Reactivity of Hydroxy and Amino Derivatives of 2-Phenyl-1*H*-imidazoline and 2-Phenyl-1*H*-imidazole toward Isocyanates: Synthesis of Appropriate Carbamates and Ureas

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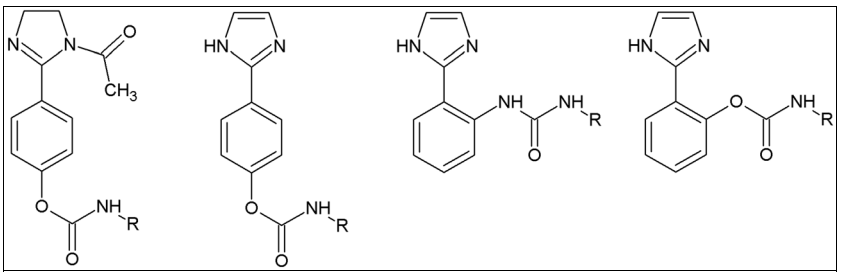

Reactivity of 2-(4-hydroxyphenyl)-1*H*-imidazoline and 2-(4-hydroxyphenyl)-1*H*-imidazole toward substituted phenyl isocyanates was studied. When mentioned imidazoline was treated with 2.5 equiv of substituted phenyl isocyanate, three *N*,*O*-dicarboxamides were prepared (substituents are H, 4-NO_2, and 4-CH_3). Subsequently, *N*,*O*-diacetylated 2-(4-hydroxyphenyl)-1*H*-imidazoline was prepared and selective deprotection method was developed for preparation of 1-acetyl-2-(4-hydroxyphenyl)-1*H*-imidazoline using diethylamine in acetone. Six carbamates derived from this imidazoline were then prepared using 1.1 equiv of substituted phenyl isocyanates (substituents are H, 4-CH_3, 4-OCH_3, 4-NO_2, 4-CN, and 3-CF_3). Finally, two carbamates were prepared from 2-(4-hydroxyphenyl)-1*H*-imidazole (substituents are 4-NO_2 and 4-CN). No reactivity to imidazole ring was observed in this case. Eight derivatives were subjected to antimycobacterial screening. Concurrently, reactivity of 2-(2-aminophenyl)- and 2-(2-hydroxyphenyl)-1*H*-imidazole toward aliphatic and aromatic isocyanates was studied. Eight ureas were prepared using equivalent mixture of 2-(2-aminophenyl)-1*H*-imidazole and isocyanate (Et, Pr, isoPr, terc-Bu, Cy, Ph, 4-$CH_3C_6H_4$, 4-CNC_6H_4). Similar attempts to obtain related carbamates from 2-(2-hydroxyphenyl)-1*H*-imidazole lead only to three substituted phenyl carbamates (substituents are 4-CH_3, 4-NO_2, and 4-CN). In both cases, no reactivity to imidazole ring was observed again.

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INTRODUCTION

Imidazoline and imidazole derivatives play important role in biological processes. They have substantial biological activity and its structural motive makes a part of many types of medical drugs [1, 2]. Nowadays, new compounds are developed in which imidazole or imidazoline derivatives acts as a chiral ligands for enantioselective catalysis [3–6]. In addition, carbamates are fundamental fragments of many polymers, pesticides, and drugs, and are tested as acetylcholinesterase inhibitors [7]. Derivatives based on ureas as the next derivatives of carbonic acid are usually used as agrochemicals, pharmaceuticals, or in petrochemical industry. Such compounds are also utilized as additives to fuels, detergents, polymers, inhibitors of corrosion, or as hair colors. Modern trend in catalysis is searching and testing of urea and thiourea-based derivatives as organocatalysts [8].

Recently, we have studied some synthetic possibilities leading to derivatives based on 2-(2-hydroxyphenyl)-1*H*-imidazoline and 2-(2-hydroxyphenyl)-1*H*-imidazole skeleton [9]. Now, we have also focused on related 2-amino and 4-hydroxy analogs. 2-(4-Hydroxyphenyl)-1*H*-imidazoline and 2-(4-hydroxyphenyl)-1*H*-imidazole have been prepared by Roger and Bruice [10], for example, but their carbamates have not been described in the literature yet. Also, carbamates derived from 2-(2-hydroxyphenyl)-1*H*-imidazole have not been described yet. On the other hand, wide group of ureas based on 2-(4-aminophenyl)-1*H*-imidazoline was synthesized and tested as chemotherapeutics [11, 12]; however,

no ureas derived from 2-(2-aminophenyl)-1*H*-imidazole were developed yet. Reactions of some 2-substituted imidazolines with phenyl isocyanate and isothiocyanate have been studied, corresponding ureas and thioureas have been prepared [13]. Kinetic (reversible N-substitution) and thermodynamic (irreversible C2-substitution) control have been observed in the case of reaction of imidazole with isocyanates [14]. Mentioned 2-(4-hydroxyphenyl)-1*H*-imidazole motive also includes Hoechst 33258 entity, which exhibits antitumor activity. Carbamate derivatives of Hoechst 33258 have been prepared as potential anticancer agents [15].

In this study, we have investigated reactivity of 2-(4-hydroxyphenyl)-1*H*-imidazoline, 2-(4-hydroxy-phenyl)-1*H*-imidazole, 2-(2-hydroxyphenyl)-1*H*-imidazole, and 2-(2-amino-phenyl)-1*H*-imidazole toward different isocyanates, leading to new group of species bearing imidazoline or imidazole ring together with carbamate or urea group. Low selectivity of carbamoylation was observed in the case of mentioned imidazoline, so we have studied methods for selective imidazoline *N*-protection.

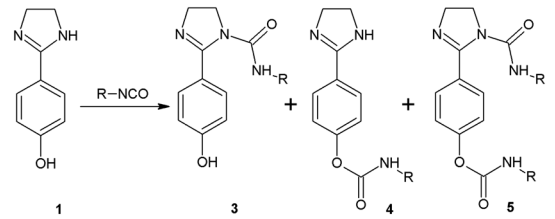
In addition to the synthetic study, compounds **9a–f** and starting imidazolines **1** and **8** were subjected to antimycobacterial screening. Compounds were evaluated *in vitro* against *Mycobacterium tuberculosis* and nontuberculous mycobacterial strains (*M. avium* and *M. kansasii)*. The aim of this study was find out a new scaffold of antimycobacterially active compunds.

RESULTS AND DISCUSSION

***para*-Analogs.** 2-(4-Hydroxyphenyl)-1*H*-imidazoline **1** was prepared from methyl 4-hydroxybenzoate and ethane-1,2-diamine (three times excess) by modification of literature procedure [10] in 78% yield. For transformation of **1** to 2-(4-hydroxyphenyl)-1*H*-imidazole **2**, we have used dehydrogenation by means of Pd/C. Because of low solubility of **1** in nonpolar solvents, we succesfully used *n*-BuOH for this dehydrogenation instead of toluene [9] or DMSO [16], which were previously used. Oxidative reagents we did not tested with regard to our previous experience [9] concerned oxidative aromatization of 2-hydroxy analog in which use of oxidation agents caused formation of quinones, for example, the use of Fremy's salt [17].

