New approach to 5-arylamino-4-(5-aryloxyfuran-2-yl)pyrimidines: synthesis and antibacterial activity

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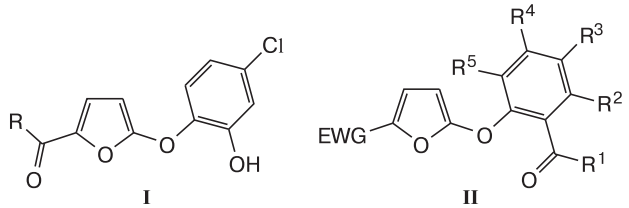
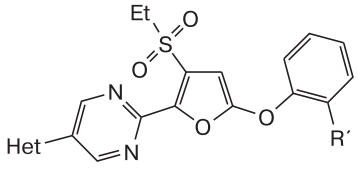
A method for the synthesis of previously unknown 5-arylamino-substituted 4-(5-aryloxyfuran-2-yl)pyrimidines containing methyl and methoxy groups at different positions of the aryl substituents was developed. The method is based on the combination of the Buchwald-Hartwig cross-coupling reaction with various anilines and nucleophilic substitution of the nitro group by phenolate anions. All the new compounds were screened against 15 different pathogenic bacterial strains. 4-[5-(3,4,5-Trimethoxyphenoxy)furan-2-yl]-substituted pyrimidines were found to possess high antibacterial activity against gonococcal infections, in some cases ten times higher than that of the commercial drug Spectinomycin.

Key words: pyrimidines, furans, antibacterial activity, Buchwald-Hartwig reaction.

Aryloxy-substituted furans are interesting objects for medicinal chemistry, since they exhibit a wide range of biological activities, for example, antiparasitic against toxoplasmosis[1] (**I**), antiplatelet,[2] antiallergic,[2] and anti-inflammatory[2] (**II**), and can also be used to combat insect pests[3] *Aphis gossypii*, *Spodoptera litura*, and others (**III**).



I **II**



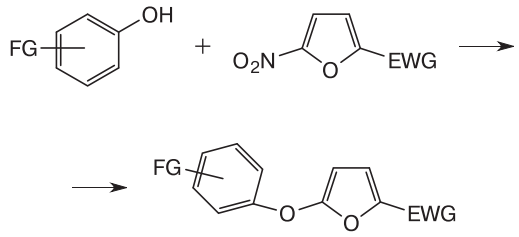
III

EWG = —CH=O, —COOEt
R^1—R^5 = H, Me, Et, OMe, Cl, Br, I
Het is a heterocyclic substituent; R′ = H, F

At the same time, there is considerable interest in substituted C(4)- and/or C(5)-mono- and di(het)aryl-substituted pyrimidines, especially in their 4-(5-nitrofuran-2-yl)-substituted derivatives as to promising wide-range antibacterial agents.[4—7]

Note that the nitro group in furans is prone to substitution by various nucleophilic agents.[8] However, the substitution reactions in nitrofurans under the action of phenolate anion are presented by only a small number of publications for a limited range of derivatives (Scheme 1).[2,9—11]

Scheme 1



FG is a functional group; EWG is an electron-withdrawing group: NO_2, C≡N, CHO, Ac, R—O—R′.

Conditions: base, solvent.

Continuing the works on synthetic approaches to the modification of 4,5-di(het)aryl-substituted pyrimidines for the subsequent study of their antibacterial activity, we synthesized new 5-arylamino-substituted 4-(5-aryloxyfuran-2-yl)pyrimidines using a combination of the Buchwald—Hartwig cross-coupling reaction with various anilines and nucleophilic substitution of the nitro group with phenolate anions.

Initially, we attempted to obtain the corresponding 5-phenoxy-4-(5-nitrofuran-2-yl)pyrimidine by the reaction of 5-bromo-4-(5-nitrofuran-2-yl)pyrimidine (**1**) with phenol (**2a**) at 85 °C in 1,4-dioxane under the conditions of the Buchwald—Hartwig cross-coupling reaction, which

