Synthesis of 5-(het)aryl- and 4,5-di(het)aryl-2-(thio)morpholinopyrimidines from 2-chloropyrimidine *via* S_N^H and cross-coupling reactions*

E. M. Cheprakova,[a] E. V. Verbitskiy,[a,b] M. A. Ezhikova,[a] M. I. Kodess,[a] M. G. Pervova,[a] P. A. Slepukhin,[a] M. S. Toporova,[a] M. A. Kravchenko,[c] I. D. Medvinskiy,[c] G. L. Rusinov,[a,b] and V. N. Charushin[a,b]*

[a] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 20 ul. Akademicheskaya/22 ul. S. Kovalevskoy, 620990 Ekaterinburg, Russian Federation. E-mail: Verbitsky@ios.uran.ru*

[b] *Ural Federal University named after the First President of Russia B. N. Yeltsin, 19 ul. Mira, 620002 Ekaterinburg, Russian Federation*

[c] *Ural Research Institute for Phthisiopulmonology, 50 ul. XXII Parts'ezda, 620039 Ekaterinburg, Russian Federation*

It has been shown that various combinations of nucleophilic aromatic substitution of hydrogen (S_N^H), S_N^{ipso} and the microwave-assisted Suzuki cross-coupling reactions are a versatile method for the synthesis of 5-(het)aryl-2-(thio)morpholinopyrimidine and 4,5-di(het)aryl-2-(thio)morpholinopyrimidine derivatives. All synthesized pyrimidines were found to be active in micromolar concentrations *in vitro* against *Mycobacterium tuberculosis* $H_{37}Rv$.

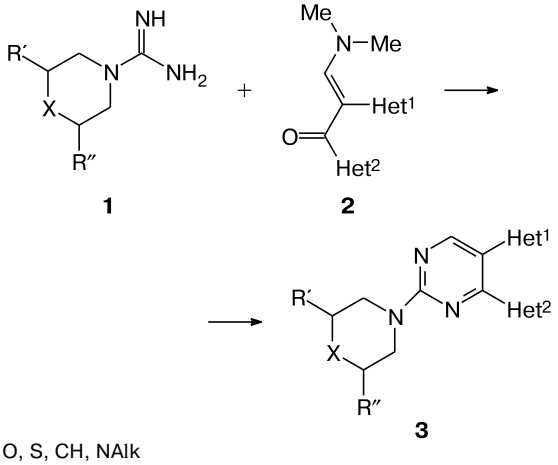
Key words: pyrimidines, morpholine, thiomorpholine, cross-coupling, microwave irradiation, nucleophilic aromatic substitution of hydrogen, antituberculosis activity.

Pyrimidines belong to an important class of heteroaromatic compounds that have found wide applications as effective pharmaceuticals, agrochemicals, and organic materials.[1] For instance, 5-(het)aryl-2-dialkylamino- and 4,5-di(het)aryl-2-dialkylaminopyrimidines bearing either morpholine or thiomorpholine moiety at the C(2) atom have attracted great interest due to the wide range of biological activities, *e.g.*, herbicidal[2] and antimicrobic[3] activities. These compounds can affect the activities of specific proteins, *e.g.*, the activity of atonal homolog 1 (ATOH-1)[4] regulating the DNA-templated transcription and neuron differentiation, as well as the epidermal growth factor (EGF),[5] which promotes the cell growth and epidermal cell differentiation. They also can be used in treatment of heurodegenerative diseases, cognitive disorders, and Alzheimer´s disease.[6]

Condensation of (thio)morpholinocarboxamidines **1** with 1,2-dihetaryl-3-dimethylaminopropenones **2** results in 2-morpholine-substituted pyrimidines **3** and their thio analogs (Scheme 1).[6]

It has been shown earlier that the combination of nucleophilic aromatic substitution of hydrogen (S_N^H) and microwave-assisted Suzuki cross-coupling reactions is an efficient pathway to 4,5-di(het)aryl-substituted pyrimidines.[7,8] The aim of the present work was to investigate the new synthetic procedures towards 5-(het)aryl- and 4,5-di(het)-aryl-2-(thio)morpholinopyrimidines from available 2-chloropyrimidine using various combinations of the S_N^{ipso} or S_N^H and Suzuki cross-couplings reactions.

Scheme 1



X = O, S, CH, NAlk

Initially, the replacement of chlorine in 2-chloropyrimidine (**4**) by the morpholine (**5a**) and thiomorpholine (**5b**) moieties and subsequent mild bromination of thus obtained 2-(thio)morpholine-substituted pyrimidines **6a**,**b** with bromine (20—25 °C, CH_2Cl_2) gives 5-bromo-2-(thio)morpholinopyrimidines **7a**,**b** (Scheme 2). Structures of compounds **7a**,**b** were unambiguously established by NMR spectroscopy and elemen-

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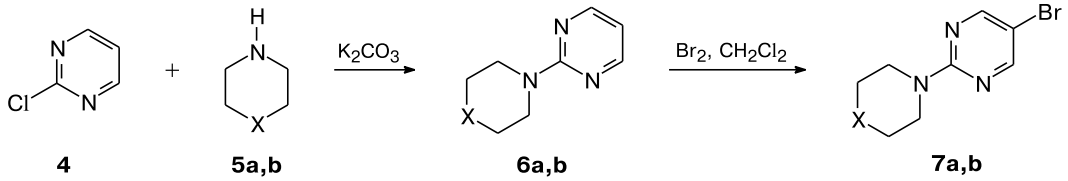
Scheme 2



tal analysis and confirmed by X-ray diffraction of compound **7a** (Fig. 1).

5-Bromo-2-(thio)morpholinopyrimidines **7a,b** were further involved in the Suzuki cross-coupling reaction with arylboronic acids **8**—**11**. Reactions of compounds **7a**,**b** with 3-nitrophenylboronic acid (**8**) result in 5-(3-nitrophenyl)-2-(thio)morpholinopyrimidines **12a**,**b** in the yields of ~10% (Scheme 3). Structures of compounds **12a**,**b** were confirmed by X-ray diffraction of **12a** (Fig. 2).

The conditions of these cross-couplings reactions were optimized using different combinations of palladium catalysts ($Pd(PPh_3)_4$ or $Pd(OAc)_2$) and phosphine ligands (PPh_3 or PCy_3, Cy is cyclohexyl) (Table 1). According to data from Table 1, the use of $Pd(PPh_3)_4$ as a catalyst and a THF—H_2O mixture in a 3 : 4 ratio as a solvent are optimal reaction conditions (see Table 1, entries *3* and *6*). It should be noted that the use of palladium(II) acetate in the presence of PPh_3 or PCy_3 gives the comparable yields but the content of by-products is higher.

Similar reactions of 5-bromo-2-(thio)morpholinopyrimidines **7a**,**b** with 2-thienylboronic (**9**), 2-benzo[*b*]thienylboronic (**10**), and 3-benzo[*b*]thienylboronic (**11**) acids carried out under optimal conditions led to novel

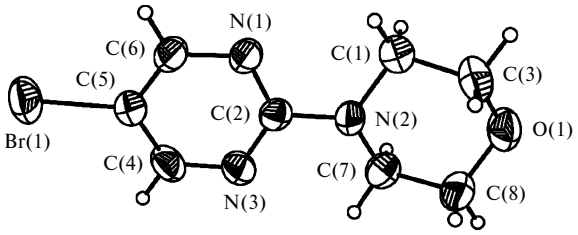


Fig. 2. Crystal structure of **7a**.

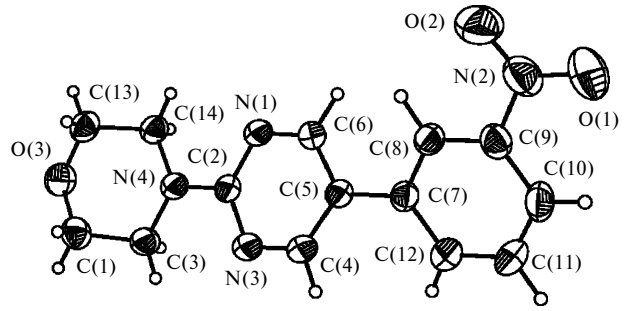
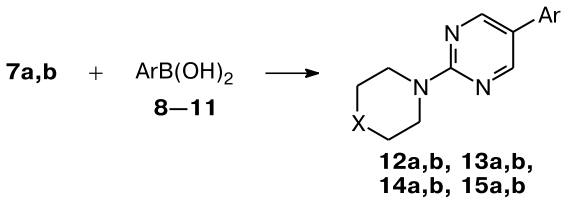
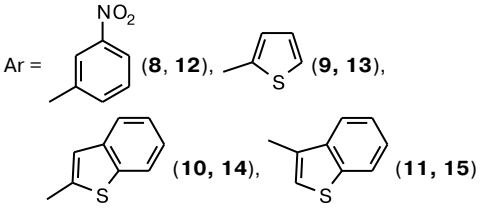


Fig. 2. Crystal structure of **12a**.

