The Synthesis and Antibacterial Activity of Novel 4-Pyrrolidin-3-cyanopyridine Derivatives

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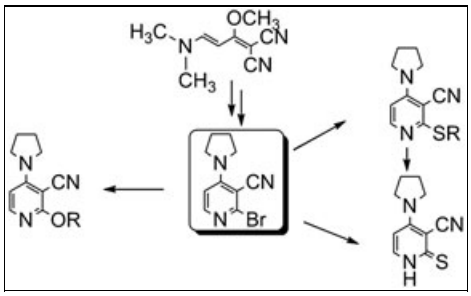

2-Bromo-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile obtained from 2-(1,3-bis(pyrrolidin-1-yl)allylidene) malononitrile has been used as a substrate for the synthesis of new cyanopyridine derivatives: 2-methoxy, 2-phenoxy, 2-aminoethylthio, and 2-thioxo. 4-(Pyrrolidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile **7** in reaction with suitable alkyl and aminoalkyl halides gave respective sulfides. All synthesized compounds were evaluated for their antimicrobial activity against 26 aerobic and anaerobic bacteria. Determined minimal inhibitory concentration values ranged from 6.2 to 100 μg/mL. Derivatives **1**, **3**, **4**, **6**, and **12** were the most active compounds.

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INTRODUCTION

Bacterial infections caused by pathogenic strains (*Myobacterium tuberculosis*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*) are known to express multidrug resistance [1,2]. This phenomenon is a worrying cause of treatment failure and carries great danger especially for HIV-positive patients [3]. Thus, there is an urgent need for novel chemotherapeutics active against resistant strains.

For many years, interest in pyridine derivatives as potential antimicrobial agents has not diminished. Isoniazid having 4-pyridine system in its structure is one of the front-line antituberculous drugs. Activity of pyridine derivatives against other bacterial species has been also reported [4–6].

The present work is a continuation of our investigation on 3-cyanopyridine derivatives with special consideration of compounds containing sulfur and oxygen in α-position in the pyridine ring. Our main goal was the synthesis of new pyridine derivatives with potential antibacterial activity. The studies of Dunn and Norrie showed various reactivities of cyanopyridines containing halogen atoms. Reactivity of halogen atoms depends on their position in pyridine ring [7]. Substitution of the halogen atom by thioalkyl or thioamide groups gives rise to tuberculostatic activity of the resulting compounds [8]. 2-Mercaptopyridine derivatives are key starting materials for the synthesis of more complex compounds comprising three-membered rings, which are important groups in tumor treatment [9], whereas acyclic 2-mercaptopyridine derivatives are used in the treatment of blood circulation diseases [10]. Studies on compounds obtained from nucleophilic substitution of the halogen atom by aliphatic alcohols and phenols revealed activity in reducing of blood pressure by blocking β-adrenergic receptors [11] and chemotherapeutic activity against picornaviruses [12].

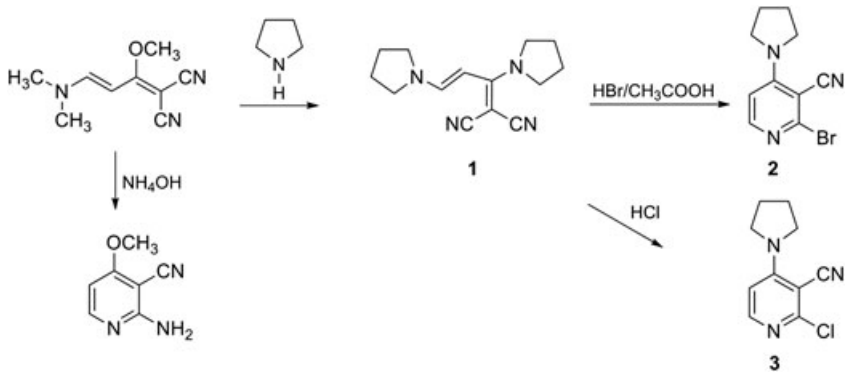
RESULTS AND DISCUSSION

Mittelbach [13] reported the cyclization of 1,1-dicyano-4-(*N*,*N*-dimethylamino)-2-methoxy-1,3-butadiene with ammonia to give 2-amino-3-cyano-4-methoxypyridine (Scheme 1). We attempted the analogous cyclization of 1,1-dicyano-4-(*N*, *N*-dimethylamino)-2-methoxy-1,3-butadiene with pyrrolidine.

The pyrrolidine ring should end up in 2-position of the pyridine ring, keeping the methoxy group in 4-position. Surprisingly, instead of the expected product, we obtained butadiene **1**, the structure of which was confirmed by ^{1}H NMR spectroscopy and X-ray crystallography.

The skeleton of **1** consists of conjugated system of single and multiple bonds including two pyrrolidine N atoms, which participate in the conjugation through their

Scheme 1



lone pairs. The conjugation promotes general planarity of the molecule (Figure 1) and is confirmed clearly by shortening of formally single C–C bonds to 1.414(2) (two C1–CN) and 1.435(2) (C2–C3) as well as of the single C–N bonds to 1.327(2) and 1.339(2) Å for C4–N5 and C2–N10, respectively, with simultaneous elongation of double (C1═C2, C3═C4) and triple CN bonds (Table 1). Flattening of **1** results in spatial clash between H(C4) and the nitrile group comprising N18 atom. The tension is eased by significant twist along C2–C3 bond as evidenced by C1–C2–C3–C4 torsion angle of −27.1(2)° (Table 1). Because of the twist, the nitrile group is placed out (above in Figure 1) of C3═C4 plane with easier access to C4 (sp^2) atom, which is not shielded any longer by its H atom, allowing a cyclization reaction leading to pyridine ring formation (Scheme 1).