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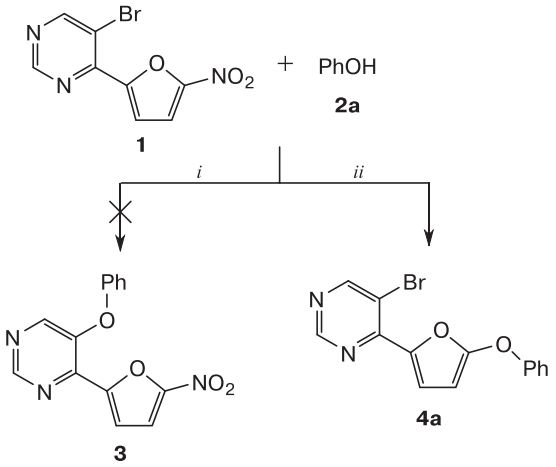
we found earlier for the reactions with anilines (Scheme 2, Table 1, entry *1*).[7] However, instead of the expected cross-coupling product **3**, the formation of which was not detected by GLC-MS, the corresponding 5-bromo-4-(5-phenyloxyfuran-2-yl)pyrimidine (**4a**) was isolated in 46% yield. The subsequent optimization of the conditions showed that the product of *ipso*-substitution of the NO_2 group **4a** can be obtained in up to 73% yields in the presence of various bases (see Table 1, entries *5*—*8*). Note that in the absence of a base, irrespective of the presence or absence of a palladium catalyst, no substitution of the NO_2 group occurs (see Table 1, entries *3* and *4*).

Scheme 2



Reagents and conditions: 2a (1.5 equiv.), 85 °C, 1.5 h, 1,4-dioxane; *i*. Pd catalyst, phosphine ligand, base, Buchwald—Hartwig cross-coupling; *ii*. base, *ipso*-substitution.

The optimal conditions found were used in the reaction of bromo-substituted pyrimidine (**1**) with 3,4,5-trimethoxyphenol (**2b**) for the synthesis of 5-bromo-4-[5-(3,4,5-trimethoxyphenoxy)furan-2-yl]pyrimidine (**4b**) (Scheme 3).

Table 1. Optimization of the reaction conditions of 5-bromo-4-(5-nitrofuran-2-yl)pyrimidine (**1**) with phenol (**2a**)

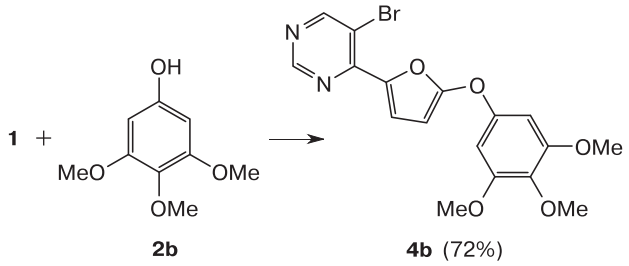
Entry	Base (2.5 equiv.)	[Pd][a] (10 mol.%)	L[b] (5 mol.%)	Yield of **4a** (%)
1	K_3PO_4	$Pd(OAc)_2$	Xanthphos	46
2	K_3PO_4	$Pd(OAc)_2$	dppf	32
3	—	$Pd(OAc)_2$	dppf	0
4	—	—	—	0
5	K_3PO_4	—	—	73 (12)[c]
6	NEt_3	—	—	71
7	KOH	—	—	56
8	Bu^tONa	—	—	37

[a] [Pd] is a Pd catalyst.

[b] L is a phosphine ligand, dppf is the 1,1′-bis(diphenylphosphino)-ferrocene; Xanthphos is the 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

[c] Carrying out this reaction at room temperature for 15 h gave product **4a** in only 12% yield.

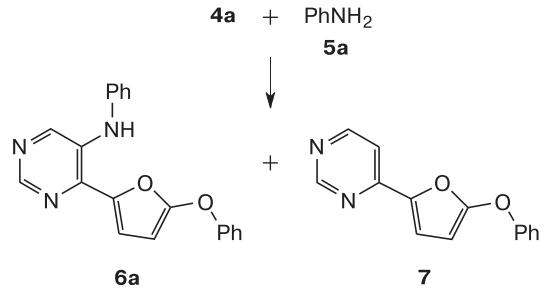
Scheme 3



Reagents and conditions: K_3PO_4 (2 equiv.), 85 °C, 15 h, 1,4-dioxane.

Further Buchwald—Hartwig amination of bromo-substituted pyrimidines **4a,b** with aniline (**5a**) leads to a mixture of the target compound **6a** and the by-product of reductive debromination **7** (Scheme 4). 4-(5-Phenoxyfuran-2-yl)pyrimidine (**7**) was not isolated in the pure form, and its content in the reaction mixtures was estimated by GLC-MS. The reaction conditions were further optimized in order to minimize the formation of undesired product **7** (Table 2).

Scheme 4



Reagents and conditions: 5a (1.5 equiv.), $Pd(OAc)_2$ (10 mol.%), phosphine ligand, K_3PO_4 (2.5 equiv.), heating, 15 h, 1,4-dioxane, Buchwald—Hartwig cross-coupling.

An overall yield of 4-(5-phenoxyfuran-2-yl)-*N*-phenylpyrimidin-5-amine (**6a**) in two sequential steps, namely, the *ipso*-substitution of the nitro group with a phenolate anion and the Buchwald—Hartwig amination, was 55%.