Scheme 3



Reagents and conditions: catalyst ($Pd(OAc)_2$—PPh_3/PCy_3 or $Pd(PPh_3)_4$), K_2CO_3, solvent (DMF or THF—H_2O), microwave irradiation, 20 min.



5-hetaryl-2-(thio)morpholinopyrimidines **13**—**15** in the yields of 40—60% (Scheme 3, Table 2).

The possibility to involve the synthesized compounds into the nucleophilic substitution of hydrogen was studied on the example of compounds **12a**,**b** (Scheme 4). According to GC/MS data, reaction mixtures obtained by stirring of 5-(3-nitrophenyl)-2-(thio)morpholinopyrimidines **12a**,**b** with thiophene (**16**) in CF_3COOH for 3 days followed by oxidation with aqueous $K_3Fe(CN)_6$ (2 equiv.) contain small amounts of the S_NH products, namely, 2-morpholino-5-(3-nitrophenyl)-4-(2-thienyl)pyrimidine (**17a**, 14%) and 5-(3-nitrophenyl)-4-(2-thienyl)-2-thiomorpholinopyrimidine (**17b**, 4%) (Table 3).

Prolongation of the reaction time up to 1 month does not result in the noticeable increase in content of the target products **17a**,**b** in the reaction mixture sufficient for their preparative isolation (see Table 3). 2-Morpholino-5-(3-nitrophenyl)-4-(2-thienyl)pyrimidine (**17a**) was isolated by preparative HPLC in 21% yield. Besides, the starting 2-morpholino-5-(3-nitrophenyl)pyrimidine (**12a**) was recovered in 55% yield from the reaction mixture.

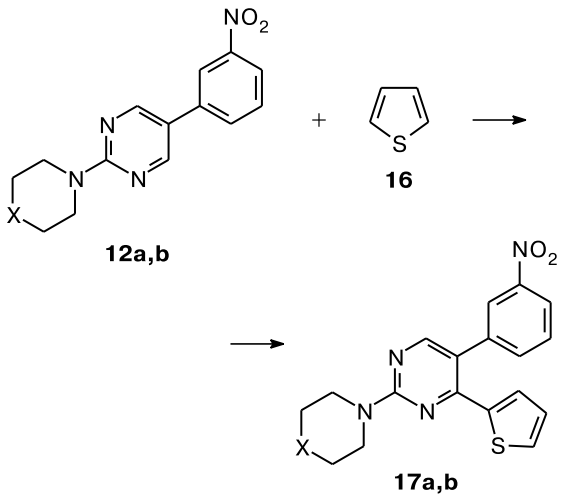
Apparently, low yields of compounds **17a**,**b** in S_NH reactions can be explained by electron-donating character of the (thio)morpholinyl substituent at the position 2 of

Table 1. GC-MS data on compositions of the reaction mixtures obtained by the reactions of 3-nitrophenylboronic acid (**8**) with 5-bromo-2-(thio)morpholinopyrimidines **7a,b** under different reaction conditions*

Entry	Reaction	Catalytic system	Solvent	Reaction mixture composition**
1	**7a** + **8**	$Pd(OAc)_2/PPh_3$ (10 mol.%)	DMF	**7a** (20.11), **12a** (32.10), Ph_3PO (30.65), impurities (17.14)
2	**7a** + **8**	$Pd(OAc)_2/PCy_3$ (10 mol.%)	DMF	**7a** (3.15), **12a** (26.12), PCy_3 (14.91), impurities (55.8)
3	**7a** + **8**	$Pd(PPh_3)_4$	THF/H_2O	**7a** (1.9), **12a** (38.5), Ph_3PO (28.2), impurities (31.4)
4	**7b** + **8**	$Pd(OAc)_2/PPh_3$ (10 mol.%)	DMF	**7b** (3.62), **12b** (32.67), Ph_3PO (34.14), impurities (29.57)
5	**7b** + **8**	$Pd(OAc)_2/PCy_3$ (10 mol.%)	DMF	**7b** (4.17), **12b** (42.02), PCy_3 (14.73), impurities (39.08)
6	**7b** + **8**	$Pd(PPh_3)_4$	THF/H_2O	**7b** (6.6), **12b** (73.5), Ph_3PO (9.5), impurities (10.4)

* Reaction time 20 min, temperature 185 °C, content of the Pd^{II} derivative in the catalytic system 5 mol.%.
** Component contents (%) are given in parenthesis.

Scheme 4



Reagents: 1) CF_3COOH, 2) $K_3Fe(CN)_6$, KOH, H_2O.

X = O (**a**), S (**b**)

the starting pyrimidines **12a**,**b**. This leads to decrease in electrophilicity of the pyrimidine cycle due to increase in an impact of the resonance structure **B** deactivating the pyrimidine cycle towards nucleophilic attack (Scheme 5).

Since attempts of acid activation of pyrimidines under S_N^H reaction conditions failed, these reactions were studied under nucleophilic activation conditions (Scheme 6). 5-Bromo-2-(thio)morpholinopyrimidines **7a**,**b** were involved in the reaction with 2-thienyllithium (**18**) generated *in situ* by treatment of thiophene (**16**) with butyllithium. This reaction gave the intermediate σ^H adducts **19a**,**b**, which further were oxidized with the $K_3Fe(CN)_6$/KOH aqueous solution. Compositions of the reaction mixtures were determined by GC-MS (Table 4). Conversions of the starting pyrimidines **7a**,**b** in S_N^H reactions under described conditions were nearly 100%. Note that along with target 5-bromo-4-(2-thienyl)-2-(thio)morpholinopyrimidines **20a**,**b**, the reaction involving 5-bromo-2-morpholinopyrimidine (**7a**) produced by-product, 5-bromo-4-butyl-

Table 2. GC-MS data on compositions of the reaction mixtures and yields of 5-(het)aryl-2-(thio)morpholinopyrimidines **13—15**

Entry	Reaction	Product (Yield (%))	Reaction mixture composition*
1	**7a** + **9**	**13a** (44)	**7a** (15.8), Ph_3PO (14.1), **13a** (42.7), impurities(27.4)
2	**7a** + **10**	**14a** (40)	**7a** (2.9), Ph_3PO (21.1), **14a** (52.3), impurities (23.7)
3	**7a** + **11**	**15a** (53)	**7a** (3.5), Ph_3PO (7.4), **15a** (73.5), impurities (15.6)
4	**7b** + **9**	**13b** (41)	**7b** (12.3), Ph_3PO (18.9), **13b** (49.1), impurities (19.7)
5	**7b** + **10**	**14b** (40)	**7b** (13.6), Ph_3PO (15.9), **14b** (54.1), impurities (16.4)
6	**7b** + **11**	**15b** (57)	**7b** (4.9), Ph_3PO (6.2), **15b** (73.9), impurities (15)

* Component contents (%) are given in parenthesis.

