Glycolurils in α-ureido- and α-aminoalkylation reactions
1. α-Ureidoalkylation of sulfamides with *N*-(hydroxymethyl)glycolurils

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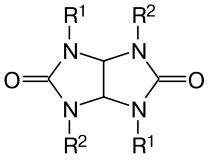
α-Ureidoalkylation of sulfamides with 2-hydroxymethyl-, 2,6- and 2,8-bis(hydroxymethyl)-, and 2,4,6,8-tetrakis(hydroxymethyl)glycolurils gave novel bi-, tri-, and tetracyclic fused systems combining the glycoluril and sulfamide fragments.

Key words: α-ureidoalkylation, *N*-(hydroxymethyl)glycolurils, *N*-(arylsulfonylaminomethyl)glycolurils, 9,11-dialkyl-8,12-dioxo-4-thia-1,3,5,7,9,11-hexaazatricyclo[5.5.1.$0^{10,13}$]tridecane 4,4-dioxides, 3,5,11,13-tetramethyl-8,16-dioxo-4,12-dithia-1,3,5,7,9,11,13,15-octaazatetracyclo[7.7.2.0.^{7,17}$0^{15,18}$]octadecane 4,4,12,12-tetraoxide.

Earlier, we have studied in detail α-ureidoalkylation of ureas[1,2] and their analogs (thiosemicarbazide and aminoguanidine[3,4]) with 4,5-dihydroxyimidazolidin-2-ones. Based on the results obtained, we have developed general methods for the targeted synthesis of various *N*-substituted glycolurils (2,4,6,8-tetraazabicyclo[3.3.0]-octane-3,7-diones) **1** (including hydroxy(carboxy)alkylated ones)[1,5,6] and 3-thioxoperhydroimidazo[4,5-*e*]-[1,2,4]triazin-6-ones **2**.[3,4] In addition, we have discovered novel reactions leading to 4,5-bis(3-alkylureido-, thiosemicarbazido-, and 3-aminoguanidino)imidazolidin-2-ones **3**—**5** and 1,3-dialkyl-4-guanidinoiminoimidazolidin-2-ones **6**.[3,4]



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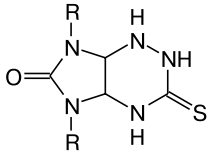

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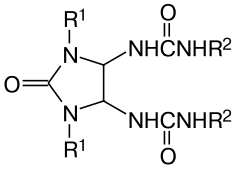

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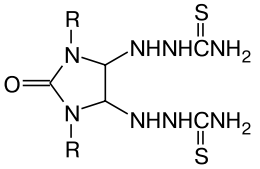

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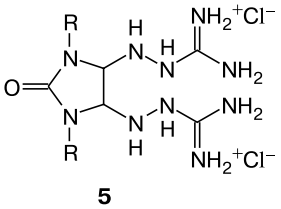

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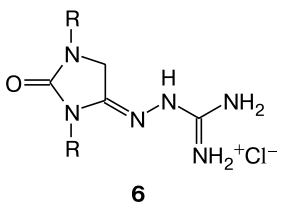

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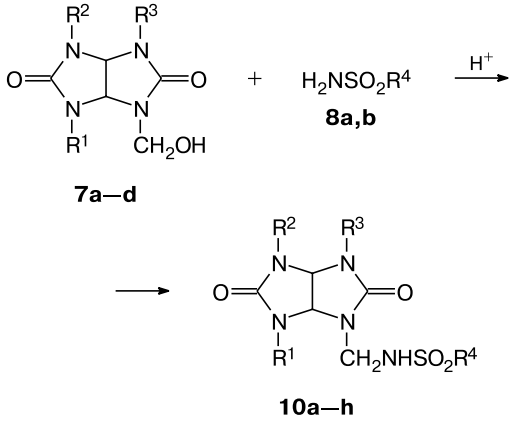
Out of *N*-(hydroxymethyl)glycolurils, only 2,4,6,8-tetrakis(hydroxymethyl)glycolurils have been used hitherto as ureidoalkylating reagents (in the synthesis of cucurbiturils).[7,8]

