.5 d (2H, $ArCH_2Ar$, *J* 14.0 Hz), 4.22 m (4H, $CH_2O$), 4.27 d (2H, $ArCH_2Ar$, *J* 14.0 Hz), 4.35 d (2H, $ArCH_2Ar$, *J* 12.45 Hz), 7.05 s (2H, OH), 7.09 s (4H, ArH), 7.14 s (4H, ArH).

**Complex of calixarene VI with benzodiazepinone I**. $^1$H NMR spectrum, δ, ppm: 0.95 m (6H, $CH_3$), 1.14 s [18H, $(CH_3)_3C$], 1.21 s [18H, $(CH_3)_3C$], 1.29–1.4 m (10H, $CH_2$), 1.69 m (6H, $CH_2$), 2.08 m (4H, $CH_2$), 3.34 d (4H, $ArCH_2Ar$, *J* 12.76 Hz), 3.98 t (4H, $CH_2O$), 4.3 d (4H, $ArCH_2Ar$), 5.1 s (2H, $CH_{2benzod}$), 7.02 s (4H, ArH), 7.04 s (4H, ArH), 7.08, 7.18 d.d (1H, $ArH_{benzod}$), 7.41 m, 7.52–7.59 m (6H, $ArH_{benzod}$), 8.42 br.s (2H, OH), 8.45 br.s (1H, NH).

**Complex of calixarene VI with benzodiazepinone II.** $^1$H NMR spectrum, δ, ppm: 0.96 m (6H, $CH_3$), 1.16 s [18H, $(CH_3)_3C$], 1.2 s [18H, $(CH_3)_3C$], 1.25–1.34 m (10H, $CH_2$), 1.7 m (6H, $CH_2$), 2.1 m (4H, $CH_2$), 3.40 d (4H, $ArCH_2Ar$, *J* 13.6 Hz), 3.89 d (1H, $CH_{2benzod}$, *J* 10.56 Hz), 4.2 t (4H, $CH_2O$), 4.43 d (4H, $ArCH_2Ar$, *J* 13.6 Hz), 4.65 d (1H, $CH_{2benzod}$, *J* 15.3 Hz), 4.8 d (1H, $CH_{2benzod}$, *J* 10.56 Hz), 5.0 d (1H, $CH_{2benzod}$, *J* 15.3 Hz), 7.08 s (4H, ArH), 7.10 s (4H, ArH), 7.26, 7.29 d.d (1H, $ArH_{benzod}$), 7.5 m (3H, $ArH_{benzod}$), 7.64 m (4H, $ArH_{benzod}$), 8.34 s (2H, OH), 8.45 br.s (1H, NH), 8.67 br.s (2H, $NH_2$).

**25,27-Diheptyloxy-26,28-bis[(methoxycarbonyl)methoxy]-*p*-*tert*-butylcalix[4]arene VII**. $^1$H NMR spectrum, δ, ppm: 0.91 m (10H, $CH_2CH_3$), 1.14 s [9H, $(CH_3)_3C$], 1.95 s [9H, $(CH_3)_3C$], 1.2 s [9H, $(CH_3)_3C$], 1.26 m (8H, $CH_2$), 1.3 s [9H, $(CH_3)_3C$], 1.9 m (8H, $CH_2$), 3.17 d (2H, $ArCH_2Ar$, *J* 13.07 Hz), 3.23 d (2H, $ArCH_2Ar$, *J* 12.76 Hz), 3.66 m (4H, $CH_2O$), 3.74 s (3H, $OCH_3$), 3.77 s (3H, $OCH_3$), 4.22 d (2H, $ArCH_2Ar$, *J* 12.76 Hz), 4.6 d (2H, $ArCH_2Ar$, *J* 13.07 Hz), 4.84 s (2H, $CH_2O$), 4.9 s (2H, $CH_2O$), 6.62 s (2H, ArH), 6.65 d (2H, ArH), 6.96 s (2H, ArH), 7.18 d (2H, ArH).

**Complex of calixarene VII with benzodiazepinone I.** $^1$H NMR spectrum, δ, ppm: 0.87–0.96 m [28H, $CH_3$, $CH_2$, $(CH_3)_3C$], 1.22 m (8H, $CH_2$), 1.34 s [18H, $(CH_3)_3C$], 1.89 m (8H, $CH_2$), 3.23 d (4H, $ArCH_2Ar$, *J* 13.07 Hz), 3.69–3.91 m (10H, $CH_2O$, $OCH_3$), 4.22 d (2H, $ArCH_2Ar$, *J* 12.77 Hz), 4.34 s (2H, $CH_2O$), 4.51 s (2H, $CH_2O$), 4.63 d (2H, $ArCH_2Ar$, *J* 12.77 Hz), 4.83 d (1H, $CH_{2benzod}$, *J* 9.6 Hz), 4.86 d (1H, $CH_{2benzod}$, *J* 9.6 Hz), 6.96 s (2H, ArH), 7.08 s (2H, ArH), 7.1 s (2H, ArH), 7.18 s (2H, ArH), 7.22, 7.28 d.d (1H, $ArH_{benzod}$), 7.4 m, 7.57 m (6H, $ArH_{benzod}$), 8.6 br.s (1H, NH).