Table 3. GC-MS data on compositions of the reaction mixtures obtained by the reactions of 5-(3-nitrophenyl)-2-(thio)morpholinopyrimidines **12a**,**b** with thiophene (**16**) at different duration of treatment with TFA and subsequent oxidation

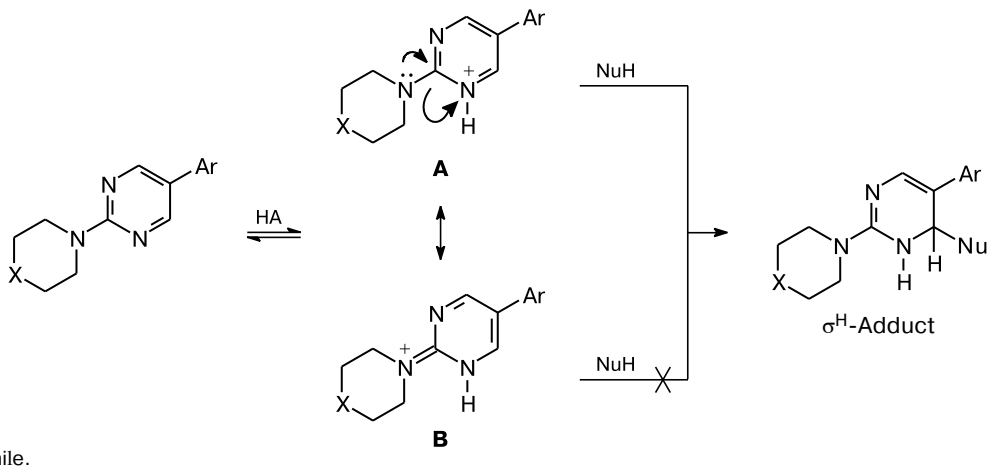
Entry	Reaction	Dutarion of treatment CF_3COOH	Reaction mixture composition*
1	**12a + 16**	3 days	**12a** (86), **17a** (14)
2	**12a + 16**	1 month	**12a** (71), **17a** (29)
3	**12b + 16**	3 days	**12b** (96), **17b** (4)
4	**12b + 16**	1 month	**12b** (87), **17b** (13)

* Component contents (%) are given in parenthesis.

2-morpholinopyrimidine (**21a**), due to the reaction with butyllithium; while in the reaction involving 5-bromo-2-thiomorpholinopyrimidine (**7b**), elimination of HBr gave rise to the product of *kine* substitution of hydrogen, 4-(2-thienyl)-2-thiomorpholinopyrimidine (**22b**) (see Table 4). Moreover, GC-MS indicated that the reaction mixture obtained by the reaction of 5-bromo-2-morpholinopyrimidine (**7a**) with 2-thienyllithium (**18**) contained compound **23** (*m/z* 489 $[M]^+$) together with unidentified impurities. Compound **23** was isolated by preparative HPLC in the yield of 3%. According to ^1H, ^{13}C, and 2D NMR experiments, compound **23** was identified as bromo-2,2′-dimorpholino-4′-(2-thienyl)-4,5′-bipyrimidine.

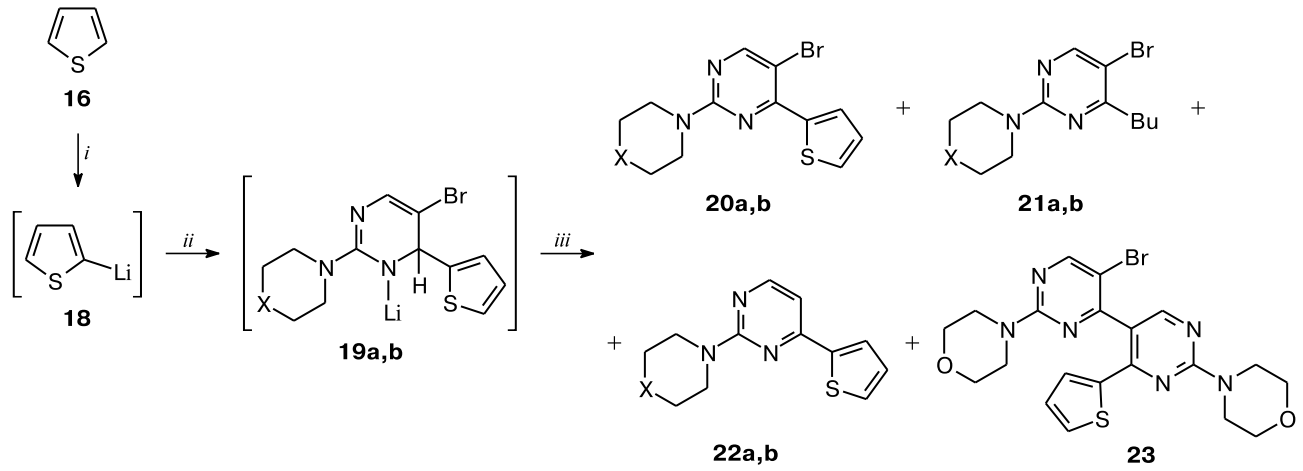
On the next step of our research, bromo-substituted pyrimidines **20a**,**b** were involved in microwave-assisted

Scheme 5



NuH is nucleophile.
HA is acid.

Scheme 6



Reagents and conditions: *i.* BuLi, Et_2O, 0 °C; *ii.* **7a,b**, Et_2O, −20 °C; *iii.* $K_3Fe(CN)_6$, KOH, H_2O.
X = O (**a**), S (**b**)

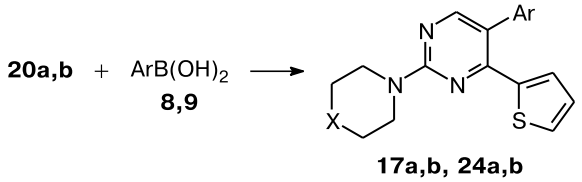
Table 4. GC-MS data on compositions of the reaction mixtures and product yields in the reactions of 5-bromo-2-(thio)morpholinopyrimidines (**7a**,**b**) with 2-thienyllithium (**18**) and subsequent oxidation

OEntry	Reaction	Product (Yields (%))	Reaction mixture composition*
1	**7a** + **16**/BuLi	**20a** (51), **21a** (19), **23** (3)	**7a** (1.2), **20a** (67.0), **21a** (23.2), **22a** (0), **23** (4.0), impurities (4.6)
2	**7b** + **16**/BuLi	**20b** (69), **22b** (3)	**7b** (0), **20b** (90.3), **21b** (0), **22b** (5.1), impurities (4.6)

* Component contents (%) are given in parenthesis.

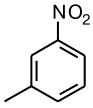
Suzuki cross-coupling reactions (155 °C, 20 min) with 3-nitrophenylboronic (**8**) and 2-thienylboronic (**9**) acids (Scheme 7). Yields of 5-hetaryl-4-(2-thienyl)-2-(thio)-morpholinopyrimidines **17a**,**b** and **24a**,**b** (42—80%) depend on the starting arylboronic acid (Table 5).

Scheme 7



Reagents and conditions: $Pd(PPh_3)_4$, K_3CO_3, THF, H_2O, microwave irradiation, 20 min.

X = O (**a**), S (**b**)

Ar =  (**8, 17**),  (**9, 24**)

Wide range of antibacterial activity[1] exhibited by a series of pyrimidine derivatives prompted us to study antituberculosis activity of the synthesized compounds. Thus, we determined tuberculostatic activity of some 5-(het)-aryl-2-(thio)morpholinopyrimidines (**12a**,**b**, **14a**, **15a**,**b**), 5-bromo-4-(2-thienyl)-2-(thio)morpholino- (**20a**,**b**) and 5-(het)aryl-4-(2-thienyl)-2-(thio)morpholinopyrimidines (**17a**,**b** and **24a**,**b**), and 5-bromo-2,2´-dimorpholino-4´-(2-thienyl)-4,5´-bipyrimidine (**23**) against *Mycobacterium tuberculosis* $H_{37}Rv$ *in vitro*. Isoniazid and Pyrazinamide were used as positive controls (Table 6). All compounds have a bacteriostatic effect comparable and even higher than that of Pyrazinamide with minimum inhibiting concentration (MIC) of 12.5 μg mL^{-1}.

In summary, tandem and more complicated sequences of the reactions of nucleophilic substitution of hydrogen (S_NH, S_N^{ipso}) and Suzuki cross-coupling reactions are effective strategy towards novel 2,5-disubstituted and 2,4,5-trisubstituted pyrimidines. Indeed, these compounds can be regarded as promising potential candidates for the further development of new antitubercular agents.

Table 5. GC-MS data on compositions of the reaction mixtures and product yields in the reactions of 5-(het)aryl-4-(2-thienyl)-2-(thio)morpholinopyrimidines **17a**,**b** and **24a**,**b**

Entry	Reaction	Product (Yield (%))	Reaction mixture composition*
1	**20a** + **8**	**17a** (70)	**17a** (63.4), Ph_3PO (31.6), impurities (5.0)
2	**20a** + **9**	**24a** (80)	**24a** (80.8), Ph_3PO (19.0), impurities (0.2)
3	**20b** + **8**	**17a** (42), **22b** (34)	**7b** (40.8), **22b** (32.6), Ph_3PO (24.4), impurities (2.2)
4	**20b** + **9**	**24b** (73)	**22b** (2.1), **24b** (71.4), Ph_3PO (22.3), impurities (4.2)

* Component contents (%) are given in parenthesis.