Because glycolurils belong to a novel class of neurotropic compounds[9—11] and exhibit other types of biological activity,[12,13] it was of practical interest to design a molecule combining the glycoluril fragment and other pharmacophore (*e.g.*, sulfamide[14]) groups. The fundamental possibility of the synthesis of such compounds has been demonstrated earlier with single examples.[15] Here we studied α-ureidoalkylation with various 2-hydroxymethyl-, 2,6- and 2,8-bis(hydroxymethyl)-, and 2,4,6,8-tetrakis(hydroxymethyl)glycolurils **7** of sulfonamides **8**, sulfamide, and *N*,*N*′-dialkylsulfamides **9** with the aim of obtaining novel bi-, tri-, and tetracyclic fused systems combining the glycoluril and sulfamide fragments.

Conditions for the synthesis of bicyclic compounds **10a**—**h** (Scheme 1) were optimized with a reaction of 2-hydroxymethyl-4,6,8-trimethylglycoluril (**7a**) with benzenesulfonamide (**8a**) in boiling methanol in the presence of HCl as an example, by analogy with acid-catalyzed α-ureidoalkylation with 4,5-dihydroxyimidazolidin-2-ones conducted in either water or lower alcohols. Methanol was used as a solvent because the starting sulfamides are soluble in methanol better than in water. The course of the reaction was monitored by ^{1}H NMR spectroscopy regarding disappearance of the signals for the OH protons in the starting glycoluril **7a**. The optimized reaction time was 1 h. α-Ureidoalkylation of

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2195—2199, November, 2007.

Scheme 1



Compound	R^1	R^2	R^3	R^4
7a	Me	Me	Me	—
7b	Me	Me	Et	—
7c	Me	CH_2OH	Me	—
7d	Et	CH_2OH	Et	—
10a	Me	Me	Me	Ph
10b	Me	Me	Me	4-MeC_6H_4
10c	Me	Me	Et	Ph
10d	Me	Me	Et	4-MeC_6H_4
10e	Me	$CH_2NHSO_2R^4$	Me	Ph
10f	Me	$CH_2NHSO_2R^4$	Me	4-MeC_6H_4
10g	Et	$CH_2NHSO_2R^4$	Et	Ph
10h	Et	$CH_2NHSO_2R^4$	Et	4-MeC_6H_4

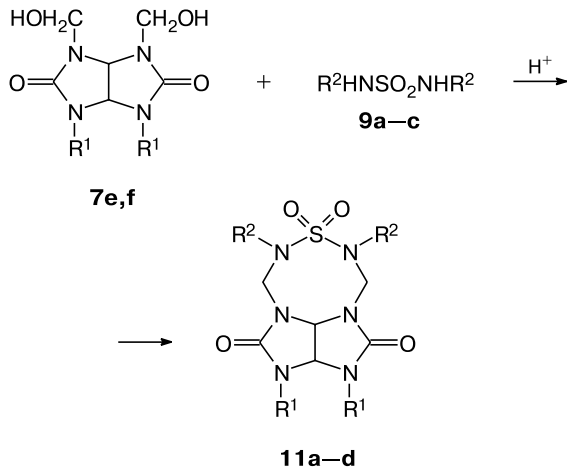
8: R^4 = Ph (**a**), 4-MeC_6H_4 (**b**)

sulfonamides **8a,b** with 2-hydroxymethyl- (**7a,b**) and 2,6-bis(hydroxymethyl)glycolurils (**7c,d**) under the optimized conditions gave 2-(arylsulfonylaminomethyl)- and 2,6-bis(arylsulfonylaminomethyl)glycolurils **10a—h** in 27—50% yields (Table 1).

