DOI 10.1007/s10593-017-2029-5

Chemistry of Heterocyclic Compounds **2017**, *53*(2), 116–122

Glycolurils in the synthesis of fused polyheterocyclic compounds

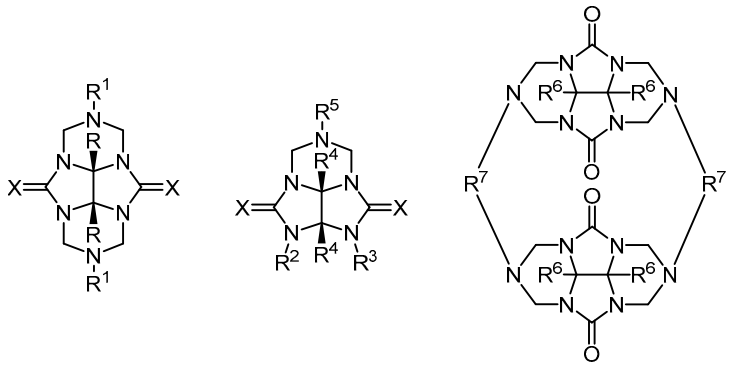
Yana A. Barsegyan[1,2]*, Vladimir V. Baranov[1], Angelina N. Kravchenko[1]

[1] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Ave., Moscow 119991, Russia; e-mail: kani@server.ioc.ac.ru*

[2] *D. I. Mendeleev Chemical Technology University of Russia, 9 Miusskaya Sq., Moscow 125047, Russia*

Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2017, *53*(2), 116–122

Submitted November 8, 2016
Accepted November 22, 2016



We present a comprehensive analysis of data published over the last decade about the methods applicable to the synthesis of fused polyheterocyclic compounds on the basis of glycolurils.

Keywords: amines, amino acids, diamines, formaldehyde, fused polyheterocycles, glycolurils, condensation.

Glycolurils and their derivatives have attracted the attention of chemists for more than one hundred years. The reactions of glycolurils with formaldehyde have served as a basis for rapid progress in the chemistry of fused polycyclic derivatives of glycolurils – cucurbiturils[1] and bambusurils,[2–6] which are of interest as objects for supramolecular chemistry research. Relatively simpler fused polyheterocyclic compounds also represent significant topics of study: 2,6-disubstituted hexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8-diones (**I**), their 3a[1],4a[1]-tetramethylene-substituted (**I**, $R^1 + R^2 = (CH_2)_4$) derivatives, including enantiomerically pure compounds, their 4,8-dithio analogs (**I**, X = S), and 2a,2a[1]-disubstituted 6-alkyltetrahydro-5*H*-2,3,4a,6,7a-pentaazacyclopenta[*cd*]indene-1,4-(2*H*,3*H*)-diones (thiones) (**II**),[7–49] obtained in a reaction of glycolurils, formaldehyde, and various amines or amino acids. Besides that, glycolurils and formaldehyde have been used in the synthesis of macrocyclic polyamines **III**[8] (Fig. 1). The aforementioned compounds have found applications in medicine, technology, polymer manufacturing, and the majority of their useful properties have been patented,[9–11] pointing to the value of future research regarding such compounds.

The tetracyclic compounds **I** have shown biological activity: they suppress multidrug resistance[9] of various bacteria, viruses, fungi, as well as cancer cells, and have been found to exhibit neuroprotective properties.[12] Besides that, such molecules have been patented as photostabilizers of polymers, stabilizers that can be used in the manufacturing of plastics, coatings, and organic materials useful for protecting surfaces from oxidative and thermal factors.[10,11] Certain representatives of this class of compounds are used as fluorescent chemosensors.[13] One of the compounds, 2,6-di(*tert*-butyl)-substituted tetracycle of type **I**, serves as the starting material in the synthesis of new energetic materials.[14] In some cases glycolurils have been used in the role of molecular clips.[13,15] Tricyclic derivatives of glycolurils belonging to the type **II** represent promising objects for supramolecular chemistry research.[16,17] For example, certain tricyclic compounds of type **II** (R^6, $R^7 = CO_2Et$, Ph) have shown a tendency toward self-assembly: based on homochiral recognition effects,

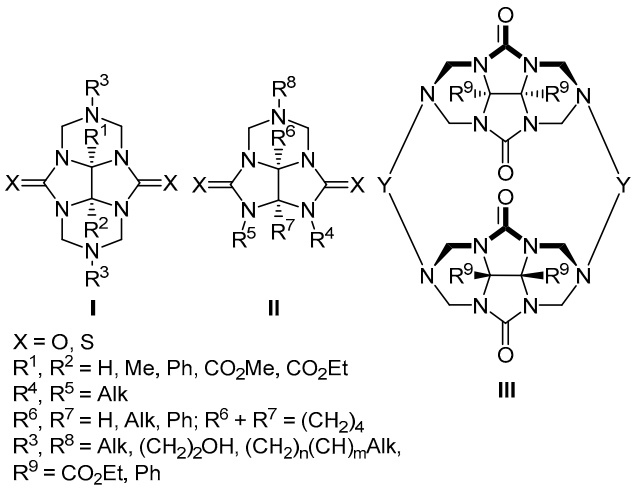


Figure 1. Known polyfused polyheterocyclic compounds derived from glycolurils.

they form one-dimensional ribbons, which can further aggregate into two-dimensional networks.[16] In another example, molecular conglomerates were formed from tricyclic glycolurils.[17]

Despite the fact that the first patents about the synthesis of compounds belonging to type **I** were published at the end of last century,[9–11,18] the interest toward developing methods for their preparation and extending the range of similar compounds is still very high.[19–49] At the same time, no reviews are available on the synthesis of such compounds.

