Synthesis and antineoplastic properties of (1*H*-1,2,3-triazol-1-yl)furazans*

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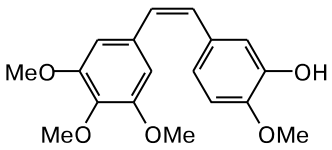
A method of 3-amino-4-[5-aryl(heteroaryl)-1*H*-1,2,3-triazol-1-yl)]furazan synthesis was optimized. Condensation of these compounds with 2,5-dimethoxytetrahydrofuran resulted in a series of previously unknown 4-[5-aryl(heteroaryl)-1*H*-1,2,3-triazol-1-yl)]-3-(pyrrol-1-yl)furazans. All target compounds were evaluated for both antimitotic microtubule destabilizing effect in a phenotypic sea urchin embryo assay and cytotoxicity in a panel of 60 human cancer cell lines. Pyrrolyl derivatives of triazolylfurazans were determined as antiproliferative compounds. The most potent microtubule targeting compounds **7a** and **7e** are of interest for further trials as antineoplastic agents.

Key words: azidofurazans, 1,3-dicarbonyl compounds, 1,3-dipolar cycloaddition, 2,5-dimethoxytetrahydrofuran, 3-amino(pyrrol-1-yl)-4-[5-aryl(hetaryl)-1*H*-1,2,3-triazol-1-yl]-furazans, antineoplastic activity, sea urchin embryos.

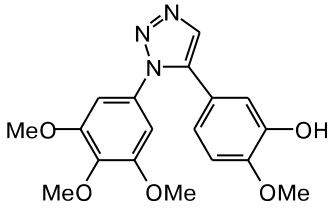
Five-membered heterocycles are frequently used in the synthesis of antimitotics that was studied in detail[1] for the analogs of natural compound combretastatin A-4 (CA-4). A water-soluble phosphorylated prodrug of CA-4 is currently undergoes clinical trials in the USA as antitumor agent.[2,3] An introduction of 1,2,3-triazole (1,2,3-triazolocombretastatin)[4,5] and furazan (combretafurazan)[6] rings into combretastatin framework was regarded as a non-isomerizable and metabolically stable bioisosteric replacement of the double bond in *cis*-stilbenes allowing the synthesis of new promising anticancer compounds.

Compared to combretastatin, combretafurazan is a more potent cytotoxic compound *in vitro* against neuroblastoma cells, yet maintaining similar pharmacokinetic properties.[6] 1,2,3-Triazole-bridged combretastatin analog[4,5] exhibits both strong cytotoxicity against ovarian cancer cells and vascular disrupting activity in tumors.[6] Moreover, this compound is more water-soluble than combretafurazan.

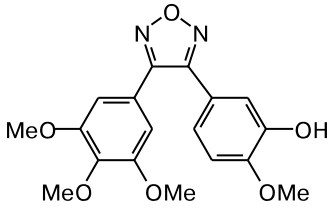
Water-soluble biologically active compounds containing both cycles, *e.g.*, (1,2,3-triazol-1-yl)furazans **1**, exhibiting other mechanisms of action were synthesized. Thus, compounds with the (1,2,3-triazol-1-yl)furazan moieties inhibit glycogen synthase kinase (GSK-3), a target in the treatment of Alzheimer's disease and type 2 diabetes.[7] Other analogs of (1,2,3-triazol-1-yl)furazans inhibit the SARS CoV M^{pro} cysteine protease, an important enzyme responsible for the intracellular replication of severe acute respiratory syndrome coronavirus.[8a] Several (1,2,3-triazol-1-yl)furazan derivatives selectively stimu-



Combretastatin A-4



1,2,3-Triazole-bridged combretastatin analog



Combretafurazan

* Dedicated to Academician of the Russian Academy of Sciences I. P. Beletskaya on the occasion of her anniversary.

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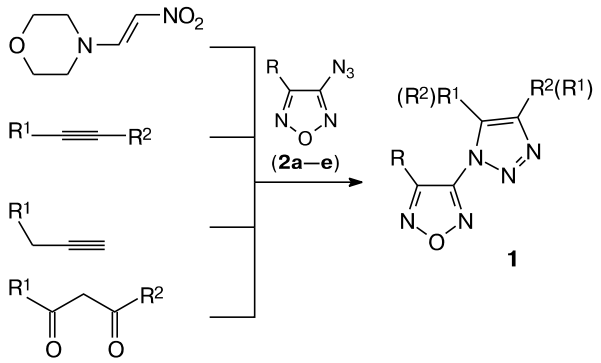
late NO-dependent activation of soluble guanylate cyclase (sGC).[8b]

In the present work we aimed to study a series of (1,2,3-triazol-1-yl)furazans **1** as potential antineoplastic agents, since these compounds can be synthesized by well elaborated methods.[9—15] Synthesis of these compounds involved 1,3-dipolar cycloaddition of azidofurazans **2** to various dipolarophiles, *e.g.*, acetylenes, morpholinonitroethylene, or compounds with the activated methylene group, *e.g.*, activated nitriles and 1,3-dicarbonyl compounds. The disadvantage of majority of these methods is the formation of 1,2,3-triazole regioisomers. Depending on the type of the substituents, dipolarophiles add differently to the azidofurazans yielding isomeric 4,5- or 5,4-derivatives (Scheme 1).

Scheme 1



2: NH_2 (**a**), Me (**b**), OMe (**c**), Ph (**d**), (**e**)

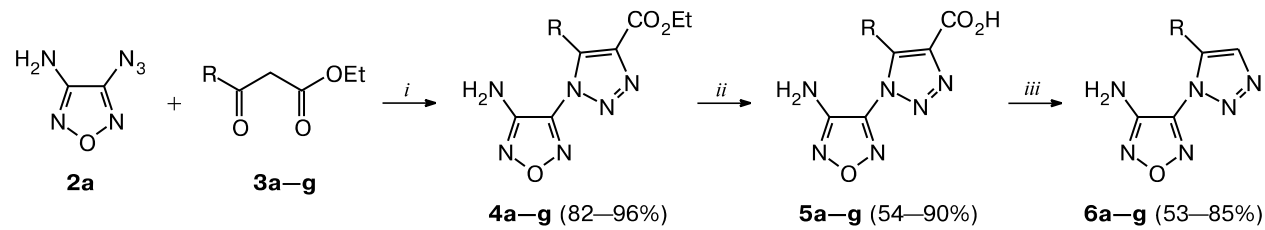
The regioselective cycloaddition of aroylacetic esters to azidofurazans was described; in the cycloaddition products, the aryl substituent and the ester group were located, respectively, at the positions 5 and 4 of the triazole ring.[10] However, only two compounds of this type with Ar = Ph and 4-ClC_6H_4 synthesized from the corresponding aroylacetates are known. To provide feasible antineoplastic properties, it is necessary to introduce into the triazolylfurazan structure either alkoxybenzene moieties or heterocyclic pharmacophores and to remove the ester group.

Thereby, the aim of the present work was the optimization of the synthetic procedure for [5-aryl(hetaryl)-1*H*-1,2,3-triazol-1-yl]furazan derivatives and biological evaluation of the target compounds for antiproliferative properties. It was also necessary to clarify whether the regioselectivity of cycloaddition of azidofurazan to aroyl(hetaroyl)acetates **3** with other aromatic or heteroaromatic substituents will be retained. In addition, to extend the scope of triazolylfurazan derivatives with potential antineoplastic activity, we used the Clauson—Kaas pyrrole synthesis involving the reaction of primary amino group of the furazan ring with dimethoxytetrahydrofuran.