We studied the reactivity of some aromatic isocyanates toward **1**. When 1.05 equiv of isocyanate in acetone was used, products **3** of *N*- (72–85%), **4** of *O*- (12–28%), eventually **5** of *N*,*O*-dicarbamoylation (0–12%) were detected by 1H-NMR (Scheme 1). Constitution of reaction mixture depends on substitution of aromatic isocyanate. Products were not separated. Scheme 1 summarizes respective amount of individual products estimated by 1H-NMR measurements realized immediately after sample preparation.

Scheme 1. Reaction of 2-(4-hydroxyphenyl)-1*H*-imidazoline **1** with 1.05 equiv of substituted phenyl isocyanates.



Generally, *N*-substitution of imidazoline ring was easily recognized, because two triplets of imidazoline methylene groups appeared due to blocking of imidazoline tautomerism.

Respective amount of individual products estimated by 1H-NMR is: when R = 4-$NO_2C_6H_4$ ratio of **3**, **4**, and **5** is 76, 12, and 12%; when R = 4-CNC_6H_4 ratio is 72, 28, 0%; when R = 4-$CH_3OC_4H_6$ ratio is 85, 15, and 0%.

This result correspond with higher nucleofilicity of nitrogen, but it is interesting when compared to alkylation of 2-(2-hydroxyphenyl)-1*H*-imidazoline in which no *N*-alkylation was observed [9, 18]. Reaction of related 2-phenyl-1*H*-imidazoline with phenyl isocyanate was presented in literature [13]. Finally, when 2.5 equiv of isocyanate in refluxing acetone was used, pure *N*,*O*-dicarboxamides **5a–c** were obtained in 56–88% yield.

Products of type **3**, **4**, and **5** depicted in Scheme 1 were unstable in DMSO-d_6, probably due to known basicity/nucleophilicity of imidazoline and/or presence of water in DMSO-d_6. NMR spectra were recorded promptly after mixing the sample. Decomposition was studied by 1H-NMR in case of **5c** (Scheme 2).

Decomposition products were starting imidazoline **1** and corresponding aniline **6**, eventually corresponding urea **3** as intermediate. Decomposition of carbamate group was faster than urea (Table 1), carbamate **4** was not observed during this experiment. After 24 h staying in DMSO-d_6, only imidazoline **1** and corresponding aniline **6** was observed in reaction mixture in case of decomposition of **5a–c**.

As the reactivity of **1** toward isocyanates is in favor of *N*-carbamoylation, we have tried to realize selective *N*-protection of **1**. *N*-Protective methods are summarized in

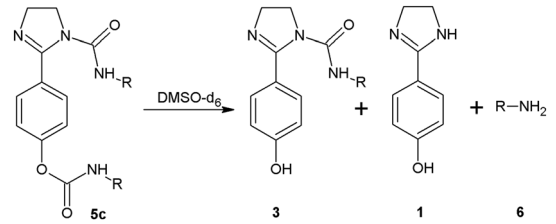
Table 1

Decomposition of 4-{1-[(4-nitrophenyl)carbamoyl]-1*H*-imidazoline-2-yl} phenyl *N*-(4-nitrophenyl)carbamate **5c**: time-dependent composition of its DMSO-d_6 solution (detected by 1H-NMR).

Time[a] (min)	**5c** (%)	**3** (%)	**1** (%)	**6** (%)
3	90	5	0	5
10	80	10	0	10
180	0	46	13	41

[a]Time after mixing the sample.

Scheme 2. Decomposition of 4-{1-[(4-Nitrophenyl)carbamoyl]-1*H*-imidazoline-2-yl}phenyl *N*-(4-nitrophenyl)carbamate **5c** (R = 4-$NO_2C_6H_4$) in DMSO-d_6 (1H-NMR experiment).



Scheme 3. First, the hydrochloride of **1** was synthesized [19]. Unfortunately, the hydroxy group of this compound was probably too deactivated to react with all isocyanates. Only 4-nitrophenyl and 4-cyanophenyl isocyanate react with this hydrochloride with 100% selectivity toward hydroxy group. Decomposition of these imidazoline hydrochloride carbamates in DMSO-d_6 was also observed, failing the hypothesis of base induced decomposition. Unfortunately, these products were not obtained in quite pure form.

Reductive methylation of **1** with formaldehyde [20] was 100% *N*-selective (observed by 1H-NMR) but not complete. Attempts to isolate pure 1-methyl-2-(4-hydroxyphenyl)-1*H*-imidazoline by recrystallization or column chromatography failed.

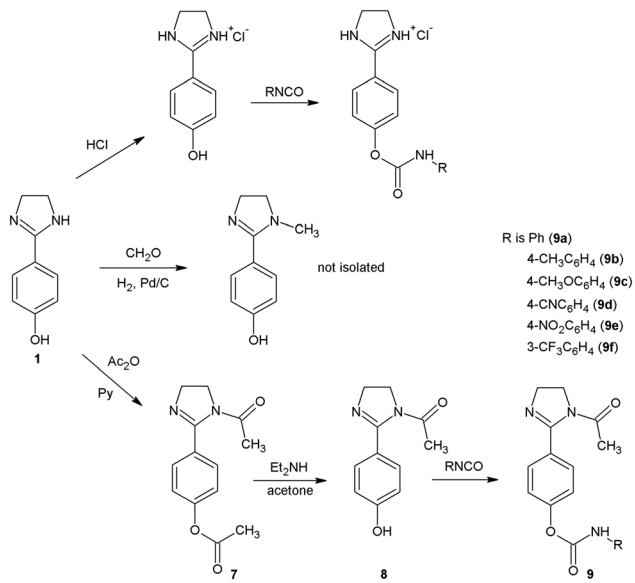
Acetylation of **1** with acetanhydride in pyridine proceed well and even when 1.5 equiv of acetanhydride was used, only *N,O*-diacetyl derivate **7** was isolated. Therefore, this reaction was conducted to yield this product and try its selective *O*-deprotection. Many reagents were tested for this reaction. Products obtained by reaction of **7** with ammonia or ethylamine miscarried to be identified. When methanolysis with basic reagents was tested (NaOH, K_2CO_3, $NaHCO_3$, Et_3N, Et_2NH), pure *N,O*-deacetylation product **1** was observed. Finally, when diacetyl derivate **7** was refluxed with the excess of diethylamine in acetone, pure *N*-acetylderivate **8** was obtained in 79% yield. This reaction probably proceeds as aminolysis in comparison with methanolysis reaction, when diethylamine was used in methanol and both acetyl groups were cleaved.

Six carbamates **9a–f** were obtained by reaction of **8** with substituted phenyl isocyanates in 67–83% yield. These products were soluble and fully stable in $CDCl_3$. Stability of **9f** in DMSO was checked for the reason of its interesting antimycobacterial activity. NMR measurements realized immediately, 7 days, and 36 days after mixing the sample in DMSO-d_6 confirmed its stability.

