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Synthesis and evaluation of antitubercular activity of fluorinated 5-aryl-4-(hetero)aryl substituted pyrimidines

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ABSTRACT

Various 5-(fluoroaryl)-4-(hetero)aryl substituted pyrimidines have been synthesized based on the Suzuki cross-coupling and nucleophilic aromatic substitution of hydrogen (S_N^H) reactions starting from commercially available 5-bromopyrimidine and their antitubercular activity against *Mycobacterium tuberculosis H37Rv* has been explored. The outcome of the study disclose that, some of the compounds have showed promising activity in micromolar concentration against *Mycobacterium tuberculosis H37Rv*, *Mycobacterium avium*, *Mycobacterium terrae*, and multidrug-resistant strains isolated from tuberculosis patients in Ural region (Russia).The data concerning the "structure - activity" relationship for fluorinated compounds have been discussed.

1. Introduction[1]

Fluorine-containing compounds, especially of heterocyclic nature, have gained attention as biologically actives, and, indeed, many of them are well presented in pharmaceutical market [1-11]. In particular, a great variety of effective antibacterial agents have the structure of fluoroquinolones [1,2,7-14]. In fact, some of the anti-microbial compounds have fluorine atom in their structure [15]. The presence of a fluorine atom in the structure of organic molecules has been shown to modulate their stereoelectronic parameters [14,15]. Further incorporation of fluorine atom not only alters their electronic environment, but also affects pKa value of the neighboring Brønsted acid/base centers, polarity, and lipophilicity, as expressed by the distribution coefficient. Fluorine substituents in bioactive molecules appear to improve often their pharmacological properties, such as better membrane permeability, enhanced hydrophobic binding, and a good stability towards metabolic transformation. This is why development of new fluorine-containing antimycobacterial agents is continued interest for chemists and biologists [18-23].

In continuation of our previous studies in the field of pyrimidine derivatives, as potential antimycobacterial compounds [24-26], we wish to report the synthesis of new 5-(fluoroaryl)-4-(hetero)aryl substituted pyrimidines. In this paper we intend to discuss the effects a fluorine atom or CF_3-group at C(2) and/or C(4) positions on the phenyl substituent in 5-(fluoroaryl)-4-(hetero)arylpyrimidines on their antibacterial activity against *M. tuberculosis*, and other pathogenic strains, such as *M. avium*, *M. terrae*.

2. Results and discussion

2.1. Chemistry

The desired 5-(fluoroaryl)-4-(hetero)aryl substituted pyrimidines have been synthesized based on the palladium-catalyzed Suzuki cross-coupling reaction and nucleophilic aromatic substitution of hydrogen (the S_N^H reaction) [27,28].

Initially 5-(fluoro-aryl)pyrimidines (**3b-k)** were obtained by reacting 5-bromopyrimidine (**1**) with various fluorinated benzeneboronic acids **(2b-k)** by using the aerobic Suzuki cross-coupling reaction conditions in the presence of a new catalyst, namely *trans*-bis(dicyclohexylamine)palladium(II) acetate (DAPCy) (Scheme 1, Table 1) [28]. Whereas 5-phenyl-pyrimidine (**3a**) was obtained from unsubstituted phenylboronic acid (**2a**) by using the method A, as a reference compound for comparison of biological activity (Scheme 1).

Here, we would like to mention that, when the benzeneboronic acid with fluorine substitution at C(2) position (e.g. 2-F-, 2,4-F-, 2-CF_3- or 2,4-CF_3-) reacted with 5-bromopyridine under

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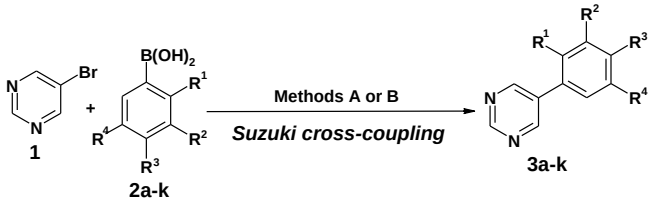
aforesaid reaction condition, the yields of the target products **3b,e,g,j** were found to be poor. However, they were prepared in good yields, according to the procedure described in our previous publication [29]. The starting 5-bromopyrimidine was coupled with the corresponding boronic acid (**2b,e,g,j**) under microwave irradiation, by using 1,4-dioxane-H_2O (4:3) as solvent, and K_2CO_3 and $Pd(PPh_3)_4$, as catalyst (Scheme 1, method B).



a: R^1= H, R^2= H, R^3= H, R^4= H;
b: R^1= F, R^2= H, R^3= H, R^4= H;
c: R^1= H, R^2= F, R^3= , R^4= H;
d: R^1= H, R^2= H, R^3= F, R^4= H;
e: R^1= F, R^2= H, R^3= F, R^4= H;
f: R^1= H, R^2= F, R^3= H, R^4= F;
g: R^2= CF_3, R^2= H, R^3= H, R^4= H;
h: R^1= H, R^2= CF_3, R^3= H, R^4= H;
i: R^1= H, R^2= H, R^3= CF_3, R^4= H;
j: R^1= CF_3, R^2= H, R^3= CF_3, R^4= H;
k: R^1= H, R^2= CF_3, R^3= H, R^4= CF_3

Method A: DAPCy (5 mol.%), K_3PO_4 (2,5 equiv.), EtOH, r.t., 24 h;

Method B: $Pd(PPh_3)_4$ (5 mol.%), K_2CO_3 (2,5 equiv.), 1,4-dioxane - H_2O (4:3), 165 °C, MW, 20 min.

Scheme 1. Synthesis of 5-phenylpyrimidine (3a) and 5-(fluoroaryl)-pyrimidines 3b-k.

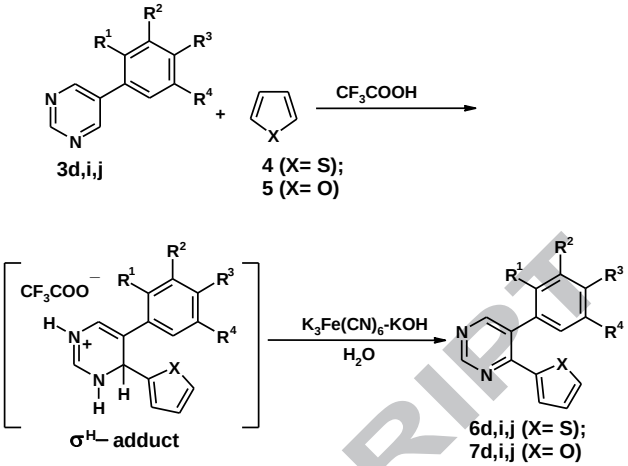
Table 1. Yields of 5-phenylpyrimidine **(3a)** and 5-(fluoroaryl)pyrimidines **3b-k** under the Suzuki cross-coupling reaction.

Entry	Reactants	Conditions	Product –Isolated yield
1	1+2a	Method A	3a – 92 %
2	1+2b	Method A	3b – 37 %[a]
3		Method B	3b – 44 %
4	1+2c	Method A	3c – 61 %
5	1+2d	Method A	3d – 71 %
6	1+2e	Method A	3e – 11 %[a]
7		Method B	3e – 57 %
8	1+2f	Method A	3f – 79 %
9	1+2g	Method A	n.d.
10		Method B	3g – 49 %
11	1+2h	Method A	3h – 63 %
12	1+2i	Method A	3i – 77 %
12	1+2j	Method A	n.d.
13		Method B	3g – 35 %
14	1+2k	Method A	3k – 53%

[a]Quantity of the target product in the reaction mixture according to the GC-MS data.

[b]n.d. – not determined.

At the next stage we have tried to realize nucleophilic substitution of hydrogen at C-4 (the S_N^H-reaction) in 5-aryl substituted pyrimidines by action of thiophene (**4**) and furan (**5**) resulted. It has been shown that the S_N^H reactions of compounds **3d,i,j** with thiophene (**4**) and furan (**5**) result in the formation of 5-(fluoroaryl)-4-(hetero)arylpyrimidines **6d** and **7d** in moderate yields, whereas products **6i,j** and **7i,j** have been obtained in low yields (Scheme 2, Table 2).



Scheme 2. Synthesis of 5-(fluoroaryl)-4-(hetero)aryl substituted pyrimidines **6d,i,j** and **7d,i,j** through the S_N^H-methodology.

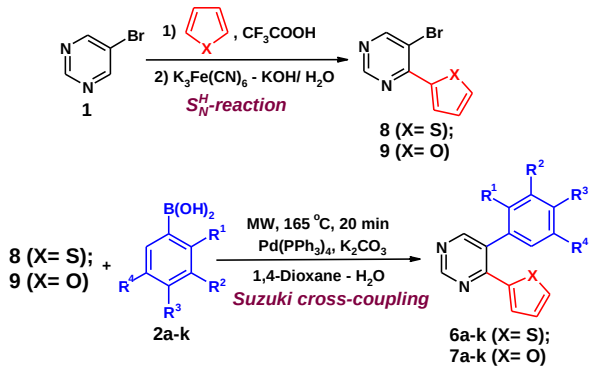
Table 2. Reaction of 5-(fluoroaryl)pyrimidines **3d,i,j** with thiophene (4) and furan (5). Composition of the reaction mixtures and yields of 5-(fluoroaryl)-4-(hetero)aryl substituted pyrimidines **6d,i,j** and **7d,i,j**.

Entry	Reactants	Reaction mixtures[a]	Isolated yield
1	3d+4	3d – 0.3 % σ^H-adduct – 0 % 6d – 99.7 %	6d – 80 %
2	3i+4	3i – 0.6 % σ^H-adduct – 57.5 % 6i– 41.9 %	6i – 36 %
3	3j+4	3j – 41.1 % σ^H-adduct – 1.4 % 6j – 57.5 %	3j – 21 % 6j – 39 %
4	3d+5	3d – 1.7 % σ^H-adduct – 0 % 7d – 98.3 %	7d – 57 %
5	3i+5	3i – 1.2 % σ^H-adduct – 68.5 % 7i – 30.3 %	7i – 26 %
6	3j+5	3j – 41.5 % σ^H-adduct – 11.7 % 7j – 46.8 %	3j – 19 % 7j– 11 %

[a] Reaction mixtures were analyzed by GC-MS after oxidation with $K_3Fe(CN)_6$.

