Heteroatom Chemistry
Volume 23, Number 2, 2012

Synthesis and Tuberculostatic Activity of Novel *N′*-Methyl-4-(pyrrolidin-1-yl)picolinohydrazide and *N′*-Methylpyrimidine-2-carbohydrazide Derivatives

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Received 8 November 2011; revised 13 January 2012

ABSTRACT: *The synthesis of N′-methyl-4-(pyrrolidin-1-yl)picolinohydrazide and N′-methylpyrimidine-2-carbohydrazide derivatives (***5a** *and* **5b***) was carried out. These compounds were used as starting materials to obtain methyl N′-methylhydrazinecarbodithioates* **6a** *and* **6b***, which, on reaction with either triethylamine or hydrazine, gave corresponding 1,3,4-oxadiazioles* **7a** *and* **7b** *or 1,2,4-triazoles* **9a** *and* **9b** *with the free NH_2 group at the N-4 position, respectively. Compounds* **8a**–**e***, particularly containing cyclic amines at N-4 of the 1,2,4-triazole ring, were also obtained. Synthesized compounds were tested in vitro for their activity against* Mycobacterium tuberculosis. *The structure–activity relationship analysis for obtained compounds was done.* © 2012 Wiley Periodicals, Inc. Heteroatom Chem 23:223–230, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21008

INTRODUCTION

Tuberculosis (TB) still remains a major public heath problem. More than 2 billion people are infected with *Mycobacterium tuberculosis* [1]. The treatment is complicated due to the long-term administration of a few antituberculotic agents, which altogether cause serious side effects [2,3].

1,3,4-Oxadiazoles and 1,2,4-triazoles containing a pyridine moiety possess antibacterial and antitubercular activities [4]. The antibacterial properties of some 3-(pyridin-3-yl)-1*H*-1,2,4-triazole-5(4*H*)-thiones [5,6] (**A, B**) and antimycobacterial activity of some 3-(pyridin-2-yl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thiols were found (**C**) [7] (Fig. 1).

Our previous research has shown that mono- and dithioesters of pyrazinoylhydrazinecarbodithioic acid undergo reactions with amines, and the structure of their products depends on the amine type and reaction conditions [8–10]. Derivatives of thiosemicarbazide as well as heterocyclic compounds such as 1,3,4-oxadiazoles, 1,2,4-triazoles, and triazolepyrimidine condensed structures can be the products of the reactions [11–13]. Two sulfur atoms present in the 2-acylhydrazinecarbodithioate molecule play a key role in the compound reactivity that makes it an excellent starting material for the synthesis of various heterocyclic systems.

Since many other 1,2,4-triazole derivatives were described as biologically active, it seemed interesting to obtain new 3,4-disubstituted derivatives of this heterocyclic system and to evaluate their activity against *M. tuberculosis*.

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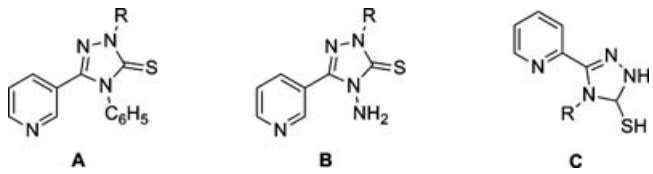
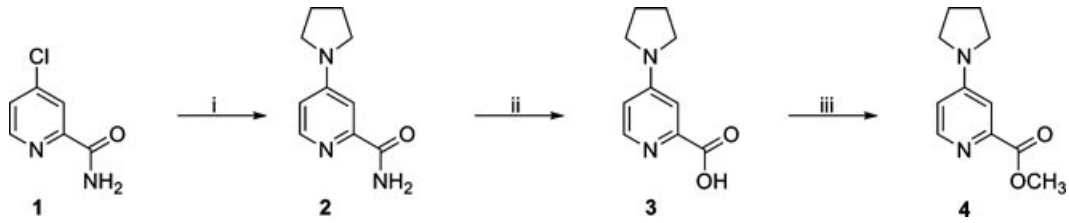


FIGURE 1 Structures of antibacterial and antimycobacterial pyridine derivatives.



