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Synthesis of 5-(arylaminomethyl)furo[2,3-*d*] pyrimidine derivatives and cytotoxicity evaluation against some human solid tumor cell lines

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5-(Arylaminomethyl)furo[2,3-*d*]pyrimidines were synthesized via the Mitsunobu reaction from 5-hydroxymethylfuro[2,3-*d*]pyrimidine derivative and *N*-sulphonylanilines as acidic components of the Mitsunobu reaction. Substituents on the phenyl moiety, the methylenamino bridge and the 2nd position of furo[2,3-*d*]pyrimidine scaffold were marked as of particular interest, so synthesis protocols for modification of these positions were suggested. The selected compounds were evaluated in vitro against a panel of six human solid tumor cell lines: A2780 (ovarian), HBL-100 (breast), HeLa (cervix), SW (non-small cell lung), T47D (breast) and WiDr (colon).

Key words: furo[2,3-*d*]pyrimidines, Mitsunobu reaction, nitrogen heterocycles, C–N bond formation, anti-cancer drugs

INTRODUCTION

The fused pyrimidines are a class of compounds with a wide diversity of biological activity on account of the relationship to the natural substrates of enzymes and similarity to the purine bases of nucleic acids. Among these heterocycles are compounds containing the furo[2,3-*d*] pyrimidine moiety. Derivatives of furo[2,3-*d*]pyrimidine as an oxygen 7-deaza analogue of biogenic purine are of particular interest as a research object in organic chemistry and medicine. A. Gangjee et al. synthesized and studied various furo[2,3-*d*]pyrimidines as potential inhibitors of folic acid cycle enzymes such as DHFR and TS [1–5]. They also investigated furo[2,3-*d*]pyrimidines as multireceptor tyrosine kinase (EGFR, VEGFR-2, PDGFR-β) inhibitors [4]. Although the 2-aminopyrimidine moiety is considered obligatory for dihydrofolate reductase inhibitors, other enzymes of the folic acid cycle are not strictly bound to this fragment, so variation of substituents on this position is also welcomed [6, 7]. Folic cycle enzymes and their inhibitors had enjoyed attention from various research groups in last decades thanks to four enzymes of folic cycle inhibiting drug – Pemetrexed, which is now being used in treating metastatic non-small cell lung cancer (NSCLC) [8, 9]. The present paper describes the synthesis of some 5-arylaminomethylfuro[2,3-*d*]pyrimidine derivatives and also deals with the cytotoxicity evaluation of these compounds against certain cancer cells.

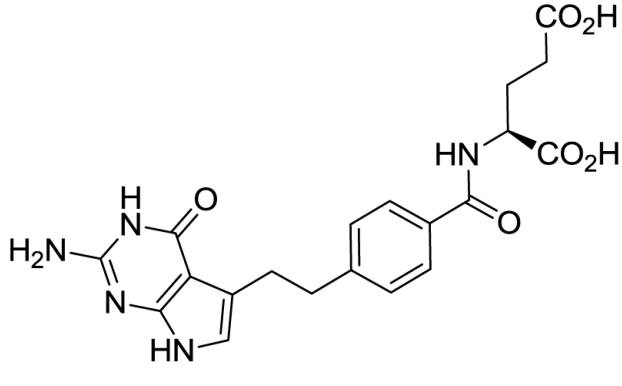

Fig. 1. Pemetrexed (Alimta™) (four enzymes of folic cycle inhibiting drug)

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EXPERIMENTAL

Melting points were determined in open capillaries with a digital melting point IA9100 series apparatus (Thermo Fischer Scientific). All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F_{254} aluminium plates (Merck). Visualization was accomplished by UV light. Column chromatography was performed using Silica gel 60 (0.040–0.063 mm) (Merck). Infrared spectra were recorded on an FTIR spectrophotometer Spectrum BX II (Perkin Elmer). NMR spectra were recorded on a Varian Inova (300 MHz and 75 MHz, respectively) or Bruker Ascend 400 (400 MHz and 100 MHz, respectively). ^{1}H NMR and ^{13}C NMR were referenced to residual solvent peaks. High Resolution Mass Spectrometry (HRMS) analyses were carried out on an ESI TOF 6230 (Agilent Technologies) mass spectrometer. Melting points and spectroscopic data of some 5-arylaminomethylfuro[2,3-*d*]pyrimidines (**5a–d**, **6a–d**, **7a–d**) are reported in our earlier paper [10].