In order to increase the yield of the target product **6a**, we considered an alternative sequence of the implemented processes. We used 4-(5-nitrofuran-2-yl)-5-phenylaminopyrimidine (**8a**) as a starting compound, which we obtained earlier in 76% yield by the reaction of bromo-substituted pyrimidine **1** with aniline (**5a**) in the presence of 2.5 equiv. of K_3PO_4, 10 mol.% of $Pd(OAc)_2$ as a catalyst, and 20 mol.% of Xanthphos as a ligand.[7] The substitution of

Table 2. Optimization of the reaction conditions of 5-bromo-4-(5-phenoxyfuran-2-yl)pyrimidine (**4a**) with aniline (**5a**)

Entry	Ligand (equiv.)	*T*/°C	Composition of the reaction mixture[a] (%)	Yield of **6a** (%)
1	dppf (0.2)	85	**4a** (66.0), **6a** (18.0), **7** (8.1), UI (7.9)[b]	23
2	dppf (0.4)	85	**4a** (6.2), **6a** (8.4), **7** (79.5), UI (5.9)[b]	4
3	Xanthphos (0.2)	85	**4a** (38.1), **6a** (54.2), **7** (7.7)	53
4	Xanthphos (0.2)	Reflux	**6a** (88.8), UI (11.2)[b]	76

[a] According to GLC-MS.
[b] Unidentified impurities.

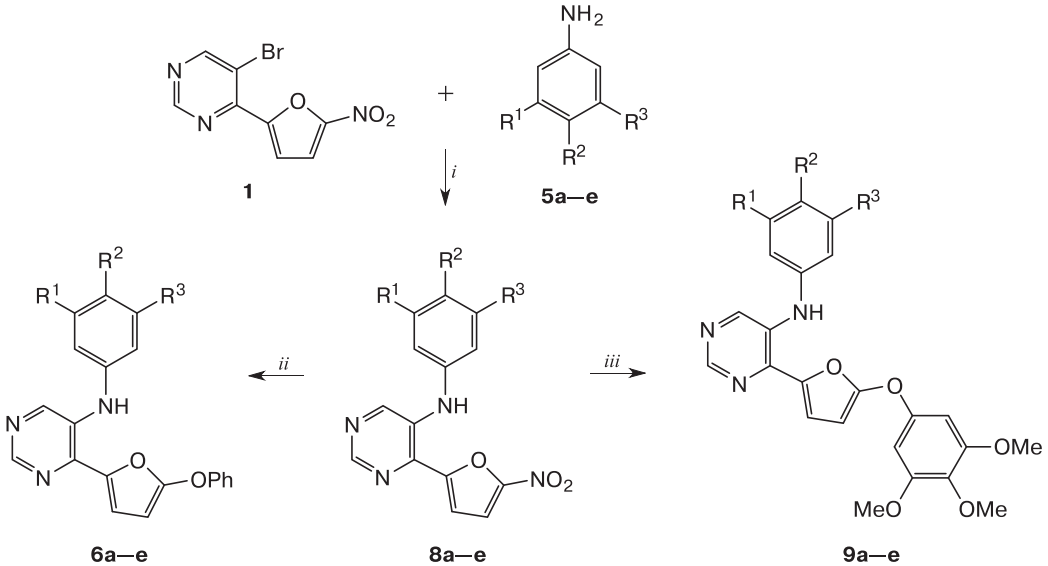
the nitro group in **8a** by the reaction with phenol gave the corresponding product **6a** in 80% yield, with its overall yield on two steps being 61% (Scheme 5).

Since the total yield on two steps in the second case was higher, we used this version to synthesize a series of 5-arylamino-4-(5-aryloxyfuran-2-yl)pyrimidines containing phenoxy- (**6a—e**) and 3,4,5-trimethoxyphenoxy substituents (**9a—e**) in moderate to high yields (Scheme 5). In the case of 3,4,5-trimethoxyphenoxy-substituted derivatives, the yields were much lower, apparently, due to the greater steric hindrances. In addition, the reaction time in this case had to be increased from 15 to 30 h, since after heating for 15 h, the content of products **9a—e** in the reaction mixtures according to GLC-MS data did not exceed 9—14%.