1. Methods for the synthesis of 2,6-dialkylhexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a–hexaazacyclopenta[*def*]fluorene-4,8-diones (dithiones) and their 3a^1,4a^1-tetramethylene-substituted derivatives

Synthesis of 2,6-dialkylhexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8-diones **1**–**5** (compounds of type **I**, Fig. 1) has been accomplished according to three routes (Scheme 1):

– a three-component one-pot condensation of tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones (glycolurils) **7a**–**e** with formaldehyde and amines (method I);[7,8,10,14,15,18–35]

– a reaction of 1,3,4,6-tetrakis(hydroxymethyl)tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (**8a**) or its 3a,6a-tetramethylene-substituted analog (**8b**) with amines and amino acids (method II);[10,18,19,36–39]

– a condensation of glycoluril **7a** with *N*,*N*-bis(methoxymethyl)alkylamines in the presence of $SmCl_3 \cdot 6H_2O$ as a catalyst (method III).[40]

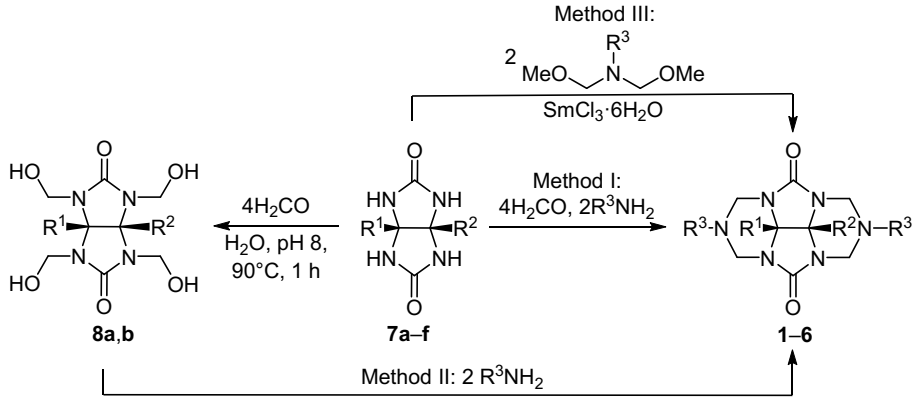
1.1. A three-component one-pot condensation of glycolurils with formaldehyde and amines (method I)

Method I has been used in the synthesis of tetracyclic compounds **1**–**5**. It consists of a three-component condensation of glycolurils **7a**,**c**–**e** containing various substituents at the bridgehead carbon atoms with formaldehyde and amines. For example, this approach was used in the synthesis of three tetracyclic compounds **1a**,**b**,**v** by reacting the glycoluril **7a** with formaldehyde (4 mol) and 2 mol of the appropriate amine (methylamine, 2-(hydroxyethyl)amine, or 4-phenyltriazol-2-amine).[18,19] The tetracyclic compound **1a** was synthesized in a 33% yield, but the conditions required for the reaction of glycoluril **7a** with formaldehyde and methylamine were not described in that patent.[18] For the synthesis of the second tetracyclic compound **1b** in 80% yield, the reaction mixture was heated for 2.5 h at 80°C.[18] Compound **1v** was obtained in 17% yield, but the reaction conditions were not described in that work.[19]

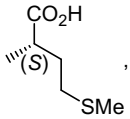
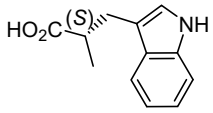
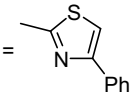
Method I has been used mainly for the preparation of diethyl 2,6-dialkyl-4,8-dioxo-1,3,5,7-tetrahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-3a^1,4a^1-dicarboxylates **5a**–**j** (22 examples) by the condensation of diethyl 2,5-dioxotetrahydroimidazo[4,5-*d*]imidazole-3a,6a(1*H*,4*H*)-dicarboxylate (**7e**) with 37% aqueous formaldehyde solution and alkyl-, aryl-, or alkylarylamines.[7,8,15,20–31] Several procedures for the preparation of compounds **5a**–**j** have been described in the literature. During the synthesis of compounds **5a**–**i**, solutions of the appropriate amines in MeOH or MeCN were added dropwise to a mixture of glycoluril with formaldehyde.[7,8,20–23,29–31] When MeOH was used, amine solutions were added dropwise over 1 h, and the reaction mixture was refluxed for 9–24 h. The yields of the tetracyclic compounds obtained according to this procedure ranged from 10 to 76%.[8,15,29–31] In order to increase the yields of the tetracyclic compounds **5b**–**e**,**h**, acetonitrile was used as the solvent for amines and the reaction mixture was stirred for 12 h at room temperature.[20–23,31] This approach enabled the preparation of tetracyclic compounds **5b**–**e**,**h** in 90% yield. The synthesis of tetracycles **5j** was accomplished in various solvents (MeOH, EtOH, THF, DMF)[24–28] and the authors were able to establish that the optimum conditions for reactions of diethoxycarbonylglycoluril **7e** with formaldehyde and aromatic amines (aniline, *p*-toluidine, *m*-toluidine, *p*-methoxyaniline, *p*-isopropylaniline, *p*-chloroaniline, *p*-bromoaniline, *p*-iodoaniline, *p*-ethynylaniline) was DMF as solvent and maintaining the reaction mixture at 120°C for 16 h, while the yields of products **5j** were in the range of 24–61%.[25,27] When *p*-nitroaniline and *p*-aminopyridine were used in analogous reactions, the expected tetracyclic compounds could not be obtained.[25] In other studies,[24,26] compounds **5j** (R^3 = Ph, *p*-Tol) were obtained in 70 and 60% yields, respectively, but the only reported reaction parameter was its duration (12 h).