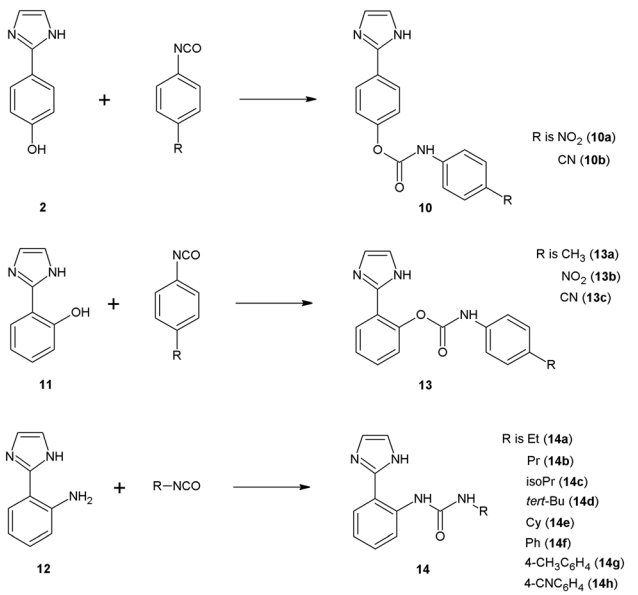
When the imidazole **2** reacted with substituted phenyl isocyanates (Scheme 4), no *N*-carbamoylation was observed. Formation of urea from 2-phenylimidazole was reported as reversible reaction [14, 21]. Two carbamates **10a–b** were obtained by reaction of **2** with 1.2 equiv of 4-nitro or 4-cyanophenyl isocyanate in dichloromethane in very good yields. These products are also unstable in DMSO-d_6, products of hydrolysis were detected. Presence of strong electron-withdrawing substituent is probably crucial because differently substituted phenyl isocyanates were also tested but without success. Heterogeneous realization of the reaction can be also limitative.

Generally, tested reactions of **1** and **2** with aliphatic isocyanates and sulfonylisocyanates afforded no carbamates.

Scheme 3. Synthesis of *N*-protected carbamates derived from 2-(4-hydroxyphenyl)-1*H*-imidazoline **1**.



Scheme 4. Synthesis of carbamates and ureas from 2-(4-hydroxyphenyl)-1*H*-imidazole **2**, 2-(2-hydroxyphenyl)-1*H*-imidazole **11** and 2-(2-aminophenyl)-1*H*-imidazole **12**.



Attempts to analyze all prepared carbamates **9a–f** and **10a–b** using GC-MS technique failed because of decomposition of derivatives during analyses.

***ortho*-Analogs.** Starting 2-(2-hydroxyphenyl)-1*H*-imidazole **11** was already used as main substrate in our previous article, this derivative was prepared using procedure described in prior work [9]. Second starting material for *ortho*-analogs, 2-(2-aminophenyl)-1*H*-imidazole **12**, was synthesized using small modifications of literature procedure. 2-Nitrobenzaldehyde reacted with glyoxal trimer dihydrate (instead of 30% aqueous glyoxal solution used in [22]) in glacial acetic acid as a solvent in the presence of ammonium acetate to afford 2-(2-nitrophenyl)-1*H*-imidazole. The yield of 19% is quite low but better than previous reported (7.6%) [22]. This nitro derivative was hydrogenated overnight at pressure 40 bar (instead of atmospheric pressure applied in [22]) using Pd/C (10%) as catalyst, product **12** was prepared in 91% yield.

Reactions of 2-(2-hydroxyphenyl)-1*H*-imidazole **11** with nine various aliphatic and aromatic isocyanates (aliphatic are Et, Pr, isoPr, *tert*-Bu, Cy; aromatic are Ph, 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 4-CNC_6H_4) were tested (Scheme 4). Syntheses were realized using equimolar mixture of starting compounds in toluene, which appeared as convenient solvent. Only three target carbamates **13a–c** were prepared in moderate to good yields using substituted phenyl isocyanates (substituents are 4-CH_3, 4-NO_2, and 4-CN). Miscarriages in the cases of using aliphatic isocyanates can be caused by their lower reactivity coming from electron-donating inductive effect of aliphatic moiety. Surprisingly, no carbamate was obtained using phenyl isocyanate, and desired product was never detected in the reaction mixture.

Reactions of 2-(2-aminophenyl)-1*H*-imidazole **12** with eight same aliphatic and aromatic isocyanates (except 4-$NO_2C_6H_4$) were realized without problems (Scheme 4). Acetonitrile was found as suitable solvent, equimolar mixture of starting compounds was used and all new target ureas **14a–h** were obtained in poorer yields but very good purity, which required no further purification. 4-Nitrophenyl isocyanate and 3,5-bis(trifluoromethyl) phenyl isocyanate were also tested, appropriate ureas were succesfully prepared and described in our previous article concerned in their testing in homogeneous and heterogeneous catalysis [23].

No *N*-carbamoylated imidazole derivatives were isolated or detected as products of reactions of hydroxy derivative **11** or amino derivative **12** with isocyanates analogously to reactions of 2-(4-hydroxyphenyl)-1*H*-imidazole **2** with isocyanates. It is in great contrast to reactivity of imidazoline ring in 2-(4-hydroxyphenyl)-1*H*-imidazoline **1** in which isocyanate attacks imidazoline N atom together with hydroxy O atom very readily.

Attempts to analyze all prepared carbamates **13a–c** and ureas **14a–h** using GC-MS technique failed because of decomposition of derivatives during analyses. Furthermore, no carbamates **13a–c** were analyzed applying NMR technique, because these carbamates are unstable in all tested solvents (DMSO-d_6, $CDCl_3$, CD_3CN, CD_3OD, and toluene-d_8) in which hydrolysis was observed. Proton numbering for assignment of ^{1}H-NMR shifts of ureas **14a–h** is stated in Scheme 5.

Antimycobacterial activity. The newly prepared derivatives **9a–f** were tested for antimycobacterial activity against four mycobacterial strains. The minimum inhibitory concentrations (MICs) given in μmol/L are summarized in Table 2. As reference the starting molecules **1** and **8**, and isoniazide (INH) were included in the assay.

As seen from the data of Table 2, 4-(1-Acetyl-1*H*-imidazoline-2-yl)phenyl *N*-(3-trifluoro-methylphenyl) carbamate **9f** exhibited very interesting activity, especially against *M. tuberculosis* and *M. kansasii*. The derivative **9f** differs from the others carbamates **9** in phenylcarbamate moiety, where phenyl is substituted in the position meta. This steric change of molecule can play significant role in the biological activity.

Because many low-molecular weight drugs cross biological membranes through passive transport, which strongly depends on their lipophilicity, we calculated the lipophilicity parameters values (log P) for evaluated compounds. Log *P* of the compounds **1**, **8**, and **9** were calculated using the commercially available program ChemBioDraw. Compound **9f** exhibited the highest lipofilicity from all tested compounds.

CONCLUSIONS

Reactivity of 2-(4-hydroxyphenyl)-1*H*-imidazoline and corresponding imidazole towards substituted phenyl isocyanates was studied. By using of 1.05 equiv of isocyanate the mixture of three products of *N*-, and *O*-carbamoylation, and *N*,*O*-dicarbamoylation was obtained. When 2.5 equiv of

Scheme 5. Proton numbering for assignment of ^{1}H-NMR shifts of 1-alkyl- and 1-substituted aryl-3-[2-(1*H*-imidazol-2-yl)phenyl]ureas **14a–h**.

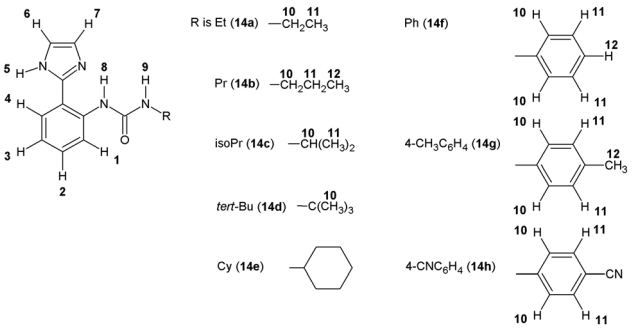


Table 2

Antimycobacterial activities expressed as MIC (μmol/L).