The study of antibacterial activity *in vitro* against gram-negative (*N. gonorrhoeae*, *E. coli, C. braakii, S. flexneri*, *P. vulgaris*, *S. marcescens*, *K. pneumoniae*, *P. aeruginosa*) and gram-positive (*S. pyogenes, S. aureus*) bacteria showed that the replacement of the NO_2 group in the furan fragment of 5-bromo- and 5-arylamino-substituted pyrimidines (**1** and **8a—c**) by the phenoxy group leads to a sharp decrease in the antibacterial activity of compounds **4a** and **6a,b,e** (the minimum inhibitory concentration (MIC) changes from 62.5 to 25 μg mL^{-1} for the strain *Neisseria gonorrhoeae* NCTC12700/ATCC49226), while compound **9c** with the 3,4,5-trimethoxyphenoxy group at the same position, compared to spectinomycin, had a higher MIC which is comparable to the MIC of the previously obtained analogous nitrofuryl derivative **8e** (Table 3). This indicates that it is reasonable to further search for antibacterial agents in the series of 4-[5-(3,4,5-trimethoxyphenoxy)-furan-2-yl]-substituted pyrimidines.

In conclusion, we proposed a convenient method for the synthesis of earlier unknown 5-arylamino-4-(5-aryloxyfuran-2-yl)pyrimidines containing methyl and methoxy groups at various positions of aryl substituents which is based on a combination of the Buchwald—Hartwig cross-

Scheme 5



5, **6**, **8**, **9**	R^1	R^2	R^3	Yield (%)		
				6	**8**	**9**
a	H	H	H	80	76	46
b	H	Me	H	90	67	27
c	H	OMe	H	32	45	13
d	OMe	OMe	H	31	55	10
e	OMe	OMe	OMe	34	50	8

Reagents and conditions: *i*. $Pd(OAc)_2$ (10 mol.%), Xanthphos (20 mol.%), K_3PO_4 (2.5 equiv.), 85 °C, 15 h, 1,4-dioxane, Buchwald—Hartwig cross-coupling; *ii*. **2a** (1.5 equiv.), K_3PO_4 (2.5 equiv.), 85 °C, 15 h, 1,4-dioxane, *ipso*-substitution; *iii*. **2b** (1.5 equiv.), K_3PO_4 (2.5 equiv.), 85 °C, 30 h, 1,4-dioxane, *ipso*-substitution.

Table 3. Antibacterial activity of 5-bromo- and 5-arylamino-substituted pyrimidines (**1**, **4a**, **6a,b,e**, **8a,b,c,e**, and **9c**) against the strain *Neisseria gonorrhoeae* NCTC12700/ATCC49226

Compound	MIC/mg mL^{-1}
Spectinomycin	15.6
1	0.9
4a	62.5
6a	62.5
6b	125
6e	250
8a	0.9
8b	0.9
8c	0.9
8e	0.45
9c	<1.9

coupling and the substitution of the nitro group. The results of tests of a wide spectrum of antibacterial activity, as well as the absence of the data on the existence of derivatives of 2-substituted 5-(3,4,5-trimethoxyphenoxy)furans in the *SciFinder* database, indicate that the search for anticoccal agents in the series of 4-(5-aryloxyfuran-2-yl)pyrimidines is promising.

Experimental

Compounds **8a—e** were synthesized according to a known procedure.[7] 1,4-Dioxane for cross-coupling reactions was preliminarily distilled over calcium hydride and then degassed by passing argon for 1 h.

^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-400 (400 and 101 MHz) and Bruker AVANCE^{III}-500 spectrometers (500 and 126 MHz) in DMSO-d_6, using $SiMe_4$ as an internal standard. Elemental analysis was performed on a Perkin—Elmer PE-2400 automatic analyzer. Melting points were determined on a Boetius heating block and were not corrected.

GLC/MS analysis of all samples was performed using an Agilent GC 7890A MS 5975C Inert XL EI/CI gas chromatograph-mass spectrometer with a quadrupole mass spectrometric detector and a HP-5MS quartz capillary column, 30 m×0.25 mm, film thickness 0.25 μm. Mass spectra were recorded under conditions of electron ionization (70 eV) by scanning over the total ion current in the range of *m/z* 20—1000. Carrier gas helium, flow splitting 1 : 50, flow rate through the column 1.0 mL min^{-1}; initial column temperature 40 °C (plateau for 3 min), programming at a rate of 10 deg min^{-1} up to 290 °C (plateau for 20 min), injector temperature 250 °C, source temperature 230 °C, quadrupole temperature 150 °C, transition chamber temperature 280 °C. Sample solutions with a concentration of 3—4 mg mL^{-1} were prepared in THF.

High-resolution mass spectra were obtained using a Bruker maXis Impact HD spectrometer.

All microwave experiments were performed in a Discover SP single-mode microwave system (CEM, USA) with an operating frequency of 2.45 GHz and a microwave power range from 0 to 300 W. The reactions were carried out in a 10-mL test-tube with a sealed silicone stopper. The reaction temperature was monitored using a built-in IR sensor on the outer surface of the reaction vessel. Flash chromatography was performed using Kieselgel 60 silica gel, 0.040—0.063 mm (230—400 mesh).

