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Synthesis and cytotoxic activities of substituted *N*-{4-[4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N*'-arylureas

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Abstract

Substituted *N*-{4-[4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl] phenyl}-*N*'-aryl ureas were derived by condensation of aryl isocyanates with 2-substituted 2-(4-aminophenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes. The cytotoxic activity of some of the compounds was determined in three lines of tumor cells.

Keywords: adenocarcinoma, arylurea, anticarcinogenicactivity, cytotoxicity, 1,3-dioxolane, fibroblast, myeloleukemia, 1,2,4-triazole, urea.

INTRODUCTION

Modern pharmaceutics has a number of successful and effective methods of treatment of a large number of malignant tumors, and now drugs with this type of active placed near 20 percent of top 200 of most selling drugs [1]. However, the low specificity of such drugs, the time-related resistance, and side effects complicate the use of known chemotherapeutic regimens [2–4]. Currently, in practical oncology there are several groups of drugs (taxanes, hydroxyurea derivatives), which main mode of action is due to the ability to disrupt the fission (mitosis) processes of tumor cells and induce their subsequent death [5]. Among other classes of compounds, active cytostatics have been found [6–29]. Molecular-biological mechanisms to provide the phenotype of multiple drug resistance of the tumor process have not been fully studied [5]. In this regard, the search for new effective compounds for the treatment of cancer is an urgent challenge.

Aryl ureas are promising targets for the search for anticancer drugs, since compounds have been found for which six mechanisms of cytotoxic activity have been studied [30].

Among the substituted 4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes [31-37] and 2-aryl-1,3-dioxolanes containing fragments of substituted ureas in the molecule [38–41], compounds with a wide spectrum of biological activity have been found, but the antitumor activity of these series have not been studied and substituted 4-aminomethyl-1,3-dioxolanes containing fragments of substituted aryl ureas have not been studied too. It should be noted that the derivatives of 1,3-dioxolane and 1,2,4-triazole have low toxicity [42, 43]. All of the above causes an interest in the search for cytotoxically active compounds containing fragments of aryl urea, 1,3-dioxolane and 1,2,4-triazole.

MATERIALS AND METHODS

^{1}H NMR spectra were recorded on a Bruker AM-300 instrument (300.13 MHz). IR spectra were recorded on a Specord M-80 instrument (Nujol). The course of the reaction was monitored and the purity of the compounds was checked by TLC (Sorbfil A-UF). 2-(4-aminophenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes have been synthesized by the technique which is earlier developed by us [36].

Substituted *N*-{4-[2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N*'-arylureas (general procedure). The 1.45 mmol of substituted arylisocyanate were added with stirring to a solution of 1.45 mmol of 2-(4-aminophenyl)-2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane in 3 ml of absolute acetonitrile. The mixture was held for 10–15 minutes, then the precipitated crystals were filtered off, washed with 10 ml of hexane, and air-dried. A product with a yield of 89–93% was derived.

***N*-{4-[2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N*'-[3-(trifluoromethyl)phenyl]urea (1).** Yield 89%, m.p. 170-171 ^{o}C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.49 (s, 3H, CH_3); 3.71 (d.d, 1H, CH_2O, ^3J = 7.0, ^2J = 7.8); 3.84 (d.d, 1H, CH_2O, ^3J = 5.4, ^2J = 8.0); 4.26 (q, 1H, CHO, ^3J = 5.6); 4.30-4.43 (m, 2H, CH_2N); 6.83 (t, $C^5HC_6H_3F_2$, ^3J = 8.6, ^4J = 2.8); 7.09-7.56 (m, 7H, Ar); 7.83 (s, 1HC^3Htriaz.), 7.88 (s, 1H, $C^2HC_6H_4CF_3$); 8.30 (s, 1H, C^5Htriaz.). 8.42 (br.s, 1H, NH); 8.67 (br.s, 1H, NH). IR (Nujol, ν/sm^{-1}): 3358, 3314 (NH); 1607 (CO); 1270 (βCHtriaz.); 1245, 1190, 1085 (COCOC).