Compounds	Strains				log*P*
	Mycobacterium tuberculosis My 331/88	*Mycobacterium kansasii* My 235/80	*Mycobacterium kansasii* 6509/96	*Mycobacterium avium* My 330/88	
	14 d/21 d	7 d/14 d/21 d	7 d/14 d/21 d	14 d/21 d	
1	>1000/>1000	500/>1000/>1000	125/500/1000	1000/>1000	1.3
8	>1000/>1000	500/>1000/>1000	250/1000/1000	1000/>1000	0.95
9a	>1000/>1000	1000/>1000/>1000	500/500/1000	500/1000	2.49
9b	1000/n.d.	n.d./n.d./n.d.	500/n.d./n.d.	n.d./n.d.	2.98
9c	n.d./n.d.	n.d./n.d./n.d.	n.d./n.d./n.d.	n.d./n.d.	2.37
9d	>1000/>1000	1000/>1000/>1000	500/500/>1000	>1000/>1000	2.53
9e	250/500	250/1000/1000	125/500/1000	500/1000	2.08
9f	2/2	4/8/8	4/4/4	>250/>250	3.42
INH	0.5/1.0	>250/>250/>250	4/8/8	>250/>250	–

n.d., not determined (due to the limited solubility of the compounds in the test medium).

isocyanate was used three pure *N*,*O*-dicarboxamides were prepared. Their decomposition in DMSO-d_6 solution during NMR measurement was observed. Sequentially, *N*,*O*-diacetylated 2-(4-hydroxyphenyl)-1*H*-imidazoline was prepared and its selective *O*-deprotection was developed for preparation of 1-acetyl-2-(4-hydroxyphenyl)-1*H*-imidazoline using diethylamine in acetone. Six carbamates derived from last imidazoline were then prepared using 1.1 equiv of substituted phenyl isocyanates as reactants. Finally, two carbamates were prepared from 2-(4-hydroxyphenyl)-1*H*-imidazole. No *N*-carbamoylation was observed during reaction of this imidazole with slight excess of isocyanate.

Concurrently, reactivity of 2-(2-aminophenyl)- and 2-(2-hydroxyphenyl)-1*H*-imidazole toward aliphatic and aromatic isocyanates was studied. In the case of amino derivative, eight ureas were prepared using equivalent amount of aliphatic or aromatic isocyanates. No carbamoylations proceed on imidazole N atom were observed. Accomplished attempts realized on reactions of 2-(2-hydroxyphenyl)-1*H*-imidazole with equivalent amount of aliphatic or aromatic isocyanates show that only three substituted phenyl isocyanates produce desired carbamates. Repeatedly, no carbamoylation to imidazole ring was observed in this case.

The preliminary antimycobacterial screening found out the significant activity of 4-(1-acetyl-1*H*-imidazoline-2-yl)phenyl *N*-(3-trifluoromethylphenyl)carbamate **9f** (MIC 2–8 μmol/L). This structure can create a new scaffold of antimycobacterially active compounds.

EXPERIMENTAL

General data. NMR spectra of model compounds were measured at 25°C on Bruker AMX 360 spectrometer at 360 MHz (^{1}H) and 90 MHz (^{13}C) or Bruker Avance 500 spectrometer at 500 MHz (^{1}H) and 125 MHz (^{13}C) using solutions in DMSO-d_6 or $CDCl_3$. Chemical shifts are relative to TMS, residual solvent signal was used as an internal standard. MS spectra were recorded on GC/MS configuration Agilent Technologies 6890N (HP-5MS, 30 m × 0.25 mm × 0.25 μm) with Network MS detector 5973 (EI = 70 eV, 33–550 Da). The mid-infrared spectra were obtained on Perkin Elmer 2000 Fourier transform infrared spectrometer in the 4000–400 cm^{-1} spectral range with a resolution of 4 cm^{-1} at room temperature using the KBr pressed disc technique. Elemental analysis was carried out using an automatic analyser EA 1108 (Fisons). Thin-layer chromatography was performed on SiO_2 60 F_{254} (Merck) with UV detection at 254 nm. Melting points were determined on Büchi B-540 apparatus.

2-(4-Hydroxyphenyl)-1*H*-imidazoline (1). The mixture of 20 g (0.13 mol) of methyl 4-hydroxybenzoate and 27 mL (0.40 mol) of ethane-1,2-diamine was stirred under reflux for 24 h. Volatile matter was removed under reduced pressure, the residue was heated for 30 min to maximum 150°C and then refluxed with 100 mL of water-ethanol (2:1) mixture for 10 min to remove unreacted *N*-(2-aminoethyl)-4-hydroxybenzamide. After cooling the product was filtered and washed with 50 mL of water-ethanol (2:1) mixture to yield white powder, 16.6 g (78 %), mp 281–285°C (290–292°C [24]), R_f = 0.1 (MeOH). ^{1}H-NMR (360 MHz, DMSO-d_6): δ 3.61 (s, 4H, CH_2CH_2), 6.76 (d, *J* = 8.0 Hz, 2H, ArH), 7.66 (d, *J* = 8.0 Hz, 2H, ArH). *Anal*. Calcd. for $C_9H_{10}N_2O$ (162.19): C, 66.65; H, 6.21; N, 17.27. Found: C, 66.70; H 6.43; N, 17.03.

***2-(4-Hydroxyphenyl)-1H*-imidazole (2).** The mixture of 1 g (6.17 mmol) of **1** and 0.5 g of 10 % Pd/C in 150 ml of *n*-BuOH was stirred at reflux under argon atmosphere for 3 days (progress was monitored by TLC). After, the hot solution was filtered and solvent was removed under reduced pressure. Column chromatography on silicagel (Silicagel 60, 0.040–0.063 mm, Merck) with MeOH as eluent provided 0.44 g (45 %) of yellow crystals, which were used for next step without further purification. Analytical sample was crystallized from MeOH, mp 270–276°C (267–270°C [25], R_f = 0.58 (MeOH). ^{1}H-NMR (360 MHz, DMSO-d_6): δ 6.87 (d, *J* = 8.4 Hz, 2H, ArH), 7.09 (s, 2H, CHCH), 7.80 (d, *J* = 8.4 Hz, 2H, ArH), 9.70–10.00 (br s, 1H, OH), 11.80-12.50 (br s, 1H, NH). *Anal*. Calcd. for $C_9H_8N_2O$ (160.17): C, 67.49; H, 5.03; N, 17.49. Found: C, 67.40; H, 5.09; N, 17.63.

***General procedure for synthesis of N,O*-dicarboxamides 5 derived from 1.** The mixture of 0.20 g (1.25 mmol) of **1** and 0.34 mL (3.12 mmol) of phenyl isocyanate in 50 mL of dry acetone was stirred at reflux under argon atmosphere for 24 h. The mixture was concentrated to 10–20 mL and cooled to −15° C. Product **5a** was filtered and washed with diethylether (diethylether in the case of **5b**, acetone in case of **5c**).