For these purposes, aroylacetic esters **3a—g** were involved in the cyclocondensations with aminoazidofurazan **2a** under conditions developed earlier.[10] The ^1H and ^{13}C NMR spectra of synthesized triazolylfurazans **4a—g** indicated formation of single regioisomer in high yield; no signals for the second possible regioisomer were detected. The spectral characteristics also indicated high purity of the crude products. Therefore, unpurified esters **4a—g** were hydrolyzed to the corresponding acids **5a—g**, which also without further purification were subsequently thermally decarboxylated to target 3-amino-4-[5-aryl(hetaryl)-1*H*-1,2,3-triazol-1-yl]furazans **6a—g** in high yields. Thus, we developed a preparative procedure for the synthesis of triazolylfurazans **6a—g** without purification of the intermediates (Scheme 2).

To transform the amino group of triazolylfurazans **6** into the pyrrole ring, compounds **6a—f** and **6h**[15] were involved in the Clauson—Kaas pyrrole synthesis with 2,5-dimethyltetrahydrofuran. The reaction was carried out in refluxing acetic acid.[14] Pyrrole-containing triazolylfurazans **7a—f**,**h** were obtained in 64—98% yields (Scheme 3).

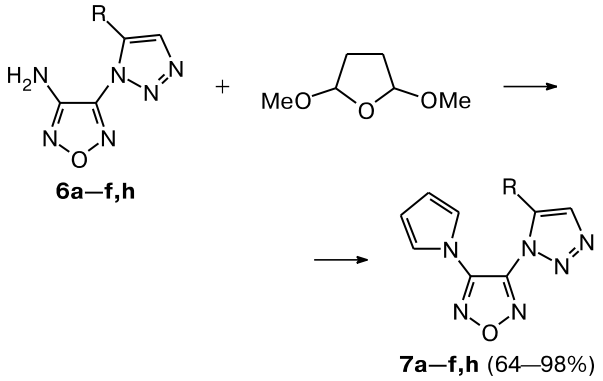
Scheme 2



3—6: R = 4-$MeOC_6H_4$ (**a**), 3,4-$(MeO)_2C_6H_3$ (**b**), 3,4,5-$(MeO)_3C_6H_2$ (**c**), 3,4-$(OCH_2O)C_6H_3$ (**d**), 4-$EtOC_6H_4$ (**e**), 4-FC_6H_4 (**f**), 2-thienyl (**g**)

Reagents and conditions: *i*. $MgCO_3$, EtOH, reflux, 8—10 h; *ii*. NaOH, H_2O, reflux, 1 h; *iii*. AcOH, reflux, 45 min.

Scheme 3

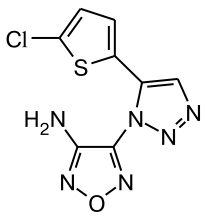


6, 7: R = 4-$MeOC_6H_4$ (**a**), 3,4-$(MeO)_2C_6H_3$ (**b**), 3,4,5-$(MeO)_3C_6H_2$ (**c**), 3,4-$(OCH_2O)C_6H_3$ (**d**), 4-$EtOC_6H_4$ (**e**), 4-FC_6H_4 (**f**), 4-ClC_6H_4 (**h**)

Reagents and conditions: AcOH, reflux, 1 h.

Biological trials

The biological activity of seven triazolylfurazan derivatives bearing amino groups **6a—d,g,i**, ester **4c** (a precursor of compound **6c**), and seven pyrrole derivatives **7a—f,h** was studied. The initial trials were carried out on the sea urchin embryos widely used as a model in screening for compounds with antiproliferative effect.[16,17] Recently a simple and efficient phenotypic sea urchin embryo assay has been developed. The assay allows identification of compounds with antiproliferative properties and provides information about the mechanism of antimitotic activity.[18] Specific changes of sea urchin embryo swimming pattern, namely, settlement to the bottom of the culture vessel and rapid spinning around the animal—vegetal axis, suggest a microtubule destabilizing activity of a tested compound.* Typical developmental abnormalities caused by triazolylfurazan **7** are shown in Fig. 1.



6i

Note that the compounds at effective concentrations leading to the alteration of sea urchin egg cleavage were comparable with the IC_{50} for the cultured mammalian and human tumor cells.[18,19] Target compounds were further selected for cytotoxicity test in 60 human tumor cell lines (Developmental Therapeutics Program at the National Cancer Institute of USA). The results are given in Table 1.

Triazolylfurazans **6a—d,g,i** bearing alkoxybenzene moieties and the unsubstituted amino group, as well as ester **4c**, did not affect cell division in both test systems. Their analogs **7a—f,h** bearing the pyrrole ring instead of the amino group exhibited moderate activity. The most potent compounds **7a** and **7e** altered cleavage of the sea urchin eggs at concentration of 50 nmol L^{-1}. Compound **7e** caused the sea urchin embryo spinning suggesting the antitubulin mechanism of action, namely, the ability to destabilize microtubules. Apparently, compound **7a** exhibited similar mechanism of action. Although, compound **7a** failed to affect the sea urchin embryo swimming, the arrested eggs acquired tuberculate shape typical of microtubule destabilizers.[18] The pyrrole ring was shown to be essential for antiproliferative effect, since the related structures **6** containing the amino group instead of the pyrrole ring were inactive. It is worth noting that the increase in the number of methoxy groups in the benzene ring (compounds **7a—d**) resulted in reduction of the antimitotic properties. In this respect, triazolylfurazans **7** is distinguished from the known analogs of plant antimitotics combretastatin and podophyllotoxin interacting with the colchicine site of tubulin. Specifically, trimethoxybenzene

Table 1. Antiproliferative activity of compounds **4c**, **6a—d,g,i** and **7a—f,h**

Compound	Sea urchin embryo, EC/μmol L^{-1}			Inhibition of human cancer cell growth (%) (GI_{50}/μmol L^{-1})
	Cleavage alteration	Cleavage arrest	Embryo spinning	
4c	>4	>4	>4	105.15
6a	4	>4	>4	103.97
6b	>4	>4	>4	95.88
6c	>4	>4	>4	101.33
6d	>4	>4	>4	100.34
6g	>4	>4	>4	102.88
6i[a]	>4	>4	>4	103.66
7a	0.05	0.5	>5	(0.389)
7b	0.5	>5	>5	50.83
7c	1	>5	>5	98.26
7d	5	>5	>4	—[b]
7e	0.05	0.5	5	(0.295)
7f	4	>4	>4	89.97
7h	>4	>4	>4	99.63

Note. The effect of compounds on the sea urchin embryos was studied according to the described method.[18] Repeated measurements showed no differences in effective threshold concentration. Inhibition of human cancer cell growth (percentage to control) was determined for the concentration of the tested compound of 10 μmol L^{-1}. GI_{50} is compound concentration required for 50% cell growth inhibition. The average GI_{50} values and percent of inhibition of cancer cell growth for 60 human cancer cell lines (NCI60 screen, http://dtp.cancer.gov) are given.