We have suggested that an aryl substituent at C(5) causes a significant steric hindrance for the S_N^H-reaction which has to be proceeding at the neighboring C(4) position of the pyrimidine ring. Therefore, we have decided to use the opposite sequence of the Suzuki cross-coupling and nucleophilic aromatic substitution of hydrogen for the syntheses of 5-(fluoroaryl)-4-(hetero)aryl-pyrimidines **6b-k** and **7b-k**. It has previously been shown that 5-bromopyrimidine (**1**) reacts with thiophene (**4**) and furan (**5**) in CF_3COOH with subsequent oxidation of the intermediate σ^H-adducts to afford the corresponding 5-bromo-4-(thien-2-yl)-pyrimidine (**8**) and 5-bromo-4-(furan-2-yl)pyrimidine (**9**) in good yields (Scheme 3) [25,27,30]. Also it is worth noting that use of DAPCy in the aerobic Suzuki cross-coupling reaction of 5-bromopyrimidines, bearing electron-donating thiophenyl substituents at C-4, leads to the corresponding products in rather

low yields [31]. For this reason 5-bromopyrimidines **8** and **9** have been involved in the Suzuki reaction with arylboronic acids **2a-k** under microwave irradiation (165 ºC, 20 min). Under these reaction conditions the corresponding cross-coupling products, *viz.* 5-(fluoroaryl)-4-(thien-2-yl)pyrimidines (**6b-k**) and 5-(fluoroaryl)-4-(furan-2-yl)pyrimidines (**7b-k**), have been obtained in good yields (Scheme 3, Table 3).



a: R^1= H, R^2= H, R^3= H, R^4= H;
b: R^1= F, R^2= H, R^3= H, R^4= H;
c: R^1= H, R^2= F, R^3= , R^4= H;
d: R^1= H, R^2= H, R^3= F, R^4= H;
e: R^1= F, R^2= H, R^3= F, R^4= H;
f: R^1= H, R^2= F, R^3= H, R^4= F;
g: R^1= CF_3, R^2= H, R^3= H, R^4= H;
h: R^1= H, R^2= CF_3, R^3= H, R^4= H;
i: R^1= H, R^2= H, R^3= CF_3, R^4= H;
j: R^1= CF_3, R^2= H, R^3= CF_3, R^4= H;
k: R^1= H, R^2= CF_3, R^3= H, R^4= CF_3

Scheme 3. Synthesis of 4-(hetero)aryl-5-phenylpyrimidines **6a** and **7a** 5-(fluoroaryl)-4-(hetero)aryl substituted pyrimidines **6b-k** and **7b-k** through the sequence of S_N^H and the Suzuki cross-coupling reactions.

Table 3. The microwave-assisted Suzuki cross-coupling reaction of 5-bromo-4-(hetero)aryl substituted pyrimidines **8** and **9** with various arylboronic acids **2a-k**.

Entry	Reactants	Product –Isolated yield
1	8+2a	6a – 93 %
2	8+2b	6b – 99 %
3	8+2c	6c – 94 %
4	8+2d	6d – 99 %
5	8+2e	6e – 86 %
6	8+2f	6f – 94 %
7	8+2g	6g – 94 %
8	8+2h	6h – 96 %
9	8+2i	6i – 96 %
10	8+2j	6j – 49 %
11	8+2k	6k – 84 %
12	9+2a	7a – 91 %
13	9+2b	7b – 80 %
14	9+2c	7c – 88 %
15	9+2d	7d – 85 %
16	9+2e	7e – 81 %
17	9+2f	7f – 84 %
18	9+2g	7g – 87 %
19	9+2h	7h – 90 %
20	9+2i	7i – 92 %
21	9+2j	7j – 39 %
22	9+2k	7k – 97 %

2.2. Antimycobacterial in vitro activity

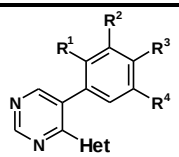
The series of 33 compounds were screened for their activity *in vitro* against *M. tuberculosis* $H_{37}Rv$, *M. avium*, *M. terrae*, and multi-drug-resistant strains, and the data on the minimal inhibitory concentrations (MICs) of these compounds are presented in Table 4. All new pyrimidines were compared with the commercially available drugs Isoniazid, Ofloxacine and Pyrazinamide, tested under the same experimental conditions.

It follows from the experimental results that many compounds (**3a,b,d,h-j**, **6b-f,i,k** and **7b,d,e,g,h,i**) are active at a relatively low MIC (12.5 μg/mL). Besides that, we have observed that incorporation of a fluoro atom in the phenyl substituent at C(5) of pyrimidines (**3b-d**, **6b-f** and **7b,d-f**) does not enhance their antituberular activity, with the exception of compound **7c,** bearing a fluoro atom at C(3) of the phenyl group. The exceptions are the presence of either one fluoro atom at C(5) of the phenyl substituent (compound **7c**, MIC = 1.5 μg/mL), or two fluoro atoms at C(2) and C(4) of 5-aryl substituent in compound **3e** (see Table 4, entry 5), or two fluoro atoms at C(3) and C(5) of 5-aryl substituent in compound **3f** (see Table 4, entry 6). On the contrary, 5-aryl substituted pyrimidines **3k, 6h, 7g** and **7k**, bearing one or two CF_3-groups, proved to exhibit a significant level of inhibitory properties against *Mycobacterium tuberculosis* $H_{37}Rv$ and other strains (MIC from 3.1 to 0.7 μg/mL). Non-fluorinated 5-phenylpyrimidines **6a** and **7a** have also demonstrated a high MIC 6.25 and 0.35 μg/mL, correspondingly.

It is noteworthy that in the series of both 5-phenyl substituted (**3a**, **6a** and **7a**) and 5-(2,4-*bis*-thrifluoromethylphenyl) substituted (**3j**, **6j** and **7j**) pyrimidines the antitubercular activity is growing in the following sequence **3a,j** < **6a,j** < **7a,j**: from C(4) unsubstituted (**3a,j**) to 4-(furan-2-yl) substituted (**7a,j**) pyrimidines (see Table 4, entries 1,10,12,21,23 and 32). This sequence and the recently obtained data for 4-furanyl substituted pyrimidines [25] make compounds **7a** and **7j** as promising leads for further development of new antitubercular agents. In the series of C(3) and C(5)-fluoro or trifluoromethyl substituted pyrimidines such clear sequences are not available, but it should be noted that pyrimidines bearing a fluoro substituent at C(3) position of the phenyl group are commonly more active than their analogues with the CF_3-group (for example, compare **3c** and **3h**, **7c** and **7h**, **3f** and **3k**). Besides that, C(4) unsubstituted pyrimidine **3f** has a high MIC (0.7 μg/mL), and it can also be regarded as a candidate for development of new antitubercular agents.

For the most active compounds **3f**, **7a** and **7j** having MIC ≤0.7 μg/mL against *M. tuberculosis* $H_{37}Rv$, the data on their acute toxicities on white mice have been obtained (Table 1). All tested pyrimidines **3f**, **7a** and **7j** proved to be less toxic in experiments with white mice than Isoniazid. It should be noted that in case of non-fluorinated 4-furan-2-yl-5-phenylpyrimidine **(7a)** the acute oral toxicity proved to be two and four times lower the fluorinated derivatives **3f** and **7j**. The structure of these compounds has to be modified substantially in order to reduce their toxicity with retention of the existing level of activity.

Table 4. *In vitro* antituberculosis activity of 5-arylpyrimidines (**3a-k**) and 5-aryl-4-heteroarylpyrimidines (**6a-k** and **7a-k**).

Entry	Compound						Molecular Mass	Antimycobacterial activity against different strains of *Mycobacterium* (MIC), μg/mL								LD_{50} mouse, mg/kg
								$H_{37}Rv$		*M. avium*		*M. terrae*		MDR[a]		
		Het	R^1	R^2	R^3	R^4		μg/mL	μM	μg/mL	μM	μg/mL	μM	μg/mL	μM	
1	**3a**	H	H	H	H	H	156.19	12.5	80.03	12.5	80.03	12.5	80.03	12.5	80.03	n.d.
2	**3b**	H	F	H	H	H	174.18	12.5	71.76	12.5	71.76	12.5	71.76	12.5	71.76	n.d.
3	**3c**	H	H	F	H	H	174.18	6.25	35.88	6.25	35.88	6.25	35.88	6.25	35.88	n.d.
4	**3d**	H	H	H	F	H	174.18	12.5	71.76	12.5	71.76	12.5	71.76	12.5	71.76	n.d.
5	**3e**	H	F	H	F	H	192.17	3.1	16.13	3.1	16.13	3.1	16.13	3.1	16.13	n.d.
6	**3f**	H	H	F	H	F	192.17	0.7	3.64	0.7	3.64	0.7	3.64	0.7	3.64	300
7	**3g**	H	CF_3	H	H	H	224.19	6.2	27.66	6.2	27.66	6.2	27.66	6.2	27.66	n.d.
8	**3h**	H	H	CF_3	H	H	224.19	12.5	55.76	12.5	55.76	12.5	55.76	12.5	55.76	n.d.
9	**3i**	H	H	H	CF_3	H	224.19	12.5	55.76	12.5	55.76	12.5	55.76	12.5	55.76	n.d.
10	**3j**	H	CF_3	H	CF_3	H	292.19	12.5	42.78	12.5	42.78	12.5	42.78	12.5	42.78	n.d.
11	**3k**	H	H	CF_3	H	CF_3	292.19	1.5	5.13	1.5	5.13	1.5	5.13	1.5	5.13	n.d.
12	**6a**	thien-2-yl	H	H	H	H	238.31	6.2	26.02	6.2	26.02	6.2	26.02	6.2	26.02	n.d.
13	**6b**	thien-2-yl	F	H	H	H	256.30	12.5	48.77	12.5	12.5	12.5	12.5	12.5	12.5	n.d.
14	**6c**	thien-2-yl	H	F	H	H	256.30	12.5	48.77	12.5	12.5	12.5	12.5	12.5	12.5	n.d.
15	**6d**	thien-2-yl	H	H	F	H	256.30	12.5	48.77	12.5	12.5	12.5	12.5	12.5	12.5	n.d.
16	**6e**	thien-2-yl	F	H	F	H	274.29	12.5	45.57	12.5	45.57	12.5	45.57	12.5	45.57	n.d.
17	**6f**	thien-2-yl	H	F	H	F	274.29	12.5	45.57	12.5	45.57	12.5	45.57	12.5	45.57	n.d.
18	**6g**	thien-2-yl	CF_3	H	H	H	306.31	6.2	20.24	6.2	20.24	6.2	20.24	6.2	20.24	n.d.
19	**6h**	thien-2-yl	H	CF_3	H	H	306.31	1.5	4.90	1.5	4.90	1.5	4.90	1.5	4.90	n.d.
20	**6i**	thien-2-yl	H	H	CF_3	H	306.31	12.5	40.81	12.5	40.81	12.5	40.81	12.5	40.81	n.d.
21	**6j**	thien-2-yl	CF_3	H	CF_3	H	374.31	6.2	16.56	6.2	16.56	6.2	16.56	6.2	16.56	n.d.
22	**6k**	thien-2-yl	H	CF_3	H	CF_3	374.31	12.5	33.39	12.5	33.39	12.5	33.39	12.5	33.39	n.d.
23	**7a**	furan-2-yl	H	H	H	H	222.25	0.35	1.57	0.35	1.57	0.35	1.57	0.35	1.57	150
24	**7b**	furan-2-yl	F	H	H	H	240.24	12.5	52.03	12.5	52.03	12.5	52.03	12.5	52.03	n.d.
25	**7c**	furan-2-yl	H	F	H	H	240.24	1.5	6.24	1.5	6.24	1.5	6.24	1.5	6.24	n.d.
26	**7d**	furan-2-yl	H	H	F	H	240.24	12.5	52.03	12.5	52.03	12.5	52.03	12.5	52.03	n.d.