Semi-preparative HPLC was performed using an Agilent 1200 Series semi-preparative liquid chromatograph (Agilent Technologies, USA). The device was equipped with an autosampler (900 μL), a diode array detector (the selected analytical wavelength was 280 nm), and a fraction collector. The column was ZORBAX Eclipse XDB-C18 PrepHT, 21.2 mm×150 mm, particle size 5 μm (Agilent Technologies, USA), the column temperature was ambient. A mixture of acetonitrile—water in various ratios was used as the mobile phase, the flow rate of the mobile phase was 20 mL min^{-1}, and the isocratic elution mode.

Reaction progress and purity of products were monitored by TLC on Sorbfil plates, visualization under the UV light.

Synthesis of 5-bromo-4-(5-aryloxyfuran-2-yl)pyrimidines 4 (general procedure). Phenol (**2a**) or 3,4,5-trimethoxyphenol (**2b**) (1.5 mmol) and K_3PO_4 (531 mg, 2.5 mmol) were added to a solution of 5-bromo-4-(5-nitrofuran-2-yl)pyrimidine (**1**) (270 mg, 1.0 mmol) in 1,4-dioxane (15 mL). The reaction mixture was heated at 85 °C for 15 h. The solvent was evaporated under reduced pressure, the residue was purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate—hexane (1 : 3).

5-Bromo-4-(5-phenoxyfuran-2-yl)pyrimidine (4a) was obtained by the reaction of 5-bromo-4-(5-nitrofuran-2-yl)pyrimidine (**1**) with phenol (**2a**). The yield was 231 mg (73%), a beige powder, m.p. 73—74 °C. ^{1}H NMR (500 MHz), δ: 9.06 (s, 1 H, C(6)H); 8.98 (s, 1 H, C(2)H); 7.77 (d, 1 H, $C_{fur}H$, J = 3.7 Hz)*; 7.51—7.45 (m, 2 H, $C_{Ar}H$); 7.31—7.25 (m, 3 H, $C_{Ar}H$); 5.99 (d, 1 H, $C_{fur}H$, J = 3.7 Hz). ^{13}C NMR (126 MHz), δ: 160.6, 159.1, 156.4, 154.8, 150.9, 140.9, 130.3, 125.3, 120.6, 118.0, 113.0, 91.3. Found (%): C, 53.21; H, 2.94; N, 8.72. $C_{14}H_9BrN_2O_2$ (317.14). Calculated (%): C, 53.02; H, 2.86; N, 8.83. GLC: t_R = 24.32 min. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 316 $[M]^+$ (100) for ^{79}Br, 318 $[M]^+$ (97) for ^{81}Br.

5-Bromo-4-[5-(3,4,5-trimethoxyphenoxy)furan-2-yl]pyrimidine (4b) was obtained by the reaction of 5-bromo-4-(5-nitrofuran-2-yl)pyrimidine (**1**) with 3,4,5-trimethoxyphenol (**2b**). The yield was 293 mg (72%), a beige powder, m.p. 77—79 °C. ^{1}H NMR (500 MHz), δ: 9.06 (s, 1 H, C(6)H); 8.98 (s, 1 H, C(2)H); 7.75 (d, 1 H, $C_{fur}H$, J = 3.7 Hz); 6.66 (s, 2 H, $C_{Ar}H$); 5.94 (d, 1 H, $C_{fur}H$, J = 3.7 Hz); 3.77 (s, 6 H, OMe); 3.66 (s, 3 H, OMe). Found (%): C, 50.24; H, 3.57; N, 6.93. $C_{17}H_{15}BrN_2O_5$ (407.22). Calculated (%): C, 50.14; H, 3.71; N, 6.88. GLC: t_R = 28.83 min. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 406 $[M]^+$ (100) for ^{79}Br, 408 $[M]^+$ (96) for ^{81}Br.

Synthesis of *N*-aryl-4-(5-phenoxyfuran-2-yl)pyrimidin-5-amines 6a—e and *N*-aryl-4-[5-(3,4,5-trimethoxyphenoxy)furan-2-yl]pyrimidin-5-amines 9a—e (general procedure). Method *A*. A mixture of 5-bromo-4-(5-phenoxyfuran-2-yl)pyrimidine (**4a**) (407 mg, 1.0 mmol), aniline (**5a**) (137 μL, 1.5 mmol), phosphine ligand (Xanthphos or dppf) (0.2 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), and K_3PO_4 (2.5 mmol) was dissolved in 1,4-dioxane (20 mL). The resulting mixture was heated at 85 °C for 15 h. The solvent was evaporated under reduced pressure, the residue was purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate—hexane (1 : 3).