[a] Compound **6i** was kindly provided for the studies by Chemical Block Ltd (www.chemblock.com).

[b] Not determined.

* Video illustrations of sea urchin embryo swimming are presented at http://www.chemblock.com.

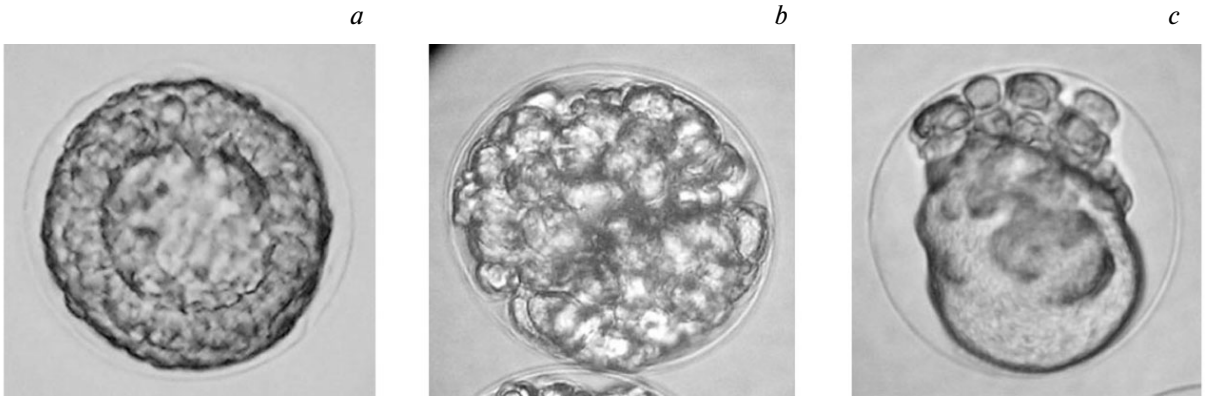


Fig. 1. Effect of triazolylfurazans on the sea urchin *Paracentrotus lividus* embryo development with compound **7e** as an example. (*a*) Intact blastula. (*b*) and (*c*) Typical developmental alterations caused by compound **7e** at concentration of 0.1 μmol L^{-1} (*b*, abnormal cleavage) and 0.5 μmol L^{-1} (*c*, arrested tuberculate egg). The observations were carried out 6 h after fertilization. The average embryo diameter was 115 μm.

derivatives of combretastatin and podophyllotoxin exhibit the strongest antimitotic activity.[19,20]

According to the data of the National Cancer Institute (NCI) of USA, compounds **7a** and **7e** inhibited cancer cell growth at relatively low concentrations (GI_{50} = 389 and 295 nmol L^{-1}, respectively). These compounds were referred to the biological expert committee of NCI as promising for further studies. Leukemia SR cells (**7a**), melanoma MDA-MB-435 cells (**7a** and **7e**), and the colon cancer cells (**7e**) were the most sensitive to triazolylfurazans **7a** and **7e**. The "doze—effect" curves for seven colon cancer cell lines exposed to compound **7e** are given in Fig. 2.

In summary, the preparative synthesis of furazans **6** by 1,3-dipolar cycloaddition of azidoaminofurazan **2a** to aroyl(hetaroyl)acetates **3a—g** followed by further modification was developed. The procedure does not require purification of the intermediates. Subsequent Clauson—Kaas condensation of synthesized triazolylfurazans **6** with dimethoxytetrahydrofuran yielded a series of 4-[5-aryl-(hetaryl)-1*H*-1,2,3-triazol-1-yl]-(3-pyrrol-1-yl)furazans **7**. The antiproliferative properties of both types of compounds were evaluated using the sea urchin embryo assay. It was found that the amino derivatives of triazolylfurazans **6** failed to affect cell division. However, their analogs **7** bearing the pyrrole ring exhibited moderate antimitotic activity. Two compounds, **7a** and **7c**, were referred to the NCI biological expert committee as promising compounds for further trials.

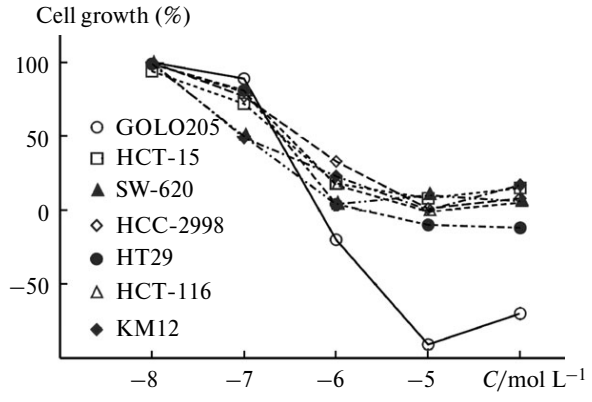


Fig. 2. Inhibition of colon cancer cell growth (COLO205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620 cell lines) caused by triazolylfurazan **7e**. *C* is concentration of **7e**.

Experimental

NMR spectra were recorded on Bruker WM-250 (^{1}H, 250 MHz) and Bruker AM-300 (^{13}C, 75.5 MHz) spectrometers. Chemical shifts are given in the δ scale relative to Me_4Si (internal standard). Mass spectra were obtained on a Varian MAT CH 6 instrument (EI, 70 eV). Thin-layer chromatography was performed on Silufol UV-254 plate (elution with $CHCl_3$), spots were visualized under UV light. Elemental analyses were carried out on a Perkin—Elmer 2400 CHN analyzer.

Ethyl aroylacetates with 4-methoxyphenyl- (**3a**), 3,4-dimethoxyphenyl- (**3b**), 3,4,5-trimethoxyphenyl- (**3c**), 4-fluorophenyl substituents (**3f**) were commercially available (Aldrich). 4-Azidofurazan-3-amine (**2a**), ethyl aroylacetates with 3,4-methylenedioxyphenyl- (**3d**),[21] 4-ethoxyphenyl- (**3e**),[22] and 2-thienyl substituents (**3g**)[23] and 4-[5-(4-chlorophenyl)-1*H*-1,2,3-triazol-1-yl]furazane-3-amine (**6h**)[15] were synthesized by the known procedures.

Synthesis of ethyl 1-(4-aminofurazan-3-yl)-5-R-1*H*-1,2,3-triazole-4-carboxylates 4a—g (general procedure). A mixture of 4-azidofurazan-3-amine **2a** (0.88 g, 7 mol), aroylacetate **3a—g** (7 mmol), and $MgCO_3$ (0.34 g, 4 mmol) in ethanol (20 mL) was refluxed for 8—10 h (until complete consumption of **2a**, TLC monitoring). The reaction mixture was filtered hot, the solvent was evaporated *in vacuo*. The precipitate was filtered off, washed with cold EtOH, and dried in air.

Ethyl 1-(4-aminofurazan-3-yl)-5-(4-methoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylate (4a). The yield was 96%, m.p.

