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Synthesis and cytotoxicity of novel γ-piperidone-containing dibenzo-1,7-diaza-14-crown-4 ethers

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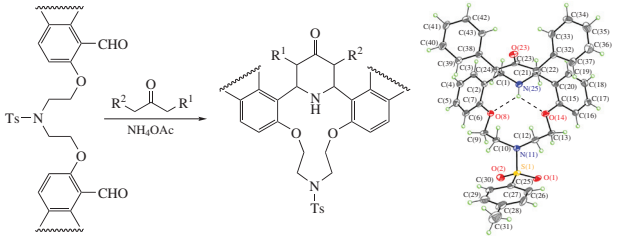
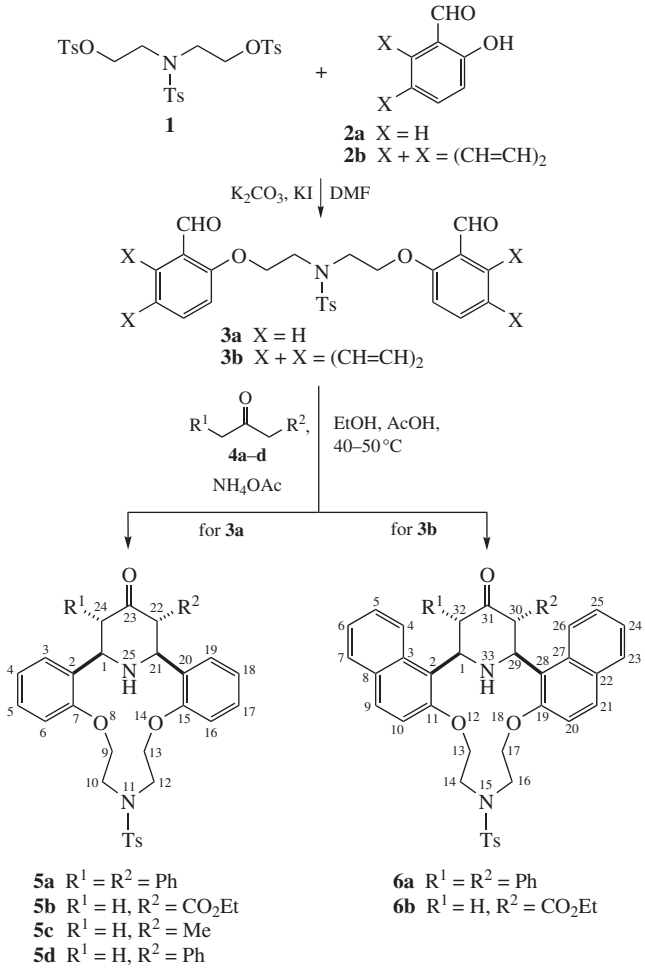
For the development of new antitumor agents, novel dibenzo-1,7-diaza-14-crown-4 ethers containing γ-piperidone moiety were synthesized by a domino condensation of new podands, ketones and ammonium acetate. The crystal structure of one of them was studied by X-ray diffraction. Four crown compounds were evaluated *in vitro* for cytotoxic activity against 5 human cancer cell lines.



At present, the domino reactions were applied to the synthesis of N-macroheterocycles being of interest to researchers[1–6]. Azacrown ethers form metal complexes[3,7,8] possessing high cytotoxicity against several human cancer cell lines.[9,10] Herein, we employed a simple one-pot multicomponent condensation reaction to access novel 1,7-diaza-14-crown-4 ethers containing γ-piperidone moiety from special podands, ammonium acetate and ketones. The combination of γ-piperidone and diazacrown ether moieties in one molecule promises to bring a novel chemotype of macromolecular host for metal cations.

Podands **3a**,**b** were prepared from *N*,*N*-bis(2-tosyloxyethyl)-*N*-tosylamine **1** and hydroxy aldehydes **2a**,**b** according to known procedure[9,10] (Scheme 1). The multicomponent condensation of podands **3a**,**b**, ketones **4a–d** and ammonium acetate taken in the ratio of 1 : 1 : 10, respectively, gave γ-piperidone-containing 4,11-diaza-14-crown-4 ethers **5**, **6**.† Their structures were determined by IR, ^{1}H NMR, ^{13}C NMR, HRMS spectroscopy and X-ray analysis.



Scheme 1

† *General procedure for the synthesis of γ-piperidone-containing 1,7-diaza-14-crown-4-ethers* **5**, **6**. Equimolar amounts of podands **3a**,**b** (0.64 mmol) and ketones **4a–d** (0.64 mmol) were stirred in ethanol/acetic acid mixture at 40–50 °C in the presence of ammonium acetate (0.49 g, 6.4 mmol). The reaction was monitored by TLC and completed after 24 h. The mixture was cooled to room temperature (25 °C) and neutralized with K_2CO_3 solution; then, the product was extracted with dichloromethane (3 × 30 ml) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure; the residue was purified by column chromatography and recrystallized from ethanol to obtain pure 1,7-diaza-14-crown-4-ether product.