Method I was also used in the synthesis of dimethyl 2,6-bis(*tert*-butyl)-4,8-dioxotetrahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-3a^1,4a^1-dicarboxylate (**4**)[32] (90% yield), as well as 2,6-dialkyl-3a^1,4a^1-diphenylhexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]-fluorene-4,8-diones **3a**–**c**.[14,33–35] Dicarboxylate **4** was obtained by a condensation reaction of dimethyl 2,5-dioxotetrahydroimidazo[4,5-*d*]imidazole-3a,6a(1*H*,4*H*)-dicarboxylate (**7d**), paraformaldehyde, and *tert*-butylamine in acetonitrile at room temperature. Compound **3a** (12%

Scheme 1



1a–v $R^1 = R^2 = H$, **a** $R^3 = Me$, **b** $R^3 = (CH_2)_2OH$, **c** $R^3 = n\text{-}C_{12}H_{25}$, **d** $R^3 = n\text{-}C_{18}H_{35}$, **e** $R^3 = Cy$, **f** $R^3 = All$, **g** $R^3 = Bu$, **h** $R^3 = CH_2CO_2H$, **i** $R^3 = (CH_2)_5CO_2H$, **j** $R^3 = (CH_2)_{10}CO_2H$, **k** $R^3 = Bn$, **l** $R^3 = t\text{-}Bu$, **m** $R^3 = i\text{-}Pr$, **n** $R^3 = Et$, **o** $R^3 = (CH_2)_2CO_2H$, **p** $R^3 = (CH_2)_3CO_2H$, **q** $R^3 = CH_2CONHCH_2CO_2H$,

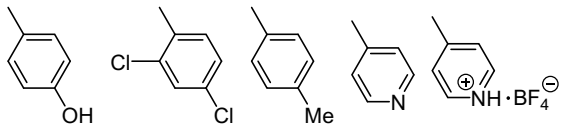
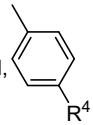
r R^3 =  , **s** R^3 =  , **t** R^3 =  , **u** R^3 =  , **v** R^3 = 

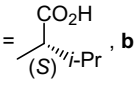
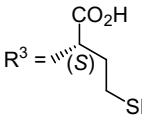
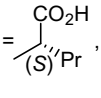
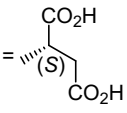
2 $R^1 = R^2 = Me$, $R^3 = Cy$

3 $R^1 = R^2 = Ph$, **a** $R^3 = Et$, **b** $R^3 = Bn$, **c** $R^3 = Ph_2CH$

4 $R^1 = R^2 = CO_2Me$, $R^3 = t\text{-}Bu$

5 $R^1 = R^2 = CO_2Et$, **a** $R^3 = Et$, **b** $R^3 = i\text{-}Pr$, **c** $R^3 = i\text{-}Bu$, **d** $R^3 = (CH_2)_2OH$, **e** $R^3 = Bn$, **f** $R^3 = Bu$, **g** $R^3 = Pr$, **h** $R^3 = Cy$, **i** $R^3 = CH_2Ar^1$, **j** $R^3 = Ar^2$

Ar^1 =  ; Ar^2 = Ph, *p*-Tol, *m*-Tol,  , R^4 = Br, Cl, I, *i*-Pr, C≡CH

6 $R^1 + R^2 = (CH_2)_4$, **a** R^3 =  , **b** R^3 =  , **c** R^3 =  , **d** R^3 = 

e $R^3 = Et$, **f** $R^3 = C_2H_4OH$, **g–i** $R^3 = (CH_2)_mCO_2H$, **g** $m = 1$, **h** $m = 2$, **i** $m = 3$

7 a $R^1 = R^2 = H$, **b** $R^1 = R^2 = Me$, **c** $R^1 = R^2 = Ph$, **d** $R^1 = R^2 = CO_2Me$, **e** $R^1 = R^2 = CO_2Et$, **f** $R^1 + R^2 = (CH_2)_4$

8 a $R^1 = R^2 = H$, **b** $R^1 + R^2 = (CH_2)_4$

yield) was obtained by condensation of 3a,6a-diphenylglycoluril **7c** with formaldehyde and ethylamine by refluxing the starting materials in MeOH solution.[14,33] The synthesis of compounds **3b**,**c** was also accomplished in 90% yield in acetonitrile at room temperature.[34,35]