184—185 °C, R_f 0.57. Found (%): C, 50.76; H, 4.40; N, 25.33. $C_{14}H_{14}N_6O_4$. Calculated (%): C, 50.91; H, 4.27; N, 25.44. MS, *m/z* (I_{rel} (%)): 330 $[M]^+$ (83); 285 $[M - EtO]^+$ (13); 272 (18); 256 $[M - HCO_2Et]^+$ (12); 247 [M – aminofurazanyl + 1]$^+$ (27); 245 (42); 227 (20); 217 (20); 202 (17); 175 $[ArC{\equiv}CCO_2H - 1]^+$ (100); 157 (37); 147 (48); 135 (52). ^{1}H NMR (DMSO-d_6), δ: 1.30 (t, 3 H, Me, ^3J = 4.2 Hz); 3.85 (s, 3 H, OMe); 4.30 (q, 2 H, CH_2, ^3J = 4.2 Hz); 6.31 (s, 2 H, NH_2); 6.94, 7.34 (both d, 2 H each, Ar, ^3J = 8.4 Hz). ^{13}C NMR (DMSO-d_6), δ: 13.90 (Me); 55.28 (OMe); 60.79 (CH_2); 113.82; 115.41; 131.51; 135.99; 142.32; 143.40; 153.30; 159.83 (CNH_2); 160.87 (CO).

Ethyl 1-(4-aminofurazan-3-yl)-5-(3,4-dimethoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylate (4b). The yield was 82%, m.p. 192—194 °C, R_f 0.62. Found (%): C, 50.19; H, 4.34; N, 23.22. $C_{15}H_{16}N_6O_5$. Calculated (%): C, 50.00; H, 4.48; N, 23.32. MS, *m/z* (I_{rel} (%)): 360 $[M]^+$ (89); 315 $[M - EtO]^+$ (3); 275 [M – aminofurazanyl – 1]$^+$ (25); 256 (26); 247 (71); 205 $[ArC{\equiv}CCO_2H - 1]^+$ (71); 177 (100); 149 (18). ^{1}H NMR (DMSO-d_6), δ: 1.28 (t, 3 H, Me, ^3J = 4.2 Hz); 3.73, 3.83 (both s, 3 H each, 2 OMe); 4.31 (q, 2 H, CH_2, ^3J = 4.2 Hz); 6.51 (s, 2 H, NH_2); 6.96, 7.02 (both d, 2 H, Ar, ^3J = 8.0 Hz); 7.03 (s, 1 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 14.06 (Me); 55.33 (OMe); 55.43 (OMe); 60.58 (CH_2); 111.35; 112.44; 127.70; 130.01; 141.88; 142.93; 147.17; 153.22; 158.64 (CNH_2); 161.12 (CO).

Ethyl 1-(4-aminofurazan-3-yl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylate (4c). The yield was 94%, m.p. 186—187 °C, R_f 0.47. Found (%): C, 49.12; H, 4.62; N, 21.58. $C_{16}H_{18}N_6O_6$. Calculated (%): C, 49.28; H, 4.65; N, 21.53. MS, *m/z* (I_{rel} (%)): 390 $[M]^+$ (90); 305 [M – aminofurazanyl – 1]$^+$ (29); 286 (15); 235 $[ArC{\equiv}CCO_2H - 1]^+$ (39); 207 (100); 177 (15). ^{1}H NMR (DMSO-d_6), δ: 1.28 (t, 3 H, Me, ^3J = 4.0 Hz); 3.74 (s, 6 H, 2 OMe, C(3) and C(5) in Ar); 3.76 (s, 3 H, OMe, C(4) in Ar); 4.31 (q, 2 H, CH_2, ^3J = 4.0 Hz); 6.62 (s, 2 H, NH_2); 6.76 (s, 2 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 13.67 (Me); 56.04 (OMe); 60.15 (OMe); 60.89 (CH_2); 108.18; 119.85; 136.15; 139.12; 141.98; 145.13; 153.30; 157.72 (CNH_2); 160.79 (CO).

Ethyl 1-(4-aminofurazan-3-yl)-5-(3,4-methylenedioxyphenyl)-1*H*-1,2,3-triazole-4-carboxylate (4d). The yield was 95%, m.p. 178—179 °C, R_f 0.56. Found (%): C, 49.01; H, 3.61; N, 24.27. $C_{14}H_{12}N_6O_5$. Calculated (%): C, 48.84; H, 3.51; N, 24.41. MS, *m/z* (I_{rel} (%)): 344 $[M]^+$ (21); 259 (18); 231 (19); 189 $[ArC{\equiv}CCO_2H - 1]^+$ (100); 170 (22); 161 (74). ^{1}H NMR (DMSO-d_6), δ: 1.25 (t, 3 H, Me, ^3J = 4.3 Hz); 4.30 (q, 2 H, CH_2, ^3J = 4.3 Hz); 6.09 (s, 2 H, OCH_2O); 6.56 (s, 2 H, NH_2); 6.86—6.99 (m, 3 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 13.91 (Me); 60.36 (OCH_2); 101.70 (OCH_2O); 108.95; 113.36; 115.55; 124.33; 125.23; 137.49; 143.15; 149.11; 149.46; 156.80 (CNH_2); 161.12 (CO).

Ethyl 1-(4-aminofurazan-3-yl)-5-(4-ethoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylate (4e). The yield was 94%, m.p. 140—141 °C, R_f 0.60. Found (%): C, 52.03; H, 4.57; N, 24.21. $C_{15}H_{16}N_6O_4$. Calculated (%): C, 52.32; H, 4.68; N, 24.41. MS, *m/z* (I_{rel} (%)): 344 $[M]^+$ (28); 286 (11); 259 (35); 240 (17); 231 (35); 189 $[ArC{\equiv}CCO_2H - 1]^+$ (100); 161 (94). ^{1}H NMR (DMSO-d_6), δ: 1.29 (t, 3 H, $\underline{Me}CH_2OCO$, ^3J = 4.0 Hz); 1.42 (t, 3 H, $\underline{Me}CH_2O$, ^3J = 4.1 Hz); 4.08 (q, 2 H, $MeC\underline{H}_2O$, ^3J = 4.1 Hz); 4.30 (q, 2 H, $MeCH_2OCO$, ^3J = 4.0 Hz); 6.37 (s, 2 H, NH_2); 6.92, 7.32 (both d, 2 H each, Ar, ^3J = 8.2 Hz). ^{13}C NMR (DMSO-d_6), δ: 13.34 (Me); 13.78 (Me); 60.36 (CO_2CH_2); 62.15 ($ArOCH_2$); 110.62; 114.11; 132.37; 137.98; 142.56; 146.60; 155.24; 158.12 (CNH_2); 161.00 (CO).

Ethyl 1-(4-aminofurazan-3-yl)-5-(4-fluorophenyl)-1*H*-1,2,3-triazole-4-carboxylate (4f). The yield was 88%, m.p. 150—151 °C, R_f 0.49. Found (%): C, 49.30; H, 3.35; N, 26.36. $C_{13}H_{11}FN_6O_3$. Calculated (%): C, 49.06; H, 3.48; N, 26.41. MS, *m/z* (I_{rel} (%)): 318 $[M]^+$ (19); 233 $[M - CO_2 - N_3 + 1]^+$ (44); 214 (15); 205 (32); 163 $[ArC{\equiv}CCO_2H - 1]^+$ 100); 135 (18); 133 (23). ^{1}H NMR (DMSO-d_6), δ: 1.28 (t, 3 H, Me, ^3J = 4.0 Hz); 4.29 (q, 2 H, CH_2, ^3J = 4.0 Hz); 6.41 (s, 2 H, NH_2); 7.19, 7.48 (both d, 2 H each, Ar, ^3J = 8.2 Hz). ^{13}C NMR (DMSO-d_6), δ: 14.31 (Me); 61.19 (CH_2); 117.84; 120.66; 134.22; 138.04; 145.18; 146.43; 158.80 (CNH_2); 161.22 (CO); 164.52.