***4-[1-(Phenylcarbamoyl)-1H*-imidazoline-2-yl]phenyl *N*-phenylcarbamate (5a).** White crystals, yield 0.44 g (88%), mp 167.5–171°C, R_f 0.31 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (360 MHz, DMSO-d_6): δ 4.00 (t, *J* = 8.0 Hz, 2H, CH_2), 4.12 (t, *J* = 8.0 Hz, 2H, CH_2), 7.07 (m, 2H, ArH), 7.30 (m, 4H, ArH), 7.38 (t, *J* = 7.8 Hz, 2H, ArH), 7.51 (d, *J* = 8.0 Hz, 2H, ArH), 7.57 (d, *J* = 7.5 Hz, 2H, ArH), 7.63 (d, *J* = 8.2 Hz, 2H, ArH), 9.23 (s, 1H, NCONH), 10.34 (s, 1H, OCONH); ^{13}C-NMR (90 MHz, DMSO-d_6): δ 48.8, 53.9, 118.5, 119.7, 121.1, 122.8, 123.1, 128.5, 128.9, 129.1, 129.6, 138.5, 139.2, 151.4, 151.4, 152.6, 159.5. *Anal*. Calcd. for $C_{23}H_{20}N_4O_3$ (400.42): C, 68.99; H, 5.03; N, 13.99. Found: C, 69.29; H, 5.22; N, 13.92.

***4-{1-[(4-Methylphenyl)carbamoyl]-1H-imidazoline-2-yl}phenyl N-(4-methylphenyl)-carbamate (5b).** White crystals, yield 0.34 g (68%), mp 174-176°C, R_f = 0.34 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (360 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.99 (t, *J* = 8.0 Hz, 2H, CH_2), 4.10 (t, *J* = 8.1 Hz, 2H, CH_2), 7.11 (d, *J* = 8.1 Hz, 2H, ArH), 7.18 (d, *J* = 8.0 Hz, 2H, ArH), 7.26 (d, *J* = 8.4 Hz, 2H, ArH), 7.39 (d, *J* = 8.2 Hz, 2H, ArH), 7.45 (d, *J* = 7.9 Hz, 2H, ArH), 7.61 (d, *J* = 8.4 Hz, 2H, ArH), 9.13 (s, 1H, NCONH), 10.24 (s, 1H, OCONH); ^{13}C-NMR (90 MHz, DMSO-d_6): δ 20.4, 48.7, 53.8, 118.5, 119.6, 119.8, 121.1, 128.9, 129.1, 129.3, 129.6, 131.7, 131.0, 136.0, 136.6, 151.4, 152.5, 159.5. *Anal*. Calcd. for $C_{25}H_{24}N_4O_3$ (428.48): C, 70.08; H, 5.65; N, 13.08. Found: C, 69.90; H, 5.77; N, 12.93.

***4-{1-[(4-Nitrophenyl)carbamoyl]-1H-imidazoline-2-yl}phenyl N-(4-nitrophenyl)car-bamate (5c).** Light yellow crystals, yield 0.28 g (56 %), mp 174-176°C. ^{1}H-NMR (360 MHz, DMSO-d_6): δ 4.03 (t, *J* = 8.0 Hz, 2H, CH_2), 4.14 (t, *J* = 8.1 Hz, 2H, CH_2), 7.33 (d, *J* = 8.3 Hz, 2H, ArH), 7.66 (d, *J* = 8.2 Hz, 2H, ArH), 7.79 (m, 4H, ArH), 8.21 (d, *J* = 8.8 Hz, 2H, ArH), 8.29 (d, *J* = 8.7 Hz, 2H, ArH), 9.85 (s, 1H, NCONH), 11.05, (s, 1H, OCONH). *Anal*. Calcd. for $C_{23}H_{18}N_6O_7$ (490.42): C, 56.33; H, 3.70; N 17.14. Found: C, 56.45; H, 4.00; N, 17.29.

4-(1-Acetyl-1H-imidazoline-2-yl)phenyl acetate (7). To a suspension of 5 g (30.83 mmol) of **1** in 30 mL of pyridine was added 6.4 mL (67.83 mmol) of acetanhydride at 0–5°C. The mixture was stirred for 3 h at 10°C, then diluted with 200 mL of water and extracted three times with dichloromethane. Organic phase was washed with water and brine, and the solvent was evaporated to yield off-white crystals of product, which was used for the next synthetic step without purification.

Yield 6.8 g (90%), mp 139–142°C (ethanol-water 1:1), R_f = 0.41 ($CHCl_3$/MeOH 10:1), ^{1}H-NMR (360 MHz, DMSO-d_6): δ 2.03 (s, 3H, $NCOCH_3$), 2.33 (s, 3H, $OCOCH_3$), 3.91 (t, *J* = 8.2 Hz, 2H, CH_2), 4.05 (t, *J* = 8.2 Hz, 2H, CH_2), 7.20 (d, *J* = 7.6 Hz, 2H, ArH), 7.58 (d, *J* = 7.6 Hz, 2H, ArH); ^{13}C-NMR (90 MHz, DMSO-d_6): δ 20.9, 24.8, 47.8, 53.16, 121.1, 129.6, 130.0, 151.4, 158.1, 167.7, 169.1; MS: *m/z* 246 (M^+, 9), 204 (83), 162 (68), 161 (47), 133 (100), 43 (28). *Anal*. Calcd. for $C_{13}H_{14}N_2O_3$ (246.26): C, 63.40; H, 5.73; N, 11.38. Found: C, 63.69; H, 5.94; N, 11.55.

1-Acetyl-2-(4-hydroxyphenyl)-1H-imidazoline (8). To the solution of 5 g (20.30 mmol) of **5** in 250 mL of acetone was added 12.5 mL (0.121 mol) of diethylamine. The mixture was stirred at reflux for 24 h. The mixture was concentrated under reduced pressure to ∼50 mL and cooled to –15°C. Product was filtered and washed twice with cold acetone to yield 3.29 g (79 %) of white crystals, mp 182–183.5°C, R_f = 0.26 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.95 (s, 3H, $NCOCH_3$), 3.82 (t, *J* = 8.5 Hz, 2H, CH_2), 3.99 (t, *J* = 8.5 Hz, 2H, CH_2), 6.81 (d, *J* = 8.5 Hz, 2H, ArH), 7.38 (d, *J* = 8.5 Hz, 2H, ArH), 9.70–10.20 (br s, 1H, OH); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 24.9, 48.0, 52.6, 114.6, 122.9, 130.0, 158.7, 159.0, 167,8. *Anal*. Calcd. for $C_{11}H_{12}N_2O_2$ (204.23): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.56; H, 6.15; N, 13.58.

General procedure for synthesis of 4-(1-Acetyl-1*H*-imidazoline-2-yl)phenyl *N*-(substituted phenyl)carbamates 9. The mixture of 0.19 g (0.93 mmol) of **8** and 0.11 mL (1.02 mmol) of appropriate phenyl isocyanate in 20 mL of dry acetone was stirred at room temperature under argon atmosphere for 24 h (progress was monitored by TLC). After cooling to –15°C, the product was filtered and washed with diethylether. In case of **9f**, the reaction mixture was concentrated to ∼5 mL, and this solution was diluted with 50 mL of hexane. Precipitated product was filtered, washed with 5 mL of ether and with 20 mL of hexane.