***N*-({4-Aminofuro[2,3-*d*]pyrimidin-5-yl}methyl)-*N*-phenylmethanesulfonamide (8a)**. To a suspension of crushed nickel-aluminum alloy (0.35 g) in water (11 mL) potassium hydroxide (2.35 g) was added very slowly. After the exothermic phase of reaction, the prepared Raney nickel was left for 10–15 min. at r. t., and later mixture was heated at 70 °C (water bath) for another 30 min. When activation of Raney nickel was completed, the solution was decanted, in addition Raney nickel was washed two times with dist. H_2O (10 mL) and 2–3 times with methanol (10 mL). The residue was poured to methanol (5 mL) and *N*-({4-amino-2-(methylthio)furo[2,3-*d*]pyrimidin-5-yl}methyl)-*N*-phenylmethanesulfonamide (**5a**) (0.04 g, 0.11 mmol) was added to the suspension. The reaction mixture was stirred under reflux for 3 h, then the hot reaction mixture was filtrated and the filtrate was cooled. The resulting precipitate was collected by filtration, washed with water and recrystallized. Yield 15 mg (43%), yellowish solid; mp 266.5–268.5 °C (*i*-PrOH); IR (KBr), ν, cm^{-1}: 3436, 3321, 3107 (NH); ^{1}H NMR (300 MHz, DMSO-D_6), δ, ppm: 3.19 (s, 3H, SO_2CH_3), 5.01 (s, 2H, CH_2), 6.90–7.40 (m, 7H, Ar-H + NH_2), 7.56 (s, 1H, $C_{(6)}$H), 8.16 (s, 1H, $C_{(2)}$H); ^{13}C NMR (75 MHz, DMSO-D_6), δ, ppm: 36.9, 45.2, 99.9, 115.1, 128.8, 129.0, 129.9, 138.8, 140.8, 154.8, 159.4, 167.8; HRMS (ESI): calculated for $C_{14}H_{14}N_4O_3S$ $[M+H]^+$ = 319.0859; found 319.0862.

***N*-({4-Aminofuro[2,3-*d*]pyrimidin-5-yl}methyl)-*N*-(3,4,5-trimethoxyphenyl)methanesulfonamide (8b)**. Compound **8b** was synthesized from *N*-({4-amino-2-(methylthio)furo[2,3-*d*]pyrimidin-5-yl}methyl)-*N*-(3,4,5-trimethoxyphenyl)methanesulfonamide (**5b**) (0.2 g, 0.44 mmol) according to the procedure described for **8a**. Yield 62 mg (34%), white solid; mp 226–229 °C (MeOH); IR (KBr), ν, cm^{-1}: 3317, 3306 (NH); ^{1}H NMR (300 MHz, DMSO-D_6), δ, ppm: 3.22 (s, 3H, SO_2CH_3), 3.63 (s, 3H, OCH_3), 3.71 (s, 6H, 2×OCH_3), 5.00 (s, 2H, CH_2), 6.65 (s, 2H, Ar-H), 7.12 (br s, 2H, NH_2), 7.70 (s, 1H, $C_{(6)}$H), 8.18 (s, 1H, $C_{(2)}$H); ^{13}C NMR (75 MHz, DMSO-D_6), δ, ppm: 37.1, 45.3, 56.8, 60.7, 100.1, 106.9, 115.2, 134.4, 138.0, 140.8, 153.4, 154.7, 159.4, 167.7; HRMS (ESI): calculated for $C_{17}H_{20}N_4O_6S$ $[M+H]^+$ = 409.1176; found 409.1183.