Compound **2** was obtained by a reaction of 3a,6a-dimethylglycoluril **7b** with 30% formaldehyde solution and cyclohexylamine upon refluxing in isobutanol.[10]

1.2. Condensation of 1,3,4,6-tetrakis(hydroxymethyl)-tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones with amines and amino acids (method II)

Method II, based on the reaction between 1,3,4,6-tetrakis(hydroxymethyl)tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (**8a**) or its 3a,6a-tetramethylene-substituted analog **8b**, obtained according to known procedures,[36,37] with amines (methylamine, ethylamine, isopropylamine, *n*-butylamine, cyclohexylamine, allylamine, benzylamine, dodecan-1-amine, octadecan-1-amine, 2-(hydroxyethyl)amine, 4-phenyltriazol-2-amine) or amino acids (glycine, ε-aminocaproic acid, 11-aminoundecanoic acid, β-alanine, γ-aminobutyric acid, glycylglycine, valine, methionine, norvaline, tryptophan, and aspartic acid in the form of potassium salts) has been used for the synthesis of tetra- and pentacyclic compounds **1** and **6**[10,18,19,36–39] (31 examples). The reactions were performed in several variations, using different solvents (H_2O, MeOH, MeOH–H_2O, MeOH–C_7H_{16}, EtOH, MeCN, 2:3 H_2O–2-PrOH, 2-PrOH, 2-methylpropan-1-ol), temperature regimes (90 and 60°C, room temperature, reflux conditions) and reaction duration from 0.5 to 12 h. The yields of products **1a**–**v** were in the range of 37–91%. A patent[18] describes various methods applicable to the preparation of ten tetracyclic compounds **1a**–**j** (Table 1). Another patent[10] claims the synthesis of tetracyclic compounds **1a**,**m**, but fails to specify the yields. The tetracyclic compounds **1b**,**n**–**u**, including enantiomerically pure products **1r**–**u**, were obtained by heating the reagents **8a**,**b** and amines or amino acids as potassium salts in aqueous medium at 90°C for 2 h.[37,38] The tetracyclic product **1m** containing isopropyl substituents

Table 1. Synthesis conditions and yields of compounds **1a**–**j**

Compound	R	Reaction conditions	Yield, %
1a	Me	H_2O, Δ	78
1b	CH_2CO_2H	H_2O, Δ, 1 h	59
1c	$(CH_2)_5CO_2H$	H_2O, 60°C, 2 h	61
1d	$(CH_2)_{10}CO_2H$	H_2O, Δ, 0.5 h	70
1e	All	MeOH, Δ, 1 h	82
1f	Bn	EtOH, Δ, 1 h	37
1g	*n*-$C_{18}H_{37}$	2-PrOH, Δ	85
1h	*n*-$C_{12}H_{25}$	2-methylpropan-1-ol, Δ	77
1i	Cy	H_2O–2-PrOH, 2:3, Δ	91
1j	Bu	MeOH, C_7H_{16}	90

was synthesized in 90% yield by maintaining glycoluril **8a** with isopropylamine for 12 h in acetonitrile at room temperature.[39]

Synthesis of the tetracyclic compound **1l** was performed in 2 steps: aqueous suspension of glycoluril **7a** with paraformaldehyde was at first maintained for 12 h at 70°C in the presence of NaOH (pH 8–10); then the obtained reaction mixture was treated with *tert*-butylamine and maintained for 16 h at 40°C.[14] The reaction product **1l** was isolated in 61% yield.

1.3. Condensation of glycoluril with *N*,*N*-bis-(methoxymethyl)alkylamines in the presence of $SmCl_3·6H_2O$ catalyst (method III)

A new method was proposed in 2015 for the synthesis of compounds **1b**,**e**,**l**,**m**, based on the condensation of glycoluril **7a** with *N*,*N*-bis(methoxymethyl)alkylamines (R^3 = Cy, 2-Pr, *t*-Bu, $(CH_2)_2OH$) in $CHCl_3$–EtOH medium and using $SmCl_3·6H_2O$ in the role of a catalyst (Scheme 1).[40] The target compounds were isolated by using column chromatography, resulting in 70–81% yields of compounds **1b**,**e**,**l**,**m**.

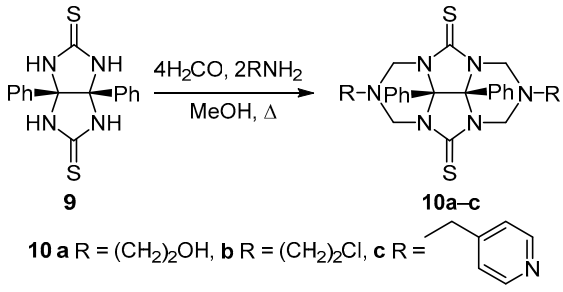
1.4. Modification of the tetracyclic compound **5d** by using click chemistry approach

In order to prepare fused tetracyclic compounds **5m**–**s**, which can be used as molecular clips, a three-stage synthetic route was developed[13] (Scheme 2), based on chemical transformations of diethoxycarbonylglycoluril **5d**.[41] As a first step, the dihydroxyethyl derivative **5d** was tosylated with TsCl in CH_2Cl_2 in the presence of Et_3N at room temperature. In the second step, the obtained tetracyclic compound **5k** was converted to azide **5l** by the action of NaN_3 in DMF. After the treatment of azide **5l** with various arylacetylenes in the medium of 1:1 *t*-BuOH–H_2O mixture in the presence of $CuSO_4$ and ascorbic acid (click reaction), the products were identified as compounds **5m**–**s** (obtained in 70–82% yields), which showed the properties of fluorescent chemosensors.