27	**7e**	furan-2-yl	F	H	F	H	258.23	12.5	48.41	12.5	48.41	12.5	48.41	12.5	48.41	n.d.
28	**7f**	furan-2-yl	H	F	H	F	258.23	6.2	24.01	6.2	24.01	6.2	24.01	6.2	24.01	n.d.
29	**7g**	furan-2-yl	CF_3	H	H	H	290.25	12.5	43.07	12.5	43.07	12.5	43.07	12.5	43.07	n.d.
30	**7h**	furan-2-yl	H	CF_3	H	H	290.25	12.5	43.07	12.5	43.07	12.5	43.07	12.5	43.07	n.d.
31	**7i**	furan-2-yl	H	H	CF_3	H	290.25	12.5	43.07	12.5	43.07	12.5	43.07	12.5	43.07	n.d.
32	**7j**	furan-2-yl	CF_3	H	CF_3	H	358.25	0.7	1.95	0.7	1.95	0.35	0.98	0.7	1.95	600
33	**7k**	furan-2-yl	H	CF_3	H	CF_3	358.25	3.1	8.65	3.1	8.65	3.1	8.65	3.1	8.65	n.d.
	INH						137.14	0.1	0.73	0.1	0.73	0.1	0.73	-	-	133[b] 151[c]
	PZA						123.12	12.5	101.53	n.d.	n.d.	n.d.	n.d.	-	-	n.a[b] 1680[c]
	OFL						361.37	0.1	0.28	0.1	0.28	0.1	0.28	0.1	0.28	5450[d]

n.d. – not determined; n.a. – data not available; INH – Isoniazid; PZA – Pyrazinamide; OFL – Ofloxacine.

[a]MDR (multi-drug-resistant tuberculosis strain) – Rifampin and Isoniazid resistant *Mycobacterium tuberculosis* strain having Beijing genotype with a combination of mutations *Ser 531 - Leu 315* and *Ser-Thr* in *rpoB* and *katG* genes, respectively.

[b]LD_{50} Oral mouse [32].

[c]LD_{50} Intraperitoneal mouse [32].

[d]LD_{50} Oral mouse [33].

3. Conclusions

In summary, a simple and efficient way for the synthesis of new family of 5-(fluoroaryl)-4-(hetero)aryl substituted pyrimidines from commercially available 5-bromopyrimidine has been advanced by using the sequence of nucleophilic aromatic substitution of hydrogen (S_N^H) and the Suzuki cross-coupling reactions. In the series of pyrimidines screened, compounds bearing two fluoro atoms at C(3) and C(5) or CF_3-groups at C(2) and C(4) positions of the phenyl substituent, and also containing the furanyl substituent at C(4) of the pyrimidine ring have shown the most promising antitubercular activity. Further studies are needed to explore the mechanism of antimicobacterial activity of these compounds in detail.

4. Experimental section

4.1. General information

All reagents and solvents were obtained from commercial sources and dried by using the standard procedures before use. 5-Bromopyrimidine **(1)** and all arylboronic acids were purchased from Sigma-Aldrich. 5-Bromo-4-(thien-2-yl)pyrimidine (**8**) [27,30] and 5-bromo-4-(furan-2-yl)pyrimidine (**9**) [25] were synthesized as described previously. Solvents (1,4-dioxane and H_2O) for the microwave-assisted Suzuki cross-coupling reaction were deoxygenated by bubbling argon for 1h.

The ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker DRX-400 and AVANCE-500 instruments using Me_4Si and C_6F_6 as an internal standards. Elemental analysis was carried on a Eurovector EA 3000 automated analyzer. Melting points were determined on Boetius combined heating stages and were not corrected.

The GC-MS analysis of all samples was carried out using an Agilent GC 7890A MS 5975C Inert XL EI/CI GC-MS spectrometer 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. Samples of 1 mL of the obtained solutions were analyzed.

Column chromatography was carried out using Alfa Aesar silica gel 0.040-0.063 mm (230–400 mesh), eluting with ethyl acetate-hexane., 1:1 or 1:3. The progress of reactions and the purity of compounds were checked by TLC on Sorbfil plates (Russia), in which the spots were visualized with UV light (λ 254 or 365 nm).

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 reaction temperature was monitored, using an inserted IR sensor by the external surface of the reaction vessel.

*4.2. Synthesis of 5-phenylpyrimidine (**3a**) and 5-(fluoroaryl)pyrimidines (**3b-k**).*

Method A: K_3PO_4 (531 mg, 2.5 mmol) was added to a solution of 5-bromopyrimidine (**1**) (159 mg, 1.0 mmol), phenylboronic (**2a**) [2-fluorobenzeneboronic acid (**2b**), 3-fluorobenzeneboronic (**2c**), 4-fluorobenzeneboronic (**2d**), 2,4-difluorobenzeneboronic (**2e**), 3,5-difluorobenzeneboronic (**2f**), 2-(trifluoromethyl)benzeneboronic (**2g**), 3-(trifluoromethyl)benzeneboronic (**2h**), 4-(trifluoromethyl)benzeneboronic (**2i**), 2,4-*bis*(trifluoromethyl)benzeneboronic (**2j**), or 3,5-*bis*(trifluoromethyl)benzeneboronic (**2k**) acids] (1.2 mmol) and *trans*-bis(dicyclohexylamine)palladium(II) acetate (29 mg, 0.05 mmol) in EtOH (10 mL). The resulting suspension was stirred at ambient temperature for 24 h. EtOH was evaporated under a reduced pressure and the residue was suspended in CH_2Cl_2 (20 mL) and filtered from inorganic salts. After that solvent was distilled off under a reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 1:3) to afford the desired cross-coupling products (**3a-k**).

Method B: A solution of K_2CO_3 (346 mg, 2.5 mmol) in H_2O (3 mL) was added to a mixture of a 5-bromopyrimidine (**1**) (159 mg, 1.0 mmol), the corresponding (hetero)arylboronic acid (**2a-k**) (1.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 5 mol %) in 1,4-dioxane (4 mL). The resulting mixture was irradiated in a microwave apparatus at 165 °C (250 W) for 20 min. After that solvent was distilled off *in vacuo*, and the residue was purified by flash column chromatography (hexane/ethyl acetate, 1:3) to afford the desired cross-coupling products (**3a-k**).

*4.2.1. 5-Phenylpyrimidine **(3a)** [34].*

It has been obtained by the reaction of **1** with phenylboronic (**2a**) acid. Yield (see Table 1, entry 1), white solid; mp 38-40 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45-7.49 (m, 1H, Ph), 7.51-7.55 (m, 2H, Ph), 7.58-7.60 (m, 2H, Ph), 8.92 (s, 2H, H-4 and H-6), 9.17 (s, 1H, H-2) ppm. GC t_R 15.76 min; MS m/z (rel intensity) 156 (M^+, 100). Anal. Calcd for $C_{10}H_8N_2$ (156.19): C, 76.90; H, 5.16; N, 17.94. Found: C, 59.18; H, 3.63; N, 17.55.

*4.2.2. 5-(2-Fluorophenyl)pyrimidine **(3b)**.*

It has been obtained by the reaction of **1** with 2-fluorobenzenboronic (**2b**) acid. Yield (see Table 1, entries 2 and 3), white solid; m.p. 75-78 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21-7.32 (m, 2H, Ph), 7.43-7.47 (m, 2H, Ph), 8.94 (d, 2H, J = 1.2 Hz, H-4 and H-6), 9.22 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 116.52 (d, $^2J_{C,F}$ = 22.0 Hz), 122.14 (d, $^2J_{C,F}$ = 13.8 Hz), 125.04 (d, $^4J_{C,F}$ = 3.8 Hz), 129.75 (d, $^4J_{C,F}$ = 1.8 Hz), 130.06 (d, $^4J_{C,F}$ = 3.0 Hz), 130.98 (d, $^3J_{C,F}$ = 8.3 Hz), 156.33 (d, $^3J_{C,F}$ = 3.9 Hz), 157.66, 158.82, 160.80 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 44.17-44.22 (m, 1F) ppm. GC t_R 15.57 min; MS m/z (rel intensity): 174 (M^+, 100). Anal. Calcd for $C_{10}H_7FN_2$ (174.18): C 68.96, H 4.05, N, 16.08. Found: C 68.93; H, 3.96; N, 15.82.