***N*-({4-Aminofuro[2,3-*d*]pyrimidin-5-yl}methyl)-*N*-(naphthalen-1-yl)methanesulfonamide (8c)**. Compound **8c** was synthesized from *N*-({4-amino-2-(methylthio) furo[2,3-*d*]pyrimidin-5-yl}methyl)-*N*-(naphthalen-1-yl) methanesulfonamide (**5c**) (0.1 g, 0.24 mmol) according to the procedure described for **8a**. Yield 30 mg (34%), white solid; mp ~260 °C dec. (*n*-BuOH); IR (KBr), ν, cm^{-1}: 3409, 3333 (NH); ^{1}H NMR (300 MHz, DMSO-D_6), δ, ppm: 3.36 (s, 3H, SO_2CH_3), 4.93 (d, ^2J = 14.4 Hz, 1H, CH_aH_b), 5.29 (d, ^2J = 14.4 Hz, 1H, CH_aH_b), 7.20–7.50 (m, 5H, NH_2 + $C_{(6)}$H + Ar-H), 7.50–7.65 (m, 1H, Ar-H), 7.84–7.96 (m, 3H, Ar-H), 8.04 (d, ^3J = 8.4 Hz, 1H, Ar-H), 8.15 (s, 1H, $C_{(2)}$H); ^{13}C NMR (75 MHz, DMSO-D_6), δ, ppm: 37.1, 46.8, 100.3, 114.4, 124.0, 125.9, 126.4, 126.8, 127.0, 128.4, 129.6, 133.7, 134.5, 135.9, 140.9, 154.7, 159.3, 167.5; HRMS (ESI): calculated for $C_{18}H_{16}N_4O_3S$ $[M+H]^+$ = 369.1016; found 369.1020.

***N*-((Biphenyl-4-yl)-*N*-({4-aminofuro[2,3-*d*]pyrimidin-5-yl}methyl)methanesulfonamide (8d)**. Compound **8d** was synthesized from *N*-({4-amino-2-(methylthio) furo[2,3-*d*]pyrimidin-5-yl}methyl)-*N*-(biphenyl-1-yl)methanesulfonamide (**5d**) (0.1 g, 0.23 mmol) according to the procedure described for **8a**. Yield 40 mg (44%), white solid; mp 226–228.5 °C (*i*-PrOH); ^{1}H NMR (300 MHz, DMSO-D_6), δ, ppm: 3.23 (s, 3H, CH_3), 5.07 (s, 2H, CH_2), 7.17 (br s, 2H, NH_2), 7.30–7.50 (m, 5H, Ar-H), 7.61–7.78 (m, 5H, Ar-H + $C_{(6)}$H), 8.18 (s, 1H, $C_{(2)}$H); ^{13}C NMR (75 MHz, DMSO-D_6), δ, ppm: 37.0, 45.1, 100.0, 115.2, 127.4, 128.0, 128.5, 129.4, 129.7, 138.0, 139.7, 140.4, 140.8, 154.8, 159.4, 167.8; HRMS (ESI): calculated for $C_{20}H_{18}N_4O_3S$ $[M+H]^+$ = 395.1172; found 395.1177.

5-((Phenylamino)methyl)furo[2,3-*d*]pyrimidin-4-amine (9a). Compound **9a** was synthesized from 2-(methylthio)-5-(phenylaminomethyl)furo[2,3-*d*]pyrimidin-4-amine (**7a**) (0.1 g, 0.35 mmol) according to the procedure described for **8a**. Yield 36 mg (43%), white solid: mp 213.5–215.5 °C (benzene); IR (KBr), ν, cm^{-1}: 3382, 3295 (NH); ^{1}H NMR (300 MHz, DMSO-D_6), δ, ppm: 4.32 (d, ^3J = 5.1 Hz, 2H, CH_2), 6.19 (t, ^3J = 5.1 Hz, 1H, NH), 6.66 (t, ^3J = 7.2 Hz, 1H, Ar-H), 6.77 (d, ^3J = 7.2 Hz, 2H, Ar-H), 7.05–7.20 (m, 4H, Ar-H + NH_2), 7.82 (s, 1H, $C_{(6)}$H), 8.19 (s, 1H, $C_{(2)}$H); ^{13}C NMR (75 MHz, DMSO-D_6), δ, ppm: 39.0, 101.0, 114.1, 118.1, 118.7, 129.6, 139.1, 149.0, 154.6, 159.8, 167.8; HRMS (ESI): calculated for $C_{31}H_{12}N_4O$ $[M+H]^+$ = 241.1084; found: 241.1086.