* Hereinafter, fur stands for furanyl.

Method *B*. Phenol (**2a**) or 3,4,5-trimethoxyphenol (**2b**) (0.75 mmol) and K_3PO_4 (266 mg, 1.25 mmol) were added to a solution of 5-arylamino-4-(5-nitrofuran-2-yl)pyrimidine **8a—e** (0.5 mmol) in 1,4-dioxane (10 mL). The resulting mixture was heated at 85 °C for 15 h (for the reaction with **2a**) or 30 h (for the reaction with **2b**). The solvent was evaporated under reduced pressure, the residue was purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate—hexane (1 : 3). Products **9b—e** were additionally purified by semi-preparative HPLC.

4-(5-Phenoxyfuran-2-yl)-*N*-phenylpyrimidin-5-amine (6a). The yield was 250 mg (76%) (method ***A***); 132 mg, 80% (method ***B***), a dark yellow powder, m.p. 99—100 °C. ^{1}H NMR (500 MHz), δ: 8.80 (s, 1 H, C(6)H); 8.63 (s, 1 H, C(2)H); 7.85 (s, 1 H, NH); 7.48—7.39 (m, 2 H, $C_{Ar}H$); 7.26 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 7.24—7.16 (m, 5 H, $C_{Ar}H$); 6.91—6.81 (m, 3 H, $C_{Ar}H$); 5.90 (d, 1 H, $C_{fur}H$, J = 3.6 Hz). ^{13}C NMR (126 MHz), δ: 157.9, 155.2, 152.4, 151.5, 146.2, 143.5, 141.5, 131.9, 130.2, 129.3, 124.9, 120.2, 117.8, 117.6, 116.2, 91.2. MS (ESI): found m/z 330.1236 $[M + H]^+$; calculated for $C_{20}H_{16}N_3O_2^+$ 330.1237. GLC: t_R = 29.99 min. MS (EI, 70 eV), m/z (I_{rel} (%)): 329 $[M]^+$ (100).

4-(5-Phenoxyfuran-2-yl)-*N*-(*para*-tolyl)pyrimidin-5-amine (6b) was synthesized by method ***B***. The yield was 155 mg (90%), a dark yellow oil. ^{1}H NMR (400 MHz), δ: 8.74 (s, 1 H, C(6)H); 8.56 (s, 1 H, C(2)H); 7.68 (s, 1 H, NH); 7.48—7.40 (m, 2 H, $C_{Ar}H$); 7.26 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 7.25—7.16 (m, 3 H, $C_{Ar}H$); 7.07—7.02 (m, 2 H, $C_{Ar}H$); 6.86—6.80 (m, 2 H, $C_{Ar}H$); 5.91 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 2.22 (s, 3 H, Me). ^{13}C NMR (101 MHz), δ: 157.8, 155.2, 151.6, 150.0, 145.1, 141.7, 140.5, 132.7, 130.2, 129.7, 129.6, 124.9, 117.6, 117.4, 117.3, 91.2, 20.2. MS (APCI): found m/z 344.1394 $[M + H]^+$; calculated for $C_{21}H_{18}N_3O_2^+$ 344.1394. GLC: t_R = 29.98 min. MS (EI, 70 eV), m/z (I_{rel} (%)): 343 $[M]^+$ (100).

N*-(4-Methoxyphenyl)-4-(5-phenoxyfuran-2-yl)pyrimidin-5-amine (6c)** was synthesized by method ***B. The yield was 58 mg (32%), a dark orange oil. ^{1}H NMR (400 MHz), δ: 8.74 (s, 1 H, C(6)H); 8.57 (s, 1 H, C(2)H); 7.70 (s, 1 H, NH); 7.50—7.41 (m, 2 H, $C_{Ar}H$); 7.28 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 7.28—7.18 (m, 3 H, $C_{Ar}H$); 7.08—7.03 (m, 2 H, $C_{Ar}H$); 6.88—6.82 (m, 2 H, $C_{Ar}H$); 5.90 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 3.72 (s, 3 H, OMe). MS (APCI): found m/z 360.1343 $[M + H]^+$; calculated for $C_{21}H_{18}N_3O_3^+$ 360.1345. GLC: t_R = 31.72 min. MS (EI, 70 eV), m/z (I_{rel} (%)): 359 $[M]^+$ (100).