*4.2.3. 5-(3-Fluorophenyl)pyrimidine **(3c)**.*

It has been obtained by the reaction of **1** with 3-fluorobenzenboronic (**2c**) acid. Yield (see Table 1, entry 4), pale yellow solid; m.p. 63-64 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.33 (m, 1H, Ph), 7.59 (td, 1H, J = 8.0, 6.2 Hz, Ph), 7.69 (ddd, 1H, J = 7.7, 1.5, 0.9 Hz, Ph), 7.75 (ddd, 1H, J = 10.4, 2.4, 1.9 Hz, Ph), 9.20 (s, 2H, H-4 and H-6), 9.22 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 113.81 (d, $^2J_{C,F}$ = 22.8 Hz), 115.66 (d, $^2J_{C,F}$ = 21.00 Hz), 123.04 (d, $^4J_{C,F}$ = 2.8 Hz), 131.28 (d, $^3J_{C,F}$ = 6.8 Hz), 131.93 (d, $^4J_{C,F}$ = 2.4 Hz), 136.15 (d, $^3J_{C,F}$ = 8.2 Hz), 154.89, 157.67, 162.69 (d, $^1J_{C,F}$ = 244.0 Hz) ppm. ^{19}F NMR (470.5 MHz, DMSO-d_6) 50.51 (ddd, J = 10.1, 9.1, 6.2 Hz) ppm. GC t_R 15.58 min; MS m/z (rel intensity): 174 (M^+, 100). Anal.

Calcd for $C_{10}H_7FN_2$ (174.18): C 68.96, H 4.05, N, 16.08. Found: C 68.85; H, 3.91; N, 15.87.

*4.2.4. 5-(4-Fluorophenyl)pyrimidine **(3d)** [34].*

It has been obtained by the reaction of **1** with 4-fluorobenzenboronic (**2d**) acid. Yield (see Table 1, entry 5), white solid; m.p. 96-98 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (m, 2H, H-2' and H-6'), 7.56 (m, 2H, H-3' and H-5'), 8.92 (s, 2H, H-4 and H-6), 9.21 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 116.54 (d, $^2J_{C,F}$ = 21.8 Hz), 128.78 (d, $^3J_{C,F}$ = 8.4 Hz), 130.39 (d, $^4J_{C,F}$ = 3.4 Hz), 133.44, 154.72, 157.49, 162.40, 164.39 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 49.34 (tt, 1F, *J* = 8.4, 5.1 Hz) ppm. GC t_R 15.84 min; MS m/z (rel intensity): 174 (M^+, 100). Anal. Calcd for $C_{10}H_7FN_2$ (174.18): C 68.96, H 4.05, N, 16.08. Found: C 68.90; H, 3.89; N, 15.96.

*4.2.5. 5-(2,4-Difluorophenyl)pyrimidine **(3e)** [35].*

It has been obtained by the reaction of **1** with 2,4-difluorobenzenboronic (**2e**) acid. Yield (see Table 1, entries 6 and 7), white solid; m.p. 93-95 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.98-7.08 (m, 2H, H-5' and H-6'), 7.74 (td, 1H, *J* = 8.6, 6.2 Hz, H-3'), 8.90 (d, 2H, *J* = 1.3 Hz, H-4 and H-6), 9.23 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 105.02 (t, $^2J_{C,F}$ = 25.7 Hz), 112.51 (dd, $^2J_{C,F}$ = 21.5 Hz, $^4J_{C,F}$ = 3.8 Hz), 113.46 (dd, $^2J_{C,F}$ = 14.2 Hz, $^3J_{C,F}$ = 4.0 Hz), 129.01 (d, $^3J_{C,F}$ = 2.0 Hz), 130.95 (dd, $^2J_{C,F}$ = 9.8 Hz, $^3J_{C,F}$ = 4.5 Hz), 156.20 (d, $^4J_{C,F}$ = 3.7 Hz), 157.75, 160.01 (dd, $^1J_{C,F}$ = 252.2 Hz, $^2J_{C,F}$ = 12.0 Hz), 163.45 (dd, $^1J_{C,F}$ = 252.2 Hz, $^2J_{C,F}$ = 12.0 Hz) ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 48.85 (td, 1F, *J* = 9.7, 1.1 Hz), 54.07 (qd, 1F, *J* = 8.3, 6.3 Hz) ppm. GC t_R 15.15 min; MS m/z (rel intensity): 192 (M^+, 100). Anal. Calcd for $C_{10}H_6F_2N_2$ (192.17): C 62.50, H 3.15, N, 14.58. Found: C 62.58; H, 3.20; N, 14.52.

*4.2.6. 5-(3,5-Difluorophenyl)pyrimidine **(3f)**.*

It has been obtained by the reaction of **1** with 3,5-difluorobenzenboronic (**2f**) acid. Yield (see Table 1, entry 8), white solid; m.p. 150-151 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.93 (tt, 1H, *J* = 8.8, 2.3 Hz, H-4'), 7.13 (m, 2H, H-2' and H-6'), 8.94 (s, 2H, H-4 and H-6), 9.27 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 104.43 (t, $^2J_{C,F}$ = 25.2 Hz), 110.06 (dd, $^2J_{C,F}$ = 20.0 Hz, $^3J_{C,F}$ = 6.6 Hz), 132.32, 137.44 (t, $^3J_{C,F}$ = 9.7 Hz), 154.82, 158.39, 163.62 (dd, $^1J_{C,F}$ = 250.5 Hz, $^2J_{C,F}$ = 12.9 Hz) ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 54.13-54.21 (m, 2F) ppm. GC t_R 14.95 min; MS m/z (rel intensity): 192 (M^+, 100). Anal. Calcd for $C_{10}H_6F_2N_2$ (192.17): C 62.50, H 3.15, N, 14.58. Found: C 62.52; H, 3.27; N, 14.33.

*4.2.7. 5-(2-Trifluorometylphenyl)pyrimidine **(3g)**.*

It has been obtained by the reaction of **1** with 2-(trifluoromethyl)benzeneboronic (**2g**) acid. Yield (see Table 1, entries 9 and 10), pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (d, 1H, *J* = 7.5 Hz, H-6'), 7.64 (dt, 2H, *J* = 15.0, 7.4 Hz, H-4' and H-5'), 7.84 (d, 1H, *J* = 7.8 Hz, H-3'), 8.74 (s, 2H, H-4 and H-6), 9.27 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 123.70 (d, $^1J_{C,F}$ = 252.2 Hz), 126.54 (q, $^3J_{C,F}$ = 5.2 Hz), 129.00, 129.06, 129.24, 131.93 (d, $^4J_{C,F}$ = 2.6 Hz), 133.56, 133.63 (d, $^4J_{C,F}$ = 1.7 Hz), 156.11 (q, $^4J_{C,F}$ = 1.6 Hz), 158.03 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 104.91 (s, CF_3) ppm. GC t_R 15.03 min; MS m/z (rel intensity): 224 (M^+, 100). Anal. Calcd for $C_{11}H_7F_3N_2$ (224.19): C 58.93, H 3.15, N, 12.50. Found: C 58.86; H, 3.05; N, 12.70.

*4.2.8. 5-(3-Trifluorometylphenyl)pyrimidine **(3h)**.*

It has been obtained by the reaction of **1** with 3-(trifluoromethyl)benzeneboronic (**2h**) acid. Yield (see Table 1, entry 11), white solid; m.p. 103-105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, 1H, *J* = 7.8 Hz, H-4'), 7.76 (d, 1H, *J* = 15.1 Hz, Ph), 7.77 (d, 1H, *J* = 14.9 Hz, Ph), 7.84 (s, 1H, H-2'), 8.99 (s, 2H, H-4 and H-6), 9.28 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 123.73 (d, $^1J_{C,F}$ = 272.5 Hz), 124.79 (dq, $^1J_{C,F}$ = 241.5 Hz , $^4J_{C,F}$ = 3.7 Hz), 130.05, 130.33, 131.87, 132.13, 133.16, 135.19, 154.98, 158.11 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 98.96 (s, CF_3) ppm. GC t_R 15.56 min; MS m/z (rel intensity): 224 (M^+, 100). Anal. Calcd for $C_{11}H_7F_3N_2$ (224.19): C 58.93, H 3.15, N, 12.50. Found: C 59.03; H, 3.06; N, 12.55.

*4.2.9. 5-(4-Trifluorometylphenyl)pyrimidine **(3i)**.*

It has been obtained by the reaction of **1** with 4-(trifluoromethyl)benzeneboronic (**2i**) acid. Yield (see Table 1, entry 12), white solid; m.p. 110-112 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, 2H, *J* = 8.1 Hz, H-2' and H-6'), 7.80 (d, 2H, *J* = 8.1 Hz, H-3' and H-5'), 8.99 (s, 2H, H-4 and H-6), 9.28 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 123.84 (d, $^1J_{C,F}$ = 272.3 Hz), 126.40 (q, $^4J_{C,F}$ = 3.7 Hz), 127.41, 131.17 (q, $^2J_{C,F}$ = 32.8 Hz), 133.10, 137.86 (d, $^4J_{C,F}$ = 0.8 Hz), 155.02, 158.24 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 98.98 (s, CF_3) ppm. GC t_R 15.89 min; MS m/z (rel intensity): 224 (M^+, 100). Anal. Calcd for $C_{11}H_7F_3N_2$ (224.19): C 58.93, H 3.15, N, 12.50. Found: C 58.72; H, 3.13; N, 12.64.