Table 6. Tuberculostatic activity of substituted pyrimidines **12a**,**b**, **14a**, **15a**,**b**, **17a**,**b**, **23**, and **24a**,**b** against *Mycobacterium tuberculosis* $H_{37}Rv$ *in vitro*

Compound	MIC/μg mL^{-1}	Compound	MIC/μg mL^{-1}
12a	6.25	**20a**	6.25
12b	12.5	**20b**	12.5
14a	12.5	**23**	1.5
15a	12.5	**24a**	3.1
15b	12.5	**24b**	12.5
17a	12.5	Pyrazinamide	12.5
17b	6.25	Isoniazid	0.1

Experimental

Solvents and reactants were purified and dried as earlier described.[9]

^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 500 spectrometer (working frequencies of 500 and 126 MHz, respectively) in $CDCl_3$ relative to Me_4Si (internal standard). All signals in ^1H and ^{13}C NMR spectra were ascribed using 2D NMR experiments (^1H—^1H COSY, ^1H—^{13}C HSQC/HMBC). Elemental analyses were performed with a Perkin—Elmer PE-240 elemental analyzer. Melting points were determined on a Boetius apparatus and are uncorrected.

The GC-MS analyses of all samples were carried out using an Agilent GC 7890A MS 5975C Inert XL EI/CI GC-MS spec-

trometer with a quadrupole mass-spectrometric detector with electron ionization (70 eV) and scan over the total ionic current in the range *m/z* 20—1000 and a quartz capillary column HP-5MS (30 m×0.25 mm, film thickness 0.25 mm). Helium served as a carrier gas, the split ratio of the flow was 1 : 50, and the consumption through the column was 1.0 mL min^{-1}; the initial temperature of the column was 40 °C (storage 3 min), programming rate was 10 °C min^{-1} to 290 °C (storage 20 min), the temperature of the evaporator was 250 °C, the temperature of the source was 230 °C, the temperature of the quadrupole was 150 °C, and the temperature of the transition chamber was 280 °C. Solutions of the samples with a concentration of 3—4 mg mL^{-1} were prepared in THF. Aliquots of 1 mL of the obtained solutions were analyzed.

Preparative HPLC was performed with semi-preparative Agilent 1200 Series liquid chromatography system (Agilent Technologies, USA), equipped with autosampler (900 μL), diode array detector (analytical wavelength of 280 nm), and fraction collector. Column was ZORBAX Eclipse XDB-C18 PrepHT 21.2 mm×150 mm, particles size of 5 μm (Agilent Technologies, USA), ambient column temperature, isocratic elution with acetonitrile—water (65 : 35), flow rate was 20 mL min^{-1}.

Microwave experiments were carried out in a Discover unimodal microwave system (CEM, USA) with a working frequency of 2.45 GHz and the power of microwave radiation ranged from 0 to 300 W. The reactions were carried out in a 10 mL reaction tube with the hermetic Teflon cork. The temperature of the reaction was monitored using an inserted IR sensor by the external surface of the reaction vessel.

Flash chromatography was performed using Kieselgel 60, 0.040—0.063 mm (230—400 mesh).

The progress of the reactions and purity of the products were checked by TLC on Sorbfil plates (Russia), in which the spot were visualized under UV light (λ = 254 or 365 nm).

X-ray diffraction analyses were carried out on an Xcalibur S automatized 4-circle diffractometer, equipped with a CCD detector following the standard procedure (λ(MoKα), graphite monochromator, ω scanning mode, step 1°, 295(2) K).

X-ray diffraction of compound **7a** was performed for a colorless crystal fragment of 0.24×0.18×0.10 mm in size. Correction for absorption was done analytically using a multifaceted crystal model (μ = 4.310 mm^{-1})[10]. The crystals are monoclinic, space group is $P2_1/n$. The unit cell parameters are as follows: a = = 4.6316(6) Å, b = 13.496(2) Å, c = 15.184(2) Å, β = 94.864(12)°, V = 945.7(2) $Å^3$, Z = 4, d_{calc} = 1.714 g cm^{-3}. At angles of 2.69° ≤ θ ≤ 33.22°, 3233 reflections (R_{int} = 0.0358) were measured (1372 reflections with $I > 2\sigma(I)$). The structure was solved and refined using SHELXTL software[10] by the full-matrix least-squares method on F^2. Nonhydrogen atoms were included in the model in anisotropic approximation. Hydrogen atoms were located by peaks of the spatial distribution of electron density and refined using a riding model in isotropic approximation. Final R-factors: R_1 = 0.0322, wR_2 = 0.0560 (based on reflections with $I > 2\sigma(I)$), R_1 = 0.1041, wR_2 = 0.0586 (based on all reflections) at Q-factor of S = 1.004 and number of refined parameters of 118. The peaks of maximum and minimum electron density are Δρ = 0.348/−0.560 e $Å^{-3}$.

X-ray diffraction of compound **12a** was carried out for an yellow crystal of 0.25×0.12×0.04 mm in size. Correction for absorption was very small (μ = 0.106 mm^{-1}) and was not introduced. The crystal is rhombic, space group is $Pca2_1$. The unit cell parameters are as follows: a = 22.1710(15) Å, b = 4.1344(3) Å, c = 14.2241(11) Å, V = 1303.83(16) $Å^3$, Z = 4, d_{calc} = = 1.458 g cm^{-3}. At angles of 2.86° ≤ θ ≤ 28.32°, 3175 reflections (R_{int} = 0.0358) were measured (2540 reflections with $I > 2\sigma(I)$). The structure was solved and refined using SHELXTL software[10] by the full-matrix least-squares method on F^2. Nonhydrogen atoms were included in the model in anisotropic approximation. Hydrogen atoms were located by peaks of the spatial distribution of electron density; some H-atoms were calculated independently and refined in isotropic approximation, remained H-atoms were refined using a riding model with fixed isotropic thermal parameters of the parent atoms. The final R-factors are as follows: R_1 = 0.0325, wR_2 = 0.0706 (based on reflections with $I > 2\sigma(I)$), R_1 = 0.0452, wR_2 = 0.0738 (based on all reflections) at Q-factor of S = 1.003 and number of the refined parameters of 214. The peaks of maximum and minimum electron density are Δρ = 0.141/−0.109 e $Å^{-3}$.

All X-ray analyses data (CIF files) were deposited with the Cambridge Crystallographic Data Center under CCDC 978028 (compound **7a**) and CCDC 978034 (compound **12a**) and are available free of charge at *http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx?*.

Antimicrobial assay of compounds **12**, **14**, **15**, **17**, **20**, **23**, and **24** were carried out *in vitro* against the $H_{37}Rv$ strain of *Mycobacterium tuberculosis* (MBT) by vertical diffusion technique using solid culture medium Novaya. Culture medium (5 mL) was distributed into the test tubes in sloping positions leaving an 1/2 of the test tube bottom free. The slopes were inoculated delivering suspension of MBT, strain $H_{37}Rv$ (0.1 mL, turbidity standard of 100 millions of bacteria in 1 mL of suspension), and transferred to incubator for growing. After 24 h, the test tubes were placed in the upright positions and the solutions of the studied compounds (0.3 mL) with concentrations of 12.5, 6.25, 3.1, 1.5, and 0.75 μg mL^{-1} were delivered dropwise by the side wall of the test tube. The test tubes were incubated at 37 °C for 10 days. Growth of MBT was estimated following standard procedure[11], *e.g.*, appearance of the zones of growth inhibition (more than 10 mm in size) indicated the tuberculostatic properties of the compound in the tested concentration. The size of the growth inhibition zone (in mm) is proportional to the degree of tuberculostatic activity of the compound. The growth inhibition equal to 100 mm was regarded as complete inhibition of the MBT growth. For studying tuberculostatic activity of the synthesized compounds, three slopes for each concentration were used. The data obtained are summarized in Table 6.