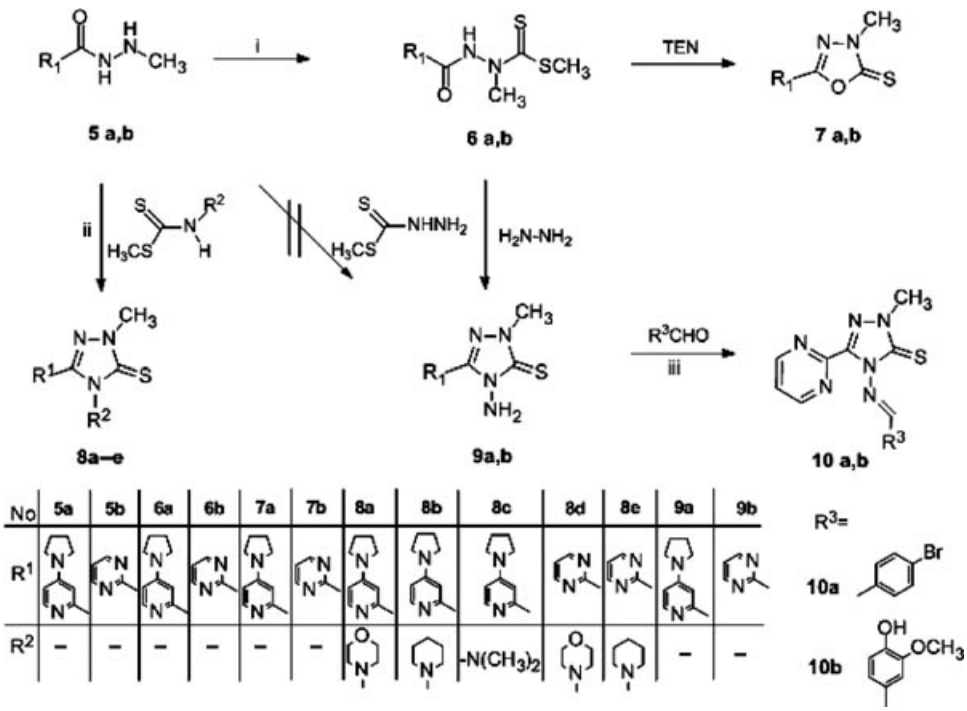
SCHEME 1 Reagent conditions and yields: (i) pyrrolidine (8 molar equiv.), dioxane, reflux 3 h, 82%; (ii) NaOH (5 molar equiv.), reflux 2 h, H^+, 66%; (iii) MeOH/$SOCl_2$, reflux 3 h, 49%.

RESULTS AND DISCUSSION

The main goal of the present work was to obtain novel *N′*-methyl-4-(pyrrolidin-1-yl) picolinohydrazide and *N′*-methylpyrimidine-2-carbohydrazide and to conduct research on their usefulness for the syntheses of new derivatives with tuberculostatic activity. Thus, 4-chloropicolinamide(**1**) [14] was converted to 4-(pyrrolidin-1-yl)picolinamide (**2**) by refluxing it with pyrrolidine in dioxane. Alkaline hydrolysis of the amide **2** furnished the acid **3**, which was transformed into methyl 4-(pyrrolidin-1-yl)picolinate (**4**) by a reaction with methanol in the presence of thionyl chloride [15] (Scheme 1).

The treatment of methyl 4-(pyrrolidin-1-yl) picolinate (**4**) or methyl pyrimidine-2-carboxylate [16] with methylhydrazine gave *N′*-methyl-4-(pyrrolidin-1-yl)picolinohydrazide (**5a**) or *N′*-methylpyrimidine-2-carbohydrazide (**5b**), respectively. Monothioesters **6a** and **6b** were obtained by treating compounds **5a** and **5b** with carbon disulfide and methyl iodide in ethanol containing a 1.2 molar equivalent of triethylamine (TEA). On the other hand, heating of monomethylthioesters **6a** and **6b** in ethanol in excess of triethylamine for 4 h led to the desired 1,3,4-oxadiazoles **7a** and 7**b**. Acid properties of sulfur atom and basic conditions make the carbon atom of the thiocarbonyl group more susceptible to a nucleophilic attack of the enol form of carbonyl oxygen. The result is intermolecular substitution of the methylthio group, which, in these reactions appeared, to be a good leaving one (yields ~70%).

Next, we examined the effect of various carbamoditioates possessing the NH_2 group either free or substituted with the methyl moiety or with cyclic amines in their structure on methylhydrazides **5a** and **5b**. Thus we used methyl morpholinocarbamodithioate, methyl piperidin-1-ylcarbamodithioate, methyl 2,2-dimethylhydrazinecarbodithioate, and methyl hydrazinecarbodithioate, respectively. Heating of *N′*-methyl-4-(pyrrolidin-1-yl)picolinohydrazide (**5a**) or *N′*-methylpyrimidine-2-carbohydrazide (**5b**) with the mentioned substrates in dioxane in the presence of 10% K_2CO_3 led to 1,2,4-triazoles substituted at the N-4 position with *N*, *N*-dimethylamine, pyrrolidine or morpholine **8a**–**e**. Generally the methylthio group easily underwent substitution with the NH_2 group of carbohydrazide, as evidenced by, the reaction yields (~80%). That confirmed thiomethyl as a good leaving group. Moreover, this method seems to be a convenient way to obtain novel 1,2,4-triazoles possessing cyclic amines at the N-4 position. An attempt to obtain 4-amino-1-methyl-3-[4-(pyrrolidin-1-yl)pyridin-2-yl]-1*H*-1,2,4-triazole-5(4*H*)-thione (**9a**) from compound **5a** with methyl hydrazinecarbodithioate failed. However, compound **9a** was synthesized by the reaction of **6a** in hydrazine monohydrate under reflux. The IR spectrum of **9a** showed the disappearance of the absorption band of the C=O (1687 cm^{-1}) group, and its ^1H NMR spectrum revealed the absence of SCH_3 (δ = 2.53 ppm) and NH (δ = 9.58 ppm) protons, and instead, the signal of NH_2 of the 1,2,4-triazole moiety was detected at δ = 6.57 ppm. Based on the obtained data, the reaction product was formulated as 4-amino-1-methyl-3-[4-(pyrrolidin-1-yl)pyridin-2-yl]-1*H*-1,2,4-triazole-5(4*H*)-thione (**9a**). A similar trial was performed for compound **6b** and



SCHEME 2 Reagent conditions and yields: (i) CS_2 (1.2 molar equiv.), TEA (1.2 molar equiv.), MeI (1 molar equiv.), EtOH, room temperature (rt) 4 h, 25%–71%; (ii) $R^2NHCSSCH_3$ (1 molar equiv.), K_2CO_3 (2 molar equiv.), dioxane, reflux 6–20 h, 27–87%; (iii) R^3CHO (1 molar equiv.), EtOH, reflux 3 h, 74–93%.