***N*-{4-[2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N*'-[3,5-dimethylphenyl]urea (2).** Yield 92%, m.p.135-136 ^{o}C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.53 (s, 3H, CH_3); 2.18 (s, 6H, CH_3Ar); 3.69 (d.d, 1H, CH_2O, ^3J = 7.8, ^2J = 8.2); 3.84 (d.d, 1H, CH_2O, ^3J = 5.4, ^2J = 8.2); 4.23 (q, 1H, CHO, ^3J = 5.6); 4.29-4.43 (m, 2H, CH_2N); 6.63 (s, C^4H $C_6H_3(CH_3)_2$); 6.86 (s, 2H, $C^{2,6}H$ $C_6H_3(CH_3)_2$); 7.18-7.36 (m, 4H, $C_6\underline{H_4}NH_2$); 7.69 (br.s, 1H, NH); 7.91 (br.s, 1H, NH); 7.98 (s, 1H C^3Htriaz.); 8.26 (s, 1H C^5Htriaz.). IR (Nujol, ν/sm^{-1}): 3378, 3305 (NH); 1621 (CO); 1272 (β CHtriaz.); 1242, 1185, 1088 (COCOC).

***N*-{4-[2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N*'-[2,4-difluorophenyl]urea (3)**. Yield 90%, m.p. 131-132 ^{o}C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.58 (s, 3H, CH_3); 3.70 (d.d, 1H, CH_2O, ^3J = 7.0, ^2J = 7.8); 3.84 (d.d, 1H, CH_2O, ^3J = 5.4, ^2J = 8.0); 4.26 (q, 1H, CHO, ^3J = 5.6); 4.30-4.43 (m, 2H, CH_2N); 6.83 (t, C^5H $C_6H_3F_2$, ^3J = 8.6, ^4J = 2.8); 7.12 (t, C^3H $C_6H_3F_2$, ^3J = 8.9); 7.20-7.37 (m, 4H, $C_6\underline{H_4}NH_2$); 7.96 (s, 1HC^3Htriaz.); 8.29 (c, 1HC^5Htriaz.). 8.48 (br.s, 1H, NH); 8.60 (br.s, 1H, NH). IR (Nujol, ν/sm^{-1}): 3366, 3315 (NH); 1632 (CO); 1278 (β CHtriaz.); 1245, 1190, 1090 (COCOC).

***N*-{4-[2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N*'-[3-chloro-4-fluorophenyl]urea (4)**. Yield 92%, m.p. 182-183 ^{o}C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.55 (s, 3H, CH_3); 3.73 (d.d, 1H, CH_2O, ^3J = 7.4, ^2J = 8.4); 3.88 (d.d, 1H, CH_2O, ^3J = 5.4, ^2J = 8.4); 4.33 (q, 1H, CHO, ^3J = 5.4); 4.89 (d, 2H, CH_2N, ^3J = 6.4); 7.25-7.35 (m, 4H, C_6H_5NH); 7.4 (d, 2H, $C^{5,6}H$, C_6H_3FCl, ^3J = 8.6); 7.97 (d, 1H, C^2H, C_6H_3FCl, ^4J = 2.2); 7.97 (s, 1H, C^3H triaz.); 8.52 (s, H, C^5Htriaz.); 8.70 (br.s, 1H, NHC_6H_4); 8.78 (br.s, 1H, NHC_6H_3FCl). IR (Nujol, ν/sm^{-1}): 3356, 3295 (NH); 1643 (CO); 1272 (β CHtriaz.). 1242, 1188, 1088 (COCOC); 736 (C-Cl).