1.5. Synthesis of 2,6-dialkyl-3a^1,4a^1-diphenyl-1,3,5,7-tetrahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8-dithiones

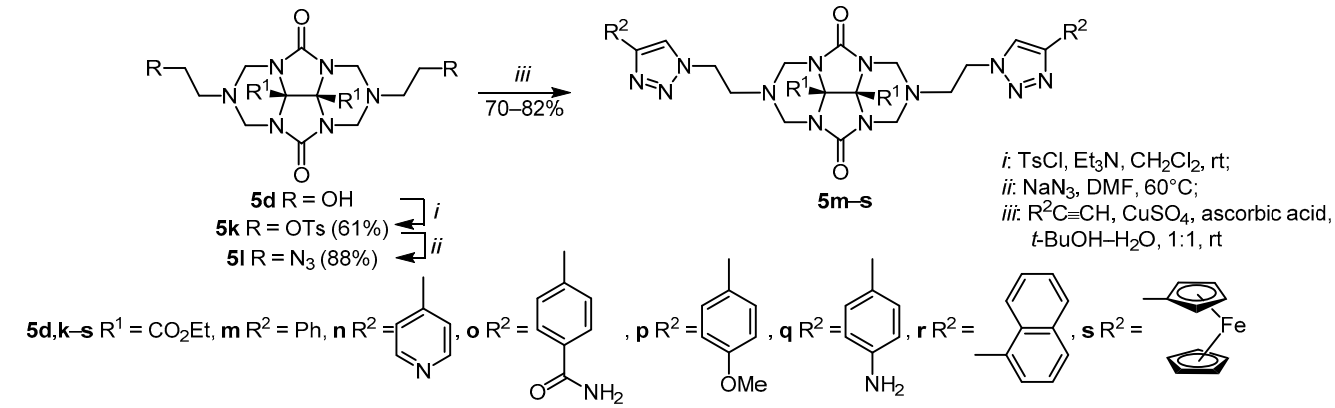
Thio analogs of the tetracyclic compounds **6a**–**c** were synthesized by using the method I (Scheme 1). 3a,6a-Diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dithione (**9**), aqueous 37% formaldehyde, and amines ((2-hydroxyethyl)amine, (2-chloroethyl)amine, and (4-pyridinyl)-methylamine)[14,15,42–44] were refluxed in MeOH (Scheme 3). Unfortunately, the reaction duration and yields were not reported in the publications, although the structure of the obtained 3a^1,4a^1-diphenylhexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8-dithiones **10a**–**c** was proved by X-ray structural analysis.

Scheme 3



Thus, a three-component one-pot condensation reaction of tetrahydroimidazo[4,5-*d*]imidazole-2,5-(1*H*,3*H*)-diones (glycolurils) **7a**–**e** with formaldehyde and amines (method I) serves as the main route for the synthesis of tetracyclic compounds **5a**–**j**. Among the other tetracyclic compounds **1**–**4**, **6**, **10**, only isolated examples (compounds **1a**,**b**, **2**–**4**, **10a**–**c**) were obtained by this method. Method II (the

Scheme 2

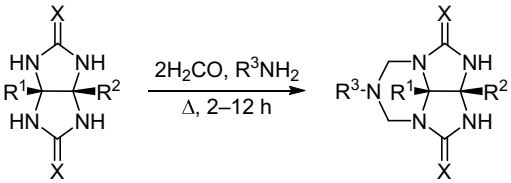


reaction of 1,3,4,6-tetrakis(hydroxymethyl)tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (**8a**) and its 3a,6a-tetramethylene-substituted analog **8b** with amines and amino acids) was used for the synthesis of compounds **1a**–**u** and **6a**–**i**. Method III (the condensation of glycoluril **7a** with *N*,*N*-bis(methoxymethyl)alkylamines in the presence of $SmCl_3 \cdot 6H_2O$ as catalyst) allowed to obtain four compounds: **1b**,**e**,**l**,**m**. The accessible range of tetracyclic compounds was expanded by employing the approach of click chemistry.

2. Synthesis of 2a,2a[1]-disubstituted (2-substituted) 6-alkyltetrahydro-5*H*-2,3,4a,6,7a-pentaazacyclopenta-[*cd*]indene-1,4(2*H*,3*H*)-diones(thiones)

The synthesis of tricyclic glycoluril derivatives, 2a,2a[1]-disubstituted 6-alkyltetrahydro-5*H*-2,3,4a,6,7a-pentaazacyclopenta[*cd*]indene-1,4(2*H*,3*H*)-diones(thiones) **11**–**14**, and their tetracyclic analog **15** was accomplished by a three-component condensation of 3a,6a-disubstituted tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones **7a**,**c**,**e** or their thio analog **9**, or compound **8b** with formaldehyde (used as solutions in an appropriate solvent) and amines or potassium salts of amino acids (Scheme 4).[8,16,25,37,45–48]