*(1*RS*, 21*SR*, 22*RS*, 24*SR*)-22,24-Diphenyl-11-tosyl-8,14-dioxa-11,25-diazatetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18-hexaen-23-one* **5a**. Yield 53%, mp 275–277 °C. R_f = 0.53 (hexane–ethyl acetate, 1 : 1). IR (KBr, ν/cm^{-1}): 3296.35, 2926.01, 2875.86, 1695.43 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.80 (d, 2H, H-26, H-30, ^3J 8.0 Hz), 7.35 (d, 2H, H-27, H-29, ^3J 8.0 Hz), 7.12–7.14 (br. m, 4H, H-4, H-18), 7.02–7.08

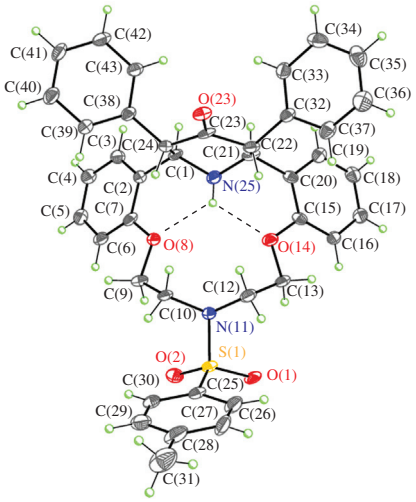


Figure 1 Molecular structure of **5a** (50% displacement ellipsoids). The intramolecular N–H···O hydrogen bonds are depicted by dashed lines.

Structural features of 1,7-diaza-14-crown-4 ether **5a** have been ultimately established by single crystal X-ray diffraction study (Figure 1).‡ The molecule of **5a** possesses the idealized C_s (m) intrinsic symmetry. However, in the crystal the geometry of **5a** is slightly distinguished from the idealized one due to the crystal packing effects. Compound **5a** crystallizes as a chloroform disolvate, *i.e.*, **5a**·2$CHCl_3$. The molecule of **5a** comprises a fused tetracyclic system containing the diaza-14-crown-2-ether macrocycle, piperidone and two benzene rings. The diaza-14-crown-2-ether ring adopts a bowl conformation which is stabilized by the two intramolecular N–H···O hydrogen bonds (Table S1, see Online Supplementary Materials). The configuration of the C(7)–O(8)–C(9)–C(10)–N(11)–C(12)–C(13)–O(14)–C(15) azapolyether chain is t–g^-–g^-–g^+–g^+–t (t = *trans*, 180°; g = *gauche*, ±60°). The central piperidone ring has a distorted (flattened from a side of the carbonyl group) *chair* conformation. Two phenyl substituents occupy the sterically more favorable equatorial positions. The dihedral angles between the basal C(1)–C(21)–C(22)–C(24) plane of the piperidone ring and planes of the two benzene rings fused to the diaza-14-crown-2-ether moiety are 81.66(13) and 81.08(13)°. Both nitrogen atoms have a trigonal pyramidal configuration.

The molecule of **5a** possesses four asymmetric centers at the C(1), C(21), C(22) and C(24) carbon atoms and potentially can have sixteen diastereomers. The crystal of **5a** is racemic and consists of enantiomeric pairs with the following relative configuration of the centers: 1*RS*,21*SR*,22*RS*,24*SR*. Such a diastereoselectivity of multicomponent assembling of complex molecule of types **5**,**6** is worthwhile of note.

In the crystal, the molecules of **5a** form centrosymmetrical dimers *via* the intermolecular C–H···O hydrogen bonds. The H-bonded dimers are arranged at van der Waals distances (Table S1, Figures S1 and S2, see Online Supplementary Materials).

In the search for new antitumor agents, some representatives among herein synthesized γ-piperidone-containing 1,7-diaza-14-crown-4 ethers were tested towards cytotoxicity against five human tumor cell lines, namely, Hep-G2 (Human hepatocellular carcinoma), Lu-1 (Human lung adenocarcinoma), RD (Human rhabdomyosarcoma), MCF-7 (Human breast adenocarcinoma), HeLa (HeLa cervical cancer cells) and on the Vero cell line. Compounds **5a**,**b**,**d** and **6a** have been selected due to their high solubility. (Tables 1 and 2). Crown compound **5b** has inhibited the Hep-G2 and Lu-1 cell line with IC_{50} of 4.32 and 6.64 μg ml^{-1}, respectively (see Table 2). In continuation of biological evaluation of potential antitumor agents, compound **5b** was tested for cytotoxicity on the Vero cell line (normal African green monkey kidney cell line) and it did not show activity on the Vero cell line.