***N*-{4-[2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N*'-[2,5-dichlorophenyl]urea (5)**. Yield 93%, m.p.

221-222 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.51 (s, 3H, CH_3); 3.72 (d.d, 1H, CH_2O, ^3J = 6.9, ^2J = 8.0); 3.91 (d.d, 1H, CH_2O, ^3J = 5.4, ^2J = 8.0); 4.28-4.46 (m, 3H, CH_2N+CHO); 7.08 (d.d, 1H, C^4H $C_6H_3Cl_2$, ^3J = 8.6; ^4J = 2.1); 7.29 (d, 2H, C^2H, C^6H, C_6H_4N, ^3J = 8.6); 7.46 (d, 1H, C^2H $C_6H_3Cl_2$, ^3J = 8.6); 8.00 (s, 1H, C^3Htriaz.); 8.32 (d, 1H, C^6H $C_6H_3Cl_2$, ^4J = 2.6); 8.44 (s, 1H, C^5H triaz.); 8.55 (s, 1H, NHC_6H_4); 9.56 (s, 1H, NH $C_6H_3Cl_2$). IR (Nujol, ν/sm^{-1}): 3360, 3320 (NH); 1610 (CO); 1272 (β CHtriaz.); 1245, 1180, 1075 (COCOC).740 (C-Cl).

***N*-{4-[2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[1-naphthyl]urea (6)**. Yield 91%, m.p. 192-193 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.52 (s, 3H, CH_3); 3.70 (d.d, 1H, CH_2O, ^3J = 7.6, ^2J = 8.2); 3.88 (d.d, 1H, CH_2O, ^3J = 5.6, ^2J = 8.2); 4.25 (q, 1H, CHO, ^3J = 5.4); 4.28-4.46 (m, 2H, CH_2N); 7.34-7.49 (m,5H, $C_6\underline{H}_4NH_2$ + C^3H napht.); 7.51-7.55 (m, 2H, $C^{6,7}H$ napht.); 7.88-7.96 (m, 3H, C^4H napht. + C^3Htriaz.); 8.01-8.30 (m, 5H, $C^{2,5,8}H$ napht. + 2 NH); 8.45 (s, 1H C^5H triaz.). IR (Nujol, ν/sm^{-1}): 3346, 3320 (NH); 1614 (CO); 1270 (β CHtriaz.); 1245, 1170, 1088 (COCOC).

Substituted *N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-arylurea (general procedure).

The 1.45 mmol of substituted arylisocyanate were added at room temperature to 1.45 mmol of 2-(4-aminophenyl)-2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3--dioxolane, dissolved by heating in 1.5 ml of absolute toluene. The mixture was held for 5 minutes, then the toluene was decanted from the product released as an oil. The product was repeatedly mashed with hexane (10x5 ml). The precipitated crystals were filtered off and air-dried. A product with a yield of 72–94% was derived.

***N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[2-(trifluoromethyl)phenyl]urea (7).** Yield 92%, m.p. 95-96 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.93-4.13 (m, 2H, CH_2O); 4.25-4.42 (m, 2H, CH_2N); 4.58 (q, 1H, CHO, ^3J = 5.2); 7.05-7.55 (m, 12H, C_6H_5, $C_6\underline{H}_4NH$, $C_6\underline{H}_4CF_3NH$); 7.95 (s, 1H, C^3Htriaz.); 8.03 (s, 1H, C^5H triaz.); 8.08 (br.s, 1H, $C_6H_4N\underline{H}$); 8.20 (br.s, 1H, $NHC_6H_4CF_3$). IR (Nujol, ν/sm^{-1}): 3368, 3315 (NH); 1627 (CO); 1270 (β CHtriaz.); 1245, 1164, 1089 (COCOC).

***N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[4-ethylphenyl]urea (8).** Yield 76%, m.p. 72-73 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.34 (t, 3H, CH_3, ^3J = 7.3); 2.56 (q, 2H, $\underline{CH_2}CH_3$, ^3J = 7.1); 4.13 (q, 1H, CHO, ^3J = 5.4); 4.23-4.53 (m, 2H, CH_2N); 7.02-7.52 (m, 9H, Ar); 7.66 (br.s, 1H, NH); 7.84 (br.s, 1H, NH); 7.95 (s, 1H C^3Htriaz.); 8.21 (s, 1HC^5Htriaz.). IR (Nujol, ν/sm^{-1}): 3339, 3296 (NH); 1649 (CO); 1240, 1180, 1080 (COCOC).