*4.2.10. 5-(2,4-Bis-trifluoromethylphenyl)pyrimidine **(3j)** [36].*

It has been obtained by the reaction of **1** with 2,4-bis(trifluoromethyl)benzeneboronic (**2j**) acid. Yield (see Table 1, entries 12 and 13), white solid; m.p. 58-59 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (d, 1H, *J* = 8.0 Hz, H-6'), 7.95 (d, 1H, *J* = 8.0 Hz, H-5'), 8.10 (s, 1H, H-3'), 8.75 (s, 2H, H-4 and H-6), 9.32 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 121.89 (d, $^2J_{C,F}$ = 18.4 Hz), 123.87 (dt, $^3J_{C,F}$ = 8.8 Hz, $^3J_{C,F}$ = 3.9 Hz), 124.07 (d, $^2J_{C,F}$ = 17.0 Hz), 128.88 (d, $^4J_{C,F}$ = 3.3 Hz), 130.20 (d, $^2J_{C,F}$ = 31.4 Hz), 131.82 (d, $^2J_{C,F}$ = 33.8 Hz), 132.31, 132.86, 137.45, 155.86, 158.65 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 98.72 (s, CF_3), 104.47 (s, CF_3) ppm. GC t_R 14.13 min; MS m/z (rel intensity): 292 (M^+, 100). Anal. Calcd for $C_{12}H_6F_6N_2$ (292.19): C 49.33, H 2.07, N, 9.59. Found: C 49.18; H, 2.21; N, 9.52.

*4.2.11. 5-(3,5-Bis-trifluoromethylphenyl)pyrimidine **(3k)**.*

It has been obtained by the reaction of **1** with 3,5-bis(trifluoromethyl)benzeneboronic (**2k**) acid. Yield (see Table 1, entry 14), off-white solid; m.p. 152-154 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (s, 1H, H-4'), 8.03 (s, 2H, H-2' and H-6'), 9.01 (s, 2H, H-4 and H-6), 9.33 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 122.77 (dt, $^3J_{C,F}$ = 7.4 Hz, $^4J_{C,F}$ = 3.6 Hz), 122.96 (d, $^1J_{C,F}$ = 273.0 Hz), 127.20 (d, $^4J_{C,F}$ = 2.9 Hz), 131.93, 133.10 (d, $^2J_{C,F}$ = 33.8 Hz), 136.70, 155.06, 158.87 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 98.81 (s, CF_3) ppm. GC t_R 14.31 min; MS m/z (rel intensity): 292 (M^+, 100). Anal. Calcd for $C_{12}H_6F_6N_2$ (292.19): C 49.33, H 2.07, N, 9.59. Found: C 49.44; H, 2.24; N, 9.57.

*4.3. Synthesis of 4-(hetero)aryl-5-phenylpyrimidines **6a** and **7a** 5-(fluoroaryl)-4-(hetero)arylpyrimidines **6b-k** and **7b-k**.*

A solution of K_2CO_3 (346 mg, 2.5 mmol) in 3 mL H_2O was added to a mixture of 5-bromo-4-(thien-2-yl)pyrimidine **(8)** [or 5-bromo-4-(furan-2-yl)pyrimidine **(9)**] (0.5 mmol), the corresponding arylboronic acid **(2a-k)** (0.6 mmol) and $Pd(PPh_3)_4$ (29 mg, 5 mol %) in 1,4-dioxane (4 mL). The resulting mixture was irradiated in a microwave apparatus at 165 °C (250 W) for 20 min. After that solvent was distilled off *in vacuo*, and the residue was purified by flash column chromatography (hexane/ethyl acetate, 1:3) to afford the desired 5-aryl-4-(hetero)arylpyrimidines **6a-k** and **7a-k**..

4.3.1. 5-Phenyl-4-(thien-2-yl)pyrimidine ***(6a)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with phenylboronic (**2a**) acid. Yield (see Table 3, entry 1), pale yellow solid; mp 104-106 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 6.81 (dd, 1H, *J* = 3.8, 0.7 Hz, H-3''), 6.86 (dd, 1H, *J* = 5.0, 3.8 Hz, H-4''), 7.34-7.39 (m, 2H, Ph), 7.41 (dd, 1H, *J* = 5.0, 0.7 Hz, H-5''), 7.47-7.52 (m, 3H, Ph), 8.55 (s, 1H, H-6), 9.12 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): 128.02, 128.79, 129.12, 129.16, 130.29, 130.81, 130.91, 136.29, 141.78, 156.25, 157.35, 158.20 ppm. GC t_R 22.74 min; MS m/z (rel intensity) 238 (M^+, 100). Anal. Calcd for $C_{14}H_{10}N_2S$ (238.31): C, 70.56; H, 4.23; N, 11.75. Found: C, 70.36; H, 4.30; N, 11.71.

4.3.2. 5-(2-Fluorophenyl)-4-(thien-2-yl)pyrimidine ***(6b)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with 2-fluorobenzeneboronic (**2b**) acid. Yield (see Table 3, entry 2), pale yellow solid; m.p. 90-92 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.89-6.91 (m, 2H, H-3'' and H-4''), 7.21 (t, 1H, *J* = 8.9 Hz, Ph), 7.28-7.38 (m, 2H, Ph), 7.43 (dd, 1H, *J* = 4.6, 1.5 Hz, H-5''), 7.51 (tdd, 1H, *J* = 7.2, 5.2, 2.0 Hz, H-3), 8.57 (s, 1H, H-6), 9.16 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 116.35 (d, $^{2}J_{C,F}$ = 21.3 Hz), 123.95 (d, $^{2}J_{C,F}$ = 16.3 Hz), 124.74, 125.00 (d, $^{4}J_{C,F}$ = 3.7 Hz), 128.15, 129.91, 130.56, 131.18 (d, $^{3}J_{C,F}$ = 7.9 Hz), 131.29 (d, $^{4}J_{C,F}$ = 2.6 Hz), 141.64, 156.95, 157.91, 158.68, 159.86 (d, $^{1}J_{C,F}$ = 248.5 Hz) ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 44.98 (dt, 1F, *J* = 9.2, 6.7 Hz) ppm. GC t_R 22.53 min; MS m/z (rel intensity): 256 (M^+, 100). Anal. Calcd for $C_{14}H_9FN_2S$ (256.30): C 65.61, H 3.54, N, 10.93. Found: C 65.32; H, 3.52; N, 10.65.

4.3.3. 5-(3-Fluorophenyl)-4-(thien-2-yl)pyrimidine ***(6c)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with 3-fluorobenzeneboronic (**2c**) acid. Yield (see Table 3, entry 3), white solid; m.p. 60-61 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.86 (dd, 1H, *J* = 3.9, 1.1 Hz, H-3''), 6.90 (dd, 1H, *J* = 5.0, 3.9 Hz, H-4''), 7.10 (ddd, 1H, *J* = 9.2, 2.3, 1.7 Hz, Ph), 7.16 (ddd, 1H, *J* = 7.6, 1.4, 1.0 Hz, Ph), 7.20 (tdd, 1H, *J* = 8.5, 2.6, 0.9 Hz, Ph), 7.44 (dd, 1H, *J* = 5.0, 1.1 Hz, H-5''), 7.48 (td, 1H, *J* = 8.0, 5.9 Hz, Ph), 8.54 (s, 1H, H-6), 9.14 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 115.87 (d, $^{2}J_{C,F}$ = 20.9 Hz), 116.35 (d, $^{2}J_{C,F}$ = 22.1 Hz), 125.02 (d, $^{4}J_{C,F}$ = 3.0 Hz), 128.12, 129.67, 130.61, 130.84, 130.92 (d, $^{3}J_{C,F}$ = 8.4 Hz), 138.37 (d, $^{3}J_{C,F}$ = 7.8 Hz), 141.37, 156.20, 157.69, 158.01, 163.04 (d, $^{1}J_{C,F}$ = 248.4 Hz) ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 50.39 (dt, 1F, *J* = 8.9, 5.8 Hz) ppm. GC t_R 22.38 min; MS m/z (rel intensity): 256 (M^+, 100). Anal. Calcd for $C_{14}H_9FN_2S$ (256.30): C 65.61, H 3.54, N, 10.93. Found: C 65.50; H, 3.52; N, 10.90.

4.3.4. 5-(4-Fluorophenyl)-4-(thien-2-yl)pyrimidine ***(6d)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with 4-fluoro-benzeneboronic (**2d**) acid. Yield (see Table 3, entry 4), pale yellow solid; m.p. 102-103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.86 (dd, 1H, *J* = 3.8, 1.0 Hz, H-3''), 6.90 (dd, 1H, *J* = 5.0, 3.8 Hz, H-4''), 7.20 (m, 2H, H-2' and H-6'), 7.34 (m, 2H, H-3' and H-5'), 7.43 (dd, 1H, *J* = 5.0, 1.0 Hz, H-5''), 8.53 (s, H, H-4), 9.12 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 116.33 (d, $^{2}J_{C,F}$ = 21.6 Hz), 128.02, 129.93, 130.60 (d, $^{2}J_{C,F}$ = 33.1 Hz), 133.01 (d, $^{3}J_{C,F}$ = 8.2 Hz), 132.20 (d, $^{4}J_{C,F}$ = 3.5 Hz), 141.56, 156.40, 157.49, 158.23, 162.09, 164.07 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 49.39 (tt, 1F, *J* = 8.6, 5.3 Hz) ppm. GC t_R 22.60 min; MS m/z (rel intensity): 256 (M^+, 100). Anal. Calcd for $C_{14}H_9FN_2S$ (256.30): C 65.61, H 3.54, N, 10.93. Found: C 65.41; H, 3.53; N, 10.87.

4.3.5. 5-(2,4-Difluorophenyl)-4-(thien-2-yl)pyrimidine ***(6e)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with 2,4-difluorobenzenboronic (**2e**) acid. Yield (see Table 3, entry 5), beige solid; m.p. 67-69 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.94 (dd, 1H, *J* = 5.0, 3.8 Hz, H-4''), 6.95-7.01 (m, 2H, H-5' and H-3''), 7.06 (m, 1H, H-6'), 7.33 (td, 1H, *J* = 8.3, 6.4 Hz, H-3'), 7.45 (dd, 1H, *J* = 5.0, 0.9 Hz, H-5''), 8.55 (s, 1H, H-6), 9.16 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 105.00 (t, $^{2}J_{C,F}$ = 25.7 Hz), 112.46 (dd, $^{2}J_{C,F}$ = 21.4 Hz, $^{3}J_{C,F}$ = 3.9 Hz), 120.06 (dd, $^{2}J_{C,F}$ = 16.6 Hz, $^{3}J_{C,F}$ = 4.0 Hz), 123.91, 128.18, 129.91, 130.75, 132.18 (dd, $^{2}J_{C,F}$ = 9.6 Hz, $^{4}J_{C,F}$ = 4.1 Hz), 141.39, 157.16, 158.08, 158.81, 160.16 (dd, $^{1}J_{C,F}$ = 251.2 Hz, $^{2}J_{C,F}$ = 12.1 Hz), 163.70 (dd, $^{1}J_{C,F}$ = 252.2 Hz, $^{2}J_{C,F}$ = 11.5 Hz) ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 52.70 (q, 1F, *J* = 8.7 Hz), 54.27 (qd, 1F, *J* = 8.3, 6.4 Hz) ppm. GC t_R 21.99 min; MS m/z (rel intensity): 274 (M^+, 100). Anal. Calcd for $C_{14}H_8F_2N_2S$ (274.29): C 61.31, H 2.94, N, 10.21. Found: C 61.34; H, 2.84; N, 10.09.