Ethyl 1-(4-aminofurazan-3-yl)-5-(2-thienyl)-1*H*-1,2,3-triazole-4-carboxylate (4g). The yield was 85%, m.p. 130—131 °C, R_f 0.63. Found (%): C, 43.03; H, 3.20; N, 27.31. $C_{11}H_{10}N_6O_3S$. Calculated (%): C, 43.13; H, 3.29; N, 27.44. MS, *m/z* (I_{rel} (%)): 306 $[M]^+$ (21); 221 $[M - CO_2 - N_3 + 1]^+$ (14); 202 (15); 151 $[ArC{\equiv}CCO_2H - 1]^+$ (79); 135 (16); 133 (18). ^{1}H NMR (DMSO-d_6), δ: 1.34 (t, 3 H, Me, ^3J = 4.2 Hz); 4.36 (q, 2 H, CH_2, ^3J = 4.2 Hz); 6.50 (s, 2 H, NH_2); 7.15 (m, 1 H, C(4) thiophene ring); 7.44 (d, 1 H, C(3) thiophene ring, ^3J = 5.0 Hz); 7.77 (d, 1 H, C(5) thiophene ring, ^3J = 5.0 Hz). ^{13}C NMR (DMSO-d_6), δ: 13.42 (Me); 60.81 (CH_2); 115.17; 123.89; 132.31; 134.17; 135.68; 142.71; 43.52; 158.16 (CNH_2); 160.69 (CO).

Synthesis of 1-(4-aminofurazan-3-yl)-5-R-1*H*-1,2,3-triazole-4-carboxylic acids 5a—g (general procedure). A solution of NaOH (0.5 g, 12.5 mol) in water (50 mL) was added to ethyl 1-(4-aminofurazan-3-yl)-5-R-1*H*-1,2,3-triazole-4-carboxylate **4a—g** (7 mmol). The reaction mixture was refluxed for 1 h, the undissolved residue was filtered off, and the filtrate was acidified with dilute HCl to pH 2. A precipitate was filtered off, washed with water, and dried in air.

When crude carboxylic acids **4a—g** (unwashed with EtOH) were used, the yields of products **5a—g** were virtually the same.

1-(4-Aminofurazan-3-yl)-5-(4-methoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (5a). The yield was 83%, m.p. 143—145 °C. Found (%): C, 47.47; H, 3.41; N, 27.74. $C_{12}H_{10}N_6O_4$. Calculated (%): C, 47.69; H, 3.33; N, 27.81. MS, *m/z* (I_{rel} (%)): 302 $[M]^+$ (1); 259 $[M - HN_3]^+$ (23); 258 $[M - CO_2]^+$ (95); 231 (32); 230 $[M - CO_2 - N_2]^+$ (70); 175 $[ArC{\equiv}CCO_2H - 1]$ (69); 158 (100). ^{1}H NMR (DMSO-d_6), δ: 3.76 (s, 3 H, OMe); 6.64 (s, 2 H, NH_2); 6.98, 7.32 (both d, 2 H each, Ar, ^3J = 8.0 Hz); 13.40 (br.s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 55.27 (OMe); 113.84; 115.81; 131.53; 136.85; 142.45; 143.10; 153.33; 160.76 (CNH_2); 161.36 (CO).

1-(4-Aminofurazan-3-yl)-5-(3,4-dimethoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (5b). The yield was 54%, m.p. 162—163 °C. Found (%): C, 47.14; H, 3.50; N, 25.40. $C_{13}H_{12}N_6O_5$. Calculated (%): C, 46.99; H, 3.64; N, 25.29. MS, *m/z* (I_{rel} (%)): 332 $[M]^+$ (2); 288 $[M - CO_2]^+$ (71); 260 $[M - CO_2 - N_2]^+$ (38); 245 [M – aminofurazanyl – 1]$^+$ (34); 182 (74); 176 (100). ^{1}H NMR (DMSO-d_6), δ: 3.70, 3.82 (both s, 3 H each, 2 OMe); 6.67 (s, 2 H, NH_2); 6.91—7.12 (m, 3 H, Ar); 13.15 (br.s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 55.48 (OMe); 55.62 (OMe); 110.97; 111.29; 113.48; 123.01; 136.66; 142.51; 143.21; 148.29; 150.35; 153.45; 161.31 (CO).

1-(4-Aminofurazan-3-yl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (5c). The yield was 82%, m.p. 153—155 °C. Found (%): C, 46.56; H, 3.75; N, 23.38. $C_{14}H_{14}N_6O_6$. Calculated (%): C, 46.41; H, 3.89; N, 23.20. MS, *m/z* (I_{rel} (%)): 362 $[M]^+$ (1); 318 $[M - CO_2]^+$ (43); 275 [M – aminofurazanyl – 1]$^+$ (100); 206 (30). ^{1}H NMR (DMSO-d_6), δ: 3.50—3.70 (br.s, 9 H,

3 OMe and 1 H, OH); 6.82 (br.s, 4 H, 2 H in Ar and 2 H, NH_2). ^{13}C NMR (DMSO-d_6), δ: 56.03 (OMe); 60.12 (OMe); 107.78; 119.13; 136.91; 138.92; 142.48; 143.13; 152.50; 153.63; 161.22 (CO).

1-(4-Aminofurazan-3-yl)-5-(3,4-methylenedioxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (5d). The yield was 90%, m.p. 176—177 °C. Found (%): C, 45.33; H, 2.42; N, 26.50. $C_{12}H_8N_6O_5$. Calculated (%): C, 45.58; H, 2.55; N, 26.58. MS, *m/z* (I_{rel} (%)): 316 $[M]^+$ (2); 273 $[M - HN_3]^+$ (18); 272 $[M - CO_2]^+$ (60); 244 $[M - CO_2 - N_2]^+$ (55); 229 [M – aminofurazanyl – 1]$^+$ (100). ^1H NMR (DMSO-d_6), δ: 3.0—4.0 (br.s, OH); 6.10 (s, 2 H, CH_2); 6.68 (s, 2 H, NH_2); 6.82—7.07 (m, 3 H in Ar). ^{13}C NMR (DMSO-d_6), δ: 101.77 (CH_2); 108.78; 110.29; 117.24; 122.95; 124.94; 137.27; 142.68; 147.45; 148.99; 153.28; 161.44 (CO).

1-(4-Aminofurazan-3-yl)-5-(4-ethoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (5e). The yield was 89%, m.p. 133—134 °C. Found (%): C, 49.22; H, 3.88; N, 26.61. $C_{13}H_{12}N_6O_4$. Calculated (%): C, 49.37; H, 3.82; N, 26.51. MS, *m/z* (I_{rel} (%)): 316 $[M]^+$ (4); 273 $[M - HN_3]^+$ (18); 272 $[M - CO_2]^+$ (80); 245 (15); 244 $[M - CO_2 - N_2]^+$ (62); 175 $[ArC{\equiv}CCO_2H - 1]^+$ (51); 172 (100). ^1H NMR (DMSO-d_6), δ: 1.44 (t, 3 H, $\underline{Me}CH_2O$, ^3J = 4.7 Hz); 4.08 (q, 2 H, $MeC\underline{H}_2O$, ^3J = 4.7 Hz); 6.62 (s, 2 H, NH_2); 6.93, 7.28 (both d, 2 H each, Ar, ^3J = 8.2 Hz); 13.15 (br.s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 13.72 (Me); 60.40 (CH_2); 111.95; 114.90; 131.17; 137.27; 142.04; 143.52; 153.88; 160.46 (CNH_2); 161.55 (CO).