***N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[2,4-dimethylphenyl]urea (9)**. Yield 86%, m.p. 91-92 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.33 (s, 3H, 4-CH_3); 2.44 (s, 3H, 3-CH_3); 3.98 (d.d, 1H, CH_2O, ^3J = 7.4, ^2J = 8.6); 4.04 (d.d, 1H, CH_2O, ^3J = 5.9, ^2J = 8.6); 4.26-4.41 (m, 2.38H, CH_2N+CHO); 4.56 (q, 0.62H, CHO, ^3J = 5.2); 7.01-7.19 (m, 4H, $C_6\underline{H}_4NH_2$); 7.23-7.54 (m, 9H, Ar); 7.62 (br.s, 1H, NH); 7.70 (br.s,1H,NH); 7.96 (s, 1H, C^3Htriaz.); 8.14 (s, 1H, C^5Htriaz.). IR (Nujol, ν/sm^{-1}): 3355, 3307 (NH); 1620 (CO); 1273 (β CHtriaz.); 1242, 1192, 1082 (COCOC).

***N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[3,5-dimethylphenyl]urea (10)**. Yield 75%, m.p. 113-114 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.20 (s, 6H, CH_3Ar); 3.97 (d.d, 1H, CH_2O, ^3J = 7.8, ^2J = 8.2); 4.05 (d.d, 1H, CH_2O, ^3J = 6.4, ^2J = 8.2); 4.27-4.42 (m, 2H, CH_2N); 4.51 (q, 1H, CHO, ^3J = 5.4); 6.61-7.38 (m, 12H, Ar); 7.68 (br.s, 1H, NH); 7.87 (br.s, 1H, NH); 7.92 (s, 1H, C^3Htriaz.); 8.16 (s, 1H, C^5Htriaz.). IR (Nujol, ν/sm^{-1}): 3338, 3300 (NH); 1621 (CO); 1275 (β CHtriaz.); 1240, 1185, 1075(COCOC).

***N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[3-fluoro-4-methylphenyl]urea (11)**. Yield 85%, m.p. 91-92 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.11 (s, 3H, CH_3); 3.95 (d.d, 1H, CH_2O, ^3J = 5.7, ^2J = 8.7); 4.04 (d.d, 1H, CH_2O, ^3J = 7.4, ^2J = 8.7); 4.20-4.35 (m, 2H, CH_2N); 4.47 (q, 0.42H, CHO, ^3J = 5.1); 4.56 (q, 0.58H, CHO, ^3J = 5.1); 6.83 (t, 1H, C^6H C_6H_3F, ^3J = 8.8); 6.94 (t, 1H, C^5H C_6H_3F, ^3J = 8.8); 7.03 (t, 1H, C^2H C_6H_3F, $^3J_{CH\text{-}CF}$ = 11.0); 7.15-7.43 (m, 9H, Ar); 7.61 (s, 0.58H, C^3Htriaz.); 7.68 (br.s, 1H, NH); 7.72 (br.s, 0.42H, C^3Htriaz.); 7.92 (s, 0.58H, C^5Htriaz.); 7.96 (br.s, 1H, NH); 8.14 (s, 0.42H, C^5Htriaz.). IR (Nujol, ν/sm^{-1}): 3350, 3310 (NH); 1620 (CO); 1275 (β CHtriaz.); 1245, 1195, 1095 (COCOC).

***N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[3-chloro-4-fluorophenyl]urea (12).** Yield 72%, m.p. 95-96 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.90-4.08 (m, 2H, CH_2O); 4.21-4.40 (m, 2H, CH_2N); 4.50 (q, 0.51H, CHO, ^3J = 5.2); 4.57 (q, 0.49H, CHO, ^3J = 5.2); 6.88 (t, 1H, $C^5HC_6H_3FCl$, $^3J_{CH\text{-}CF}$= 8.1); 7.01 (d.t, 1H, $C^6HC_6H_3FCl$, ^3J = 9.5; $^4J_{CH\text{-}F}$= 4.8); 7.11-7.46 (m, 12H, Ar, C_6H_5, C_6H_4); 7.66 (s, 0.49H, C^3Htriaz.); 7.73 (s, 0.51H, C^3Htriaz.); 7.90 7.92, 7.96 (s, 2H, $(NH)_2$); 7.96 (s, 0.51H, C^5Htriaz.); 8.00 (s, 0.49H, C^5Htriaz.). IR (Nujol, ν/sm^{-1}): 3338, 3301 (NH); 1631 (CO); 1270 (β CHtriaz.); 1245, 1190, 1085 (COCOC), 728 (C-Cl).

