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Synthesis and cytotoxic activity of new annulated furazan derivatives

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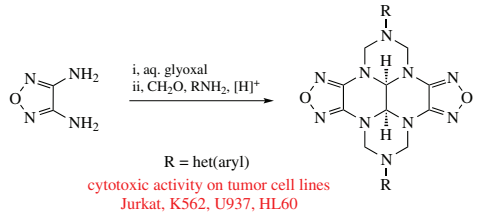
New 2,8-di(het)aryl-containing dioxadecaazadicyclopenta[*e*,*l*]pyrenes, furazan-annulated polyaza polycycles, have been synthesized by acid-catalyzed cyclocondensation of difurazanotetraazadecalin with formaldehyde and primary (het)arylamines. The cytotoxic activity of these compounds against tumor cell lines (Jurkat, K562, U937, HL60) has been estimated.



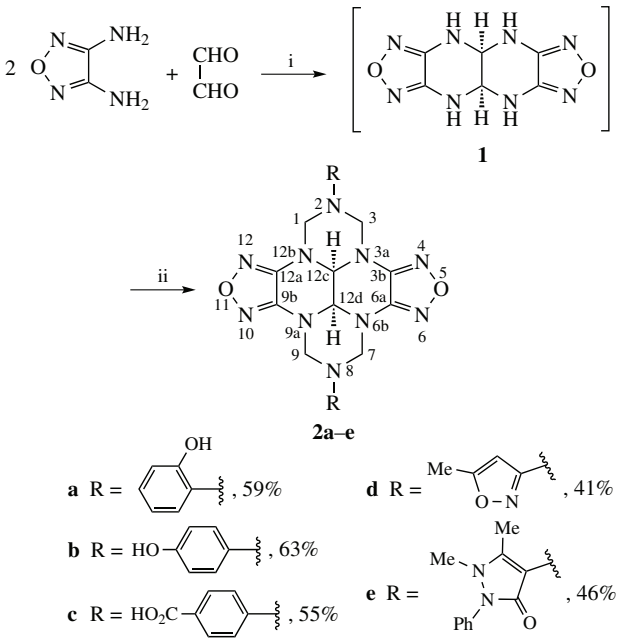
Keywords: heterocyclization, aza-acetalization, aminals, furazans, Brønsted acids, polycycles, 5,11-dioxa-2,3a,4,6,6b,8,9a,10,12,12b-decaazadicyclopenta[*e*,*l*]pyrenes, cytotoxic activity.

The development of new selective syntheses of functionalized molecules using heterocyclic reactants with specified structures as building blocks is the basis in the design of molecular systems with varying degrees of complexity. 1,2,5-Oxadiazole (furazan) is used as an efficient building block in the synthesis of heterocyclic compounds.[1] Heterocycles comprising an oxadiazole moiety possess valuable properties[2–4] and exhibit antiatherogenic,[5] antimalarial,[6] antimicrobial,[7,8] neuroprotective[9] and antiproliferative[10] activities. For this reason, the synthesis of new furazan derivatives is a promising goal. The design of heterocyclic assemblies of this class is interesting in terms of creating hybrid[11] pharmacologically active molecules.

Recently,[12] we demonstrated the possibility of the one-pot assembling of dicycloalkyl-substituted dioxadecaazadicyclopenta[*e*,*l*]pyrenes with antitumor activity by a catalytic reaction of tetraazadifurazanodecaline with 1,3,5-triazinanes as highly efficient cycloaminomethylating synthons.[13] Taking into account the results of the synthesis of annulated polyazapolycycles[14–17] and to expand the library of difurazanohexaazapyrene compounds,[12] our experiments were aimed at elucidating the possibility of a selective synthesis of new annulated furazans with pharmacologically active substituents. We turned our attention to the one-pot catalytic cyclocondensation of functionally substituted (het)arylamines with formaldehyde and 1,4,5,8-tetraazadifurazano[3,4-*c*][3,4-*h*]decalin[18] (compound **1** obtained *in situ* from 3,4-diaminofurazan and glyoxal) as the principal building block. Previously, we used salts of rare earth elements, which are hard Lewis acids, as the catalysts for the activation of the starting compounds under three-component condensation conditions.[19,20]

In this study, Lewis acids did not show activity in the attempted reaction of compound **1** with amines and formaldehyde. However, we succeeded in performing it by moving to Brønsted acid as the proton donor. In fact, the reaction between compound **1**, formaldehyde and *o*-aminophenol in MeOH–DMSO in the presence of catalytic amounts of conc. HCl (5 mol%) results in 2,8-bis(2-hydroxyphenyl)-substituted dioxadecaazadicyclopenta[*e*,*l*]pyrene **2a** in 59% yield (Scheme 1). The MeOH–DMSO mixture was the solvent of choice because of good solubility of the starting reagents in it. The optimal ratio of the MeOH–DMSO solvent mixture is 10 : 1 (v/v) since an excess of DMSO in the reaction medium makes it difficult to isolate the target product. The application of other (het)arylamines in such a reaction under the optimal conditions selectively gave analogous products **2b–e** in 41–63% yields (see Scheme 1).