4-amino-1-methyl-3-(pyrimidin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (**9b**) was obtained. For derivative **9b** possessing a free NH_2 group at the N-4 position, condensation reactions with 4-bromobenzaldehyde or 4-hydroxy-3-methoxybenzaldehyde in ethanol were performed, giving 4-(4-bromobenzylideneamino)-1-methyl-3-(pyrimidin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (**10a**) and 4-(4-hydroxy-3-methoxybenzylideneamino)-1-methyl-3-(pyrimidin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (**10b**), respectively (Scheme 2).

Tuberculostatic Activity

All newly synthesized compounds were examined for their tuberculostatic activity toward the *M. tuberculosis* $H_{37}Rv$ standard strain and two wild strains isolated from TB patients: one (Spec. 210) resistant to *p*-aminosalicylic acid, isonicotinic acid hydrazide (INH), etambutol, and rifampicine, and the other (Spec. 192), fully susceptible to the drugs administered (Table 1). Investigations were performed by a classical testtube method of successive dilution in Youmans' modification of liquid Proskauer and Beck's medium containing 10% of bovine serum [17,18]. Bacterial suspensions were prepared from 14-day-old cultures of slowly growing strains and from 48-h-old cultures of saprophytic strains [19,20]. Solutions of compounds in ethylene glycol were tested. Stock solutions contained 10 mg of compounds in 1 mL. Dilutions (in geometric

TABLE 1 In Vitro Tuberculostatic Activity of Compounds **5a–10b**[a–c]

Compound number	*Myc. Tbc. $H_{37}Rv$*	*Myc. spec. 192*	*Myc. spec. 210*
5a	50	50	50
6a	50	50	25
7a	50	50	25
8a	50	50	50
8b	50	50	50
8c	50	100	50
8d	50	100	50
8e	100	50	50
9a	50	50	50
9b	50	50	50
10a	50	50	50
10b	50	50	50
Isonicotinic acid hydrazide (INH)	0.5	0.5	1.0

[a]Minimum inhibitory concentrations for mycobacterial strains were determined by a twofold classical test-tube method of successive dilution.
[b]INH isoniazid.
[c]*M. tuberculosis* $H_{37}Rv$, Spec. 192, Spec. 210.

progression) were prepared in Youmans' medium. The medium containing no investigated substances and containing isoniazid (INH) as a reference drug was used for comparison. Incubation was performed at a temperature of 37°C. The minimum inhibitory concentration (MIC) values were determined as the minimum concentration inhibiting the growth of tested tuberculous strains in relation to the probe with no tested compound.

The tuberculostatic evaluation revealed that all the synthesized *N*′-methyl-4-(pyrrolidin-1-yl)picolinohydrazide and *N*′-methylpyrimidine-2-carbohydrazide derivatives exhibited poorer activity against *M. tuberculosis* than INH (MIC 0.5–1.0 μg/mL) used as the reference drug. Methylthioester **6a** and compound **7b** possessing the 1,3,4,-oxadiazole ring exhibited the highest activity toward tested strains. Both compounds belonged to 4-pyrrolidine-2-pyridine derivatives. MIC values for these compounds were 50 μg/mL against the H_{37}Rv standard strain and 192 sensitive strain, whereas the activity was higher against the 210 resistant strain (MIC 25 μg/mL). *N*′-Methylhydrazide **5a** and 1,2,4-triazoles **8a**, **8b**, **9a**, **9b**, **10a**, and **10b** exhibited lower activity. MIC values for these compounds were 50 μg/mL toward all tested strains. In that group, there was no difference in activity between compounds containing 2-pyrimidine or 4-pyrrolidine-2-pyridine systems (**9a** and **9b**). There was also no difference in activity between compounds **10a** and **10b**, which were derivatives of 2-pyrimidine with a different R^3 substituent, 4-bromophenyl, and 4-hydroxy-3-methoxyphenyl. The same holds for compounds **8a** and **8b**, which were derivatives of 3-[(4-pyrrolidin-1-yl)pyridin-2-yl]-1,2,4-triazole-5-thione with morpholine and piperidine systems at the N-4 position. These compounds were more active than the corresponding 2-pyrimidine derivatives (**8d** and **8e**), for which MIC values toward the H_{37}Rv strain were 50 and 100 μg/mL; μ against the 210 resistant strain was 50 μg/mL, and toward the 192 sensitive strain, were 100 and 50 μg/mL respectively. Compounds **8a** and **8b** were also more active than derivative **8c**, which in place of morpholine and piperidine in the N-4 position, has a dimethylamine group. MIC values for derivative **8c** were 50 μ (H_{37}Rv), 100 μ (Spec.192), and 50 μg/mL (Spec. 210).