**Complex of calixarene VII with benzodiazepinone II**. $^1$H NMR spectrum, δ, ppm: 0.85 s [18H, $(CH_3)_3C$], 0.95 m (6H, $CH_3$), 1.2 m (4H, $CH_2$), 1.28 m (8H, $CH_2$), 1.32 s [18H, $(CH_3)_3C$], 3.24 d (2H, $ArCH_2Ar$, *J* 12.45 Hz), 3.68–3.74 m (10H, $CH_2O$, $OCH_3$), 3.84 d (1H, $CH_{2benzod}$, *J* 10.6 Hz), 4.17 d (1H, $CH_{2benzod}$, *J* 14.95 Hz), 4.22 d (2H, $ArCH_2Ar$, *J* 12.45 Hz), 4.5 s (4H, $CH_2O$), 4.61 d (1H, $CH_{2benzod}$, *J* 10.6 Hz), 4.74 d (1H, $CH_{2benzod}$, *J* 14.94 Hz), 4.85–4.92 m (4H, $ArCH_2Ar$), 6.54 d (2H, ArH), 6.62 d (2H, ArH), 6.96 s (2H, ArH), 7.03 s (2H, ArH), 7.42 m (4H, $ArH_{benzod}$), 7.7 m (4H, $ArH_{benzod}$), 8.5 br.s (1H, NH), 8.72 br.s (2H, $NH_2$).

**25,26,27-Tripropoxy-28-[(hydrazinocarbonyl)methoxy]calix[4]arene VIII**. $^1$H NMR spectrum, δ, ppm: 0.93–1.01 m (9H, $CH_3$), 1.76–1.9 m (6H, $CH_2$), 3.19 d

(2H, $ArCH_2Ar$, *J* 13.38 Hz), 3.6 t (2H, $CH_2CH_2O$), 3.69–3.8 m (4H, $ArCH_2Ar$), 3.87 t (4H, $CH_2CH_2O$), 4.13 d (2H, $ArCH_2Ar$, *J* 13.7 Hz), 4.37 s (2H, $CH_2O$), 5.16 br.s (2H, NH), 6.35 m (2H, ArH), 6.5 m (2H, ArH), 6.84 m (2H, ArH), 6.98 m (2H, ArH), 7.1 t (2H, ArH), 7.32 t (1H, ArH), 7.39 t (1H, ArH), 8.75 br.s (4H, $NH_2$).

**Complex of calixarene VIII with benzodiazepinone I.** $^1$H NMR spectrum, δ, ppm: 1.05–1.1 m (9H, $CH_3$), 1.82–2.03 m (6H, $CH_2$), 3.3 d (2H, $ArCH_2Ar$, *J* 13.4 Hz), 3.8–4.13 m (10H, $ArCH_2Ar$, $CH_2CH_2O$), 4.2 d (2H, $ArCH_2Ar$, *J* 13.4 Hz), 4.4 s (2H, $CH_2O$), 5.03 s (2H, $CH_{2benzod}$), 5.18 br.s (2H, NH), 6.4 m (2H, ArH), 6.55 m (2H, ArH), 6.91 m (2H, ArH), 6.98 m (2H, ArH), 7.14 t (2H, ArH), 7.28, 7.31 d.d (1H, $ArH_{benzod}$), 7.38 t (1H, ArH), 7.4–7.62 m (7H, ArH, $ArH_{benzod}$), 8.54 br.s (4H, NH).

**Complex of calixarene VIII with benzodiazepinone II**. $^1$H NMR spectrum, δ, ppm: 0.86–1.0 m (9H, $CH_3$), 1.74–1.89 m (6H, $CH_2$), 3.19 d (2H, $ArCH_2Ar$, *J* 13.07 Hz), 3.57 t (2H, $CH_2CH_2O$), 3.65–3.86 m (7H, $ArCH_2Ar$, $CH_{2benzod}$), 4.12 d (2H, $ArCH_2Ar$, *J* 13.38 Hz), 4.21 d (1H, $CH_{2benzod}$, *J* 15.5 Hz), 4.32 s (2H, $CH_2O$), 4.55 d (1H, $CH_{2benzod}$, *J* 15.5 Hz), 4.78 d (1H, $CH_{2benzod}$, *J* 11.51 Hz), 6.39 m (2H, ArH), 6.52 m (2H, ArH), 6.86 m (2H, ArH), 6.98 m (2H, ArH), 7.14–7.3 m (4H, ArH), 7.42 m, 7.61 m (9H, $ArH_{benzod}$, NH), 8.66 br.s (2H, $NH_2$), 8.81 br.s (2H, $NH_2$), 9.6 br.s (1H, NH).

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