Compounds **2a–e** were isolated pure, and their structures were determined by spectral methods. The structures of derivatives **2c**,**e** were supported by X-ray diffraction analysis



Scheme 1 *Reagents and conditions*: i, H_2O, HCl, 60 °C, 1 h; ii, RNH_2 (2 equiv.), CH_2O (aq., 4 equiv.), HCl (5 mol%), MeOH–DMSO, room temperature, 3 h.

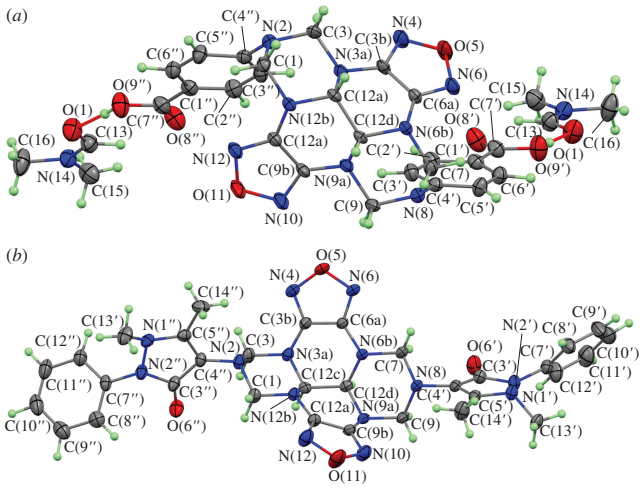


Figure 1 Molecular structure of (*a*) compound **2c** (solvate with two DMF molecules) and (*b*) compound **2e**, with the atoms presented as thermal vibration ellipsoids with 30% probability.

(Figure 1).† Crystalline solvate **2c** has a monoclinic crystal lattice, in which the independent part of the unit cell comprises one half of the molecule of the basic compound **2c** and a DMF molecule linked to each other by a strong O–H···O hydrogen bond ($Z = 4$, $Z' = 0.5$). Molecules of **2e** also form monoclinic crystals (space group $P2_1/c$), but the independent part of the unit cell contains one molecule ($Z = 4$, $Z' = 1$). The molecules of compound **2c** are in a particular position; the twofold symmetry axis passes through the middle of the C(12c)–C(12d) bond, while molecules of **2e** occupy a general position in the crystal. The piperazine rings of both samples **2c**,**e** have a *cis*-junction and the torsion angles H(12c)–C(12c)–C(12d)–H(12d) are 51.6(14) and 59.0(3)°, respectively. The triazinane rings acquire the *chair* conformation, while the piperazine rings acquire the *sofa* conformation. The substituents occupy equatorial positions relative to the heterocyclic frame in structure **2e** and an axial position in structure **2c**. The phenyl and pyrazolone rings in the antipyrine moieties of structure **2e** reside in different planes. The torsion angles C(3″)–N(2″)–C(7″)–C(12″) and C(3′)–N(2′)–C(7′)–C(8′) are 122.8(3) and 121.1(3)°, respectively. The O···O distance in the classical O–H···O hydrogen bond connecting the molecules of compound **2c** and DMF is 2.603(4) Å, which meets the criteria of a strong O–H···O hydrogen bond.[25]

Table 1 The *in vitro* cytotoxic activity of dioxadecaazadicyclopenta[*e*,*l*]pyrenes **2a–e** against tumor cell lines Jurkat, K562, U937, HL60.