4.3.6. 5-(3,5-Difluorophenyl)-4-(thien-2-yl)pyrimidine ***(6f)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with 3,5-difluorobenzenboronic (**2f**) acid. Yield (see Table 3, entry 6), pale yellow solid; m.p. 108-110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.89-6.99 (m, 5H, H-3'', H-4'' and Ph), 7.47 (dd, 1H, *J* = 4.9, 1.1 Hz, H-5''), 8.53 (s, 1H, H-6), 9.15 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 104.47 (t, $^{2}J_{C,F}$ = 25.1 Hz), 112.52 (dd, $^{2}J_{C,F}$ = 19.7 Hz, $^{3}J_{C,F}$ = 6.4 Hz), 128.24, 128.77, 130.88, 130.94, 139.42 (t, $^{3}J_{C,F}$ = 9.7 Hz), 140.94, 156.13, 157.78, 158.00, 163.40 (dd, $^{1}J_{C,F}$ = 251.2 Hz, $^{2}J_{C,F}$ = 12.9 Hz) ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 54.06-54.13 (m, 2F) ppm. GC t_R 21.67 min; MS m/z (rel intensity): 274 (M^+, 100). Anal. Calcd for $C_{14}H_8F_2N_2S$ (274.29): C 61.31, H 2.94, N, 10.21. Found: C 61.30; H, 2.96; N, 10.15.

4.3.7. 4-Thien-2-yl-5-(2-trifluorometylphenyl)pyrimidine ***(6g)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with 2-(trifluoromethyl)benzeneboronic (**2g**) acid. Yield (see Table 3, entry 7), beige solid; m.p. 97-99 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.59 (d, 1H, *J* = 3.6 Hz, H-3''), 6.86 (m, 1H, H-4''), 7.35 (dd, 1H, *J* = 6.3, 1.4 Hz, H-6'), 7.41 (d, 1H, *J* = 4.9 Hz, H-5''), 7.65-7.71 (m, 2H, H-4' and H-5'), 7.89 (dd, 1H, *J* = 6.6, 1.9 Hz, H-3'), 8.53 (s, 1H, H-6), 9.16 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 120.29, 123.56 (d, $^{1}J_{C,F}$ = 274.1 Hz), 126.92 (q, $^{3}J_{C,F}$ = 5.0 Hz), 128.12, 129.13, 129.39, 129.61, 130.56 (q, $^{2}J_{C,F}$ = 30.5 Hz), 132.01, 132.49, 134.69, 141.74, 156.28, 157.94 (d, $^{4}J_{C,F}$ = 1.2 Hz), 159.97 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 102.59 (s, CF_3) ppm. GC t_R 22.10 min; MS m/z (rel intensity): 306 (M^+, 100). Anal. Calcd for $C_{15}H_9F_3N_2S$ (306.31): C 58.82, H 2.96, N, 9.15. Found: C 58.86; H, 2.84; N, 9.04.

4.3.8. 4-Thien-2-yl-5-(3-trifluorometylphenyl)pyrimidine ***(6h)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with 3-(trifluoromethyl)benzeneboronic (**2h**) acid. Yield (see Table 3, entry 8), white solid; m.p. 73-74 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.81 (dd, 1H, *J* = 3.9 , 1.0 Hz, H-3''), 6.90 (dd, 1H, *J* = 5.1 , 3.9 Hz, H-4''), 7.45 (dd, 1H, *J* = 5.1, 1.0 Hz, H-5''), 7.58 (d, 1H, *J* = 7.7 Hz, Ph), 7.63-7.66 (m, 2H, Ph), 7.77 (d, 1H, *J* = 7.7 Hz, Ph), 8.56 (s, 1H, H-6), 9.16 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 123.71 (d, $^{1}J_{C,F}$ = 272.5 Hz), 125.68 (q, $^{4}J_{C,F}$ = 3.8 Hz), 126.13 (q, $^{4}J_{C,F}$ = 3.8 Hz), 126.96, 128.12, 129.46, 129.77, 130.79 (q, $^{4}J_{C,F}$ = 2.1 Hz), 131.78 (q, $^{2}J_{C,F}$ = 32.8 Hz), 132.73, 137.17, 141.24, 156.33,

157.89, 158.12 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 99.01 (s, CF_3) ppm. GC t_R 21.91 min; MS m/z (rel intensity): 306 (M^+, 100). Anal. Calcd for $C_{15}H_9F_3N_2S$ (306.31): C 58.82, H 2.96, N, 9.15. Found: C 58.76; H, 3.02; N, 9.04.

4.3.9. 4-Thien-2-yl-5-(4-trifluorometylphenyl)pyrimidine ***(6i)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with 4-(trifluoromethyl)benzeneboronic (**2i**) acid. Yield (see Table 3, entry 9), white solid; m.p. 125-127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.82 (dd, 1H, *J* = 3.8, 0.8 Hz, H-3''), 6.92 (dd, 1H, *J* = 5.0, 3.8 Hz, H-4''), 7.46 (dd, 1H, *J* = 5.0, 0.8 Hz, H-5''), 7.54 (d, 2H, *J* = 8.1 Hz, H-2' and H-6'), 7.78 (d, 2H, *J* = 8.1 Hz, H-3' and H-5'), 8.55 (s, 1H, H-6), 9.17 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): 123.89 (d, $^1J_{C,F}$ = 272.5 Hz), 126.18 (q, $^4J_{C,F}$ = 3.7 Hz), 128.19, 129.60, 129.71, 130.76, 130.86, 131.11 (q, $^2J_{C,F}$ = 32.7 Hz), 140.12, 141.26, 156.21, 157.88, 158.01 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 99.10 (s, CF_3) ppm. GC t_R 22.14 min; MS m/z (rel intensity): 306 (M^+, 100). Anal. Calcd for $C_{15}H_9F_3N_2S$ (306.31): C 58.82, H 2.96, N, 9.15. Found: C 58.71; H, 2.90; N, 9.09.

4.3.10. 5-(2,4-Bis-trifluoromethylphenyl)-4-(thien-2-yl)pyrimidine ***(6j)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with 2,4-bis(trifluoromethyl)benzeneboronic (**2j**) acid. Yield (see Table 3, entry 10), pale yellow solid; m.p. 117-120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.65 (d, 1H, *J* = 3.5, H-3''), 6.90 (dd, 1H, *J* = 4.9, 3.5 Hz, H-4''), 7.45 (d, 1H, *J* = 4.9 Hz, H-5''), 7.55 (d, 1H, *J* = 8.0 Hz, H-6'), 7.95 (d, 1H, *J* = 8.0 Hz, H-5'), 8.16 (s, 1H, H-3'), 8.51 (s, 1H, H-6), 9.20 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 121.86 (d, $^2J_{C,F}$ = 38.9 Hz), 123.89, 124.24 (dd, $^3J_{C,F}$ = 9.4 Hz, $^3J_{C,F}$ = 4.8 Hz), 126.24, 128.27, 129.30 (d, $^4J_{C,F}$ = 3.3 Hz), 130.52, 130.67 (d, $^2J_{C,F}$ = 31.3 Hz), 131.16, 132.08 (d, $^2J_{C,F}$ = 34.0 Hz), 133.13, 138.77, 141.26, 156.13, 157.62, 158.47 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 98.85 (s, CF_3), 102.30 (s, CF_3) ppm. GC t_R 20.64 min; MS m/z (rel intensity): 374 (M^+, 100). Anal. Calcd for $C_{16}H_8F_6N_2S$ (374.31): C 51.34, H 2.15, N, 7.48. Found: C 51.18; H, 2.35; N, 7.32.

4.3.11. 5-(3,5-Bis-trifluoromethylphenyl)-4-(thien-2-yl)pyrimidine ***(6k)***.

It has been obtained by the reaction of 5-bromo-4-(thien-2-yl)pyrimidine (**8**) with 3,5-bis(trifluoromethyl)benzeneboronic (**2k**) acid. Yield (see Table 3, entry 11), white solid; m.p. 145-147 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.85 (dd, 1H, *J* = 3.8 , 0.8 Hz, H-3''), 6.94 (dd, 1H, *J* = 5.1 , 3.8 Hz, H-4''), 7.49 (dd, 1H, *J* = 5.1, 0.8 Hz, H-5''), 7.87 (s, 2H, H-2' and H-6'), 8.03 (s, 1H, H-4'), 8.58 (s, 1H, H-6), 9.20 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 122.78 (dt, $^3J_{C,F}$ = 7.4 Hz, $^4J_{C,F}$ = 3.7 Hz), 122.91 (d, $^1J_{C,F}$ = 273.0 Hz), 128.04, 128.23, 129.74 (d, $^4J_{C,F}$ = 3.0 Hz), 130.84, 131.36, 132.78 (d, $^2J_{C,F}$ = 33.8 Hz), 138.54, 140.60, 156.42, 158.02, 158.43 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 98.82 (s, 6F, CF_3) ppm. GC t_R 20.21 min; MS m/z (rel intensity): 374 (M^+, 100). Anal. Calcd for $C_{16}H_8F_6N_2S$ (374.31): C 51.34, H 2.15, N, 7.48. Found: C 51.32; H, 1.92; N, 7.30.