The ^{1}H NMR spectra of the compounds obtained show characteristic triplets for the NH protons of the sulfamide fragments at δ 8.51—8.65 (Table 2). The signals for the CH—CH protons appear at δ 4.65—5.17 as two doublets (**10a—d**) or a singlet (**10e—h**). The diastereotopic protons of the NCH_2 groups resonate at δ 4.09—4.27 and 4.63—4.71. The ^{13}C NMR spectra contain characteristic signals for the NCH_2 groups at δ 51—52; the signals for the CH—CH and CO groups appear at δ 65—69 and 156—159, respectively. The IR spectra show intense absorption bands due to SO_2 (1320—1328 cm^{-1}), C=O (1688—1712 cm^{-1}), and NH groups (3184—3272 cm^{-1}) and bands assignable to the framework vibrations of the bicycles (1496—1508 cm^{-1}).[5]

A similar approach was used to obtain 9,11-dialkyl-8,12-dioxo-4-thia-1,3,5,7,9,11-hexaazatricyclo[5.5.1.$0^{10,13}$]tridecane 4,4-dioxides **11a—d** by condensation of sulfamides **9a—c** with 2,8-bis(hydroxymethyl)glycolurils **7e,f**. The reactions were carried out in MeOH (for sulfamides **9a,c**) or Pr^iOH (for sulfamide **9b**) (Scheme 2).

Scheme 2



7: R^1 = Me (**e**), Et (**f**); **9:** R^2 = H (**a**), Me (**b**), Pr (**c**);
11: R^1 = Me, R^2 = H (**a**); R^1 = R^2 = Me (**b**); R^1 = Me, R^2 = Pr (**c**); R^1 = Et, R^2 = H (**d**)

The ^{1}H NMR spectra of compounds **11a—d** show doublets of doublets at δ 4.26—4.80 due to the diastereotopic CH_2 protons of the eight-membered ring and doublets of doublets at δ 5.16—5.35 for the CH—CH protons. The IR spectra exhibit characteristic intense absorption bands due to the SO_2 (1144—1167 and 1320—1361 cm^{-1}) and C=O groups (1699—1728 cm^{-1}); for compounds **11a,d**, the bands for the NH groups were also observed (3239—3346 cm^{-1}). The mass spectrum of the tricyclic compound **11a** contains a sufficiently intense molecular ion peak. These peaks are absent for compounds **11b,c**: their mass spectra show peaks of the fragmentation ions [M^+ – 64] produced by elimination of an SO_2 molecule (Table 3).

2,4,6,8-Tetrakis(hydroxymethyl)glycoluril (**7g**) is soluble in water better than in MeOH; for this reason, we carried out its condensation with *N*,*N*′-dimethylsulfamide (**9b**) in water at pH 1 (HCl) (Scheme 3). The ^{1}H NMR spectrum of the compound obtained shows a singlet at δ 2.85, a doublet of doublets at δ 4.81, and a singlet at δ 5.44 with an integral intensity ratio of 6 : 4 : 1. This corresponds to the structure of tetracyclic compound **12**: 3,5,11,13-tetramethyl-8,16-dioxo-4,12-dithia-1,3,5,7,9,11,13,15-octaazatetracyclo[7.7.2.0.^{7,17}0^{15,18}]-octadecane 4,4,12,12-tetraoxide. The mass spectrum contains a peak of the ion [M^+ – 64] (due to elimination of SO_2).

Compounds **10h** and **11a** were tested for antimicrobial and fungicidal activities, respectively*. The test for

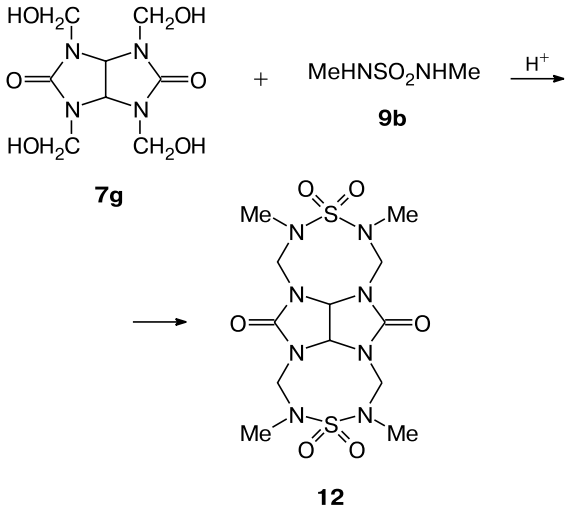
* The fungicidal activity was studied at the All-Russia Research Institute for chemical plant protectors under the supervision of V. A. Abelentsev. The antimicrobial activity was studied at the Natural-Science Institute of the Perm State University under the supervision of G. A. Aleksandrova.