Compound	Jurkat (IC_{50}/μM)	K562 (IC_{50}/μM)	HL60 (IC_{50}/μM)	U937 (IC_{50}/μM)	Fibroblasts (IC_{50}/μM)
2a	0.62±0.06	0.75±0.07	0.51±0.05	0.59±0.05	4.28±0.39
2b	3.11±0.29	3.68±0.34	2.64±0.24	2.89±0.27	21.14±1.98
2c	2.95±0.27	3.42±0.31	2.39±0.25	2.71±0.26	20.88±2.12
2d	0.49±0.05	0.42±0.04	0.39±0.04	0.46±0.04	4.11±0.43
2e	1.84±0.18	1.92±0.21	1.44±0.15	1.76±0.16	16.27±1.42

The biological study (Table 1) revealed that compounds **2a–e** exhibited a cytotoxic effect against a number of suspension tumor cell lines (Jurkat, K562, U937, HL60) in the range of 0.39–3.68 μM and against normal fibroblasts in the range of 4.11–21.14 μM. The compounds have a rather high selectivity index toward tumor cells (SI = IC_{50} fibroblasts /IC_{50} cancer cells) that ranges from 6 to 11. The highest cytotoxic activity (0.39–0.75 μM) was demonstrated by dioxadecaazadicyclopenta[*e*,*l*]pyrenes **2a**,**d** containing 2-hydroxyphenyl and 5-methylisoxazol-3-yl substituents. Compound **2d** showed the highest cytotoxicity among the compounds studied. It should be noted that a pronounced decrease in cytotoxicity is observed on passage from difurazanohexaazapyrene with 2-hydroxyphenyl substituent (**2a**) to its structural analogues with 4-hydroxy- or 4-carboxyphenyl substituents (**2b**,**c**). Compound **2e** containing antipyrine substituent exhibited cytotoxic activity in the range of 1.44–1.92 μM.

In conclusion, the one-pot cyclocondensation of 1,4,5,8-tetraazadifurazano[3,4-*c*][3,4-*h*]decalin with formaldehyde and functionally substituted (het)arylamines under Brønsted acid catalysis is an efficient method for synthesizing new 2,8-di(het)aryl-substituted dioxadecaazadicyclopenta[*e*,*l*]pyrenes with pronounced cytotoxic activity. The suggested synthesis of annulated polyazapolycycles with two oxadiazole rings along with pharmacologically active substituents, including natural metabolites with pronounced biological activity, opens up a way to a wide range of new hybrid molecules.

This study was carried out under the research plans of the IPC RAS on the subject ‘Metal-complex and heterogeneous catalysis in the design of macroheterocycles and heteroatomic compounds’, State Registration no. AAAA-A19-119022290010-9 (2019–2021), as well as with financial support from the Stipendium of the President of the Russian Federation to young scientists and graduate students (SP-197.2019.4) and Russian Foundation for Basic Research (grant no. 18-29-09068). The structural studies of the compounds were performed at the ‘Agidel’ Center for Collective Use at the Ufa Federal Research Center of the Russian Academy of Sciences with the financial support of the Russian Ministry of Education and Science (grant no. 2019-05-595-000-058).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.026.

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† *Crystal data for* **2c**. $C_{30}H_{34}N_{12}O_8$ (M = 690.69), monoclinic, space group $C2/c$: a = 11.8738(15), b = 8.6947(9) and c = 32.191(4) Å, β = 92.819(13)°, V = 3319.3(7) Å^3, Z = 4, d_{calc} = 1.382 g cm^{-3}, μ(MoKα) = 0.104 mm^{-1}, F(000) = 1448.0. A total of 6698 reflections were collected (3779 independent, R_{int} = 0.0504) and used in the refinement, which converged to wR_2 = 0.1742, GOOF = 1.074 for all independent reflections [R_1 = 0.0730 was calculated for 3779 reflections with $I > 2\sigma(I)$].

Crystal data for **2e**. $C_{32}H_{32}N_{14}O_4$ (M = 676.71), monoclinic, space group $P2_1/c$: a = 16.6130(11), b = 11.0964(5) and c = 18.7678(12) Å, β = 109.229(7)°, V = 3266.7(4) Å^3, Z = 4, d_{calc} = 1.376 g cm^{-3}, μ(MoKα) = 0.097 mm^{-1}, F(000) = 1416.0. A total of 16188 reflections were collected (7479 independent reflections, R_{int} = 0.0385) and used in the refinement, which converged to wR_2 = 0.0996, GOOF = 0.841 for all independent reflections [R_1 = 0.0524 was calculated for 7479 reflections with $I > 2\sigma(I)$].

The X-ray diffraction measurements for compounds **2c**,**e** were performed on an Agilent XCalibur (Gemini, Eos) diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The collected data were processed using the CrysAlisPro program.[21] The structures of **2c**,**e** were solved with the SHELXS[22] and SHELXT[23] programs, respectively. The structure refinement was carried out using SHELXL (full-matrix least-squares on F^2).[24] All hydrogen atoms were located in the Difference Fourier map and refined isotropically.

CCDC 2042588 and 2042590 contain 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.

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