1-(4-Aminofurazan-3-yl)-5-(4-fluorophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (5f). The yield was 79%, m.p. 170—171 °C. Found (%): C, 45.45; H, 2.38; N, 28.80. $C_{11}H_7FN_6O_3$. Calculated (%): C, 45.52; H, 2.43; N, 28.96. MS, *m/z* (I_{rel} (%)): 290 $[M]^+$ (11); 246 $[M - HN_3 - 1]^+$ (16); 218 $[M - CO_2 - N_2]^+$ (24); 163 (26); 146 (27); 134 (100). ^1H NMR (DMSO-d_6), δ: 6.40 (s, 2 H, NH_2); 7.20, 7.48 (both d, 2 H each, Ar, ^3J = 8.0 Hz); 12.96 (br.s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 118.20; 121.06; 134.83; 139.26; 147.33; 147.53; 159.00 (CNH_2); 160.65 (CO); 164.26.

1-(4-Aminofurazan-3-yl)-5-(2-thienyl)-1*H*-1,2,3-triazole-4-carboxylic acid (5g). The yield was 66%, m.p. 174—175 °C. Found (%): C, 39.05; H, 2.28; N, 30.12. $C_9H_6N_6O_3S$. Calculated (%): C, 38.85; H, 2.17; N, 30.20. MS, *m/z* (I_{rel} (%)): 278 $[M]^+$ (22); 234 $[M - CO_2]^+$ (24); 206 (14); 202 (14); 151 (25); 134 (31); 122 (100). ^1H NMR (DMSO-d_6), δ: 6.43 (s, 2 H, NH_2); 7.13 (m, 1 H, C(4) thiophene ring); 7.44 (d, 1 H, C(3) thiophene ring, ^3J = 5.2 Hz); 7.73 (d, 1 H, C(5) thiophene ring, ^3J = 5.2 Hz).

Synthesis of 3-amino-4-(5-R-1*H*-1,2,3-triazol-1-yl)furazans 6 (general procedure). A solution of carboxylic acid **5a—g** (10 mmol) in AcOH (20 mL) was refluxed for 45 min. The reaction mixture was cooled, concentrated *in vacuo*, and water (50 mL) was added to the residue. A precipitate was filtered off, washed with water, and dried in air.

4-[5-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]furazan-3-amine (6a). The yield was 71%, m.p. 166—167 °C, R_f 0.10. Found (%): C, 51.22; H, 3.81; N, 32.43. $C_{11}H_{10}N_6O_2$. Calculated (%): C, 51.16; H, 3.90; N, 32.54. MS, *m/z* (I_{rel} (%)): 258 $[M]^+$ (7); 230 $[M - N_2]^+$ (12); 158 (10); 146 (100). ^1H NMR (DMSO-d_6), δ: 3.79 (s, 3 H, OMe); 6.65 (s, 2 H, NH_2); 7.05, 7.35 (both d, 4 H in Ar, ^3J = 8.0 Hz); 8.23 (s, 1 H, triazole ring). ^{13}C NMR (DMSO-d_6), δ: 55.30 (OMe); 114.55; 116.78; 129.68; 132.60; 139.85; 143.13; 153.19; 160.49.

4-[5-(3,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl]furazan-3-amine (6b). The yield was 85%, m.p. 181—182 °C, R_f 0.12. Found (%): C, 50.26; H, 3.99; N, 29.19. $C_{12}H_{12}N_6O_3$. Calculated (%): C, 50.00; H, 4.20; N, 29.15. MS, *m/z* (I_{rel} (%)): 288 $[M]^+$ (94); 260 $[M - N_2]^+$ (42); 245 $[M - HN_3]^+$ (92); 203 (28); 188 (48); 176 (100); 162 $[ArC{\equiv}CH]^+$ (42). ^1H NMR (DMSO-d_6), δ: 3.72 (s, 3 H, OMe); 3.82 (s, 3 H, OMe); 6.68 (s, 2 H, NH_2); 6.91, 7.08 (both d, 2 H in Ar, ^3J = 7.5 Hz); 7.04 (s, 1 H, in Ar); 8.28 (s, 1 H, triazole ring). ^{13}C NMR (DMSO-d_6), δ: 55.48 (OMe); 55.53 (OMe); 111.68; 111.95; 116.80; 120.91; 132.56; 140.08; 148.73; 150.14; 153.34.

4-[5-(3,4,5-Trimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl]furazan-3-amine (6c). The yield was 69%, m.p. 213—214 °C, R_f 0.11. Found (%): C, 48.88; H, 4.61; N, 22.69. $C_{13}H_{14}N_6O_4$. Calculated (%): C, 49.06; H, 4.43; N, 22.82. MS, *m/z* (I_{rel} (%)): 318 $[M]^+$ (77); 290 $[M - N_2]^+$ (8); 275 $[M - HN_3]^+$ (100); 235 (14); 217 (18); 206 (44); 192 (29); 206 (43); 192 $[ArC{\equiv}CH]^+$ (29). ^1H NMR (DMSO-d_6), δ: 3.70 (s, 3 H, OMe); 3.73 (s, 6 H, 2 OMe); 6.74 (s, 2 H in Ar); 6.75 (s, 2 H, NH_2); 8.32 (s, 1 H, triazole ring). ^{13}C NMR (DMSO-d_6), δ: 56.04 (OMe); 60.13 (OMe); 105.93; 119.91; 132.95; 140.14; 143.21; 153.10; 153.47.

4-[5-(3,4-Methylenedioxyphenyl)-1*H*-1,2,3-triazol-1-yl]-furazan-3-amine (6d). The yield was 53%, m.p. 192—193 °C, R_f 0.13. Found (%): C, 48.51; H, 2.83; N, 31.11. $C_{11}H_8N_6O_3$. Calculated (%): C, 48.53; H, 2.96; N, 30.87. MS, *m/z* (I_{rel} (%)): 272 $[M]^+$ (67); 244 $[M - N_2]^+$ (62); 186 (14); 172 (19); 160 (100). ^1H NMR (DMSO-d_6), δ: 6.08 (s, 2 H, CH_2); 6.67 (s, 2 H, NH_2); 6.74, 7.02 (both d, 2 H, in Ar, J = 7.5 Hz); 7.00 (s, 1 H, CH in Ar); 8.22 (s, 1 H, triazole ring). ^{13}C NMR (DMSO-d_6), δ: 101.83 (CH_2); 108.46; 108.87; 118.16; 122.62; 132.99; 139.78; 143.07; 147.76; 148.81; 153.20.