2-Morpholinopyrimidine (6a). To a solution of morpholine **5a** (3.63 mL, 42 mmol) in DMF (50 mL), K_2CO_3 (5.8 g, 42 mmol) was added; after 20 min stirring, 2-chloropyrimidine (4.0 g, 35 mmol) was added. The reaction mixture was stirred for 24 h, the solvent was removed *in vacuo*, the residue was purified by column chromatography (elution with ethyl acetate—hexane, 1 : 1). Yield 6.94 g (79%), colorless oil. ^{1}H NMR, δ: 3.75—3.81 (m, 8 H, OCH_2, NCH_2); 6.52 (t, 1 H, H(5), J = 4.7 Hz); 8.32 (d, 2 H, H(4), H(6), J = 4.7 Hz). ^{13}C NMR, δ: 44.11 (NCH_2); 66.77 (OCH_2); 110.21 (C(5)); 157.66 (C(4), C(6)); 161.73 (C(2)). Found (%): C, 58.01; H, 6.67; N, 25.14. $C_8H_{11}N_3O$. Calculated (%): C, 58.17; H, 6.71; N, 25.44. GC: t_R = 15.36 min. MS, m/z (I_{rel} (%)): 165 $[M]^+$ (100).

2-Thiomorpholinopyrimidine (6b). To a solution of thiomorpholine **5b** (247 mg, 2.2 mmol) in MeCN (25 mL), K_2CO_3 (332 mg, 2.2 mmol) was added; after 20 min stirring, 2-chloropyrimidine (**4**) (229 mg, 2 mmol) was added and the mixture was re-

fluxed for 10 h. The solvent was removed *in vacuo*, the residue was dissolved in water (150 mL) and extracted with $CHCl_3$ (3×50 mL). Removal of the solvent and column chromatography of the residue (elution with ethyl acetate—hexane, 1 : 2) afforded compound **6b** in the yield of 399 mg (55%), white crystalline powder, m.p. 59—60 °C. ^{1}H NMR, δ: 2.64 (m, 4 H, SCH_2); 4.15 (m, 4 H, NCH_2); 6.47 (t, 1 H, H(5), J = 4.7 Hz); 8.29 (d, 2 H, H(4), H(6), J = 4.7 Hz). ^{13}C NMR, δ: 26.15 (SCH_2); 46.19 (NCH_2); 109.65 (C(5)); 157.63 (C(4), C(6)); 161.06 (C(2)). Found (%): C, 53.16; H, 6.02; N, 23.35. $C_8H_{11}N_3S$. Calculated (%): C, 53.01; H, 6.12; N, 23.18. GC: t_R = 17.86 min. MS, m/z (I_{rel} (%)): 181 $[M]^+$ (100).

Synthesis of 5-bromo-2-(thio)morpholinopyrimidines 7a,b (general procedure). To a solution of compound **6a** (or **6b**) (0.36 mmol) in CH_2Cl_2 (25 mL), Br_2 (22 μL, 0.43 mmol) was added, the reaction mixture was stirred at room temperature for 1 h and then treated with aqueous Na_2CO_3 for 2 h. The organic layer was separated, the solvent was removed *in vacuo* and the residue was recrystallizes from hexane.

5-Bromo-2-morpholinopyrimidine (7a), white crystalline powder. Yield 89%, m.p. 91—92 °C. ^{1}H NMR, δ: 3.73—3.77 (m, 8 H, OCH_2, NCH_2); 8.30 (s, 2 H, H(4), H(6)). ^{13}C NMR, δ: 44.28 (NCH_2); 66.62 (OCH_2); 106.15 (C(5)); 157.85 (C(4), C(6)); 159.91 (C(2)). Found (%): C, 39.40; H, 4.11; N, 17.06. $C_8H_{10}N_3OBr$. Calculated (%): C, 39.37; H, 4.13; N, 17.21. GS: t_R = 18.55 min. MS, m/z (I_{rel} (%)): 243 $[M]^+$ (100) for ^{79}Br, 245 $[M]^+$ (100) for ^{81}Br.

5-Bromo-2-thiomorpholinopyrimidine (7b), white crystalline powder. Yield 82%, m.p. 80—82 °C. ^{1}H NMR, δ: 2.64 (m, 4 H, SCH_2); 4.12 (m, 4 H, NCH_2); 8.29 (s, 2 H, H(4), H(6)). ^{13}C NMR, δ: 26.77 (SCH_2); 46.58 (NCH_2); 105.70 (C(5)); 157.93 (C(4), C(6)); 159.39 (C(2)). Found (%): C, 36.96; H, 3.75; N, 16.08. $C_8H_{10}BrN_3S$. Calculated (%): C, 36.94; H, 3.87; N, 16.15. GS: t_R = 20.92 min. MS, m/z (I_{rel} (%)): 259 $[M]^+$ (100) for ^{79}Br, 261 $[M]^+$ (100) for ^{81}Br.

Synthesis of 5-(het)aryl-2-(thio)morpholinopyrimidines 12—15 (general procedure). ***A.*** To a mixture of compound **7a** (or **7b**) (1 mmol), the corresponding (het)arylboronic acid **8** (**9**, **10** or **11**) (1.2 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in degassed THF (3 mL), a solution of K_2CO_3 (346 mg, 2.5 mL) in water (4 mL) were added. The reaction mixture was microwave irradiated at 155 °C (250 W) for 20 min, then solvent was removed *in vacuo*. Products were isolated by column chromatography (elution with ethyl acetate—hexane, 1 : 2).

B. A mixture of K_2CO_3 (346 mg, 2.5 mmol), bromopyrimidine **7a** (or **7b**) (1 mmol), 3-nitrophenylboronic acid (**8**) (200 mg, 1.2 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and PPh_3 (26 mg, 0.1 mmol) was dissolved in degassed DMF (7 mL) and microwave irradiated at 180 °C (250 W) for 20 min. Solvent was removed *in vacuo*, products were isolated by column chromatography (elution with ethyl acetate—hexane, 1 : 2).

C. A mixture of K_2CO_3 (346 mg, 2.5 mmol), bromopyrimidine **7a** (or **7b**) (1 mmol), 3-nitrophenylboronic acid (**8**) (200 mg, 1.2 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and PCy_3 (28 mg, 0.1 mmol) was dissolved in degassed DMF (7 mL) and microwave irradiated at 180 °C (250 W) for 20 min. Solvent was removed *in vacuo*, products were isolated by column chromatography (elution with ethyl acetate—hexane, 1 : 2).

2-Morpholino-5-(3-nitrophenyl)pyrimidine (12a), yellow crystalline powder. Yield 57%, m.p. 192—194 °C. ^{1}H NMR, δ: 3.80 (m, 4 H, OCH_2); 3.89 (m, 4 H, NCH_2); 7.62 (t, 1 H, H(5′), J = 7.9 Hz); 7.80 (d, 1 H, H(6′), J = 7.5 Hz); 8.19 (d, 1 H, H(4′), J = 8.2 Hz); 8.34 (s, 1 H, H(2′)); 8.60 (s, 2 H, H(4), H(6)). ^{13}C NMR, δ: 44.31 (NCH_2); 66.76 (OCH_2); 120.40 (C(2′)); 120.86 (C(5)); 121.88 (C(4′)); 130.12 (C(5′)); 131.45 (C(6′)); 137.41 (C(1′)); 148.92 (C(3′)); 155.96 (C(4), C(6)); 161.32 (C(2)). Found (%): C, 58.31; H, 5.03; N, 19.00. $C_{14}H_{14}N_4O_3$. Calculated (%): C, 58.74; H, 4.93; N, 19.57. HPLC: t_R = 4.05 min. GC: t_R = 27.96 min. MS, m/z (I_{rel} (%)): 286 $[M]^+$ (100).

5-(3-Nitrophenyl)-2-thiomorpholinopyrimidine (12b), yellow crystalline powder. Yield 60%, m.p. 149—150 °C. ^{1}H NMR, δ: 2.69 (m, 4 H, SCH_2); 4.22 (m, 4 H, NCH_2); 7.62 (t, 1 H, H(5′), J = 8.0 Hz); 7.80 (ddd, 1 H, H(6′), J = 7.8 Hz, J = 1.7 Hz, J = 1.0 Hz); 8.18 (ddd, 1 H, H(4′), J = 8.2 Hz, J = 2.2 Hz, J = 1.0 Hz); 8.34 (t, 1 H, H(2′), J = 1.9 Hz); 8.59 (s, 2 H, H(4), H(6)). ^{13}C NMR, δ: 26.99 (SCH_2); 46.60 (NCH_2); 120.38 (C(2′)); 120.50 (C(5); 121.85 (C(4′)); 130.11 (C(5′)); 131.42 (C(6′)); 137.43 (C(1′)); 148.92 (C(3′)); 156.03 (C(4), C(6)); 160.87 (C(2)). Found (%): C, 55.89; H, 4.58; N, 18.71. $C_{14}H_{14}N_4O_2S$. Calculated (%): C, 55.62; H, 4.67; N, 18.53. GC: t_R = 30.28 min. MS, m/z (I_{rel} (%)): 302 $[M]^+$ (100).