5-({(3,4,5-Trimethoxyphenyl)amino}methyl)furo[2,3-*d*]pyrimidin-4-amine (9b). Compound **9b** was synthesized from 2-(methylthio)-5-[(3,4,5-trimethoxyphenylamino)methyl]furo[2,3-*d*]pyrimidin-4-amine (**7b**) (34 mg,

0.09 mmol) according to the procedure described for **8a**. Yield 12 mg (40%), white solid; mp ~190 °C dec. (benzene); IR (KBr), ν, cm^{-1}: 3317, 3306, 3166 (NH); ^{1}H NMR (300 MHz, DMSO-D_6), δ, ppm: 3.55 (s, 3H, OCH_3), 3.71 (s, 6H, 2 × OCH_3), 4.31 (d, ^3J = 4.8 Hz, 2H, CH_2), 6.00 (br s, 1H, NH), 6.10 (s, 1H, Ar-H), 7.17 (br s, 2H, NH_2), 7.86 (s, 1H, $C_{(6)}H$), 8.19 (s, 1H, $C_{(2)}H$); ^{13}C NMR (75 MHz, DMSO-D_6), δ, ppm: 41.0, 56.3, 60.8, 92.0, 101.1, 118.7, 130.4, 139.1, 145.7, 154.1, 154.6, 159.8, 167.8.

5-((Naphthalen-1-ylamino)methyl)furo[2,3-*d*]pyrimidin-4-amine (9c). Compound **9c** was synthesized from 2-(methylthio)-5-[(naphthalen-1-ylamino)methyl] furo[2,3-*d*]pyrimidin-4-amine (**7c**) (73 mg, 0.22 mmol) according to the procedure described for **8a**. Yield 28 mg (44%), white solid; mp 263.5–266.5 °C (toluene); IR (KBr), ν, cm^{-1}: 3317, 3306, 3166 (NH); ^{1}H NMR (300 MHz, DMSO-D_6), δ, ppm: 4.54 (d, ^3J = 4.5 Hz, 2H, CH_2), 6.74–6.84 (m, 2H, Ar-H + NH), 7.18–7.34 (m, 4H, Ar-H + NH_2), 7.42–7.52 (m, 2H, Ar-H), 7.77–7.84 (m, 1H, Ar-H), 7.92 (s, 1H, $C_{(6)}H$), 8.17 (s, 1H, $C_{(2)}H$), 8.18–8.24 (m, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-D_6), δ, ppm: 38.9, 101.0, 105.6, 117.9, 118.4, 122.2, 124.5, 125.2, 126.5, 127.2, 128.8, 134.6, 139.9, 143.9, 154.5, 159.7, 167.9; HRMS (ESI): calculated for $C_{17}H_{14}N_4O$ $[M+H]^+$ 291.1240; found 291.1246.

5-[(Biphenyl-4-ylamino)methyl]furo[2,3-*d*]pyrimidin-4-amine (9d). Compound **9d** was synthesized from 5-[(biphenyl-4-ylamino)methyl]-2-(methylthio)[2,3-*d*] pyrimidin-4-amine (**7d**) (70 mg, 0.19 mmol) according to the procedure described for **8a**. Yield 22 mg (36%), white solid; mp 224.5–226.5 °C (MeOH); IR (KBr), ν, cm^{-1}: 3295, 3269 (NH); ^{1}H NMR (300 MHz, DMSO-D_6), δ, ppm: 4.39 (d, ^3J = 4.8 Hz, 2H, CH_2), 6.38 (br s, 1H, NH), 6.86 (d, ^3J = 8.1 Hz, 2H, Ar-H), 7.10–7.28 (m, 3H, Ar-H + NH_2), 7.32–7.52 (m, 4H, Ar-H), 7.57 (d, ^3J = 8,1 Hz, 2H, Ar-H), 7.40 (s, 1H, $C_{(6)}H$), 8.20 (s, 1H, $C_{(2)}H$); ^{13}C NMR (75 MHz, DMSO-D_6), δ, ppm: 39.0, 101.0, 114.4, 118.6, 126.3, 126.7, 128.0, 129.5, 129.8, 139.2, 141.1, 148.6, 154.6, 159.8, 167.8; HRMS (ESI): calculated for $C_{19}H_{16}N_4O$ $[M+H]^+$ 317.1397; found 317.1403.