4-[5-(4-Ethoxyphenyl)-1*H*-1,2,3-triazol-1-yl]furazan-3-amine (6e). The yield was 63%, m.p. 158—159 °C, R_f 0.10. Found (%): C, 52.41; H, 4.59; N, 31.02. $C_{12}H_{12}N_6O_2$. Calculated (%): C, 52.94; H, 4.44; N, 30.87. MS, *m/z* (I_{rel} (%)): 272 $[M]^+$ (5); 244 $[M - N_2]^+$ (16); 214 (30); 172 (21); 160 (100); 146 $[ArC{\equiv}CH]^+$ (37). ^1H NMR (DMSO-d_6), δ: 1.42 (t, 3 H, $\underline{Me}CH_2O$, J = 6.4); 4.07 (q, 2 H, $MeC\underline{H}_2O$, J = 6.4); 6.58 (s, 2 H, NH_2); 6.97, 7.30 (both d, 2 H each, Ar, J = 8.3 Hz); 8.18 (s, 1 H, triazole ring). ^{13}C NMR (DMSO-d_6), δ: 13.50 (Me); 62.07 (OCH_2); 112.15; 114.92; 131.08; 136.44; 142.07; 147.26; 153.61; 158.48.

4-[5-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]furazan-3-amine (6f). The yield was 68%, m.p. 191—192 °C, R_f 0.11. Found (%): C, 48.23; H, 3.01; N, 34.36. $C_{10}H_7FN_6O$. Calculated (%): C, 48.48; H, 2.87; N, 34.13. MS, *m/z* (I_{rel} (%)): 246 $[M]^+$ (45); 218 $[M - N_2]^+$ (13); 188 (23); 176 (20); 134 (100%); 120 $[ArC{\equiv}CH]^+$ (66). ^1H NMR (DMSO-d_6), δ: 6.63 (s, 2 H, NH_2); 7.22, 7.49 (both d, 2 H each, Ar, J = 8.3 Hz); 8.33 (s, 1 H, triazole ring). ^{13}C NMR (DMSO-d_6), δ: 118.90; 121.56; 135.79; 114.92; 141.21; 145.38; 148.54; 158.60; 164.92.

4-[5-(2-Thienyl)-1*H*-1,2,3-triazol-1-yl]furazan-3-amine (6g). The yield was 73%, m.p. 81—82 °C, R_f 0.13. Found (%): C, 41.21; H, 2.47; N, 36.02. $C_8H_6N_6OS$. Calculated (%): C, 41.02; H, 2.58; N, 35.88. ^1H NMR (DMSO-d_6), δ: 6.63 (s, 2 H, NH_2); 7.20 (m, 1 H, C(4) thiophene ring); 7.40 (d, 1 H, C(3) thiophene ring, ^3J = 5.0 Hz); 7.77 (d, 1 H, C(2) thiophene ring, ^3J = 5.0 Hz); 8,36 (s, 1 H, triazole ring). ^{13}C NMR (DMSO-d_6), δ: 118.15; 123.92; 133.26; 135.21; 138.62; 145.05; 146.37; 158.93.

3-[5-(5-Chloro-2-thienyl)-1*H*-1,2,3-triazol-1-yl]furazan-3-amine (6i). M.p. 127—128 °C, R_f 0.08. Found (%): C, 48.66; H, 2.75; N, 34.00. $C_8H_5ClN_6OS$. Calculated (%): C, 35.76; H, 1.88; N, 31.28. MS, *m/z* (I_{rel} (%)): 270 $[M(Cl^{37})]^+$ (6); 268

$[M(Cl^{35})]^+$ (18); 268; 242 $[M(Cl^{37}) - N_2]^+$ (4); 240 $[M(Cl^{35}) - N_2]^+$ (11); 198 (12); 170 (8); 168 (23); 158 (41); 156 (100). ^{1}H NMR (DMSO-d_6), δ: 6.76 (s, 2 H, NH_2); 7.27, 7.85 (both m, 2 H, thiophene ring); 8.44 (s, 1 H, triazole ring). ^{13}C NMR (DMSO-d_6), δ: 120.31; 125.18; 134.16; 137.72; 140.33; 146.21; 147.57; 160.13.

Synthesis of 4-(5-R-1*H*-1,2,3-triazol-1-yl)-3-(pyrrol-1-yl)furazans 7 (general procedure). A solution of 3-amino-4-(5-R-1*H*-1,2,3-triazol-1-yl)furazan **6** (2.0 mmol) and 2,5-dimethoxytetrahydrofuran (2.64 g, 2.0 mmol) in AcOH (10 mL) was refluxed for 1 h, the reaction mixture was concentrated. The residue was diluted with water (10 mL), extracted with CH_2Cl_2 (4×20 mL), dried with $MgSO_4$. The filtered solution was passed through a layer of SiO_2 and the solvent was removed to dryness.

4-[5-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-3-(pyrrol-1-yl)furazan (7a). The yield was 83%, m.p. 71—72 °C, R_f 0.51. Found (%): C, 58.80; H, 3.79; N, 27.39. $C_{15}H_{12}N_6O_2$. Calculated (%): C, 58.44; H, 3.92; N, 27.26. MS, *m/z* (I_{rel} (%)): 308 $[M]^+$ (19); 281 $[M - N_2 + 1]^+$ (89); 250 (29); 224 (33); 208 (36); 158 (62); 146 (85); 135 (100); 115 (45). ^{1}H NMR ($CDCl_3$), δ: 3.82 (s, 3 H, OMe); 6.31 (br.s, 2 H, C(3) and C(4) of pyrrole ring); 6.68 (br.s, 2 H, C(2) and C(5) of pyrrole ring); 6.88, 7.16 (both d, 4 H in Ar, ^3J = 8.0 Hz); 7.94 (s, 1 H, triazole ring). ^{13}C NMR ($CDCl_3$), δ: 55.50 (OMe); 113.71; 114.93; 116.12; 129.88; 132.82; 141.44; 143.61; 149.11; 161.38.

4-[5-(3,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-3-(pyrrol-1-yl)furazan (7b). The yield was 98%, m.p. 80—81 °C, R_f 0.50. Found (%): C, 56.66; H, 4.05; N, 24.77. $C_{16}H_{14}N_6O_3$. Calculated (%): C, 56.80; H, 4.17; N, 24.84. MS, *m/z* (I_{rel} (%)): 338 $[M]^+$ (90); 310 $[M - N_2]^+$ (24); 295 $[M - HN_3]^+$ (13); 288 (100); 280 (27); 264 (38); 245 (48); 176 (60). ^{1}H NMR ($CDCl_3$), δ: 3.75 (s, 3 H, OMe); 3.88 (s, 3 H, OMe); 6.32 (s, 2 H, C(3) and C(4) of pyrrole ring); 6.68 (s, 2 H, C(2) and C(5) of pyrrole ring); 6.70, 6.82 (both d, 4 H in Ar, ^3J = 8.2 Hz); 7.95 (s, 1 H, triazole ring). ^{13}C NMR ($CDCl_3$), δ: 55.92 (OMe); 55.98 (OMe); 111.15; 111.57; 113.64; 116.15; 119.61; 121.48; 132.73; 141.43; 143.60; 149.08; 149.44; 150.91.