Table 1. Yields, melting points, and elemental analysis data for compounds **10a—h**, **11a—d**, and **12**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)				Molecular formula
			C	H	N	S	
10a	48—50	176—178	47.62	5.39	19.84	9.01	$C_{14}H_{19}N_5O_4S$
			47.58	5.42	19.82	9.07	
10b	30—35	174—176	49.05	5.78	19.03	8.67	$C_{15}H_{21}N_5O_4S$
			49.03	5.76	19.06	8.73	
10c	43—47	210—212	48.98	5.79	19.11	8.65	$C_{15}H_{21}N_5O_4S$
			49.03	5.76	19.06	8.73	
10d	30—34	174—176	50.41	6.05	18.37	8.35	$C_{16}H_{23}N_5O_4S$
			50.38	6.08	18.36	8.40	
10e	20—25	233—235	47.21	4.79	16.49	12.57	$C_{20}H_{24}N_6O_6S_2$
			47.23	4.76	16.52	12.61	
10f	27—31	238—240	49.20	5.28	15.69	11.91	$C_{22}H_{28}N_6O_6S_2$
			49.24	5.26	15.66	11.95	
10g	44—48	237—239	49.27	5.26	15.64	11.92	$C_{22}H_{28}N_6O_6S_2$
			49.24	5.26	15.66	11.95	
10h	40—45	197—199	51.03	5.76	14.89	11.33	$C_{24}H_{32}N_6O_6S_2$
			51.05	5.71	14.88	11.36	
11a	58—60	237—239 (decomp.)	32.93	4.99	29.10	10.87	$C_8H_{14}N_6O_4S$
			33.10	4.86	28.95	11.04	
11b	43—45	271—272 (decomp.)	37.61	5.76	26.45	9.93	$C_{10}H_{18}N_6O_4S$
			37.73	5.70	26.40	10.07	
11c	24—27	265—267 (decomp.)	44.87	7.03	22.47	8.48	$C_{14}H_{26}N_6O_4S$
			44.91	7.00	22.44	8.56	
11d	47—49	229—231	37.72	5.67	26.43	9.96	$C_{10}H_{18}N_6O_4S$
			37.73	5.70	26.40	10.07	
12	51—55	>300 (decomp.)	32.75	4.95	25.32	14.87	$C_{12}H_{22}N_8O_6S_2$
			32.87	5.06	25.55	14.63	

antimicrobial activity revealed that compound **10h** has no bacteriostatic effect on *Staphylococcus aureus* and *Esherichia coli*. Compound **11a** was tested for fungicidal activity against pathogens causing root rot and molding of agricultural seeds: *Botrytis cinerea*, *Fusarium oxysporum*, *Helminthosporium sativum*, and *Fusarium graminearum*. The fungicide thiram was used as a reference. According to the results of the tests (see below), compound **11a** exhibits a slight fungicidal activity. Biological testing of the compounds obtained will be continued.

Scheme 3



Compound	Growth suppression (%) of the fungi			
	Botrytis cinerea	*Fusarium oxysporum*	*Helminthosporium sativum*	*Fusarium graminearum*
11a	9	36	33	22
Thiram	100	100	100	100

In conclusion, we have studied for the first time α-ureidoalkylation of sulfamides with mono-, bis-, and tetrakis-*N*-(hydroxymethyl)glycolurils and obtained novel *N*-mono- and *N*-bis(arylsulfonylaminomethyl)-glycolurils: 9,11-dialkyl-8,12-dioxo-4-thia-1,3,5,7,9,11-hexaazatricyclo[5.5.1.$0^{10,13}$]tridecane 4,4-dioxides and 3,5,11,13-tetramethyl-8,16-dioxo-4,12-dithia-1,3,5,7,9,11,13,15-octaazatetracyclo[7.7.2.0.$^{7,17}0^{15,18}$]-octadecane 4,4,12,12-tetraoxide.