2,4-Diamino-5-(hydroxymethyl)furo[2,3-*d*]pyrimidine (10). A mixture of ethyl 2,4-diaminofuro[2,3-*d*]pyrimidine-5-carboxylate hydrobromide (2 g, 6.60 mmol) and THF (freshly distilled from $LiAlH_4$, 50 mL) was cooled to –50 °C and $LiAlH_4$ (0.7 g, 18.45 mmol) was added. The temperature of the mixture was raised to r. t. over 3 h, then the reaction mixture was neutralized with sat. NH_4Cl soln (about 30 mL). The layers were separated and the aqueous layer was washed with THF (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was recrystallized to give compound **10**. Yield 0.8 g (67%), brown solid; mp 259–262 °C (*n*-BuOH); IR (KBr), ν, cm^{-1}: 3484, 3340, 3184 (NH, OH); ^{1}H NMR (400 MHz, DMSO-D_6), δ, ppm: 4.50 (d, ^3J = 3.9 Hz, 2H, CH_2), 5.76 (t, ^3J = 3.9 Hz, 1H, OH), 6.06 (s, 2H, NH_2), 6.69 (s, 2H, NH_2), 7.27 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-D_6), δ, ppm: 55.1, 92.7, 120.7, 133.5, 159.6, 161.9, 170.1; Anal. calcd for $C_{19}H_{16}N_4O$: C, 46.67; H, 4.48. Found C, 46.60; H, 4.36.

***N*-((2,4-Diaminofuro[2,3-*d*]pyrimidin-5-yl)methyl)-*N*-(2,5-dimethoxyphenyl)benzenesulfonamide (11)**. To a cooled (ice bath) 0.6 M soln of Ph_3P (1.16 g, 4.44 mmol) in THF, DEAD (0.70 g, 0.63 mL, 4.00 mmol) was added. The mixture was stirred for 10 min, then a soln of *N*-(2,5-dimethoxyphenyl)-4-nitrobenzensulfonamide (0.93 g, 3.33 mmol) in a minimal amount of THF was added dropwise. After another 10 min, a suspension of 2,4-diamino-5-(hydroxymethyl)furo[2,3-*d*]pyrimidine (0.4 g, 2.22 mmol) in THF (8 mL) was added over 3–5 min. The reaction mixture was stirred at r. t. until full conversion of the alcohol occurred (TLC monitoring, ~1 h for reaction to complete). Then, H_2O was added to the reaction mixture, and the formed precipitate was collected by filtration, washed with Et_2O and recrystallized to give compound **11**. Yield 0.78 g (79%), beige solid; mp 253.5–256 °C (dioxane); IR (KBr), ν, cm^{-1}: 3382, 3324, 3191 (NH); ^{1}H NMR (400 MHz, DMSO-D_6), δ, ppm: 3.24 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 4.44–5.04 (br s, 2H, CH_2), 6.12 (s, 2H, NH_2), 6.42–6.70 (br s, 3H, Ar-H+NH_2), 6.86 (s, 2H, Ar-H), 7.03 (s, 1H, CH), 8.02 (d, ^3J = 8.4 Hz, 2H, Ar-H), 8.45 (d, ^3J = 8.4 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-D_6), δ, ppm: 55.7, 55.9, 91.6, 113.2, 114.4, 115.3, 118.5, 124.8, 125.2, 129.6, 137.0, 144.3, 150.5, 151.0, 152.9, 159.3, 161.8, 170.1; HRMS (ESI): calculated for $C_{21}H_{20}N_6O_7S$ $[M+H]^+$ 501.1187; found 501.1176.