CONCLUSION

In conclusion, a series of novel *N*′-methyl-4-(pyrrolidin-1-yl)picolinohydrazide and *N*′-methylpyr-imidine-2-carbohydrazide derivatives were synthesized successfully. Performed reactions used the acidic nature of the thiocarbonyl sulfur atom present in the hydrazinecarbodithioate molecule and the properties of methylthio group as a good leaving one in substitution reactions. The structure of all the new compounds was confirmed by IR and ^{1}H NMR spectra as well as elemental analyses. Their tuberculostatic activity was evaluated against the *M. tuberculosis* H_{37}Rv standard strain, 192 sensitive strain, and 210 strain resistant to drugs clinically used. The results showed that 4-pyrrolidine-2-pyridine derivatives were more active than 2-pyrimidine derivatives in vitro. One of them possessing the 1,2,4-oxadiazole system exhibited higher activity than its analogue with a 1,3,4-triazole ring and was more active against the 210 resistant strain than the 192 sensitive one. Given the current size of the phenomenon of multidrug resistance of microorganisms, this result seems to be very interesting. Therefore, further studies on this group of compounds appear to be interesting.

EXPERIMENTAL

Melting points were obtained with a Boetius apparatus (Franz Küstner Nachf. KG, Dresden, Germany) and are uncorrected. Elemental analyses for C, H, N, and S were performed on a Carlo-Erba 1108 instrument (Thermo Scientific, Waltham, MA), and the results for all the obtained compounds were in agreement with the calculated values within the ±0.3% range. The IR spectra were taken with a Satellite spectrophotometer (Mattson Instruments, Madison, WI). NMR spectra were recorded on a Varian Gemini 200 MHz instrument (Varian, Palo Alto, CA). The starting 4-chloropicolinamide (**1**) was obtained according to the method described previously [12]. Compound characteristics were found to be identical with those reported in the literature.

*4-(Pyrrolidin-1-yl)picolinamide (**2**)*

Compound **1** (0.470 g, 3 mmol) was dissolved in dioxane (10 mL), pyrrolidine (2 mL, 25 mmol) was added, and the mixture was refluxed for 3 h. After cooling down, the precipitate was filtered off and recrystallized from MeOH to give title compound **2** as a white solid (0.470 g, 82%); mp: 203–205°C; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.95 (t, $J = 6.3$ Hz, 4H, pyrrolidine), 3.29 (t, $J = 6.3$ Hz, 4H, pyrrolidine), 6.56 (dd, $J_1 = 5.3$ Hz, $J_2 = 2.4$ Hz, 1H, H-5), 7.11 (d, $J = 2.4$ Hz, 1H, H-3), 7.47 (s, 1H, NH), 7.96 (s, 1H, NH), 8.10 (d, $J = 5.3$ Hz, 1H, H-6); IR (KBr, cm^{-1}): 3360, 3147 (ν N—H), 2852 (ν C—H), 1702 (ν C=O), 1603 (ν C=C), 1389, 1290 (ν C—N), 1011, 790 (γ C—H), 652 (γ N—H), 567; Anal. Calcd for $C_{10}H_{13}N_3O$ (191.23):

C, 62.81; H, 6.85; N, 21.97. Found: C, 62.63; H, 6.89; N, 21.86.

*4-(Pyrrolidin-1-yl)picolinic acid (**3**)*

Compound **2** (1.91 g, 10 mmol) was dissolved in a 10% NaOH aqueous solution (20 mL) and refluxed for 2 h. After cooling down, the mixture was acidified with acetic acid and the precipitate was filtered off and recrystallized from MeOH to give product **3** as a white solid (1.26 g, 66%); mp: >260°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.89–1.99 (m, 4H, pyrrolidine), 3.33–3.43 (m, 4H, pyrrolidine), 6.71 (dd, $J_1 = 6.8$ Hz, $J_2 = 2.5$ Hz, 1H, H-5), 7.07 (d, $J = 2.5$ Hz, 1H, H-3), 7.92 (d, $J = 6.8$ Hz, 1H, H-6), 9.25 (s, 1H, OH); IR (KBr, cm^{-1}): 3229 (ν O—H), 1651 (ν C=O), 1557 (ν C=C), 1397 (δ O—H), 1238 (ν C—O), 1149 (ν C—N), 922 (γ O—H), 800 (γ C—H), 692, 644, 553. Anal. Calcd for $C_{10}H_{12}N_2O_2$ (192.21): C, 62.49; H, 6.29, N, 14.57. Found: C, 62.38; H, 6.27; N, 14.61.