4.3.12. 4-Furan-2-yl-5-phenylpyrimidine ***(7a)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with phenylboronic (**2a**) acid. Yield (see Table 3, entry 12), white solid; m.p. 64-66 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.26 (d, 1H, H-3'', *J* = 3.5 Hz), 6.35 (dd, 1H, H-4'', *J* = 3.5, 1.7 Hz), 7.33-7.35 (m, 2H, H-5''and Ph), 7.49-7.50 (m, 4H, Ph), 8.58 (s, 1H, H-6), 9.21 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): 111.99, 116.04, 128.65, 128.91, 130.77, 136.09, 144.95, 150.18, 152.36, 157.56, 158.16 ppm. GC t_R 20.53 min; MS m/z (rel intensity) 222 (M^+, 100). Anal. Calcd for $C_{14}H_{10}N_2O$ (222.25): C, 75.66; H, 4.54; N, 12.60. Found: C, 75.46; H, 4.34; N, 12.47.

4.3.13. 5-(2-Fluorophenyl)-4-(furan-2-yl)pyrimidine ***(7b)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with 2-fluorobenzeneboronic (**2b**) acid. Yield (see Table 3, entry 13), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.40 (br. s, 1H, H-3''), 6.56 (br. s, 1H, H-4''), 7.18-7.21 (br. m, 1H, H-5''), 7.28-7.32 (m, 2H, Ph), 7.46-7.49 (m, 2H, Ph), 8.60 (s, 1H, H-6), 9.22 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 112.12, 115.19, 115.92 (d, $^2J_{C,F}$ = 21.4 Hz), 123.92 (d, $^2J_{C,F}$ = 16.4 Hz), 124.44, 124.62 (d, $^4J_{C,F}$ = 3.6 Hz), 130.82 (d, $^3J_{C,F}$ = 8.0 Hz), 131.01 (d, $^4J_{C,F}$ = 2.5 Hz), 145.22, 150.66, 152.99, 157.99, 158.76, 159.93 (d, $^1J_{C,F}$ = 248.2 Hz) ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 47.44 (br. m, 1F) ppm. GC t_R 20.33 min; MS m/z (rel intensity): 240 (M^+, 100). Anal. Calcd for $C_{14}H_9FN_2O$ (240.24): C 70.00, H 3.78, N, 11.66. Found: C 70.18; H, 3.67; N, 11.45.

4.3.14. 5-(2-Fluorophenyl)-4-(furan-2-yl)pyrimidine ***(7c)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with 3-fluorobenzeneboronic (**2b**) acid. Yield (see Table 3, entry 14), yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.60 (dd, 1H, *J* = 3.5, 1.7 Hz, H-4''), 6.74 (dd, 1H, *J* = 3.5, 0.9 Hz, H-3''), 7.24 (d, 1H, *J* = 7.7 Hz, Ph), 7.29-7.37 (m, 2H, Ph), 7.53-7.57 (m, 1H, Ph), 7.77 (dd, 1H, *J* = 1.7, 0.9 Hz, H-5''), 8.71 (s, 1H, H-6), 9.19 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 112.29, 115.20 (d, $^2J_{C,F}$ = 20.9 Hz), 115.35, 115.98 (d, $^2J_{C,F}$ = 22.2 Hz), 125.27 (d, $^4J_{C,F}$ = 2.6 Hz), 128.76 (d, $^4J_{C,F}$ = 1.8 Hz), 130.54 (d, $^3J_{C,F}$ = 8.5 Hz), 138.26 (d, $^3J_{C,F}$ = 8.3 Hz), 145.96, 150.37, 151.38, 157.39, 158.42, 162.05 (d, $^1J_{C,F}$ = 244.3 Hz) ppm. ^{19}F NMR (470.5 MHz, DMSO-d_6) 49.70 (td, 1F, *J* = 9.4, 6.3 Hz) ppm. GC t_R 20.26 min; MS m/z (rel intensity): 240 (M^+, 100). Anal. Calcd for $C_{14}H_9FN_2O$ (240.24): C 70.00, H 3.78, N, 11.66. Found: C 69.88; H, 3.64; N, 11.46.

4.3.15. 5-(4-Fluorophenyl)-4-(furan-2-yl)pyrimidine ***(7d)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with 4-fluorobenzeneboronic (**2c**) acid. Yield (see Table 3, entry 15), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.35-6.42 (m, 2H, H-3'' and H-4''), 7.16-7.22 (m, 2H, H-5'' and Ph), 7.29-7.35 (m, 2H, Ph), 7.47-7.50 (m, 1H, Ph), 8.57 (s, H, H-4), 9.20 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 112.06, 115.94 (d, $^4J_{C,F}$ = 3.3 Hz), 129.74, 130.80 (d, $^3J_{C,F}$ = 8.2 Hz), 132.08 (d, $^4J_{C,F}$ = 3.4 Hz), 145.10, 150.29, 152.47, 157.69, 158.32, 161.99, 163.97 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 49.02 (tt, 1F, *J* = 8.6, 5.3 Hz) ppm. GC t_R 20.41 min; MS m/z (rel intensity): 240 (M^+, 100). Anal. Calcd for $C_{14}H_9FN_2O$ (240.24): C 70.00, H 3.78, N, 11.66. Found: C 70.05; H, 3.68; N, 11.68.

4.3.16. 5-(2,4-Difluorophenyl)-4-(furan-2-yl)pyrimidine ***(7e)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with 2,4-difluorobenzenboronic (**2e**) acid. Yield (see Table 3, entry 16), beige solid; m.p. 83-85 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.44 (dd, 1H, *J* = 3.5, 1.7 Hz, H-4''), 6.72 (d, 1H, *J* = 3.5 Hz, H-3''), 6.96 (td, 1H, *J* = 9.2, 2.5 Hz, H-6'), 7.04 (td, 1H, *J* = 8.0, 1.7 Hz, H-5'), 7.30 (td, 1H, *J* = 8.4, 1.7 Hz, H-5'), 7.45 (d, 1H, *J* = 1.0 Hz, H-4''), 8.58 (s, 1H, H-6), 9.21 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 104.45 (t, $^2J_{C,F}$ = 25.5 Hz), 111.91 (dd, $^2J_{C,F}$ = 21.4 Hz, $^4J_{C,F}$ = 3.8 Hz), 112.19, 115.21, 120.14 (dd, $^2J_{C,F}$ = 16.6 Hz, $^3J_{C,F}$ = 4.0 Hz),

123.51, 131.83 (dd, $^2J_{C,F}$ = 9.6 Hz, $^4J_{C,F}$ = 4.3 Hz), 145.37, 150.83, 153.12, 158.13, 158.96, 160.25 (dd, $^1J_{C,F}$ = 250.8 Hz, $^2J_{C,F}$ = 12.1 Hz), 163.43 (dd, $^1J_{C,F}$ = 251.2 Hz, $^2J_{C,F}$ = 11.6 Hz) ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 52.06 (q, 1F, *J* = 8.8 Hz), 53.45 (qd, 1F, *J* = 8.2, 6.4 Hz) ppm. GC t_R 19.83 min; MS m/z (rel intensity): 258 (M^+, 100). Anal. Calcd for $C_{14}H_8F_2N_2O$ (258.23): C 65.12, H 3.12, N, 10.85. Found: C 65.00; H, 3.01; N, 10.65.

4.3.17. 5-(3,5-Difluorophenyl)-4-(furan-2-yl)pyrimidine ***(7f)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with 3,5-difluorobenzenboronic (**2f**) acid. Yield (see Table 3, entry 17), white solid; m.p. 92-93 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.62 (dd, 1H, *J* = 3.5, 1.7 Hz, H-4''), 6.89 (d, 1H, *J* = 3.5 Hz, H-3''), 7.19-7.25 (m, 2H, Ph), 7.38 (tt, 1H, *J* = 9.5, 2.3 Hz, H-4'), 7.79 (d, 1H, *J* = 1.0 Hz, H-5''), 8.72 (s, 1H, H-6), 9.19 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 103.84 (t, $^2J_{C,F}$ = 25.8 Hz), 112.43, 112.70 (dd, $^2J_{C,F}$ = 20.0 Hz, $^3J_{C,F}$ = 6.3 Hz), 115.49, 127.81, 139.56 (t, $^2J_{C,F}$ = 10.5 Hz), 146.24, 150.32, 151.29, 157.65, 158.44, 162.22 (dd, $^1J_{C,F}$ = 246.6 Hz, $^2J_{C,F}$ = 13.6 Hz) ppm. ^{19}F NMR (470.5 MHz, DMSO-d_6) 52.90-52.97 (m, 2F) ppm. GC t_R 19.56 min; MS m/z (rel intensity): 258 (M^+, 100). Anal. Calcd for $C_{14}H_8F_2N_2O$ (258.23): C 65.12, H 3.12, N, 10.85. Found: C 64.94; H, 2.94; N, 10.72.

4.3.18. 4-Furan-2-yl-5-(2-trifluorometylphenyl)pyrimidine ***(7g)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with 2-(trifluoromethyl)benzeneboronic (**2g**) acid. Yield (see Table 3, entry 18), beige solid; m.p. 77-79 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.26 (dd, 1H, *J* = 3.5, 0.5 Hz, H-3''), 6.34 (dd, 1H, *J* = 3.5, 1.7 Hz, H-4''), 7.32 (d, 1H, *J* = 6.9 Hz, H-6'), 7.40 (dd, 1H, *J* = 1.7, 0.5 Hz, H-5''), 7.65 (m, 2H, H-4' and H-5'), 7.84-7.89 (m, 1H, H-3'), 8.55 (s, 1H, H-6), 9.23 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 112.05, 115.69, 123.62 (d, $^1J_{C,F}$ = 274.0 Hz), 126.55 (q, $^3J_{C,F}$ = 5.0 Hz), 127.33, 128.90, 129.26 (q, $^2J_{C,F}$ = 30.3 Hz), 131.68, 132.07, 134.68 (d, $^4J_{C,F}$ = 2.0 Hz), 145.24, 150.48, 152.46, 157.91 (d, $^4J_{C,F}$ = 1.5 Hz), 158.14 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 102.65 (s, CF_3) ppm. GC t_R 19.74 min; MS m/z (rel intensity): 290 (M^+, 100). Anal. Calcd for $C_{15}H_9F_3N_2O$ (290.25): C 62.07, H 3.13, N, 9.65. Found: C 62.23; H, 3.23; N, 9.60.