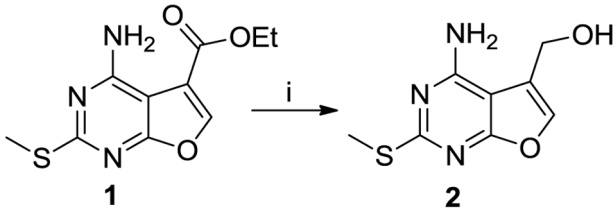
5-({(2,5-dimethoxyphenyl)amino}methyl)furo[2,3-*d*]pyrimidine-2,4-diamine (12). A compound **11** (0.29 g, 0.58 mmol) was dissolved in DMF (3 mL) and $HSCH_2COOH$ (0.1 g, 80 μL, 1.16 mmol) was added dropwise. Then, $LiOH{\cdot}H_2O$ (0.19 g, 4.64 mmol) was added to the mixture. The reaction mixture was stirred at r. t. under argon atmosphere for 1 h, then quenched with H_2O (5–10 mL). The precipitate was collected by filtration and dissolved in CH_2Cl_2 (50 mL). The solution was washed with sat. $NaHCO_3$ soln (2–50 mL) and H_2O (2–50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The obtained residue was recrystallized. Yield 0.13 g (72%). ^{1}H NMR 400 MHz, DMSO-D_6), δ, ppm: 3.62 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 4.25 (d, ^3J = 5 Hz, 2H, CH_2), 5.53 (t, ^3J = 5 Hz, 1H, NH), 6.01 (s, 2H, NH_2), 6.13 (dd, ^3J = 8.6 Hz, ^4J = 2.6 Hz, 1H, Ar-H), 6.32 (dd, ^4J = 2.6 Hz, 1H, Ar-H), 6.65 (s, 2H, NH_2), 6.71 (d, ^3J = 8.6 Hz, 1H, Ar-H), 7.39 (s, 1H, Ar-H). Other spectral data is also according to literature [11] where different protocol was invoked for the synthesis of this compound.

Compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration. Control cells were exposed to an equivalent concentration of DMSO (0.25% v/v, negative control). Each agent was tested

in triplicate at different dilutions in the range of 1–100 μM. The drug treatment was started on day 1 after plating. Drug incubation times were 48 h, after which cells were precipitated with 25 mL ice-cold TCA (50% w/v) and fixed for 60 min at 4 °C. Then the SRB assay was performed [12]. The optical density (OD) of each well was measured at 492 nm, using a BioTek's PowerWave XS Absorbance Microplate Reader. Values were corrected for the background OD from wells containing only medium.

RESULTS AND DISCUSSION

The starting material – 4-amino-5-hydroxymethyl-2-methylthiofuro[2,3-*d*]pyrimidine **2** was prepared in good yield (72%) by reduction of ethyl 4-amino-2-methylthiofuro[2,3-*d*]pyrimidine-5-carboxylate **1** [10] using $LiAlH_4$ in tetrahydrofuran. It should be mentioned that some problems due to the coordination of aluminum species with the target compound arose, due to these insoluble complexes reaction yields were below mediocre. Problems with the isolation of 5-(hydroxymethyl)furo[2,3-*d*]pyrimidine **2** from the reaction mixture were successfully addressed by using a saturated ammonium chloride solution for neutralization of the reaction mixture instead of a conventional water/acidified water procedure.



(i) 1. $LiAlH_4$, THF, –50 °C to r. t.; 2. sat. NH_4Cl.

Scheme 1. Synthesis of 4-amino-5-hydroxymethyl-2-methylthiofuro[2,3-*d*]pyrimidine

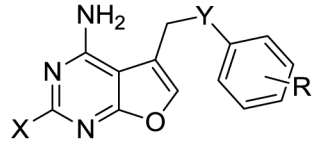
Inhibitors of folic acid cycle enzymes are and should be structurally similar to folic acid, while the 2-aminopyrimidine moiety is considered mandatory for binding to the dihydrofolate reductase catalytic center, other enzymes of the folic acid cycle are not strictly bound to this fragment. So our approach in design of antifolates includes some variation on the 2nd position of the pyrimidine moiety, the methylenamino bridge with/without electron-withdrawing groups and the aromatic moiety with electron withdrawing/donating substituents.