***N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[4-(trifluoromethyl)phenyl]urea (13).** Yield 92%, m.p. 99-100 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.96-4.11 (m, 2H, CH_2O); 4.26-4.42 (m, 2H, CH_2N); 4.59 (q, 1H, CHO, ^3J = 5.2); 7.19-7.35 (m, 7H, Ar); 7.37-7.52 (m, 7H, Ar+NH); 7.80 (s, 1H, C^3Htriaz.); 7.92 (s, 0.53H, C^5H triaz.); 7.95 (s, 0.47H, C^5H triaz.). IR (Nujol, ν/sm^{-1}): 3367, 3306 (NH); 1624 (CO); 1245, 1180, 1083 (COCOC).

***N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[4-chlorophenyl]urea (14)**. Yield 84%, m.p. 83-84 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.94-4.08 (m, 2H, CH_2O); 4.24-4.41 (m, 2H, CH_2N); 4.57 (q, 1H, CHO, ^3J = 5.2); 7.21-7.39 (m, 7H, Ar); 7.40-7.54 (m, 7H, Ar+NH); 7.89 (s, 1H, C^3Htriaz.); 8.00 (s, 0.59H, C^5H triaz.); 8.04 (s, 0.41H, C^5H triaz.). 8.13 (br.s, 1H, NHC_6H_4). IR (Nujol, ν/sm^{-1}): 3353, 3302 (NH); 1627 (CO); 1270 1245, 1190, 1085 (COCOC), 736 (C-Cl).

***N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[3-chlorophenyl]urea (15)**.Yield 94%, m.p. 84-85 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.99-4.14 (m, 2H, CH_2O); 4.28-4.44 (m, 2H, CH_2N); 4.59 (q, 1H, CHO, ^3J = 5.4); 7.22 (d, 2H, Ar, ^3J = 8.6); 7.40-7.54 (m, 12H, Ar+NH); 7.90 (s, 1H, C^3Htriaz.); 8.01 (s, 1H, C^5H triaz.); 8.09 (s, 1H, NH). IR (Nujol, ν/sm^{-1}): 3370, 3311 (NH); 1622 (CO); 1245, 1175, 1089 (COCOC), 745 (C-Cl).

***N*-{4-[2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N'*-[4-bromophenyl]urea (16)**. Yield 74%, m.p. 81-82 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.92-4.11 (m, 2H, CH_2O); 4.26-4.39 (m, 2H, CH_2N); 4.55 (q, 1H, CHO, ^3J = 5.4); 7.19-7.34 (m, 7H, Ar); 7.41-7.51 (m, 5H, Ar+NH); 7.55 (d, 2H, Ar, ^3J = 8.6); 7.90 (s, 1H, C^3Htriaz.); 8.00 (s, 1H, C^5H triaz.); 8.10 (br.s, 1H, NHC_6H_4). IR (Nujol, ν/sm^{-1}): 3355, 3304 (NH); 1623 (CO); 1245, 1165, 1090(COCOC), 658 (C-Br).

RESULTS AND DISCUSSION

The design of the target compounds included a preliminary computation of logP, since we previously showed that 4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes exhibit the greatest fungicidal activity in the range of logP of 3,0–4,0 [31, 32, 44], it has contributed to the choice of halogen and alkyl substituents in the structure of aryl isocyanates (**Tab. 1**).

The target compounds were obtained in high yields as a result of reaction of 2-(4-aminophenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes with arylisocyanates (**Fig. 1**).