Scheme 4



7a,**c**,**e**, **8b**, **9** → **11**–**14**

11 X = O, $R^1 = R^2$ = H, $R^3 = (CH_2)_mCO_2H$, **a** m = 1, **b** m = 2, **c** m = 3

12 X = O, $R^1 = R^2 = CO_2Et$, **a** $R^3 = (CH_2)_2OH$, **b** R^3 = Bn, **c** $R^3 = CH_2C_6H_4Br$-*p*, **d** R^3 = Et

13 X = O, $R^1 = R^2$ = Ph, R^3 = Et

14 X = S, $R^1 = R^2$ = Ph, R^3 = HO-CH(Me)-CH2-

15 X = O, $R^1 + R^2 = (CH_2)_4$, **a** $R^3 = (CH_2)_2OH$, **b** $R^3 = CH_2CO_2H$

The reactions were performed in H_2O, MeOH, EtOH, and MeCN solutions. The tricyclic compounds **11a**–**c** were obtained in 35–50% yields by maintaining reaction mixtures for 2 h at 90°C. The observed products were formed by oligomerization between *N*-(hydroxymethyl)-glycolurils having various degree of hydroxymethylation at the nitrogen atoms, and also by oligomerization of these compounds with amino acids.[37]

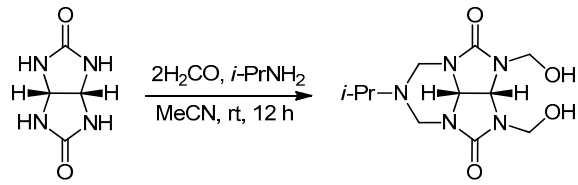
The synthesis of compound **12a** (20% yield) was performed in acetonitrile at room temperature over 12 h.[45] To synthesize compound **12b**,**c**, the reaction mixture was refluxed in MeOH.[46,47] Compounds **12d** and **13** were obtained analogously, using EtOH instead of MeOH (reaction duration 10–12 h).[16] The yields of products **12b**–**d**, **13** were in the range of 45–80%.

The condensation reaction between 3a,6a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dithione (**9**), aqueous 37% formaldehyde solution, and (*S*)-2-aminopropan-1-ol allowed to synthesize the tricyclic compound **14** (Scheme 4), but the yield was not reported.[48]

The tetracyclic compounds **15a**,**b** were obtained as by-products in the reactions of compound **8b** with (2-hydroxyethyl)amine and *N*-carbamoylglycine (in the form of potassium salt) (Scheme 4) under conditions that were analogous to those used for the synthesis of pentacyclic products **6** (H_2O, pH 9, 90°C, 2 h).[37]

It is interesting to note that performing the condensation between glycoluril **7a**, formaldehyde, and isopropylamine in acetonitrile at room temperature resulted in the synthesis of 2,3-bis(hydroxymethyl)-6-isopropylhexahydro-1*H*-2,3,4a,6,7a-pentaazacyclopenta[*cd*]indene-1,4(2*H*)-dione (**16**) in 20% yield (Scheme 5).[49]

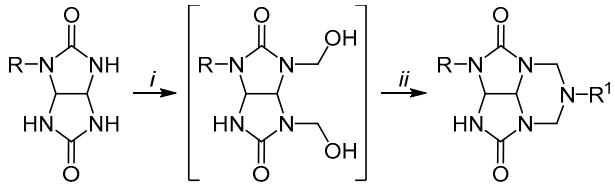
Scheme 5



7a → **16**

Our research group has performed the first one-pot two-stage condensation reactions of 1-(*tert*-butyl)- or 1-cyclohexyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones **17a**,**b** with formaldehyde and aliphatic amines (Scheme 6).[17] As a result, 2-substituted 6-alkyltetrahydro-1*H*-2,3,4a,6,7a-pentaazacyclopenta[*cd*]indene-1,4(2*H*,3*H*)-diones **18**, **19** were obtained in high yields ranging from 70 to 84% (14 examples) *via* the formation of intermediate compounds **20a**,**b**.

Scheme 6



17a,**b** → **20a**,**b** → **18**, **19**

i: H_2CO (2 equiv), *i*-PrOH–H_2O, 1:1, pH 8–9, 85°C, 1 h
ii: R^1NH_2, *i*-PrOH–H_2O, 1:1, 85°C, 1 h
17a, **18** R = *t*-Bu; **17b**, **19** R = Cy
18, **19** R^1 = Et, Pr, *n*-Bu, *sec*-Bu, *t*-Bu, Cy, $(CH_2)_2OH$

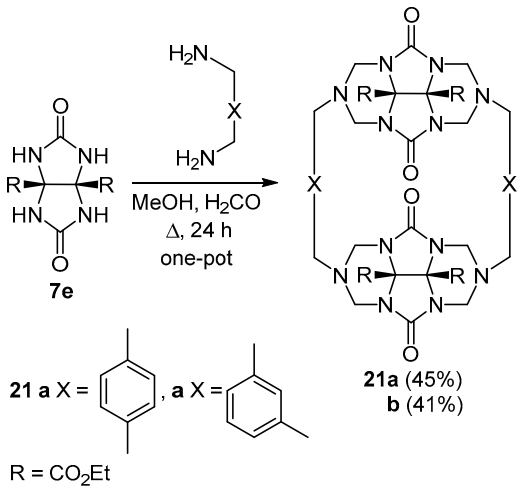
3. Synthesis of macrocyclic polyamines from glycolurils, diamines, and formaldehyde

The interest toward macrocyclic polyamines is motivated by the desire to obtain new objects for supramolecular chemistry research, characterized by the ability of self-assembly and molecular recognition. The simplest approach used for their synthesis is analogous to the method I, featuring a three-component condensation of reagents.