N*-(3,4-Dimethoxyphenyl)-4-(5-phenoxyfuran-2-yl)pyrimidin-5-amine (6d)** was synthesized by method ***B. The yield was 60 mg (31%), a brown oil. ^{1}H NMR (400 MHz), δ: 8.67 (s, 1 H, C(6)H); 8.48 (s, 1 H, C(2)H); 7.51 (s, 1 H, NH); 7.47—7.41 (m, 2 H, $C_{Ar}H$); 7.31 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 7.27—7.21 (m, 1 H, $C_{Ar}H$); 7.18 (dd, 2 H, $C_{Ar}H$, J = 8.2 Hz, J = 1.5 Hz); 6.86 (d, 1 H, $C_{Ar}H$, J = 8.5 Hz); 6.51 (dd, 1 H, $C_{Ar}H$, J = 8.5 Hz, J = 2.5 Hz); 6.27 (d, 1 H, $C_{Ar}H$, J = 2.5 Hz); 5.94 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 3.66 (s, 3 H, OMe); 3.60 (s, 3 H, OMe). MS (APCI): found m/z 390.1449 $[M + H]^+$; calculated for $C_{22}H_{20}N_3O_4^+$ 390.1448. GLC: t_R = 33.84 min. MS (EI, 70 eV), m/z (I_{rel} (%)): 389 $[M]^+$ (100).

4-(5-Phenoxyfuran-2-yl)-*N*-(3,4,5-trimethoxyphenyl)pyrimidin-5-amine (6e) was synthesized by method ***B***. The yield was 92 mg (44%), a light brown powder, m.p. 129—130 °C. ^{1}H NMR (500 MHz), δ: 8.74 (s, 1 H, C(6)H); 8.63 (s, 1 H, C(2)H); 7.67 (s, 1 H, NH); 7.46—7.41 (m, 2 H, $C_{Ar}H$); 7.30 (d, 1 H, $C_{fur}H$, J = 3.7 Hz); 7.25—7.22 (m, 1 H, $C_{Ar}H$); 7.20—7.14 (m, 2 H, $C_{Ar}H$); 6.26 (s, 2 H, $C_{Ar}H$); 5.94 (d, 1 H, $C_{fur}H$, J = 3.7 Hz); 3.67 (s, 6 H, OMe); 3.66 (s, 3 H, OMe). MS (APCI): found m/z 420.1551 $[M + H]^+$; calculated for $C_{23}H_{22}N_3O_5^+$ 420.1554. GLC: t_R = 35.55 min. MS (EI, 70 eV), m/z (I_{rel} (%)): 419 $[M]^+$ (100).

N*-Phenyl-4-[5-(3,4,5-trimethoxyphenoxy)furan-2-yl]pyrimidin-5-amine (9a)** was synthesized by method ***B. The yield was 96 mg (46%), a dark brown powder, m.p. 127—129 °C. ^{1}H NMR (500 MHz), δ: 8.80 (s, 1 H, C(6)H); 8.62 (s, 1 H, C(2)H); 7.83 (s, 1 H, NH); 7.24 (d, 1 H, $C_{fur}H$, J = 3.7 Hz); 7.22—7.19 (m, 2 H, $C_{Ar}H$); 6.87—6.82 (m, 3 H, $C_{Ar}H$); 6.57 (s, 2 H, $C_{Ar}H$); 5.86 (d, 1 H, $C_{fur}H$, J = 3.7 Hz); 3.74 (s, 6 H, OMe); 3.64 (s, 3 H, OMe). MS (APCI): found m/z 420.1551 $[M + H]^+$; calculated for $C_{23}H_{22}N_3O_5^+$ 420.1554. GLC: t_R = 35.68 min. MS (EI, 70 eV), m/z (I_{rel} (%)): 419 $[M]^+$ (100).

N*-(*para*-Tolyl)-4-[5-(3,4,5-trimethoxyphenoxy)furan-2-yl]-pyrimidin-5-amine (9b)** was synthesized by method ***B. The yield was 59 mg (27%), a brown oil. ^{1}H NMR (400 MHz), δ: 8.74 (s, 1 H, C(6)H); 8.63 (s, 1 H, C(2)H); 7.67 (s, 1 H, NH); 7.46—7.41 (m, 2 H, $C_{Ar}H$); 7.30 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 7.19—7.15 (m, 2 H, $C_{Ar}H$); 6.26 (s, 2 H, $C_{Ar}H$); 5.94 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 3.67 (s, 6 H, OMe); 3.60 (s, 3 H, OMe); 2.22 (s, 3 H, Me). MS (APCI): found m/z 434.1708 $[M + H]^+$; calculated for $C_{24}H_{24}N_3O_5^+$ 434.1710. GLC: t_R = 37.80 min. MS (EI, 70 eV), m/z (I_{rel} (%)): 433 $[M]^+$ (100).