4-(1-Acetyl-1H-imidazoline-2-yl)phenyl N-phenylcarbamate (9a). White crystals, yield 0.21 g (70%), mp 147–149°C, R_f = 0.38 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (360 MHz, $CDCl_3$): δ 1.91 (s, 3H, $NCOCH_3$), 3.96 (t, *J* = 8.2 Hz, 2H, CH_2), 4.08 (t, *J* = 8.3 Hz, 2H, CH_2), 7.09 (t, *J* = 7.3 Hz, 1H, ArH), 7.20 (d, *J* = 8.5 Hz, 2H, ArH), 7.31 (t, *J* = 7.7 Hz, 2H, ArH), 7.42 (d, *J* = 7.9 Hz, 2H, ArH), 7.53 (d, *J* = 8.5 Hz, 2H, ArH), 7.70 (s, 1H, NH); ^{13}C-NMR (90 MHz, $CDCl_3$): δ 25.4, 48.5, 53.3, 119.1, 121.7, 124.2, 129.2, 129.3, 129.7, 137.5, 151.2, 152.4, 159.1, 168.6. *Anal*. Calcd. for $C_{18}H_{17}N_3O_3$ (323.35): C, 66.86; H, 5.30; N, 13.00. Found: C, 66.61; H, 5.43; N, 13.25.

4-(1-Acetyl-1H-imidazoline-2-yl)phenyl N-(4-methylphenyl) carbamate (9b). White crystals, yield 0.20 g (67%), mp 152.5–154°C, R_f = 0.41 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (360 MHz, $CDCl_3$): δ 1.89 (s, 3H, $NCOCH_3$), 2.30 (s, 3H, CH_3), 3.95 (t, *J* = 8.3 Hz, 2H, CH_2), 4.08 (t, *J* = 8.3 Hz, 2H, CH_2), 7.11 (d, *J* = 8.2 Hz, 2H, ArH), 7.20 (d, *J* = 8.5 Hz, 2H, ArH), 7.30 (d, *J* = 7.9 Hz, 2H, ArH), 7.52 (d, *J* = 8.6 Hz, 2H, ArH), 7.60 (s, 1H, NH); ^{13}C-NMR (90 MHz, $CDCl_3$): δ 21.0, 25.4, 48.5, 53.3, 119.2, 121.7, 129.1, 129.6, 129.8, 133.8, 134.9, 151.3, 152.5, 159.1, 168.6. *Anal*. Calcd. for $C_{19}H_{19}N_3O_3$ (337.37): C, 67.64; H, 5.68; N, 12.46. Found: C, 67.62; H, 5.70; N, 12.39.

4-(1-Acetyl-1H-imidazoline-2-yl)phenyl N-(4-methoxyphenyl) carbamate (9c). White crystals, yield 0.25 g (83%), mp 164.5–166°C, R_f = 0.38 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (360 MHz, $CDCl_3$): δ 1.90 (s, 3H, N $COCH_3$), 3.79 (s, 3H, OCH_3), 3.95 (t, *J* = 8.4 Hz, 2H, CH_2), 4.09 (t, *J* = 8.3 Hz, 2H, CH_2), 6.87 (d, *J* = 9.0 Hz, 2H, ArH), 7.05 (s, 1H, NH), 7.25 (d, *J* = 8.6 Hz, 2H, ArH), 7.34 (d, *J* = 8.4 Hz, 2H, ArH), 7.54 (d, *J* = 8.6 Hz, 2H, ArH). *Anal*. Calcd. for $C_{19}H_{19}N_3O_4$ (353.37): C, 64.58; H, 5.42; N, 11.89. Found: C, 64.74; H, 5.56; N, 11.87.

4-(1-Acetyl-1H-imidazoline-2-yl)phenyl N-(4-cyanophenyl) carbamate (9d). White crystals, yield 0.25 g (83%), mp 174–175°C, R_f = 0.42 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.96 (s, 3H, $NCOCH_3$), 3.99 (t, *J* = 8.5 Hz, 2H, CH_2), 4.10 (t, *J* = 8.5 Hz, 2H, CH_2), 7.21 (d, *J* = 8.5 Hz, 2H, ArH), 7.55 (d, *J* = 8.5 Hz, 2H, ArH), 7.56 (d, *J* = 9.0 Hz, 2H, ArH), 7.62 (d, *J* = 9.0 Hz, 2H, ArH), 7.67 (s, 1H, NH). *Anal*. Calcd. for $C_{19}H_{16}N_4O_3$ (348.36): C, 65.51; H, 4.63; N, 16.08. Found: C, 65.25; H, 4.90; N, 16.35.

4-(1-Acetyl-1H-imidazoline-2-yl)phenyl N-(4-nitrophenyl) carbamate (9e). Light yellow crystals, yield 0.24 g (80%), mp 176–177°C. R_f = 0.36 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (360 MHz, $CDCl_3$): δ 1.97 (s, 3H, $NCOCH_3$), 3.99 (t, *J* = 8.8 Hz, 2H, CH_2), 4.10 (t, *J* = 8.7 Hz, 2H, CH_2), 7.24 (*d* + $CDCl_3$, 2H, ArH), 7.51 (s, 1H, NH), 7.58 (d, *J* = 8.5 Hz, 2H, ArH), 7.61 (d, *J* = 9.2 Hz, 2H, ArH), 8.24 (d, *J* = 8.8 Hz, 2H, ArH). *Anal*. Calcd. for $C_{18}H_{16}N_4O_5$ (368.34): C, 58.69; H, 4.38; N, 15.21. Found: C, 58.81; H, 4.68; N, 15.08.

4-(1-Acetyl-1H-imidazoline-2-yl)phenyl N-(3-trifluoromethylphenyl) carbamate (9f). White crystals, yield 0.26 g (87%), mp 136. 5–138° C, R_f = 0.38 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.93 (s, 3H, $NCOCH_3$), 3.98 (t, *J* = 8.5 Hz, 2H, CH_2), 4.10 (t, *J* = 8.5 Hz, 2H, CH_2), 7.15 (d, *J* = 8.5 Hz, 2H, ArH), 7.33 (d, *J* = 7.5 Hz, 1H, ArH), 7.42 (t, *J* = 8.0 Hz, 1H, ArH), 7.53 (d, *J* = 8.5 Hz, 2H, ArH), 7.62 (d, *J* = 8.5 Hz, 1H, ArH), 7.74 (s, 1H, ArH), 8.21 (s, 1H, NH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 25.3, 48.5, 53.2, 115.8, 120.4, 121.6, 122.1, 122.9, 125.1, 129.1, 129.6, 129.8, 131.3, 131.6, 138.5, 151.4, 152.2, 159.3, 168,7. *Anal.* Calcd. for $C_{19}H_{16}F_3N_3O_3$ (391.34): C, 58.31; H, 4.12; N, 10.74. Found: C, 58.11; H, 4.38; N, 10.76.

General procedure for synthesis of carbamates 10 derived from 2-(4-hydroxyphenyl)-1*H*-imidazole 2. The mixture of 0.147 g (0.92 mmol) of **2** and 1.11–1.18 mmol of 4-substituted phenyl isocyanate in 20 mL of dry dichloromethane was stirred at room temperature under argon atmosphere for 24 h. Product was filtered and washed with dichloromethane.