4.3.19. 4-Furan-2-yl-5-(3-trifluorometylphenyl)pyrimidine ***(7h)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with 3-(trifluoromethyl)benzeneboronic (**2h**) acid. Yield (see Table 3, entry 19), pale yellow solid; m.p. 67-67 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.61 (dd, 1H, *J* = 3.2, 1.5 Hz, H-4''), 6.82 (d, 1H, *J* = 3.2 Hz, H-3''), 7.73-7.86 (m, 4H, H-5'' and Ph), 7.85 (d, 1H, *J* = 7.3 Hz, Ph), 8.75 (s, 1H, H-6), 9.21(s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 112.38, 115.29, 124.03 (d, $^1J_{C,F}$ = 272.4 Hz), 124.99 (dd, $^3J_{C,F}$ = 7.2 Hz, $^4J_{C,F}$ = 3.5 Hz), 125.79 (q, $^3J_{C,F}$ = 3.7 Hz), 128.45, 129.27 (q, $^2J_{C,F}$ = 32.0 Hz), 129.55, 133.27, 137.04, 146.04, 150.56, 151.42, 157.53, 158.74 ppm. ^{19}F NMR (470.5 MHz, DMSO-d_6) 101.51 (s, CF_3) ppm. GC t_R 19.82 min; MS m/z (rel intensity): 290 (M^+, 100). Anal. Calcd for $C_{15}H_9F_3N_2O$ (290.25): C 62.07, H 3.13, N, 9.65. Found: C 62.05; H, 3.27; N, 9.81.

4.3.20. 4- Furan-2-yl-5-(4-trifluorometylphenyl)pyrimidine ***(7i)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with 4-(trifluoromethyl)benzeneboronic (**2f**) acid. Yield (see Table 3, entry 20), white solid; m.p. 100-102 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.42 (dd, 1H, *J* = 3.5, 1.7 Hz, H-4''), 6.56 (dd, 1H, *J* = 3.5 Hz, H-3''), 7.46 (dd, 1H, *J* = 1.7, 0.8 Hz, H-5''), 7.48 (d, 2H, *J* = 8.0 Hz, H-2' and H-6'), 7.76 (d, 2H, *J* = 8.0 Hz, H-3' and H-5'), 8.58 (s, 1H, H-6), 9.22 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): 112.18, 116.00, 123.94 (d, $^1J_{C,F}$ = 272.4 Hz), 125.73 (q, $^4J_{C,F}$ = 3.7 Hz), 129.24, 129.51, 130.80 (q, $^2J_{C,F}$ = 32.8 Hz), 139.98, 145.34, 150.33, 152.19, 158.00, 158.21 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 99.13 (s, CF_3) ppm. GC t_R 20.07 min; MS m/z (rel intensity): 290 (M^+, 100). Anal. Calcd for $C_{15}H_9F_3N_2O$ (290.25): C 62.07, H 3.13, N, 9.65. Found: C 62.20; H, 3.28; N, 9.54.

4.3.21. 5-(2,4-Bis-trifluoromethylphenyl)-4-(furan-2-yl)pyrimidine ***(7j)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with 2,4-bis(trifluoromethyl)benzeneboronic (**2j**) acid. Yield (see Table 3, entry 21), beige solid; m.p. 102-105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.42 (dd, 1H, *J* = 3.5, 1.7 Hz, H-4''), 6.74 (dd, 1H, *J* = 3.5 Hz, H-3''), 7.32 (dd, 1H, *J* = 1.0 Hz, H-5''), 7.49 (d, 1H, *J* = 8.0 Hz, H-6'), 7.92 (d, 1H, *J* = 8.0 Hz, H-5'), 8.11 (s, 1H, H-3'), 8.53 (s, 1H, H-6), 9.24 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 112.22, 115.73, 121.96 (d, $^2J_{C,F}$ = 37.2 Hz), 124.14 (d, $^2J_{C,F}$ = 35.4 Hz), 123.65 (dd, $^3J_{C,F}$ = 8.6 Hz, $^3J_{C,F}$ = 4.5 Hz), 125.74, 128.66, 130.33 (d, $^2J_{C,F}$ = 31.2 Hz), 131.45 (d, $^2J_{C,F}$ = 33.8 Hz), 132.69, 138.89, 145.69, 150.78, 152.20, 157.75, 158.53 ppm. ^{19}F NMR (470.5 MHz, $CDCl_3$) 98.89 (s, CF_3), 102.33 (s, CF_3) ppm. GC t_R 18.40 min; MS m/z (rel intensity): 358 (M^+, 100). Anal. Calcd for $C_{16}H_8F_6N_2O$ (358.25): C 53.64, H 2.25, N, 7.82. Found: C 53.60; H, 2.22; N, 7.75.

4.3.22. 5-(3,5-Bis-trifluoromethylphenyl)-4-(furan-2-yl)pyrimidine ***(7k)***.

It has been obtained by the reaction of 5-bromo-4-(furan-2-yl)pyrimidine (**9**) with 3,5-bis(trifluoromethyl)benzeneboronic (**2k**) acid. Yield (see Table 3, entry 22), white solid; m.p. 102-104 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.64 (dd, 1H, *J* = 3.5, 1.7 Hz, H-4''), 7.06 (dd, 1H, *J* = 3.5, 0.7 Hz, H-3''), 7.69 (dd, 1H, *J* = 1.7, 0.7 Hz, H-5''), 8.19 (s, 2H, H-2' and H-6'), 8.22 (s, 1H, H-4'), 8.83 (s, 1H, H-6), 9.23 (s, 1H, H-2) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 112.51, 115.43, 121.86 (dt, $^3J_{C,F}$ = 7.6 Hz, $^4J_{C,F}$ = 3.8 Hz), 123.23 (d, $^1J_{C,F}$ = 272.9 Hz), 126.89, 129.82-130.61 (m), 138.73, 146.23, 150.72, 151.38, 157.86, 159.04 ppm. ^{19}F NMR (470.5 MHz, DMSO-d_6) 101.38 (s, 6F, CF_3) ppm. GC t_R 18.31 min; MS m/z (rel intensity): 358 (M^+, 100). Anal. Calcd for $C_{16}H_8F_6N_2O$ (358.25): C 53.64, H 2.25, N, 7.82. Found: C 53.51; H, 2.39; N, 7.74.

4.4. General S_N^H-procedure for the synthesis of 5-(fluoroaryl)-4-(hetero)-arylpyrimidines ***6d,i,j*** *and* ***7 d,i,j***.

Thiophene **(4)** (160 μL, 2.0 mmol) [or furan **(5)** (145 μL, 2.0 mmol)] was added to a solution of corresponding 5-(fluoroaryl)pyrimidine **3d** [**3i** or **3j**] (1.0 mmol) in CF_3COOH (5 mL). The reaction mixture was stirred at room temperature for 24 h and the solvents evaporated. A solution of KOH (224 mg, 4.0 mmol, 4 equiv.) and $K_3[Fe(CN)_6]$ (658 mg, 2.0 mmol, 2 equiv.) in water (10 mL) was added to the residue. The resulting mixture was stirred for 24 h at room temperature; the semisolid formed was filtered off, washed with H_2O and air dried. The semisolid was extracted with EtOAc and the organic solution was concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 1:2) to afford the desired S_N^H-products **(6d,i,j** or **7d,i,j)**.

4.5. Antimycobacterial assay.

To evaluate the inhibitory efficiency of molecules on Mycobacterium tuberculosis (MTB), *M. tuberculosis H$_{37}$Rv*,

which is susceptible to all classical antituberculosis drugs, was used. The minimal inhibitory concentration (MIC) for *M. tuberculosis* $H_{37}Rv$ for each compound was determined by a micro broth dilution method. All molecules tested were dissolved in dimethylsulfoxide and their 1/2 dilutions were prepared in 5 mL tubes using Löwenstein-Jensen medium. A few colonies from freshly grown *M. tuberculosis* $H_{37}Rv$ were suspended in Löwenstein-Jensen medium to obtain 1.0 McFarland turbidity and diluted ten times using the same medium and the tubes were incubated at 37 °C medium with a different concentration of the tested molecule and to a positive control tube containing only clear growth medium. After 24 hours the tubes were placed in a vertical position and the free edge of the buried 0.3 mL of the substance in the test compounds concentrations: 12.5, 6.2, 3.1, 1.5, 0.7, 0.37, 0.15 μg/mL. The tubes were then placed in an thermostat at a temperature of 37 °C and incubated for 10 days. Growth estimate for the MTB were determined by standard methods, where the appearance of zones of growth retardation MTB (over 10 mm) indicated the presence of tuberculostatic properties in concentration of the compounds under study. Penetration size stunting MTB (in mm) is proportional to the degree of tuberculostatic activity. Growth delay of 100 mm or more is considered as a complete growth inhibition MTB. The multi-drug-resistant (MDR) tuberculosis strain have been isolated from tuberculosis patients in Ural Research Institute for Phthisiopulmonology (Russia). The minimal inhibitory concentrations against *M. avium*, *M. terrae*, and MDR tuberculosis strains were evaluated similarly.

4.6. Evaluation of acute toxicity in vivo.

All experimental protocols were carried out in accordance with the standard protocol approved by the Committee of the Ethical Use of Animals of the Ural Research Institute for Phthisiopulmonology (CEUA/URIP). The synthesized compounds were evaluated for their approximate LD50 in white healthy mice (17 - 20 g body weight) divided into 3 groups of 5 animals each for testing of each compound [37,38]. Toxicity tests were carried out via a single peroral administration of compound in a 1% starch aqueous solution. The volume introduced did not exceed 0.5 mL for mice. The observation period was 14 days. The median lethal doses LD_{50} were used as the criteria of toxicity.

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Supplementary Material

Supplementary material (^{1}H, ^{19}F and ^{13}C NMR spectra of the new compounds) associated with this article can be found, in the online version.

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Synthesis and evaluation of antitubercular activity of fluorinated 5-aryl-4-(hetero)aryl substituted pyrimidines

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