The 5-(arylaminomethyl) moiety was introduced to furo[2,3-*d*]pyrimidines via the Mitsunobu reaction between 5-hydroxymethylfuro[2,3-*d*]pyrimidine **2** and *N*-sulphonylanilines **3a–d** and **4a–d** as acidic components of this reaction (Scheme 1). Both *N*-mesylanilines **3a–d** and *N*-nosylanilines **4a–d** are suitable substrates for the Mitsunobu reaction, so 5-arylaminomethylfuro[2,3-*d*]pyrimidines **5a–d** and **6a–d** were synthesized in good yields (46–84%). Nosylanilines were introduced to this synthesis protocol due to harsh conditions required for deprotection of the mesyl group, while deprotection of nosylates proceeds well and under mild conditions via the Meisenheimer complex formation giving deprotection products **7a–d** in good yields (61–75%). Removal of the methylthio group was performed with Raney nickel in boiling methanol, target products **8a–d** and **9a–d** were obtained in mediocre yields (34–44%).

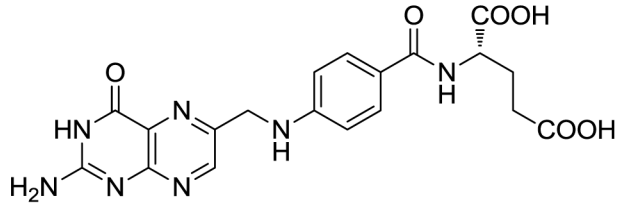
Table. **Synthesized 5-arylaminomethylfuro[2,3-*d*]pyrimidines**

Entry	R	R′		
		Ms	Ns	H
1	H	**5a**, **8a**	**6a**	**7a**, **9a**
2	3,4,5-$(OMe)_3$	**5b**, **8b**	**6b**	**7b**, **9b**
3	2,3-(-CH=CH-)$_2$	**5c**, **8c**	**6c**	**7c**, **9c**
4	4-Ph	**5d**, **5d**	**6d**	**7d**, **9d**

Synthesized compounds **5a–d**, **7a–d**, **8a–d** and **9a–d** were evaluated in vitro against a panel of six human solid tumor cell lines: A2780 (ovarian), HBL-100 (breast), HeLa (cervix), SW (non-small cell lung), T47D (breast) and WiDr (colon). The literature survey shows that antifolate activity could be enhanced via incorporation of electron withdrawing groups into the bridge between the heterocyclic scaffold and carbocyclic aromatic moiety and via expanding the carbocyclic aromatic moiety [7]. For the control purpose our synthesis protocol was applied