*Methyl 4-(Pyrrolidin-1-yl)picolinate (**4**)*

Compound **3** (1.53 g, 8 mmol) was dissolved in MeOH (20 mL), and thionyl chloride (2 mL, 25 mmol) was added. The mixture was refluxed for 3 h. Then the solvent was evaporated, and an aqueous solution of $NaHCO_3$ was added to pH 8. The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and dried with anhydrous $MgSO_4$ (3 g) for 12 h. Then dichloromethane was evaporated, and the crude product was recrystallized from MeOH to give compound **4** as a white solid (0.808 g, 49%); mp: 65–66°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.95–2.05 (m, 4H, pyrrolidine), 3.28–3.38 (m, 4H, pyrrolidine), 3.99 (s, 3H, OCH_3), 6.49 (dd, $J_1 = 5.3$ Hz, $J_2 = 1.9$ Hz, 1H, H-5), 7.28 (s, 1H, H-3), 8.30 (d, $J = 5.3$ Hz, 1H, H-6); IR (KBr, cm^{-1}): 2862 (ν C—H), 1740 (ν C=O), 1602 (ν C=C), 1538, 1393, 1302, 1240 (ν C—O), 1131 (ν C—N), 1091, 1011, 783 (γ C—H). Anal. Calcd for $C_{11}H_{14}N_2O_2$ (206.24): C, 64.06; H, 6.84; N, 13.59. Found: C, 63.88; H, 6.89; N, 13.52.

*General Procedure for the Synthesis of Compounds **5a** and **5b***

Methyl 4-(pyrrolidin-1-yl)picolinate (0.412 g, 2 mmol) (for **5a**) or methyl pyrimidine-2-carboxylate (0.276 g, 2 mmol) (for **5b**) was dissolved in EtOH (20 mL), and methylhydrazine (0.2 mL, 4 mmol) was added. The mixture was refluxed for 2 h, and then ethanol was evaporated. The residue was dissolved in boiling toluene (30 mL). After cooling down, the precipitate was filtered off and recrystallized from MeOH.

*N'-Methyl-4-(pyrrolidin-1-yl)picolinohydrazide (**5a**).* Product **5a** was isolated as a white solid (0.198 g, 45%); mp: 184–186°C; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.92–2.02 (m, 4H, pyrrolidine), 2.72 (s, 3H, NCH_3), 3.25–3.35 (m, 4H, pyrrolidine), 4.95 (s, 1H, NH), 6.46 (dd, $J_1 = 5.8$ Hz, $J_2 = 2.4$ Hz, 1H, H-5), 7.34 (d, $J = 2.4$ Hz, 1H, H-3), 8.10 (d, $J = 5.8$ Hz, 1H, H-6), 9.40 (s, 1H, NH); IR (KBr, cm^{-1}): 3256, 3156 (ν N—H), 2861 (ν C—H), 1658 (ν C=O), 1602 (ν C=C), 1503, 1392, 1216 (ν C—N), 987 (γ C—H), 706 (γ N—H) cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_4O$ (220.27): C, 59.98; H, 7.32; N, 25.44. Found: C, 59.80; H, 7.29; N, 25.39.

*N'-Methylpyrimidine-2-carbohydrazide (**5b**).* Product **5b** was isolated as a white solid (0.288 g, 95%); mp: 102–103°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 2.74 (s, 3H, NCH_3), 6.85 (bs, 2H, 2NH), 7.43 (t, $J =$ 5.1 Hz, 1H, H-5), 8.84 (d, $J = 5.1$ Hz, 2H, H-4, H-6); IR (KBr, cm^{-1}): 3386, 3246 (ν N—H), 2969 (ν C—H), 1690 (ν C=O), 1650, 1563 (ν N—H), 1476 (ν C=C), 1401, 1086, 838 (γ C—H). Anal. Calcd for $C_6H_8N_4O$ (152.15): C, 47.36; H, 5.30; N, 36.82. Found: C, 47.25; H, 5.28; N, 36.74.

*General Procedure for the Synthesis of **6a** and **6b***

Compound **5a** (1.10 g, 5 mmol) or **5b** (0.76 g, 5 mmol) was suspended in EtOH (20 mL), TEA (0.84 mL, 6 mmol) and CS_2(0.36 mL, 6 mmol) were added, and the mixture was stirred for 2 h at an ambient temperature. Then MeI (0.311 mL, 5 mmol) was added, and the mixture was stirred for another 2 h. The precipitate was filtered off and recrystallized from MeOH.

*Methyl 1-methyl-2-[4-(pyrrolidin-1-yl)picolinoyl] hydrazinecarbodithioate (**6a**).* Product **6a** was isolated as a yellow solid (1.10 g, 71%); mp: 185–186°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 1.93–2.03 (m, 4H, pyrrolidine), 2.53 (s, 3H, SCH_3), 3.27–3.37 (m, 4H, pyrrolidine), 3.79 (s, 3H, NCH_3), 6.49 (dd, $J_1 = 5.9$ Hz, $J_2 = 2.5$ Hz, 1H, H-5), 7.37 (d, $J = 2.5$ Hz, 1H, H-3), 8.13 (d, $J = 5.9$ Hz, 1H, H-6), 9.58 (s, 1H, NH); IR (KBr, cm^{-1}): 3300 (ν N—H), 2852 (ν C—H), 1687 (ν C=O), 1607 (ν C=C), 1506, 1476 (ν C=C), 1272 (ν C—N), 1095 (ν C=S), 1000, 895 (γ C—H), 782 (γ N—H), 605$^-$. Anal. Calcd for $C_{13}H_{18}N_4OS_2$ (310.44): C, 50.30; H, 5.82; N, 18.05; S, 20.66. Found: C, 50.41; H, 5.80; N, 18.10; S, 20.59.