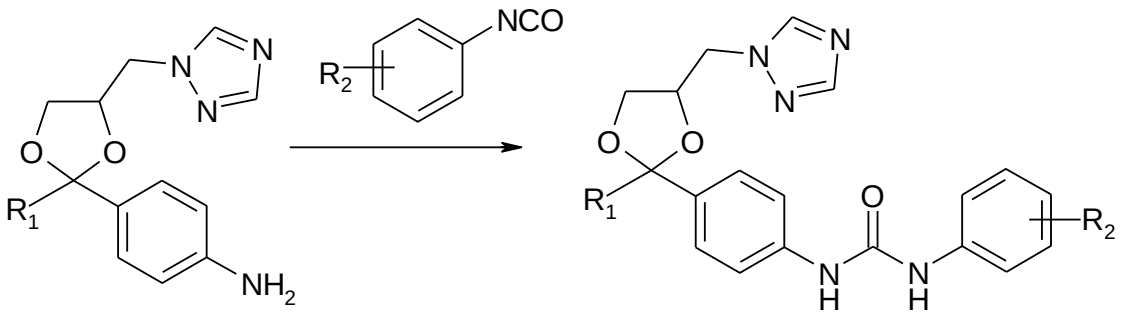

Fig. 1.

Tab. 1. Structure and lipophilicity *N*-{4-[4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N*'-arylureas

№	R_1	R_2	LogP*	№	R_1	R_2	LogP*
1	CH_3	3-CF_3	3,34	9	C_6H_5	2,4-$(CH_3)_2$	4,85
2	CH_3	3,5-$(CH_3)_2$	3,07	10	C_6H_5	3,5-$(CH_3)_2$	4,85
3	CH_3	2,4-F_2	2,60	11	C_6H_5	3-F-4-CH_3	4,88
4	CH_3	3-Cl-4-F	3,74	12	C_6H_5	3-Cl-4-F	5,52
5	CH_3	2,5-Cl_2	3,62	13	C_6H_5	4-CF_3	5,12
6	CH_3	2,3-(-CH=CH-)$_2$	3,46	14	C_6H_5	4-Cl	4,92
7	C_6H_5	2-CF_3	5,12	15	C_6H_5	3-Cl	4,92
8	C_6H_5	4-C_2H_5	4,92	16	C_6H_5	4-Br	5,10

LogP* calculated ACD Labs [45]

Tab. 2. The effect of synthesized compounds on cell lines

Compound	Cytotoxic activity		
	L-929 GI_{50},μg/ml	K-562 GI_{50},μg/ml	Hela P-388 CC_{50}, μg/ml (CC_{10}, μg/ml)
7	14,5	7,8	24,4 (13,1)
11	9,0	2,6	12,7 (5,9)

Aryl ureas based on 2- (4-aminophenyl)-2-methyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane and aryl isocyanates were synthesized in acetonitrile from which they precipitated in pure form. 2-(4-Aminophenyl)-2-phenyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane did not dissolve in acetonitrile, so the reactions were carried out in toluene, from which the desired ureas were separated as a heavy oil. The isolation of crystalline products in this case was carried out by the method of repeated washing (mashing) of the oily layer of the product with hexane, which slightly decreased the yield of the product.

The cytotoxicity of the synthesized compounds was studied at the Hans-Knoell-Institute for Natural Products Research (Germany) in lines of healthy mouse fibroblasts L-929, tumor cells of chronic myeloleukemia K-562 and cervical adrenocarcinoma Hela P-388. The results of testing *N*-{4-[4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl}-*N*'-arylureas are shown in **Tab. 2**.

CONCLUSIONS

The reaction of 2-substituted 2-(4-aminophenyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes with aryl isocyanates leads to *N*-{4-[4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl] phenyl}-*N*'-aryl ureas with high yields. It has been found that cytotoxic activity is achieved at sufficiently low concentrations of the test substances, and cytotoxicity for healthy fibroblasts is lower than for tumor cells. This class of compounds is promising for further studies of cytotoxic activity.

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