3.1. The synthesis of macrocyclic polyamines from 3a,6a-diethoxycarbonylglycoluril

Macrocyclic polyamines **21** were obtained by a condensation reaction of 3a,6a-bis(ethoxycarbonyl)-glycoluril (**7e**), formaldehyde (37% aqueous solution), and aliphatic diamines upon refluxing for 24 h in MeOH (Scheme 7).[8] The yields of products **21a**,**b** reached 45 and 41%, respectively.

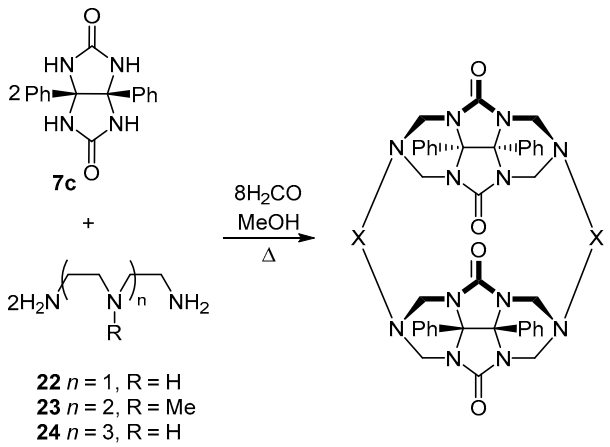
Scheme 7



3.2. Synthesis of macrocyclic polyamines from 3a,6a-diphenylglycoluril

Macrocyclic polyamines were synthesized from 3a,6a-diphenylglycoluril (**7c**), aliphatic diamines **22**–**24**, and formaldehyde (Scheme 8).[7] It is interesting to note that the use of diethylenetriamine **22** resulted in the isolation of two products: the expected macrocycle **25a** and an unexpected compound **25b**. This direction is only beginning to develop and for that reason only 6 examples of polycyclic polyamines of this type are known at this time.

Scheme 8



25 a X = $CH_2CH_2NHCH_2CH_2$ (42%),
b X = $CH_2CH_2N(CH_2CH_2NH_2)CH_2CH_2$ (6%),
c X = $CH_2CH_2N(Me)CH_2CH_2$ (76%),
d X = $CH_2CH_2NHCH_2CH_2NHCH_2CH_2$ (24%)

Overall, the analysis of literature sources indicates that the synthetic studies aimed at the preparation of fused tri-, tetra-, poly-, and macrocyclic polyamines by combining readily available reagents (glycolurils, formaldehyde, and amines or amino acids, as well as polyamines) are quite modern research. The continuing progress in this direction is driven by the practical importance of these compounds and by their applications in supramolecular chemistry research.