2-Morpholino-5-(2-thienyl)pyrimidine (13a), white crystalline powder. Yield 43%, m.p. 118—124 °C. ^{1}H NMR, δ: 3.78 (m, 4 H, OCH_2); 3.84 (m, 4 H, NCH_2); 7.08 (dd, 1 H, H(4′), J = 5.2 Hz, J = 3.6 Hz); 7.16 (dd, 1 H, H(3′), J = 3.6 Hz, J = 1.1 Hz); 7.26 (dd, 1 H, H(5′), J = 5.2 Hz, J = 1.1 Hz); 8.55 (s, 2 H, H(4), H(6)). ^{13}C NMR, δ: 44.34 (NCH_2); 66.77 (OCH_2); 117.97 (C(5)); 122.35 (C(3′)); 124.34 (C(5′)); 128.07 (C(4′)); 138.26 (C(2′)); 155.01 (C(4), C(6)); 160.86 (C(2)). Found (%): C, 58.03; H, 5.12; N, 17.04. $C_{12}H_{13}N_3OS$. Calculated (%): C, 58.28; H, 5.30; N, 16.99. GC: t_R = 23.99 min. MS, m/z (I_{rel} (%)): 247 $[M]^+$ (100).

5-(2-Thienyl)-2-thiomorpholinopyrimidine (13b), white crystalline powder. Yield 49%, m.p. 98—100 °C. ^{1}H NMR, δ: 2.67 (m, 4 H, SCH_2); 4.19 (m, 4 H, NCH_2); 7.08 (dd, 1 H, H(4′), J = 5.1 Hz, J = 3.6 Hz); 7.16 (dd, 1 H, H(3′), J = 3.6 Hz, J = 1.1 Hz); 7.26 (dd, 1 H, H(5′), J = 5.1 Hz, J = 1.1 Hz); 8.54 (s, 2 H, H(4), H(6)). ^{13}C NMR, δ: 26.92 (SCH_2); 46.59 (NCH_2); 117.58 (C(5)); 122.31 (C(3′)); 124.29 (C(5′)); 128.08 (C(4′)); 138.31 (C(2′)); 155.12 (C(4), C(6)); 160.35 (C(2)). Found (%): C, 54.80; H, 4.74; N, 16.13. $C_{12}H_{13}N_3S_2$. Calculated (%): C, 54.72; H, 4.98; N, 15.95. GC: t_R = 25.99 min. MS, m/z (I_{rel} (%)): 263 $[M]^+$ (100).

5-(2-Benzo[*b*]thienyl)-2-morpholinopyrimidine (14a), white crystalline powder. Yield 52%, m.p. 201—202 °C. ^{1}H NMR, δ: 3.79 (m, 4 H, OCH_2); 3.87 (m, 4 H, NCH_2); 7.30 (ddd, 1 H, H(6′), J = 8.2 Hz, J = 7.0 Hz, J = 1.2 Hz); 7.35 (ddd, 1 H, H(5′), J = 8.0 Hz, J = 7.0 Hz, J = 1.1 Hz); 7.39 (s, 1 H, H(3′)); 7.75 (d, 1 H, H(4′), J = 8.0 Hz); 7.81 (d, 1 H, H(7′), J = 8.2 Hz); 8.64 (s, 2 H, H(4), H(6)). ^{13}C NMR, δ: 44.35 (NCH_2); 66.77 (OCH_2); 117.68 (C(5)); 118.19 (C(3′)); 122.20 (C(7′)); 123.26 (C(4′)); 124.28 (C(6′)); 124.71 (C(5′)); 138.31 (C(2′)); 138.92 (C(7′a)); 140.53 (C(3′a)); 155.35 (C(4), C(6)); 161.03 (C(2)). Found (%): C, 64.60; H, 5.22; N, 14.10. $C_{16}H_{15}N_3OS$. Calculated (%): C, 64.62; H, 5.08; N, 14.13. GC: t_R = 29.31 min. MS, m/z (I_{rel} (%)): 297 $[M]^+$ (100).

5-(2-Benzo[*b*]thienyl)-2-thiomorpholinopyrimidine (14b) pale yellow powder. Yield 54%, m.p. 197—198 °C. ^{1}H NMR, δ: 2.69 (m, 4 H, SCH_2); 4.21 (m, 4 H, NCH_2); 7.30 (ddd, 1 H, H(6′), J = 8.0 Hz, J = 7.1 Hz, J = 1.1 Hz); 7.35 (ddd, 1 H, H(5′), J = 8.0 Hz, J = 7.1 Hz, J = 1.0 Hz); 7.37 (s, 1 H, H(3′)); 7.75 (d, 1 H, H(4′), J = 8.0 Hz); 7.81 (d, 1 H, H(7′), J = 8.0 Hz); 8.62 (s, 2 H, H(4), H(6)). ^{13}C NMR, δ: 26.96 (SCH_2); 46.61 (OCH_2); 117.28 (C(5)); 118.09 (C(3′)); 122.18 (C(7′)); 123.23

(C(4′)); 124.24 (C(6′)); 124.68 (C(5′)); 138.33 (C(2′)); 138.87 (C(7′a)); 140.52 (C(3′a)); 155.41 (C(4), C(6)); 160.523 (C(2)). Found (%): C, 61.10; H, 4.65; N, 13.23. $C_{16}H_{15}N_3S_2$. Calculated (%): C, 61.31; H, 4.82; N, 13.41. GC: t_R = 32.18 min. MS, *m/z* (I_{rel} (%)): 313 $[M]^+$ (100).

5-(3-Benzo[*b*]thienyl)-2-morpholinopyrimidine (15a), white crystalline powder. Yield 73%, m.p. 136—137 °C. ^{1}H NMR, δ: 3.81 (m, 4 H, OCH_2); 3.88 (m, 4 H, NCH_2); 7.35 (s, 1 H, H(2′)); 7.41 (m, 2 H, H(5′), H(6′)); 7.81 (m, 1 H, H(4′)); 7.92 (m, 1 H, H(7′)); 8.56 (s, 2 H, H(4), H(6)). ^{13}C NMR, δ: 44.33 (NCH_2); 66.81 (OCH_2); 118.70 (C(5)); 122.23 (C(4′)); 123.06 (C7′); 123.14 (C(2′)); 124.56 (C(5′)); 124.65 (C(6′)); 131.82 (C(3′)); 137.71 (C(3a′)); 140.57 (C(7′a)); 157.14 (C(4), C(6)); 161.00 (C(2)). Found (%): C, 64.51; H, 5.20; N, 14.05. $C_{16}H_{15}N_3OS$. Calculated (%): C, 64.62; H, 5.08; N, 14.13. GC: t_R = 28.64 min. MS, *m/z* (I_{rel} (%)): 297 $[M]^+$ (100).

5-(3-Benzo[*b*]thienyl)-2-thiomorpholinopyrimidine (15b), pale yellow powder. Yield 74%, m.p. 110—111 °C. ^{1}H NMR, δ: 2.71 (m, 4 H, SCH_2); 4.23 (m, 4 H, NCH_2); 7.35 (s, 1 H, H(2′)); 7.41 (m, 2 H, H(5′), H(6′)); 7.81 (m, 1 H, H(4′)); 7.92 (m, 1 H, H(7′)); 8.54 (s, 2 H, H(4), H(6)). ^{13}C NMR, δ: 26.96 (SCH_2); 46.55 (NCH_2); 118.29 (C(5)); 122.26 (C(4′)); 123.07, 123.09 (C(7′), C(2′)); 124.56 (C(5′)); 124.65 (C(6′)); 131.86 (C(3′)); 137.73 (C(3a′)); 140.59 (C(7′a)); 157.22 (C(4), C(6)); 161.49 (C(2)). Found (%): C, 61.25; H, 4.77; N, 13.04. $C_{16}H_{15}N_3S_2$. Calculated (%): C, 61.31; H, 4.82; N, 13.41. GC: t_R = 31.10 min. MS, *m/z* (I_{rel} (%)): 313 $[M]^+$ (100).