*Methyl 1-methyl-2-(pyrimidine-2-carbonyl) hydrazinecarbodithioate (**6b**).* Product **6b** was isolated as a white solid (0.302 g, 25%); mp: 254–255°C; ^{1}H NMR ($CDCl_3$) δ (ppm):δ.58 (s, 3H, SCH_3), 3.85 (s, 3H, NCH_3), 7.56 (t, $J = 5.2$ Hz, 1H, H-5), 8.97 (d, $J = 5.2$ Hz, 2H, H-4, H-6), 10.03 (s, 1H, NH); IR (KBr, cm^{-1}):

3172 (ν N—H), 2913 (ν C—H), 1704 (ν C=O), 1568 (ν C=C), 1505,1410 (ν C=C), 1361, 1096 (ν C=S), 958 (γ C—H), 634 (γ N—H)$^-$. Anal. Calcd for $C_8H_{10}N_4OS_2$ (242.32): C, 39.65; H, 4.16; N, 23.12; S, 26.46. Found: C, 39.61; H, 4.17; N, 23.08; S, 26.52.

General Procedure for the Synthesis of **7a** *and* **7b**

Compound **6a** (0.309 g, 1 mmol) or **6b** (0.242 g, 1 mmol) was dissolved in EtOH (5 mL), and TEA (0.5 mL, 3.5 mmol) was added. The mixture was refluxed for 4 h. After cooling down, the precipitate was filtered off and recrystallized from MeOH.

*3-Methyl-5-[4-(pyrrolidin-1-yl)pyridin-2-yl]-1,3,4-oxadiazole-2(3H)-thione (**7a**).* Product **7a** was isolated as a yellow solid (0.180 g, 69%); mp: 210–211°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 1.97–2.07 (m, 4H, pyrrolidine), 3.28–2.38 (m, 4H, pyrrolidine), 3.82 (s, 3H, NCH_3), 6.49 (dd, $J_1 = 6.1$ Hz, $J_2 = 2.5$ Hz, 1H, H-5), 7.01 (d, $J = 2.5$ Hz, 1H, H-3), 8.31 (d, $J = 6.1$ Hz, 1H, H-3); IR (KBr, cm^{-1}): 2846 (ν C—H), 1601, 1483 (ν C=C), 1391, 1183 (ν C=S), 1056 (ν C—O), 1001, 832, 814, 738 (γ C—H), 556$^-$. Anal. Calcd for $C_{12}H_{14}N_4OS$ (262.33): C, 54.94; H, 5.38; N, 21.36; S, 12.22. Found: C, 55.08; H, 5.36; N, 21.41; S, 12.19.

*3-Methyl-5-(pyrimidin-2-yl)-1,3,4-oxadiazole-2(3H)-thione (**7b**).* Product **7b** was obtained as a white solid (0.129 g, 67%); mp: 254–255°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 3.85 (s, 3H, NCH_3), 7.49 (t, $J =$ 5.1 Hz, 1H, H-5), 8.94 (d, $J = 5.1$ Hz, 2H, H-4, H-6); IR (KBr, cm^{-1}): 3068 (ν C—H), 1565, 1477, 1426 (ν C=C), 1394, 1353, 1300, 1155 (ν C=S), 1051 (ν C—O), 836, 757 (γ C—H), 692$^-$. Anal. Calcd for $C_7H_6N_4OS$ (194.21): C, 43.29; H, 3.11; N, 28.85; S, 16.51. Found: C, 43.17; H, 3.12; N, 28.78; S, 16.48.

General Procedure for the Synthesis of **8a–e**

Compound **5a** (0.220 g, 1 mmol) or **5b** (0.152 g, 1 mmol) was dissolved in dioxane (3 mL), and 1 mmol of methyl morpholinocarbamodithioate (for **8a** and **8d**), methyl piperidin-1-ylcarbamodithioate (for **8b** and **8e**), methyl 2,2-dihydrazinecarbodithioate (for **8c**), and 10% K_2CO_3 (3 mL) were added. The mixture was refluxed for 6–20 h. Then the solvent was evaporated, 10 g of ice was added, and the precipitate was filtered off and crystallized from MeOH/H_2O (1:1).

*1-Methyl-4-morpholino-3-[4-(pyrrolidin-1-yl) pyridin-2-yl]-1H-1,2,4-triazole-5(4H)-thione (**8a**). Reaction with Methyl Morpholinocarbamodithioate*: Product **8a** was isolated as a yellow solid (0.280 g, 81%); mp: 184–185°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 1.96–2.06 (m, 4H, pyrrolidine), 2.85–2.95 (m, 2H, morpholine), 3.25–2.35 (m, 4H, pyrrolidine), 3.53–3.63 (m, 2H, morpholine), 3.80 (s, 3H, NCH_3), 3.83–3.93 (m, 2H, morpholine), 4.70–4.80 (m, 2H, morpholine), 6.45 (dd, $J_1 = 5.9$ Hz, $J_2 = 2.5$ Hz, 1H, H-5), 7.20 (d, $J = 2.5$ Hz, 1H, H-3), 8.31 (d, $J = 5.9$ Hz, 1H, H-6); IR (KBr, cm^{-1}): 2845 (ν C—H), 1605 (ν C=C), 1542, 1330 (ν N=N), 1109 (ν C=S), 1002, 849, 709 (γ C—H), 535. Anal. Calcd for $C_{16}H_{22}N_6OS$ (346.45): C, 55.47; H, 6.40; N, 24.26; S, 9.26. Found: C, 55.36; H, 6.38; N, 24.33; S, 9.23.