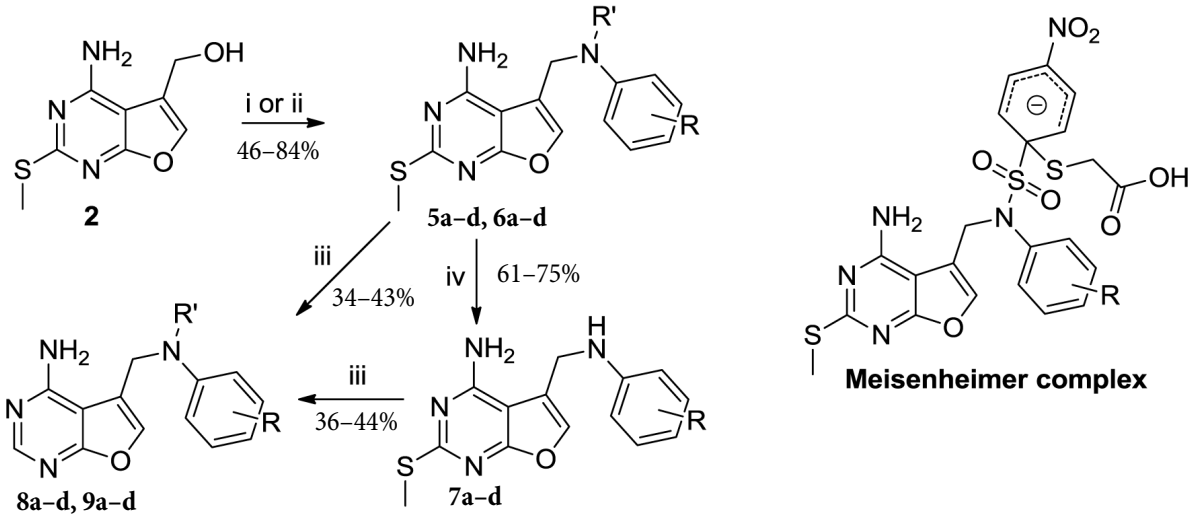


X = H; SCH_3;
Y = NH; NMs;
R = H; 3,4,5-$(OMe)_3$; 2,3-(-CH=CH-)$_2$; 4-Ph.



Folic acid

Fig. 2. Structure of synthesized/evaluated compounds and folic acid



(i) DEAD, Ph_3P, *N*-mesylaniline **3a–d**, THF, 0 °C to r. t.; (ii) DEAD, Ph_3P, *N*-nosylaniline **4a–d**, THF, 0 °C to r. t.; (iii) Raney nickel, MeOH, Δ; (iv) $HSCH_2COOH$, $LiOH{\cdot}H_2O$, DMF, r. t.

Scheme 2. Synthesis protocol of 5-arylaminomethylfuro[2,3-*d*]pyrimidines

to the synthesis of the published antifolate inhibitor **12** [11]. Unfortunately, only compound **8d** showed some growth inhibitory activity against WiDr (colon) cancer cells, no activity was seen in other compounds as well as in antifolate inhibitor **12** used for the control.

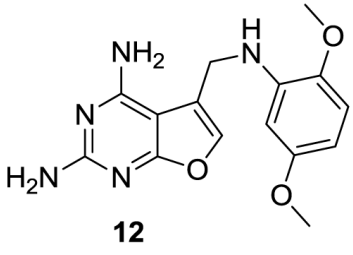


Fig. 3. Published antifolate inhibitor

CONCLUSIONS

In summary, synthesized *N*-arylaminomethylfuro[2,3-*d*] pyrimidines do not inhibit the growth of the investigated solid tumor cell lines: A2780 (ovarian), HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung) and T47D (breast). Only compound **8d** shows some degree of activity against WiDr (colon) cancer cell line – GI_{50} $8.6 \cdot 10^{-5}$ M. While the latter result is of some interest – it is not possible to evaluate valuable structural properties out of a single compound. Overall, it can be stated that the growth inhibition of solid tumor cells in search for folate cycle inhibitors is not the best way to proceed, when even the published antifolate 5-({(2,5-dimethoxyphenyl)amino}methyl)furo[2,3-*d*]pyrimidine-2,4-diamine taken for the control purpose does not show any inhibitory activity against the investigated solid tumor cell lines.

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5-ARILAMINOMETILFURO[2,3-*d*]PIRIMIDINŲ SINTEZĖ IR CITOTOKSIŠKUMO PRIEŠ KAI KURIAS VĖŽINIŲ LĄSTELIŲ GRUPES ĮVERTINIMAS

S a n t r a u k a

5-Hidroksimetilfuro[2,3-*d*]pirimidinams reaguojant su *N*-sulfonilanilinais Mitsunobu reakcijos sąlygomis gauti įvairūs 5-(arilaminometil)furo[2,3-*d*]pirimidinai. Sintetinant junginius priešvėžiniams tyrimams buvo atsižvelgiama į pakaitus, vartojamus aromatiniame karbocikliniame fragmente, metilenamino tiltelį ir antrąją pirimidino žiedo padėtį. Biologinis junginių aktyvumas buvo tirtas šešių vėžinių ląstelių grupėse – A2780 (kiaušidžių), HBL-100 (krūties), HeLa (gimdos kaklelio), SW1573 (plaučių), T-47D (krūties) ir WiDr (gaubtinės žarnos).