Table 2. IR and ^1H and ^{13}C NMR spectra of compounds **10a—h** (DMSO-d_6)

Compound	IR, ν/cm^{-1}	NMR, δ (*J*/Hz)	
		^1H	^{13}C
10a	—	2.73, 2.79, 2.81 (all s, 3 H each, NMe); 4.22, 4.65 (both dd, 1 H each, NCH_2, *J* = 6.2); 4.82, 5.12 (both d, 1 H each, CH, *J* = 7.8); 7.54—7.64 (m, 3 H, H(3)—H(5) (Ph)); 7.79 (d, 2 H, H(2), H(6) (Ph)); 8.56 (t, 1 H, NH, *J* = 5.9)	—
10b	—	2.37 (s, 3 H, Me (Ts)); 2.71, 2.78, 2.80 (all s, 3 H each, NMe); 4.23, 4.65 (both dd, 1 H each, NCH_2, *J* = 6.2); 4.76, 5.09 (both d, 1 H each, CH, *J* = 7.8); 7.39, 7.70 (both d, 2 H each, Ts, *J* = 7.8); 8.56 (t, 1 H, NH, *J* = 5.9)	—
10c	3184, 1696, 1508, 1328	1.01 (t, 3 H, Me (Et), *J* = 7.0); 2.76, 2.80 (both s, 3 H each, NMe); 3.03—3.26 (m, 2 H, NCH_2 (Et)); 4.23, 4.66 (both d, 1 H each, NCH_2, *J* = 5.5); 4.92, 5.12 (both d, 1 H each, CH, *J* = 8.6); 7.52—7.63 (m, 3 H, H(3)—H(5) (Ph)); 7.79 (d, 2 H, H(2), H(6) (Ph), *J* = 6.7); 8.63 (t, 1 H, NH, *J* = 5.8)	13.26 (Me (Et)); 29.80, 30.33 (2 MeN); 37.07 (CH_2 (Et)); 51.04 (CH_2); 67.62, 69.53 (2 CH); 126.29 (C(4) (Ph)); 129.27 (C(3), C(5) (Ph)); 132.64 (C(2), C(6) (Ph)); 140.98 (C(1) (Ph)); 156.96, 158.73 (2 CO)
10d	3188, 1700, 1500, 1320	1.03 (t, 3 H, Me (Et), *J* = 6.7); 2.39 (s, 3 H, Me (Ts)); 2.80, 2.82 (both s, 3 H each, NMe); 3.07—3.29 (m, 2 H, NCH_2 (Et)); 4.19—4.27, 4.63—4.71 (both m, 1 H each, NCH_2); 4.97, 5.17 (both d, 1 H each, CHCH, *J* = 8.5); 7.39 (d, 2 H, Ts, *J* = 8.0); 7.69 (d, 2 H, Ts, *J* = 8.6); 8.51 (t, 1 H, NH, *J* = 8.5)	13.16 (Me (Et)); 20.97 (Me (Ts)); 29.78, 30.29 (2 MeN); 36.97 (CH_2 (Et)); 50.96 (CH_2); 67.53, 69.46 (2 CH); 126.33 (C(4) (Ts)); 129.43 (C(3), C(5) (Ts)); 138.13 (C(2), C(6) (Ts)); 142.84 (C(1) (Ts)); 156.89, 158.65 (2 CO)
10e	3264, 3220, 1712, 1688, 1504, 1328	2.68 (s, 6 H, 2 NMe); 4.22 (d, 2 H, NCH_2, *J* = 14.7); 4.70 (m, 4 H, NCH_2 + CHCH); 7.58—7.68 (m, 6 H, Ph); 7.78 (d, 4 H, Ph, *J* = 7.3); 8.62 (br.s, 2 H, 2 NH)	29.07 (2 MeN); 51.06 (2 CH_2); 66.75 (2 CH); 126.31 (C(4) (Ph)); 129.16 (C(3), C(5) (Ph)); 132.61 (C(2), C(6) (Ph)); 141.01 (C(1) (Ph)); 156.83 (2 CO)
10f	3272, 3180, 1708, 1692, 1504, 1328	2.43 (s, 6 H, 2 Me (Ts)); 2.67 (s, 6 H, 2 NMe); 4.19 (d, 2 H, NCH_2, *J* = 11.1); 4.65 (m, 4 H, NCH_2 + + CHCH); 7.40, 7.64 (both d, 4 H, Ts, *J* = 6.6); 8.56 (m, 2 H, 2 NH)	20.97 (Me (Ts)); 29.33 (2 MeN); 52.19 (2 CH_2); 65.94 (2 CH); 126.14 (C(4) (Ts)); 129.57 (C(3), C(5) (Ts)); 137.96 (C(2), C(6) (Ts)); 142.34 (C(1) (Ts)); 156.43 (2 CO)
10g	3252, 3192, 1688, 1496, 1324	0.97 (t, 6 H, 2 Me (Et), *J* = 6.7); 3.02—3.29 (m, 4 H, 2 NCH_2 (Et)); 4.12, 4.66 (both dd, 2 H, NCH_2, *J* = 5.8); 4.98 (s, 2 H, CHCH); 7.61 (m, 6 H, Ph); 7.78 (d, 4 H, Ph, *J* = 6.1); 8.65 (t, 1 H, NH, *J* = 5.8)	13.41 (2 Me (Et)); 36.76 (2 CH_2 (Et)); 51.81 (2 CH_2); 65.64 (2 CH); 126.18 (C(4) (Ph)); 129.22 (C(3), C(5) (Ph)); 132.62 (C(2), C(6) (Ph)); 140.82 (C(1) (Ph)); 156.86 (2 CO)
10h	3212, 1688, 1496, 1328	0.97 (t, 6 H, 2 Me (Et), *J* = 6.7); 2.39 (s, 6 H, 2 Me (Ts)); 3.01—3.26 (m, 4 H, 2 NCH_2 (Et)); 4.09, 4.65 (both dd, 2 H, NCH_2, *J* = 5.5); 4.94 (s, 2 H, CHCH); 7.39, 7.66 (both d, 4 H each, Ts, *J* = 8.2); 8.57 (t, 1 H, NH, *J* = 5.5)	13.14 (2 Me (Et)); 21.01 (2 Me (Ts)); 36.74 (2 CH_2 (Et)); 51.08 (2 CH_2); 65.38 (2 CH); 126.26 (C(4) (Ts)); 129.67 (C(3), C(5) (Ts)); 138.07 (C(2), C(6) (Ts)); 143.00 (C(1) (Ts)); 156.85 (2 CO)