References

1. Barrow, S.J.; Kasera, S.; Rowland, M. J.; del Barrio, J.; Scherman, O. A. *Chem. Rev.* **2015**, *115*, 12320.
2. Svec, J.; Necas, M.; Sindelar, V. *Angew. Chem.*, *Int. Ed.* **2010**, *49*, 2378.
3. Svec, J.; Dusek, M.; Fejfarova, K.; Stacko, P.; Klán, P.; Kaifer, A. E.; Li, W.; Hudeckova, E.; Sindelar, V. *Chem.–Eur. J.* **2011**, *17*, 5605.
4. Havel, V.; Svec, J.; Wimmerova, M.; Dusek, M.; Pojarova, M.; Sindelar, V. *Org. Lett.* **2011**, *13*, 4000.
5. Singh, M.; Solel, E.; Keinan, E.; Reany, O. *Chem.–Eur. J.* **2015**, *21*, 536.
6. Singh, M.; Solel, E.; Keinan, E.; Reany, O. *Chem.–Eur. J.* **2016**, *22*, 8848.
7. Liu, S.; Wu, X.; Zhang, S.; Yao, J.; Liang, F.; Wu, C. *New. J. Chem.* **2004**, *28*, 562.
8. Li, Y.-T.; Wang, Y.-Z.; Wu, A.-X. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2006**, *E62*, o379.
9. Seprődi, J.; Sarkadi, B.; Hegedűs, T.; Kéri, G.; Őrfi, L.; Idei, M.; Hollósy, F.; Teplán, I.; Okada, Y. WO Patent 0220527.
10. Aumueller, A.; Neumann, P.; Trauth, H. EP Patent 0272588.
11. Aumueller, A.; Neumann, P.; Trauth, H. US Patent 4835273 A.
12. Vikharev, Yu. B.; Anikina, L. V.; Chikunov, I. E.; Sigachev, A. S.; Kravchenko, A. N.; Shklyaev, Yu. V.; Makhova, N. N. *Vopr. Biol.*, *Med. Farm. Khimii* **2006**, *4*(2), 12.
13. Gao, M.; Cao, L.; Wang, Z.; Sun, J.; She, N.; Wu, A. *Synlett* **2009**, 315.
14. Wingard, L. A.; Johnson, E. C.; Sabatini, J. J. *Tetrahedron Lett.* **2016**, *57*, 1681.
15. Li, Y.; Meng, X.; Cao, L., Wang, Y.; Yin, G.; Gao, M.; Wen, L.; Wu, A. *Cryst. Growth Des.* **2008**, *8*, 1645.
16. Cao, L.; Meng, X.; Gao, M.; She, N.; Wu, A. *Acta Crystallogr.*, *Sect. C: Cryst. Struct. Commun.* **2008**, *C64*, o69.
17. Lozhkin, B. V.; Sigachev, A. S.; Kravchenko, A. N.; Lyssenko, K. A.; Kolotyrkina, N. G.; Makhova, N. N. *Mendeleev Commun.* **2007**, *17*, 85.
18. Savostianoff, D. FR Patent 2291203.
19. Salkeeva, L. K.; Shibaeva, A. K.; Bakibaev, A. A.; Taishibekova, E. K.; Minaeva, E. V.; Zhortarova, A. A.; Sal'keeva, A. K. *Russ. J. Gen. Chem.* **2014**, *84*, 338. [*Zh. Obshch. Khim.* **2014**, *84*, 344.]
20. Li, Y.; Li, J. *Acta Crystallogr.*, *Sect. E: Struct. Rep. Online* **2006**, *E62*, o5144.
21. Li, Y.; Guo, Q. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2006**, *E62*, o3463.
22. Li, Y.; Chen, Y.; She, N.; Wu, A. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2005**, *E61*, o3364.
23. Li, Y.; Wang, Z.; Yin, G.; Wu, A. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2005**, *E61*, o2187.
24. Yin, G.; Chen, Y.; Zhou, B.; Wu A. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2005**, *E61*, o2467.
25. Yin, G.; Wang, Z.; Chen, Y.; Wu, A.; Pan, Y. *Synlett* **2006**, 49.
26. Yin, G.; Zhou, B.; Chen, Y.; Wu, A. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2005**, *E61*, o2632.

27. Hu, S.; Wang, S.; Cao, L. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2007**, *E63*, o4542.
28. Yin, G.; Zhou, B.; Wu, A. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2005**, *E61*, o2787.
29. Qin, S.; Pang, T.; Li, Y. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2008**, *E64*, o1689.
30. Guo, H.; She, N.; Li, Y. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2006**, *E62*, o5596.
31. Li, Y.; Zhou, B.; Yin, G.; Wu, A. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2005**, *E61*, o3368.
32. Li, Y.; Wang, Z.; Chen, Y.; Chen, A. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2005**, *E61*, o4128.
33. Li, J.; Hu, Y.; Wang, Z. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2007**, *E63*, o4777.
34. Li, Y.; Long, T.; Wu, A. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2005**, *E61*, o2374.
35. Li, Y.; Wang, Y.; Wu, A. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2006**, *E62*, o379.
36. Kravchenko, A. N.; Sigachev, A. S.; Gazieva, G. A.; Maksareva, E. Yu.; Trunova, N. S.; Chegaev, K. Yu.; Lyssenko, K. A.; Lyubetsky, D. V.; Struchkova, M. I.; Il'in, M. M.; Davankov, V. A.; Lebedev, O. V.; Makhova, N. N.; Tartakovsky, V. A. *Chem. Heterocycl. Compd.* **2006**, *42*, 365. [*Khim. Geterotsikl. Soedin.* **2006**, 411.]
37. Kravchenko, A. N.; Chikunov, I. E.; Lyssenko, K. A.; Baranov, V. V. *Chem. Heterocycl. Compd*. **2014**, *50*, 1322. [*Khim. Geterotsikl. Soedin.* **2014**, 1434.]
38. Chikunov, I. E.; Kravchenko, A. N.; Makhova, N. N. *Mendeleev Commun*. **2007**, *17*, 321.
39. Qin, S.; Lib Y. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2006**, *E62*, o1812.
40. Khairullina, R. R.; Geniyatova, A. R.; Meshcheryakova, E. S.; Khalilov, L. M.; Ibragimov, A. G.; Dzhemilev, U. M. *Russ. J. Org. Chem*. **2015**, *51*, 116. [*Zh. Org. Khim.* **2015**, *51*, 118.]
41. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem*., *Int. Ed*. **2001**, *40*, 2004.
42. Wang, Z.; Xi, H. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2009**, *E65*, o1426.
43. Wu, Y.; Sun, Y. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2009**, *E65*, o1715.
44. Deng, C.; Shu, W.; Zhang, D. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2010**, *E66*, o1524.
45. Li, Y. T.; Li, J., Wen, L. L. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2007**, *E63*, o287.
46. Cao, L.; Wang, Z.; Hu, Y. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2007**, *E63*, o4540.
47. Cao, L. P.; Wang, Z. G.; Hu, Y. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2007**, *E63*, o4740.
48. Wang, M.; Wang, J.; Xiang, J. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2011**, *E67*, o2060.
49. Xi, H. L.; Gao, M.; Cao, L.-P.; Li, Y.-T. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2007**, *E63*, o400.