4-(1H-imidazole-2-yl)phenyl N-(4-nitrophenyl)carbamate (10a). Yellow crystals, yield 0.26 g (87%), mp 219.5–222.5°C, R_f = 0.24 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (360 MHz, DMSO-d_6): δ 7.00–7.35 (br d, 2H, CHCH), 7.40 (d, *J* = 8.7 Hz, 2H, ArH), 7.80 (d, *J* = 9.2 Hz, 2H, ArH), 8.05 (d, *J* = 8.7 Hz, 2H, ArH), 8.30 (d, *J* = 9.2 Hz, 2H, ArH), 11.04 (s, 1H, OCONH), 12.61 (s, 1H, imidazole NH). *Anal*. Calcd. for $C_{16}H_{12}N_4O_4$ (324.29): C, 59.26; H, 3.73; N, 17.28. Found: C, 59.10; H, 3.80; N, 17.31.

4-(1H-imidazole-2-yl)phenyl N-(4-cyanophenyl)carbamate (10b). White crystals, yield 0.29 g (97%), mp 234–240°C, R_f = 0.26 ($CHCl_3$/MeOH 10:1). ^{1}H-NMR (360 MHz, DMSO-d_6): δ 7.08 (br s, 1H, CH), 7.30 (br s, 1H, CH), 7.38 (d, *J* = 8.6 Hz, 2H, ArH), 7.75 (d, *J* = 8.7 Hz, 2H, ArH), 7.90 (d, *J* = 8.7 Hz, 2H, ArH), 8.04 (d, *J* = 8.6 Hz, 2H, ArH), 10.85 (s, 1H, OCONH), 12.59 (s, 1H, imidazole NH). *Anal*. Calcd. for $C_{17}H_{12}N_4O_2$ (304.30): C, 67.10; H, 3.97; N, 18.41. Found: C, 67.02; H, 4.24; N, 18.60.

2-(2-Hydroxyphenyl)-1H-imidazole (11). This starting derivative was prepared using procedure described in our previous work [9].

2-(2-Aminophenyl)-1H-imidazole (12). 2-(2-Aminophenyl)-1 H-imidazole (**12**) was synthesized with according the procedure reported in literature. Reaction of 2-nitrobenzaldehyde with glyoxal trimer dihydrate in glacial acetic acid in the presence of ammonium acetate afforded 2-(2-nitrophenyl)-1H-imidazole in the low yield of 19% but more than two times better than in the literature (7.6%) [22], mp 180–184°C (184°C [22]). This nitro derivative was dissolved in ethanol and hydrogenated overnight at room temperature at pressure 40 bar using Pd/C (10%) as catalyst. 2-(2-Aminophenyl)-1H-imidazole **12** was prepared in 91% yield, mp 128–131°C (132–134°C [22]).

General procedure for synthesis of carbamates 13 derived from 2-(2-hydroxyphenyl)-1*H*-imidazole 11. The mixture of 1.56 mmol of 2-(2-hydroxyphenyl)-1*H*-imidazole, 1.56 mmol of aliphatic or aromatic isocyanate and 10 mL of dry toluene was refluxed for 3 h and then stirred overnight at room temperature. Products were obtained after vacuum evaporation of the solvent. Only three products were obtained using substituted phenyl isocyanate (substituents are 4-CH_3, 4-NO_2, and 4-CN).

2-(1H-Imidazol-2-yl)phenyl N-(4-methylphenyl)carbamate (13a). White crystals, yield 0.25 g (54%), mp 100–105° C; IR (potassium bromide): ν 3305 (NH), ν 1776 (CO), δ 1567 (NH in CO NH), ν_{as} 1241, ν_s 1139 (COC), γ 746 (CH arom.) cm^{-1}. *Anal*. Calcd. for $C_{17}H_{15}N_3O_2$ (293.32): C, 69.61; H, 5.15; N, 14.33. Found: C, 69.81; H, 5.27; N, 14.37.

2-(1H-Imidazol-2-yl)phenyl N-(4-nitrophenyl)carbamate (13b). Yellow crystals, yield 0.45 g (88%), mp 114–118°C; IR (potassium bromide): ν 3366, 3337 (NH), ν 1775, 1740 (CO), δ 1552 (NH in CO NH), ν 1497 (NO_2), ν_{as} 1248, ν_s 1131 (COC), γ 750 (CH arom.) cm^{-1}. *Anal*. Calcd. for $C_{16}H_{12}N_4O_4$ (324.29): C, 59.26; H, 3.73; N, 17.28. Found: C, 59.09; H, 3.99; N, 17.00.

2-(1H-Imidazol-2-yl)phenyl N-(4-cyanophenyl)carbamate (13c). White crystals, yield 0.40 g (85%), mp 121–124°C; IR (potassium bromide): ν 3377, 3309 (NH), ν 2220 (CN), 1776, ν 1732 (CO), δ 1532 (NH in CO NH), ν_{as} 1246, ν_s 1139 (COC), γ 744 (CH arom.) cm^{-1}. *Anal*. Calcd. for $C_{17}H_{12}N_4O_2$ (304.30): C, 67.10; H, 3.97; N, 18.41. Found: C, 66.96; H, 4.22; N, 18.35.

General procedure for synthesis of ureas 14 derived from 2-(2-aminophenyl)-1*H*-imidazole 12. The mixture of 1.57 mmol of 2-(2-aminophenyl)-1*H*-imidazole, 1.57 mmol of aliphatic or aromatic isocyanate and 8 mL of acetonitrile was refluxed for 5 h and then stirred overnight at room temperature. Precipitated products were filtered off. Products were obtained using all tested isocyanates.

1-Ethyl-3-[2-(1H-imidazol-2-yl)phenyl]urea (14a). White crystals, yield 0.42 g (42%), mp 146–146.5°C; ^{1}H-NMR (360 MHz, DMSO-d_6): δ 1.12 (t, 3H, H-11), 3.17 (m, 2H, H-10) , 6.99–7.07 (m, 2H, H-2, 9), 7.28 (t, 3H, H-3, 6, 7), 7.84 (d, 1H, H-4), 8.40 (d, 1H, H-1), 11.59 (s, 1H, H-5), 12.68 (s, 1H, H-8); IR (potassium bromide): ν 3311, 3262, and 3176 (NH), ν 1665 (CO), δ 1569 (NH in CO NH),γ 742 (CH arom.) cm^{-1}. *Anal*. Calcd. for $C_{12}H_{14}N_4O$ (230.27): C, 62.59; H, 6.13; N, 24.33. Found: C, 62.79; H, 6.16; N, 24.10.

1-[2-(1H-imidazol-2-yl)phenyl]-3-propylurea (14b). White crystals, yield 0.10 g (26%), mp 143–144°C; ^{1}H-NMR (360 MHz, DMSO-d_6): δ 0.92 (t, 3H, H-12), 1.52 (m, 2H, H-11), 3.10 (q, 2H, H-10), 7.02 (t, 1H, H-2), 7.18 (s, 1H, H-6[7]), 7.28 (t, 1H, H-3), 7.36 (s, 1H, H-6[7]), 7.83 (d, 1H, H-4), 8.39 (d, 1H, H-1), 7.10 (s, 1H, H-9), 11.57 (s, 1H, H-5), 12.68 (s, 1H, H-8); IR (potassium bromide): ν 3272, 3176 (NH), ν 1663 (CO), δ 1553 (NH in CO NH), γ 745 (CH arom.) cm^{-1}. *Anal*. Calcd. for $C_{13}H_{16}N_4O$ (244.29): C, 63.91; H, 6.60; N, 22.93. Found: C, 63.97; H, 6.66; N, 22.72.