Synthesis of 5-bromo-4-(2-thienyl)-2-(thio)morpholinopyrimidines (20a,b) and by-products 21a, 22b, and 23 (general procedure). 2-Thienyllithium was generated by adding of BuLi in hexane (1.6 *M*, 2.9 mL, 4.5 mmol) to thiophene (**16**) (430 μL, 5.4 mmol) in diethyl ether (20 mL) at 0 °C followed by keeping the resulting solution for 4 h. The obtained solution of 2-thienyllithium was chilled to −30 °C and a solution of **7a** (or **7b**) (3 mmol) in diethyl ether (40 mL) was slowly added. The reaction mixture was stirred at −20 °C for 1 h, then cooling was removed and stirring was continued at room temperature for 18 h. Then a solution of $K_3Fe(CN)_6$ (1.975 g, 6 mmol) and KOH (1.010 g, 18 mmol) in water (20 mL) was added and the mixture was stirred for 4 h. Solvent was removed *in vacuo*, products were isolated by column chromatography (elution with ethyl acetate—hexane, 1 : 3).

5-Bromo-2-morpholino-4-(2-thienyl)pyrimidine (20a), beige powder. Yield 67%, m.p. 122—124 °C. ^{1}H NMR, δ: 3.77 (m, 4 H, OCH_2); 3.82 (m, 4 H, NCH_2); 7.15 (dd, 1 H, H(4′), *J* = 5.1 Hz, *J* = 3.9 Hz); 7.52 (dd, 1 H, H(5′), *J* = 5.1 Hz, *J* = 1.1 Hz); 8.33 (dd, 1 H, H(3′), *J* = 3.9 Hz, *J* = 1.1 Hz); 8.40 (s, 1 H, H(6)). ^{13}C NMR, δ: 44.35 (NCH_2); 66.73 (OCH_2); 101.89 (C(5)); 127.99 (C(4′)); 130.46 (C(5′)); 131.00 (C(3′)); 142.37 (C(2′)); 155.72 (C(4)), 159.55 (C(2)); 161.38 (C(6)). Found (%): C, 44.11; H, 3.70; N, 12.63. $C_{12}H_{12}BrN_3OS$. Calculated (%): C, 44.18; H, 3.71; N, 12.88. GC: t_R = 26.01 min. MS, *m/z* (I_{rel} (%)): 325 $[M]^+$ (100) for ^{79}Br, 327 $[M]^+$ (100) for ^{81}Br.

5-Bromo-4-(2-thienyl)-2-thiomorpholinopyrimidine (20b), yellow crystalline powder. Yield 90%, m.p. 105—107 °C. ^{1}H NMR, δ: 2.67 (m, 4 H, SCH_2); 4.16 (m, 4 H, NCH_2); 7.15 (dd, 1 H, H(4′), *J* = 5.1 Hz, *J* = 3.9 Hz); 7.52 (dd, 1 H, H(5′), *J* = 5.1 Hz, *J* = 1.1 Hz); 8.33 (dd, 1 H, H(3′), *J* = 3.9 Hz, *J* = 1.1 Hz); 8.39 (s, 1 H, H(6)). ^{13}C NMR, δ: 26.84 (SCH_2); 46.64 (NCH_2); 101.47 (C(5)); 128.00 (C(4′)); 130.43 (C(5′)); 130.95 (C(3′)); 142.45 (C(2′)); 155.78 (C(4)), 159.05 (C(2)); 161.46 (C(6)). Found (%): C, 42.01; H, 3.60; N, 12.09 $C_{12}H_{12}BrN_3S_2$. Calculated (%): C, 42.11; H, 3.53; N, 12.28. GC: t_R = 27.87 min. MS, *m/z* (I_{rel} (%)): 341 $[M]^+$ (100) for ^{79}Br, 343 $[M]^+$ (100) for ^{81}Br.

5-Bromo-4-butyl-2-morpholinopyrimidine (21a), yellow crystalline powder. Yield 23%, m.p. 96—98 °C (decomp.). ^{1}H NMR, δ: 0.95 (t, 3 H, H (4′), *J* = 7.4 Hz); 1.41 (sext, 2 H, H(3′), *J* = 7.4 Hz); 1.67 (m, 2 H, H(2′)); 2.71 (m, 2 H, H(1′)); 3.72—3.77 (m, 8 H, SCH_2, NCH_2); 8.22 (s, 1 H, H(6)). ^{13}C NMR, δ: 13.73 (C(4′)); 22.29 (C(3′)); 29.18 (C(2′)); 36.34 (C(1′)); 44.23 (NCH_2); 66.58 (OCH_2); 107.07 (C(5)); 158.19 (C(6)), 160.22 (C(2)); 168.47 (C(4)). Found (%): C, 47.86; H, 6.26; N, 14.24. $C_{12}H_{18}BrN_3O$. Calculated (%): C, 48.01; H, 6.04; N, 14.00. GC: t_R = 21.73 min. MS, *m/z* (I_{rel} (%)): 299 $[M]^+$ (100) for ^{79}Br, 301 $[M]^+$ (100) for ^{81}Br.

4-(2-Thienyl)-2-thiomorpholinopyrimidine (22b), yellow crystalline powder. Yield 5%, m.p. 124—127 °C. ^{1}H NMR, δ: 2.81 (m, 2 H, SCH^B); 2.86 (m, 2 H, SCH^A); 4.25 (ddd, 2 H, NCH^B, *J* = 14.4 Hz, *J* = 10.4 Hz, *J* = 2.8 Hz); 4.60 (dt, 2 H, NCH^A, *J* = 14.4 Hz, *J* = 4.3 Hz); 6.90 (d, 1 H, H(5), *J* = 5.1 Hz); 7.13 (dd, 1 H, H(4′), *J* = 5.1 Hz, *J* = 3.8 Hz); 7.48 (dd, 1 H, H(5′), *J* = 5.1 Hz, *J* = 1.1 Hz); 7.69 (dd, 1 H, H(3′), *J* = 3.8 Hz, *J* = 1.1 Hz); 8.33 (d, 1 H, H(6), *J* = 5.1 Hz). ^{13}C NMR, δ: 35.55 (NCH_2); 45.43 (SCH_2); 104.95 (C(5)); 127.06 (C(3′)); 128.18 (C(4′)); 129.52 (C(5′)); 143.18 (C(2′)); 158.34 (C(6)); 159.56 (C(4)); 160.93 (C(2)). Found (%): C, 54.63; H, 4.86; N, 15.82. $C_{12}H_{13}N_3S_2$. Calculated (%): C, 54.72; H, 4.98; N, 15.95. GC: t_R = 25.60 min. MS, *m/z* (I_{rel} (%)): 263 $[M]^+$ (100).

5-Bromo-2,2′-dimorpholino-4′-(2-thienyl)-[4,5′]bipyrimidine (23), dark yellow powder. Yield 4%, m.p. 201—204 °C. ^{1}H NMR, δ: 3.74 (m, 4 H, OCH_2); 3.78 (m, 4 H, NCH_2); 3.81 (m, 4 H, $O'CH_2$); 3.93 (m, 4 H, $N'CH_2$); 6.93—6.96 (m, 2 H, H(4"), H(5")); 7.42 (m, 1 H, H(3"); 8.28 (s, 1 H, H(6′)); 8.38 (s, 1 H, H(6)). ^{13}C NMR, δ: 44.28 ($N'CH_2$); 44.37 (NCH_2); 66.65 (OCH_2); 66.82 ($O'CH_2$); 107.52 (C(5)); 117.72 (C(5′)); 127.90 and 129.13 (C(4"), C(5")); 129.80 (C(3")); 142.48 (C(2")); 156.75 (C(4′)); 158.84 (C(6′)); 159.79 (C(6)); 160.45 (C(2′)); 160.63 (C(2)); 163.30 (C(4)). Found (%): C, 49.05; H, 4.54; N, 17.07. $C_{20}H_{21}BrN_6O_2S$. Calculated (%): C, 49.09; H, 4.33; N, 17.17. GC: t_R = 45.29 min. MS, *m/z* (I_{rel} (%)): 488 $[M]^+$ (5) for ^{79}Br, 490 $[M]^+$ (6) for ^{81}Br, 409 $[M - thienyl]^+$ (100) for ^{79}Br, 410 $[M - thienyl]^+$ (20) for ^{81}Br.