Experimental

IR spectra were recorded on a Specord M82 instrument (KBr pellets). NMR spectra were recorded on Bruker AM-250 (250.13 MHz (^1H)) and Bruker AM-300 spectrometers (300.13 (^1H) and 75.5 MHz (^{13}C)) in DMSO-d_6. Chemical shifts are given on the δ scale with reference to Me_4Si as the internal standard. Mass spectra were recorded on a Kratos MS-30 spectrometer (70 eV). Melting points were determined on a GALLENKAMP instrument (Sanyo). 2-Hydroxymethyl-, 2,6- and 2,8-bis(hydroxymethyl)-, and 2,4,6,8-tetrakis(hydroxymethyl)glycolurils **7a—g** were prepared as described earlier.[16]

Synthesis of glycolurils 10a—d (general procedure). Appropriate 4,6,8-trialkyl-2-(hydroxymethyl)glycoluril **7a,b** (0.005 mol) and arenesulfonamide **8a,b** (0.005 mol) were dissolved in methanol (5 mL) and two drops of conc. HCl were added. The mixture was refluxed for 1 h and concentrated in a rotary evaporator. The residue was diluted with water (4 mL) and left for ~14 h. The white precipitate that formed was filtered off, washed with hot water, and crystallized from methanol—water (1 : 2).

Synthesis of glycolurils 10e—h (general procedure). Appropriate 4,8-dialkyl-2,6-bis(hydroxymethyl)glycoluril **7c,d** (0.0025 mol) and arenesulfonamide **8a,b** (0.005 mol) were dissolved in methanol (7 mL) and three drops of conc. HCl were added. The mixture was refluxed for 1 h and concentrated in a rotary evaporator to an oily residue, which was crystallized from water—methanol (1 : 2).