1-[2-(1H-imidazol-2-yl)phenyl]-3-isopropylurea (14c). White crystals, yield 0.20 g (53%), mp 192–196°C; ^{1}H-NMR (360 MHz, DMSO-d_6): δ 1.16 (d, 6H, H-11), 3.87 (m, 1H, H-10), 6.96–7.03 (m, 2H, H-2, 9), 7.19 (s, 1H, H-6[7]), 7.27 (t, 1H, H-3), 7.36 (s, 1H, H-6[7]), 7.83 (d, 1H, H-4), 8.40 (d, 1H, H-1), 11.46 (s, 1H, H-5), 12.66 (s, 1H, H-8); IR (potassium bromide): ν 3261, 3151 (NH), ν 1661 (CO), δ 1555 (NH in CO NH), γ 746 (CH arom.) cm^{-1}. *Anal.* Calcd. for $C_{13}H_{16}N_4O$ (244.29): C, 63.91; H, 6.60; N, 22.93. Found: C, 64.11; H, 6.69; N, 23.10.

1-Tert-butyl-3-[2-(1H-imidazol-2-yl)phenyl]urea (14d). White crystals, yield 0.15 g (37%), mp 195–202°C; ^{1}H-NMR (360 MHz, DMSO-d_6): δ 1.35 (s, 9H, H-10), 7.00 (t, 1H, H-2), 7.20 (s, 1H, H-6[7]), 7.26 (t, 1H, H-3), 7.35 (s, 1H, H-6[7]), 7.80 (d, 1H, H-4), 8.29 (d, 1H, H-1), 6.81 (s, 1H, H-9), 11.17 (s, 1H, H-5), 12.63 (s, 1H, H-8); IR (potassium bromide): ν 3357, 3163

(NH), v 1659 (CO), δ 1538 (NH in CO NH), γ 734 (CH arom.) cm^{-1}. *Anal*. Calcd. for $C_{14}H_{18}N_4O$ (258.32): C, 65.09; H, 7.02; N, 21.69. Found: C, 65.05; H, 7.08; N, 21.72.

1-Cyclohexyl-3-[2-(1H-imidazol-2-yl)phenyl]urea (14e). White crystals, yield 0.25 g (56%), mp 205–207°C; ^{1}H-NMR (360 MHz, DMSO-d_6): δ 1.14–1.37 (m, 6H, Cy), 1.63 (d, 1H, Cy), 1.76 (d, 2H, Cy), 1.88 (d, 2H, Cy), 6.95 (s, 1H, H-9), 7.01 (t, 1H, H-2), 7.19 (s, 1H, H-6 [7]), 7.27 (t, 1H, H-3), 7.36 (s, 1H, H-6 [7]), 7.83 (d, 1H, H-4), 8.41 (d, 1H, H-1), 11.47 (s, 1H, H-5), 12.67 (s, 1H, H-8); IR (potassium bromide): v 3306, 3199 (NH), v 1663 (CO), δ 1547 (NH in CO NH), γ 745 (CH arom.) cm^{-1}. *Anal*. Calcd. for $C_{16}H_{20}N_4O$ (284.36): C, 67.58; H, 7.09; N, 19.07. Found: C, 67.45; H, 7.15; N, 19.65.

1-[2-(1H-Imidazol-2-yl)phenyl]-3-phenylurea (14f). White crystals, yield 0.20 g (46%), mp 170–171°C; ^{1}H-NMR (360 MHz, DMSO-d_6): δ 7.02 (t, 1H, H-2), 7.11 (t, 1H, H-12), 7. 30–7.37 (m, 5H, H-3, 6, 7, 11), 7.59 (d, 2H, H-10), 7.89 (d, 1H, H-4), 8.30 (d, 1H, H-1), 9.60 (s, 1H, H-9), 11.80 (s, 1H, H-5), 12.73 (s, 1H, H-8); IR (potassium bromide): v 3352, 3191 (NH), v 1675 (CO), δ 1540 (NH in CO NH), γ 744 (CH arom.) cm^{-1}. *Anal*. Calcd. for $C_{16}H_{14}N_4O$ (278.31): C, 69.05; H, 5.07; N, 20.13. Found: C, 69.03; H, 5.18; N, 20.12.

1-[2-(1H-Imidazol-2-yl)phenyl]-3-(4-methylphenyl)urea (14g). White crystals, yield 0.20 g (43%), mp 196–198.5°C; ^{1}H-NMR (360 MHz, DMSO-d_6): δ 2.30 (s, 3H, H-12), 7.07–7.14 (m, 3H, H-2, 11), 7.21 (s, 1H, H-6[7]], 7.31–7.39 (m, 2H, H-3, 6[7]), 7.46 (d, 2H, H-10), 7.88 (d, 1H, H-4), 8.31 (s, 1H, H-1), 9.47 (s, 1H, H-9), 11.75 (s, 1H, H-5), 12.72 (s, 1H, H-8); IR (potassium bromide): v 3300, 3216 (NH), v 1676 (CO), δ 1538 (NH in CO NH), γ 734 (CH arom.) cm^{-1}. *Anal*. Calcd. for $C_{17}H_{16}N_4O$ (292.34): C, 69.85; H, 5.52; N, 19.17. Found: C, 69.68; H, 5.38; N, 19.26.

1-(4-Cyanophenyl)-3-[2-(1H-imidazol-2-yl)phenyl]urea (14h). White crystals, yield 0.15 g (32%), mp 217–219°C; ^{1}H-NMR (360 MHz, DMSO-d_6): δ 7.15 (t, 1H, H-2), 7.26 (s, 1H, H-6[7]), 7.35–7.42 (m, 2H, H-3, 6[7]), 7.78 (s, 4H, H-10, 11), 7.92 (d, 1H, H-4), 8.29 (d, 1H, H-1) 10.17 (s, 1H, H-9), 12.04 (s, 1H, H-5), 12.80 (s, 1H, H-8); IR (potassium bromide): v 3317, 3270 (NH), v 2226 (CN), v 1692 (CO), δ 1530 (NH in CO NH), γ 741 (CH arom.) cm^{-1}. *Anal*. Calcd. for $C_{17}H_{13}N_5O$ (303.32): C, 67.32; H, 4.32; N, 23.09. Found: C, 67.54; H, 4.57; N, 23.23.

Antimycobacterial activity. *In vitro* antimycobacterial activity was evaluated against *M. tuberculosis* CNCTC My 331/88, *M. kansasii* CNCTC My 235/80, *M. kansasii* 6509/96, and *M. avium* CNCTC My 330/88 using the micromethod for the determination of the MIC. All strains were obtained from the Czech National Collection of Type Cultures (CNCTC), with the exception of *M. kansasii* 6509/96, which was a clinical isolate. The activities of the compounds were determined in the Šula semisynthetic medium (SEVAC, Prague). The compounds were added to the medium in dimethylsulfoxide solutions. The following concentrations were used: 1000, 500, 250, 125, 62, 32, 16, 8, 4, 2, and 1 μmol/L. MICs were determined after incubation at 37°C for 14 and 21 days, for *M. kansasii* for 7, 14, and 21 days. MIC was the lowest concentration of a substance at which the inhibition of the growth of mycobacteria occurred. INH was used as a standard.

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