Synthesis of 5-(het)aryl-4-(2-thienyl)-2-(thio)morpholinopyrimidines (17a,b and 24a,b) (general procedure). ***A.*** Thiophene (**16**) (160 μL, 2 mmol) was added to a solution of the corresponding pyrimidine **12a** (or **12b**) (1 mmol) in TFA (10 mL). The reaction mixture was stirred for 1 month and concentrated. To the residue, a solution of $K_3Fe(CN)_6$ (658 mg, 2 mmol) and KOH (224 mg, 4 mmol) in water (10 mL) was added and mixture was stirred for 2 h. The precipitate formed was collected, washed with water, dried and analyzed by GC-MS. Compound **17a** was isolated by preparative HPLC.

B. To a mixture of **20a** (or **20b**) (1 mmol), 3-nitrophenylboronic (**8**) (or 2-thienylboronic (**9**)) acid (1.2 mmol), and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in degassed THF (3 mL), a solution of K_2CO_3 (346 mg, 2.5 mmol) in water (4 mL) was added. The reaction mixture was microwave irradiated at 155 °C (250 W) for 20 min. Solvent was removed *in vacuo*, products were isolated by column chromatography (elution with ethyl acetate—hexane, 1 : 2).

2-Morpholino-5-(3-nitrophenyl)-4-(2-thienyl)pyrimidine (17a), yellow powder. Yield 21% (method ***A***) or 70% (method ***B***), m.p. 172—174 °C. ^{1}H NMR, δ: 3.82 (m, 4 H, OCH_2); 3.92 (m, 4 H, NCH_2); 6.71 (dd, 1 H, H(3′), *J* = 3.8 Hz, *J* = 1.0 Hz); 6.85

(dd, 1 H, H(4´), *J* = 5.0 Hz, *J* = 3.8 Hz); 7.38 (dd, 1 H, H(5´), *J* = 5.0 Hz, *J* = 1.0 Hz); 7.61 (t, 1 H, H(5"), *J* = 7.9 Hz); 7.66 (dt, 1 H, H(6"), *J* = 7.7 Hz, *J* = 1.5 Hz); 8.20 (s, 1 H, H(4)); 8.21 (t, 1 H, H(2"), *J* = 1.9 Hz); 8.27 (ddd, 1 H, H(4"), *J* = 8.1 Hz, *J* = 2.1 Hz, *J* = 1.2 Hz). ^{13}C NMR, δ: 44.28 (NCH_2); 66.85 (OCH_2); 118.25 (C(5)); 122.76 (C(4")); 124.67 (C(2")); 127.80 (C(4´)); 129.74 (C(5´)); 128.82, 129.86 (C(5"), C(3´)); 136.14 (C(6")); 139.42 (C(1")); 142.60 (C(2´)); 148.63 (C(3")); 156.51 (C(6)); 159.30 (C(4)); 160.46 (C(2)). Found (%): C, 58.75; H, 4.28; N, 15.41. $C_{18}H_{16}N_4O_3S$. Calculated (%): C, 58.68; H, 4.38; N, 15.21. HPLC: t_R = 8.29 min. GC: t_R = 33.99 min. MS, *m/z* (I_{rel} (%)): 368 $[M]^+$ (100).

5-(3-Nitrophenyl)-4-(2-thienyl)-2-thiomorpholinopyrimidine (17b) was not isolated from the reaction mixture obtained following method ***A*** due to low conversion of the starting material (see Table 3) and the closeness of the retention times of the product and the starting compound **12b**. Following method ***B***, compound **17b** was obtained in 67% yield, light yellow powder, m.p. 163—164 °C. ^{1}H NMR, δ: 2.72 (m, 4 H, SCH_2); 4.25 (m, 4 H, NCH_2); 6.70 (dd, 1 H, H(3´), *J* = 3.9 Hz, *J* = 1.1 Hz); 6.85 (dd, 1 H, H(4´), *J* = 5.1 Hz, *J* = 3.9 Hz); 7.37 (dd, 1 H, H(5´), *J* = 5.1 Hz, *J* = 1.1 Hz); 7.60 (t, 1 H, H(5"), *J* = 7.9 Hz); 7.66 (dt, 1 H, H(6"), *J* = 7.7 Hz, *J* = 1.5 Hz); 8.18 (s, 1 H, H(6)); 8.21 (t, 1 H, H(2"), *J* = 1.9 Hz); 8.27 (ddd, 1 H, H(4"), *J* = 8.1 Hz, *J* = 2.2 Hz, *J* = 1.2 Hz). ^{13}C NMR, δ: 27.00 (SCH_2); 46.52 (NCH_2); 117.90 (C(5)); 122.73 (C(4")); 124.68 (C(2")); 127.80 (C(4´)); 129.70 (C(5´)); 129.79, 129.80 (C(3´), C(5")); 136.14 (C(6")); 139.43 (C(1")); 142.69 (C(2´)); 148.63 (C(3")); 156.57 (C(4)); 159.35 (C(6)); 160.28 (C(2)). Found (%): C, 56.17; H, 4.28; N, 14.49. $C_{18}H_{16}N_4O_2S_2$. Calculated (%): C, 56.23; H, 4.19; N, 14.57. GC: t_R = 39.13 min. MS, *m/z* (I_{rel} (%)): 384 $[M]^+$ (100).

2-Morpholino-4,5-di(2-thienyl)pyrimidine (24a), yellow powder. Yield 80% (method ***B***), m.p. 158—160 °C. ^{1}H NMR, δ: 3.81 (m, 4 H, OCH_2); 3.90 (m, 4 H, NCH_2); 6.89 (dd, 1 H, H(4´), *J* = 4.9 Hz, *J* = 3.8 Hz); 6.91 (dd, 1 H, H(3´), *J* = 3.8 Hz, *J* = 1.3 Hz); 7.02 (dd, 1 H, H(3"), *J* = 3.5 Hz, *J* = 1.2 Hz); 7.12 (dd, 1 H, H(4"), *J* = 5.2 Hz, *J* = 3.5 Hz); 7.36 (dd, 1 H, H(5´), *J* = 4.9 Hz, *J* = 1.3 Hz); 7.43 (dd, 1 H, H(5"), *J* = 5.2 Hz, *J* = 1.2 Hz); 8.27 (s, 1 H, H(6)). ^{13}C NMR, δ: 44.28 (NCH_2); 66.86 (OCH_2); 112.82 (C(5)); 126.85 (C(5")); 127.58 (C(4")); 127.84 (C(4´)); 128.14 (C(3")); 129.58 (C(5´)); 129.95 (C(3´)); 138.20 (C(2")); 142.83 (C(2´)); 157.53 (C(4)); 160.31 (C(6)); 160.72 (C(2)). Found (%): C, 58.45; H, 4.44; N, 12.79. $C_{16}H_{15}N_3OS_2$. Calculated (%): C, 58.33; H, 4.59; N, 12.75. GC: t_R = 28.72 min. MS, *m/z* (I_{rel} (%)): 329 $[M]^+$ (100).

4,5-Di(2-thienyl)-2-thiomorpholinopyrimidine (24b), yellow powder. Yield 73% (method ***B***), m.p. 149—152 °C. ^{1}H NMR, δ: 2.71 (m, 4 H, SCH_2); 4.24 (m, 4 H, NCH_2); 6.88—6.90 (m, 2 H, H(3´), H(4´)); 7.02 (dd, 1 H, H(3"), *J* = 3.5 Hz, *J* = 1.1 Hz); 7.12 (dd, 1 H, H(4"), *J* = 5.1 Hz, *J* = 3.5 Hz); 7.36 (m, 1 H, H(5´)); 7.43 (dd, 1 H, H(5"), *J* = 5.1 Hz, *J* = 1.1 Hz); 8.25 (s, 1 H, H(6)). ^{13}C NMR, δ: 26.98 (SCH_2); 46.53 (NCH_2); 112.45 (C(5)); 126.84 (C(5")); 127.59 (C(4")); 127.86 (C(4´)); 128.15 (C(3")); 129.57 (C(5´)); 129.91 (C(3´)); 138.24 (C(2")); 142.93 (C(2´)); 157.59 (C(4)); 160.26 (C(2)); 160.39 (C(6)). Found (%): C, 55.41; H, 4.45; N, 12.27. $C_{16}H_{15}N_3S_3$. Calculated (%): C, 55.62; H, 4.38; N, 12.16. GC: t_R = 31.03 min. MS, *m/z* (I_{rel} (%)): 345 $[M]^+$ (100).

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