*1-Methyl-4-(piperidin-1-yl)-3-[4-(pyrrolidin-1-yl) pyridin-2-yl]-1H-1,2,4-triazole-5(4H)-thione (**8b**). Reaction with Methyl Piperidin-1-ylcarbamodithioate*: Product **8b** was isolated as a white solid (0.299 g, 87%); mp: 105–107°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 1.55–1.87 (m, 6H, piperidine), 1.97–2.07 (m, 4H, pyrrolidine), 2.93–3.03 (m, 2H, piperidine), 3.34–3.44 (m, 4H, pyrrolidine), 3.82 (s, 3H, NCH_3), 4.45–4.55 (m, 2H, piperidine), 6.46 (dd, $J_1 = 6.1$ Hz, $J_2 = 2.4$ Hz, 1H, H-5), 7.45 (d, $J = 2.4$ Hz, 1H, H-3), 8.34 (d, $J = 6.1$ Hz, 1H, H-6); IR (KBr, cm^{-1}): 2852 (ν C—H), 1610 (ν C=C), 1543 (ν C=N), 1444 (ν C=C), 1329, 1207, 1001, 799 (γ C—H), 664$^-$. Anal. Calcd for $C_{17}H_{24}N_6S$ (344.48): C, 59.27; H, 7.02; N, 24.40; S, 9.31. Found: C, 59.12; H, 6.99; N, 24.47; S, 9.33.

*4-(Dimethylamino)-1-methyl-3-[4-(pyrrolidin-1-yl) pyridin-2-yl]-1H-1,2,4-triazole-5(4H)-thione (**8c**). Reaction with Methyl 2,2-Dimethylhydrazinecarbodithioate*: Product **8c** was isolated as a white solid (0.249 g, 82%); mp: 140–142°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 2.06–2.16 (m, 4H, pyrrolidine), 3.43 (s, 6H, $2\times NCH_3$), 3.49–3.59 (m, 4H, pyrrolidine), 3.81 (s, 3H, NCH_3), 6.71 (dd, $J_1 = 5.1$ Hz, $J_2 = 1.9$ Hz, 1H, H-5), 7.29 (s, 1H, H-3), 9.04 (s, 1H, H-6); IR (KBr, cm^{-1}): 2968 (ν C—H), 1609 (ν C=C), 1501, 1460 (ν C=C), 1390 (δ C—H), 1332, 1205, 999, 805 (γ C—H), 580. Anal. Calcd for $C_{14}H_{20}N_6S$ (304.41): C, 55.24; H, 6.62; N, 27.61; S, 10.53. Found: C, 55.08; H, 6.63; N, 27.69; S, 10.50.

*1-Methyl-4-morpholino-3-(pyrimidin-2-yl)-1H-1,2,4-triazole-5(4H)-thione (**8d**). Reaction with Methyl Morpholinocarbamodithioate*: Product **8d** was isolated as a white solid (75 mg, 27%); mp: 142–145°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 2.92–3.02 (m, 2H, morpholine), 3.37–3.47 (m, 2H, morpholine), 3.83 (s, 3H, NCH_3), 3.76–3.86 (m, 2H, morpholine), 4.46–4.56 (m, 2H, morpholine), 7.42 (t, $J = 4.9$ Hz, 1H, H-5), 8.90 (d, $J = 4.9$ Hz, 2H, H-4, H-6); IR (KBr, cm^{-1}): 2853 (ν C—H), 1563 (ν C=C), 1397 (δ C—H), 1328, 1217, 1108 (ν C=S), 1036, 847, 823 (γ

C—H), 717, 648, 536⁻. Anal. Calcd for $C_{11}H_{14}N_6OS$ (278.33): C, 47.44; H, 5.07; N, 30.19; S, 11.52. Found: C, 47.53; H, 5.05; N, 30.10; S, 11.49.

*1-Methyl-4-(piperidin-1-yl)-3-(pyrimidin-2-yl)-1H-1,2,4-triazole-5(4H)-thione (***8e***). Reaction with Methyl Piperidin-1-ylcarbamodithioate*: Product **8e** was obtained as a white solid (0.115 g, 42%); mp: 114–117°C. ^{1}H NMR ($CDCl_3$) δ (ppm)δ 1.15–1.25 (m, 6H, piperidine), 3.00–3.10 (m, 2H, piperidine), 3.82 (s, 3H, NCH_3), 4.14–4.28 (m, 2H, piperidine), 7.39 (t, J = 4.9 Hz, 1H, H-5), 8.88 (d, J = 4.9 Hz, 2H, H-4, H-6); IR (KBr, cm^{-1}): 2936 (ν C—H), 1565 (ν C=N), 1453 (ν C=C), 1392 (δ C—H), 1335, 1221, 1024, 821, 797 (γ C—H), 711, 644, 623. Anal. Calcd for $C_{12}H_{16}N_6S$ (276.36): C, 52.15; H, 5.84; N, 30.41; S, 11.60. Found: C, 51.99; H, 5.85; N, 30.49; S, 11.62.