In conclusion, we have synthesized six (γ-piperidone-containing 1,7-diaza-14-crown-4 ethers by three-component domino reactions of simple reactants, podands **3a**,**b**, ammonium acetate and ketones. The assembling proceeds with high diastereoselectivity. *In vitro* cytotoxicity tests revealed that compound **5b** could inhibit the

Table 1 Cytotoxicity tests performed on compounds **5a**, **5b**, **5d**, **6a** (5 μg ml^{-1}) against five cancer cell lines and Vero cell line.

Entry	Compound	Cell line with cell survival (%)						Result
		Hep-G2	LU-1	RD	MCF-7	HeLa	Vero	
1	DMSO	100	100	100	100	100	100	
2	Taxol (+)	1.34±0.82	1.66±0.95	2.12±0.38	4.71±1.55	3.42±1.63	30.07±1.51	Positive
3	**5a**	97.65±2.21	98.16±0.39	96.33±1.41	99.30±0.87	99.14±0.72	93.56±1.98	Negative
4	**5b**	31.29±2.09	48.61±1.65	99.22±0.34	84.12±2.27	97.33±0.91	95.79±1.57	Positive with Hep-G2. LU-1
5	**5d**	98.06±1.28	97.92±1.55	99.02±0.67	96.14±1.62	97.56±1.70	85.34±2.32	Negative
6	**6a**	99.12±0.57	96.89±2.51	98.39±1.12	98.77±1.60	99.60±0.14	92.98±2.08	Negative

(m, 10H, 2×Ph), 6.78 (d, 2H, H-3, H-19, ^3J 8.0 Hz), 6.75 (br. d, 2H, H-6, H-16, ^3J 6.5 Hz), 6.61 (br. t, 2H, H-5, H-17, ^3J 6.5 Hz), 4.89 (br. d, 2H, H-1, H-21, ^3J 8.5 Hz), 4.38–4.45 (br. m, 7H, H-22, H-24, 2×H-9, 2×H-13, NH-25), 3.76 (br. s, 2H, 2×H-10), 3.61 (br. m, 2H, 2×H-12), 2.42 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 156.22, 131.79, 130.01, 129.50, 128.53, 127.77, 126.35, 121.28, 51.15, 21.51. HRMS, *m/z*: 703.2441 [M+HCOO$^-$] (calc. for $C_{41}H_{39}N_2O_7S$, *m/z*: 703.2483).

‡ *Crystal data for* **5a**. The crystal of **5a** ($C_{40}H_{38}N_2O_5S·2CHCl_3$, M = 897.52) is triclinic, space group $P\bar{1}$, at T = 100 K: a = 11.606(2), b = 13.856(3) and c = 14.920(3) Å, α = 83.37(3)°, β = 67.38(3)°, γ = 71.40(3)°, V = 2099.0(9) Å^3, Z = 2, d_{calc} = 1.420 g cm^{-3}, $F(000)$ = 928, μ = 1.261 mm^{-1}. X-ray diffraction data were collected on the 'Belok' beamline (λ = 0.96330 Å) of the National Research Center 'Kurchatov Institute' using a Rayonix SX165 CCD detector. A total of 720 images for two orientations of the crystal (21088 reflections, 8513 independent reflections, R_{int} = 0.117) were collected using an oscillation range of 1.0° (φ scan mode, $2\theta_{max}$ = 76.76°) and corrected for absorption using the 'Scala' program (T_{min} = 0.830, T_{max} = 0.880).[11] The data were indexed, integrated and scaled using the utility iMOSFLM in CCP4 program.[12] The structure was determined by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The crystal was found to contain two solvate chloroform molecules in the asymmetric unit. All attempts to model and refine positions of the solvate chloroform molecules were unsuccessful. Therefore, their contribution to the total scattering pattern was removed using the utility SQUEEZE in PLATON16.[13] The hydrogen atom of the NH group was localized in the difference-Fourier map and included into the refinement with fixed positional and isotropic displacement parameters [U_{iso}(H) = = 1.2 U_{eq}(N)]. The other hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.5 U_{eq}(C) for the methyl groups and 1.2 U_{eq}(C) for the other groups]. The final divergence factors were R_1 = 0.118 for 4201 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.289 for all independent reflections, S = 0.953. The calculations were carried out using the SHELXTL program.[14]

CCDC 1888670 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Table 2 Results of IC_{50} tests for compound **5b**.

Entry	Compound	Cell line IC_{50} (μg ml^{-1})	
		Hep-G2	Lu-1
1	Taxol (+)	0.31	0.50
2	**5b**	4.32	4.64

Hep-G2 cell line (IC_{50} of 4.32 μg ml^{-1}, equivalent 7.47 μM) and Lu-1 cell line (IC_{50} of 4.64 μg ml^{-1}, equivalent 7.90 μM).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.07.004.

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