N*-(4-Methoxyphenyl)-4-[5-(3,4,5-trimethoxyphenoxy)furan-2-yl]pyrimidin-5-amine (9c)** was synthesized by method ***B. The yield was 29 mg (13%), a brown powder, m.p. 119—120 °C. ^{1}H NMR (400 MHz), δ: 8.66 (s, 1 H, C(6)H); 8.40 (s, 1 H, C(2)H); 7.47 (s, 1 H, NH); 7.29 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 7.00—6.95 (m, 2 H, $C_{Ar}H$); 6.90—6.85 (m, 2 H, $C_{Ar}H$); 6.58 (s, 2 H, $C_{Ar}H$); 5.90 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 3.74 (s, 6 H, OMe); 3.72 (s, 3 H, OMe); 3.64 (s, 3 H, OMe). MS (APCI): found m/z 450.1655 $[M + H]^+$; calculated for $C_{24}H_{24}N_3O_6^+$ 450.1660. GLC: t_R = 41.87 min. MS (EI, 70 eV), m/z (I_{rel} (%)): 449 $[M]^+$ (100).

N*-(3,4-Dimethoxyphenyl)-4-[5-(3,4,5-trimethoxyphenoxy)-furan-2-yl]pyrimidin-5-amine (9d)** was synthesized by method ***B. The yield was 24 mg (10%), a brown powder, m.p. 114—116 °C. ^{1}H NMR (400 MHz), δ: 8.67 (s, 1 H, C(6)H); 8.47 (s, 1 H, C(2)H); 7.48 (s, 1 H, NH); 7.29 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 6.86 (d, 1 H, $C_{Ar}H$, J = 8.5 Hz); 6.71 (d, 1 H, $C_{Ar}H$, J = 2.5 Hz); 6.58 (s, 2 H, $C_{Ar}H$); 6.51 (dd, 1 H, $C_{Ar}H$, J = 8.5 Hz, J = 2.5 Hz); 5.90 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 3.74 (s, 6 H, OMe); 3.70 (s, 3 H, OMe); 3.69 (s, 3 H, OMe); 3.63 (s, 3 H, OMe). MS (APCI): found m/z 480.1763 $[M + H]^+$; calculated for $C_{25}H_{26}N_3O_7^+$ 480.1765.

4-[5-(3,4,5-Trimethoxyphenoxy)furan-2-yl]-*N*-(3,4,5-trimethoxyphenyl)pyrimidin-5-amine (9e) was synthesized by method ***B***. The yield was 20 mg (8%), a dark brown powder, m.p. 125—128 °C. ^{1}H NMR (400 MHz), δ: 8.74 (s, 1 H, C(6)H); 8.62 (s, 1 H, C(2)H); 7.64 (s, 1 H, NH); 7.29 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 6.57 (s, 2 H, $C_{Ar}H$); 6.27 (s, 2 H, $C_{Ar}H$); 5.91 (d, 1 H, $C_{fur}H$, J = 3.6 Hz); 3.74 (s, 9 H, OMe); 3.68 (s, 6 H, OMe); 3.63 (s, 3 H, OMe). MS (APCI): found m/z 510.1868 $[M + H]^+$; calculated for $C_{26}H_{28}N_3O_8^+$ 510.1871.

Antibacterial activity. The assessment of the sensitivity of microorganisms to antimicrobial agents was carried out by N. A. Gerasimova and N. P. Evstigneeva, the employees of the Scientific Experimental and Laboratory Department of the Ural Research Institute for Dermatology, Venereology and Immunopathology (Ekaterinburg), using sequential microdilution method regulated by the national standard of the Russian Federation

GOST R ISO 20776-1-2010, identical to the international standard ISO 20776-1:2006. To study the antibacterial activity of pyrimidines **4a**, **6a,b,e**, and **9c**, the minimum inhibitory concentrations were determined with respect to the control strains *Neisseria gonorrhoeae* NCTC12700/ATCC49226, NCTC 8375/ATCC19424 and clinical strains *Neisseria gonorrhoeae* SpeS, AzmR and *Neisseria gonorrhoeae* SpeS, AzmS, as well as to the control strains of pathogenic and opportunistic microorganisms from the international collections ATCC and the Russian state collection of pathogenic microorganisms: gram-negative bacilli (*Escherichia coli* ATCC 8739, *Citrobacter braakii* ATCC 101/57, *Shigella flexneri* 1a8516, *Proteus vulgaris* ГКПМ 160125 (222), *Serratia marcescens* ATCC 13880, *Klebsiella pneumoniae* ATCC 13883), non-fermenting gram-negative bacilli (*Pseudomonas aeruginosa* ATCC 9027), and gram-positive cocci (*Streptococcus piogenes* ATCC 19615, *Staphylococcus aureus* ATCC 25923/NCTC 12981(F-49), *Staphylococcus aureus MRSA* NCTC12493).

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