4-[5-(3,4,5-Trimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-3-(pyrrol-1-yl)furazan (7c). The yield was 83%, m.p. 118—119 °C, R_f 0.44. Found (%): C, 55.47; H, 4.45; N, 22.70. $C_{17}H_{16}N_6O_4$. Calculated (%): C, 55.43; H, 4.38; N, 22.82. MS, *m/z* (I_{rel} (%)): 368 $[M]^+$ (100); 340 $[M - N_2]^+$ (19); 325 $[M - HN_3]^+$ (13); 309 (13); 280 (21); 206 (41). ^{1}H NMR ($CDCl_3$), δ: 3.72 (s, 6 H, 2 OMe); 3.86 (s, 3 H, OMe); 6.31 (s, 2 H, C(3) and C(4) of pyrrole ring); 6.40 (s, 2 H, C(2) and C(5) of pyrrole ring); 6.65 (s, 2 H in Ar); 7.97 (s, 1 H, triazole ring). ^{13}C NMR ($CDCl_3$), δ: 56.09 (OMe); 60.80 (OMe); 106.73; 113.63; 118.82; 119.52; 132.83; 139.85; 141.37; 143.47; 149.04; 153.63.

4-[5-(3,4-Methylenedioxyphenyl)-1*H*-1,2,3-triazol-1-yl]-3-(pyrrol-1-yl)furazan (7d). The yield was 64%, m.p. 102—103 °C, R_f 0.44. Found (%): C, 56.07; H, 3.05; N, 26.17. $C_{15}H_{10}N_6O_3$. Calculated (%): C, 55.90; H, 3.13; N, 26.08. MS, *m/z* (I_{rel} (%)): 322 $[M]^+$ (42); 294 $[M - N_2]^+$ (100); 264 (57); 237 (14); 207 (32); 179 (40). ^{1}H NMR ($CDCl_3$), δ: 5.99 (s, 2 H, CH_2); 6.32 (s, 2 H, C(3) and C(4) of pyrrole ring); 6.64—6.80 (m, 2 H, C(2) and C(5) of pyrrole ring, 3 H, Ar); 7.92 (s, 1 H, triazole ring). ^{13}C NMR ($CDCl_3$), δ: 101.92 (CH_2); 108.50; 109.12; 113.70; 117.32; 119.68; 122.94; 132.99; 141.25; 143.44; 148.49; 149.02; 149.68.

4-[5-(4-Ethoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-3-(pyrrol-1-yl)furazan (7e). The yield was 78%, m.p. 120—121 °C, R_f 0.47. Found (%): C, 59.80; H, 4.29; N, 26.19. $C_{16}H_{14}N_6O_2$. Calculated (%): C, 59.62; H, 4.38; N, 26.07. MS, *m/z* (I_{rel} (%)): 322 $[M]^+$ (32); 294 $[M - N_2]^+$ (53); 264 (21); 236 (38); 209 (52); 144 $[ArC{\equiv}CH]^+$ (28); 132 (100). ^{1}H NMR (DMSO-d_6), δ: 1.31 (t, 3 H, Me, ^3J = 7.0 Hz); 4.05 (q, 2 H, CH_2, ^3J = 7.0 Hz); 6.35 (s, 2 H, C(3) and C(4) of pyrrole ring); 6.83 (s, 2 H, C(2) and C(5) of pyrrole ring); 6.98, 7.32 (both d, 2 H each, Ar, J = 8.4 Hz); 8.37 (s, 1 H, triazole ring). ^{13}C NMR ($CDCl_3$), δ: 13.90 (Me); 62.26 (OCH_2); 113.25; 114.72; 117.33; 130.11; 133.18; 142.52; 143.92; 148.70; 161.08.

4-[5-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-3-(pyrrol-1-yl)furazan (7f). The yield was 80%, m.p. 122—123 °C, R_f 0.52. Found (%): C, 56.59; H, 2.98; N, 28.19. $C_{14}H_9FN_6O$. Calculated (%): C, 56.76; H, 3.06; N, 28.37. MS, *m/z* (I_{rel} (%)): 296 $[M]^+$ (17); 268 $[M - N_2]^+$ (80); 267 (24); 238 (51); 211 (100); 185 (58); 146 (28); 134 (74); 126 (76); 120 $[ArC{\equiv}CH]^+$ (64); 107 (79). ^{1}H NMR (DMSO-d_6), δ: 6.35 (s, 2 H, C(3) and C(4) of pyrrole ring); 6.83 (s, 2 H, C(2) and C(5) of pyrrole ring); 7.28, 7.49 (both d, 2 H each, Ar, J = 8.2 Hz); 8.40 (s, 1 H, triazole ring). ^{13}C NMR ($CDCl_3$), δ: 115.39; 117.16; 132.40; 137.73; 144.18; 145.62; 148.95; 162.29; 164.80.

4-[5-(4-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl]-3-(pyrrol-1-yl)furazan (7h). The yield was 76%, m.p. 97—98 °C, R_f 0.44. Found (%): C, 53.44; H, 3.01; N, 27.03. $C_{14}H_9ClN_6O$. Calculated (%): C, 53.77; H, 2.90; N, 26.87. MS, *m/z* (I_{rel} (%)): 314 $[M(Cl^{37})]^+$ (3); 312 $[M(Cl^{35})]^+$ (13); 286 $[M(Cl^{37}) - N_2]^+$ (18); 284 $[M(Cl^{35}) - N_2]^+$ (53); 256 (11); 254 (40); 229 (11); 227 (36); 219 (46); 192 (96); 167 (37); 150 (53); 138 (13); 136 (33). ^{1}H NMR (DMSO-d_6), δ: 6.33 (s, 2 H, C(3) and C(4) of pyrrole ring); 6.84 (s, 2 H, C(2) and C(5) of pyrrole ring); 7.45, 7.51 (both d, 2 H each, Ar, ^3J = 8.6 Hz); 8.44 (s, 1 H, triazole ring).

Study of antiproliferative activity of compounds using a sea urchin embryo assay.[18] The trials were carried out in the biological laboratory of N. K. Kol´tsov Institute of Developmental Biology of RAS in Cyprus. Adult sea urchins, *Paracentrotus lividus L.* (Echinidae), were collected from the Mediterranean Sea on the Cyprus coast and kept in an aerated seawater tank. Gametes were obtained by intracoelomic injection of 0.5 *M* KCl (1—2 mL). Eggs were washed with filtered seawater and fertilized by adding drops of diluted sperm. Embryos (600—2000 mL^{-1}) were cultured in filtered seawater at room temperature (18—23 °C) in six-well culture plates.

Stock solutions of compounds were prepared in DMSO or 95% aqueous ethanol, the maximal studied concentrations of the compounds depended on their solubility. The solubility of compounds in the solvents and seawater was controlled under microscope.

Compound treatment was carried out at the following developmental steps: (1) fertilized eggs, 8—15 min after fertilization; (2) hatched swimming blastulae, 8.5—10 h after fertilization. Aliquots of embryo suspension (5 mL) were transferred into each well followed by addition of the corresponding amount of compound solution to obtain the required final concentration. The concentration of the solvent did not exceed the maximal tolerated value (1% for ethanol and 0.05% for DMSO). In the series of trials, the concentration of compounds was sequentially decreased twofold until the effect disappeared. The activity of the compound was estimated as an effective threshold concentration, EC, resulting in cleavage alteration or developmental abnormalities. The embryo development was monitored using a Biolam LOMO light microscope (Saint-Petersburg).

Cytotoxicity in 60 human cancer cell lines was studied at the National Cancer Institute of USA according to the procedure described at http://dtp.nci.nih.gov/branches/btb/ivclsp.html.

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