Synthesis of compounds 11a—d (general procedure). Appropriate 4,6-dialkyl-2,8-bis(hydroxymethyl)glycoluril **7e—f** (0.01 mol) and sulfamide **9a—c** (0.01 mol) were dissolved in methanol (5 mL) (for **11a,c,d**) or propan-2-ol (5 mL) (for **11b**). Two drops of conc. HCl were added and the mixture was re-

Table 3. IR, ^{1}H NMR (DMSO-d_6), and mass spectra of compounds **11a—d** and **12**

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ (J/Hz)	MS, m/z (I_{rel} (%))
11a	3346, 3239, 1718, 1699, 1516, 1331, 1167	2.86 (s, 6 H, 2 NMe); 4.28 (dd, 2 H, NCH_2, J = 9.5); 4.82 (dd, 2 H, NCH_2, J = 3.6); 5.16 (dd, 2 H, CHCH, J = 8.0); 7.60 (d, 2 H, NH, J = 6.6)	290 $[M]^+$ (37), 210 (62), 183 (54), 170 (100), 141 (29), 126 (72), 98 (44), 80 (81)
11b	1723, 1710, 1320, 1155	2.88, 2.92 (both s, 6 H each, 4 NMe); 4.76 (dd, 4 H, 2 NCH_2, J = 14.5); 5.23 (dd, 2 H, CHCH, J = 9.1)	254 $[M - SO_2]^+$ (9), 239 (8), 183 (26), 167 (9), 154 (9), 139 (100), 126 (73), 98 (72)
11c	1728, 1712, 1509, 1361, 1158	0.91 (t, 6 H, 2 Me (Pr), J = 7.5); 1.58—1.72 (m, 4 H, 2 CH_2 (Pr)); 2.89 (s, 6 H, 2 NMe); 2.97—3.13, 3.22—3.37 (both m, 2 H, NCH_2 (Pr)); 4.80 (dd, 4 H, 2 NCH_2, J = 15.3); 5.17 (dd, 2 H, CHCH, J = 9.9)	345 $[M - C_2H_5]^+$ (2), 310 $[M - SO_2]^+$ (4), 253 (10), 224 (8), 183 (7), 163 (18), 151 (22), 64 (5)
11d	3300, 1720, 1700, 1488, 1340, 1144	1.07 (t, 6 H, 2 Me (Et), J = 7.0); 3.10—3.43 (m, 4 H, 2 NCH_2 (Et)); 4.26, 4.72 (both d, 2 H, NCH_2, J = 15.3); 5.16, 5.35 (both d, 1 H each, CH, J = 8.6); 7.57 (br.s, 2 H, 2 NH)	—
12	1730, 1355, 1160	2.85 (s, 12 H, 4 NMe); 4.81 (dd, 8 H, 4 CH_2, J = 15.1); 5.44 (s, 2 H, CHCH)	374 $[M - SO_2]^+$ (2), 251 (15), 196 (11), 138 (20), 124 (23), 64 (21)

fluxed with stirring for 1 h. On cooling to ~20 °C, the colorless precipitate that formed was filtered off and crystallized from methanol (**11a,c,d**) or methanol—propan-2-ol (1 : 3) (**11b**).

Compound 12. 2,4,6,8-Tetrakis(hydroxymethyl)glycoluril **7g** (2.62 g, 0.01 mol) and sulfamide **9b** (2.48 g, 0.02 mol) were dissolved in water (5 mL). The mixture was acidified with two drops of conc. HCl (pH 1) and stirred at 80—90 °C for 2 h. On cooling to ~20 °C, the white precipitate that formed was filtered off and recrystallized from DMSO.

The yields and physicochemical characteristics of compounds **10—12** are given in Tables 1—3.

This work was financially supported by the Division of Chemistry and Materials Science of the Russian Academy of Sciences (Program OKh-10).

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Received May 29, 2007;
in revised form July 5, 2007