General Procedure for the Synthesis of **9a** *and* **9b**

Compound **6a** (0.620 g, 2 mmol) or **6b** (0.484 g, 2 mmol) was dissolved in hydrazine monohydrate (3 mL, 0.06 mol), and the mixture was refluxed for 5 h. After cooling down, 30 g of ice was added and the precipitate was filtered off and recrystallized from MeOH/H_2O (1:1).

*4-Amino-1-methyl-3-[4-(pyrrolidin-1-yl)pyridin-2-yl]-1H-1,2,4-triazole-5(4H)-thione (***9a***)*. Product **9a** was obtained as a white solid (0.281 g, 51%); mp: 141–145°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 1.90–2.00 (m, 4H, pyrrolidine), 3.25–3.35 (m, 4H, pyrrolidine), 3.77 (s, 3H, NCH_3), 6.57 (s, 2H, NH_2), 6.61 (dd, J_1 = 5.8 Hz, J_2 = 2.5 Hz, 1H, H-5), 7.06 (s, 1H, H-3), 8.22 (d, J = 5.8 Hz, 1H, H-6); IR (KBr, cm^{-1}): 3448, 3288 (ν N—H), 2850 (ν C—H), 1603 (ν C=C), 1508, 1321, 1206, 1006, 819 (γ C—H), 534. Anal. Calcd for $C_{12}H_{16}N_6S$ (276.36): C, 52.15; H, 5.84; N, 30.41; S, 11.60. Found: C, 51.99; H, 5.83; N, 30.38; S, 11.57.

*4-Amino-1-methyl-3-(pyrimidin-2-yl)-1H-1,2,4-triazole-5(4H)-thione (***9b***)*. Product **9b** was isolated as a white solid (0.241 g, 58%); mp: 170–174°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 3.95 (s, 3H, NCH_3), 5.66 (s, 2H, NH_2), 7.43 (t, J = 4.9 Hz, 1H, H-5), 8.92 (d, J = 4.9 Hz, 2H, H-4, H-6); IR (KBr, cm^{-1}): 3274 (ν N—H), 1571, 1474, 1446 (ν C=C), 1321, 1197 (ν C=S), 1009, 827 (γ C—H), 678, 635, 534. Anal. Calcd for $C_7H_8N_6S$ (208.24): C, 40.37; H, 3.87; N, 40.36; S, 15.40. Found: C, 40.25; H, 3.88; N, 40.24; S, 15.43.

General Procedure for the Synthesis of **10a** *and* **10b**

Compound **9b** (0.208 g, 1 mmol) was dissolved in EtOH (10 mL), and 4-bromobenzaldehyde (0.185 g, 1 mmol) (for **10a**) or 4-hydroxy-3-methoxybenzaldehyde (0.152 g, 1 mmol) (for **10b**) was added. The mixture was refluxed for 3 h. After cooling down, the precipitate was filtered off and recrystallized from EtOH.

*4-(4-Bromobenzylideneamino)-1-methyl-3-(pyrimidin-2-yl)-1H-1,2,4-triazole-5(4H)-thione (***10a***). Reaction with 4-Bromobenzaldehyde*: Product **10a** was isolated as a white solid (0.277 g, 74%); mp: 180–181°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 3.97 (s, 3H, NCH_3), 7.38 (t, J = 4.8 Hz, 1H, H-5), 7.48–7.58 (m, 4H, 4-BrPh), 8.87 (d, J = 4.8 Hz, 2H, H-4, H-6), 9.74 (s, 1H, CH); IR (KBr, cm^{-1}): 3058 (ν C—H), 1560, 1452, 1440 (ν C=C), 1319, 1216, 1068, 1010, 836 (γ C—H), 812, 671, 628, 518. Anal. Calcd for $C_{14}H_{11}BrN_6S$ (375.2): C, 44.81; H, 2.95; N, 22.40; S, 8.55. Found: C, 44.68; H, 2.94; N, 22.37; S, 8.52.

*4-(4-Hydroxy-3-methoxybenzylideneamino)-1-methyl-3-(pyrimidin-2-yl)-1H-1,2,4-triazole-5(4H)-thione (***10b***). Reaction with 4-Hydroxy-3-methoxybenzaldehyde*: Product **10b** was obtained as a white solid (0.318 g, 93%); mp: 176–179°C; ^{1}H NMR ($CDCl_3$) δ (ppm)δ 3.96 (s, 3H, NCH_3), 3.98 (s, 3H, OCH_3), 6.97 (t, J = 8.1 Hz, 1H, H-5), 7.20–7.30 (m, 3H, arom.), 8.95 (d, J = 8.1 Hz, 2H, H-4, H-6), 9.29 (s, 1H, CH), 9.82 (s, 1H, OH); IR (KBr, cm^{-1}): 3442 (ν O—H), 1600, 1564, 1520 (ν C=C), 1393 (δ C—H), 1299, 1193 (ν C=S), 1107 (ν C—O), 1025, 860 (γ C—H), 783, 660 (γ O—H). Anal. Calcd for $C_{15}H_{14}N_6O_2S$ (342.38): C, 52.62; H, 4.12; N, 24.55; S, 9.37. Found: C, 52.48; H, 4.11; N, 24.49; S, 9.35.

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