Compound **1** was cyclized to the 2-halogenopyridine derivatives **2** and **3** with the use of concentrated HCl or 33% HBr/CH_3COOH solution, respectively (Scheme 1). Compound **2** was obtained in higher yield than compound **3** and was used in the following reactions (Scheme 2).

When the 2-bromopyridine **2** was refluxed with sodium methylate, sodium phenylate, or sodium *p*-chlorophenylate, the respective products **4–6** were formed. The bromine atom in **2** was quite easily substituted by a thiol group with the use of thiourea to form compound **7** with good yield. Both compounds **2** and **7** were used to synthesize the sulfides **8–13**. Heating of compound **2** with 2-aminoethanethiol gave the derivative **8**. The thione **7** reacted with methyl or ethyl iodide in ethanol to form the corresponding thiomethyl or thioethyl pyridine derivatives **9** and **10**. Treating compound **7** with (*N*,*N*-diethyl)-1-chloroethylamine hydrochloride, 1-(2-chloroethyl)pyrrolidine hydrochloride, and 4-(2-chloroethyl) morpholine hydrochloride gave compounds **11**, **12**, and **13**, respectively (Scheme 2).

Compounds **2** and **7** as well as the general method to convert them to their sulfur-containing derivatives have been already reported in our recent article [15]. Particular attention should be paid to the structure of compound **7**, which can occur in two tautomeric forms. Previously, it was presented as a 2-thiole. However, reanalysis of IR and ^1H NMR spectra showed something else. In IR spectrum, besides the band at 3127 cm^{-1}, which corresponds to the valence vibrations of N–H bonds, there is a band at 1244 cm^{-1}, characteristic for the C═S group. In addition, in ^1H NMR spectrum of this compound resonance signal

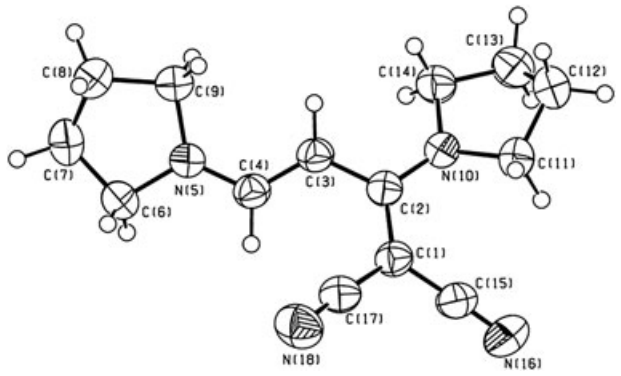


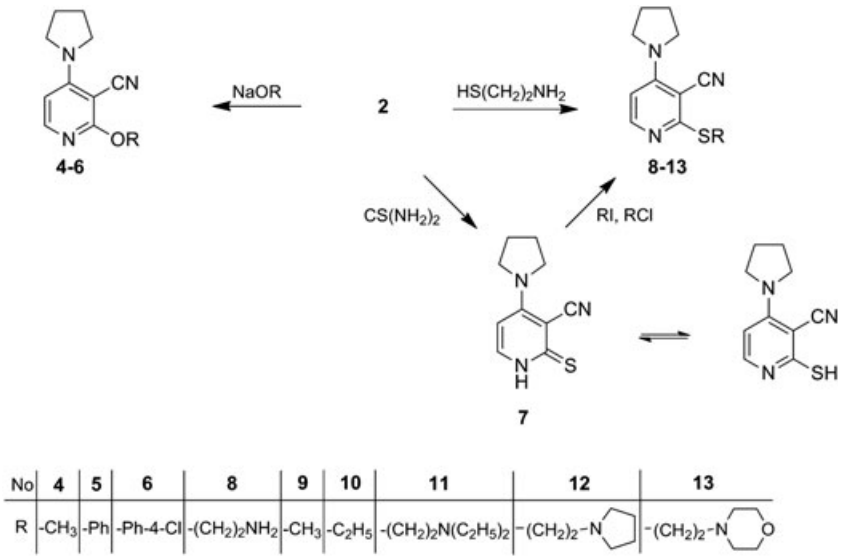
Figure 1. ORTEP view of compound **1** in the crystal. Displacement ellipsoids are shown at the 50% probability level (PLATON [14]).

Table 1

Selected bond lengths (Å) and torsion angles (°) for compound **1**.

Bond lengths	
C1–C2	1.418(2)
C1–C15	1.414(2)
C1–C17	1.414(2)
C2–C3	1.435(2)
C2–N10	1.339(2)
C3–C4	1.360(2)
C4–N5	1.327(2)
C15–N16	1.147(2)
C17–N18	1.144(2)
Torsion angles	
C1–C2–C3–C4	−27.1(2)
C2–C3–C4–N5	175.6(1)

Scheme 2



occurs at 12.60 ppm with an intensity of one proton corresponding to the N–H group, which indicates that the resulting product **7** takes thione tautomeric form.

All the synthesized compounds were evaluated for their antimicrobial activity *in vitro* (Table 2). The investigation included 26 strains of anaerobic bacteria and 26 strains of aerobic bacteria: *Escherichia coli* (6), *Pseudomonas aeruginosa* (7), *Acinetobacter baumannie* (5), *S. aureus* (3), *Enterococcus faecalis* (4), *Corynebacterium minutissimum* (2) as well as five standard strains: *S. aureus* ATCC 25923, *E. faecalis* ATCC 29212, *Serratia marcescenes* ATCC 8100, *Acinetobacter baumannie* ATCC 19606, and *E coli* ATCC 25922. The aerobic bacteria and the anaerobic bacteria were isolated from patients with infection of the oral cavity, respiratory tract, and abdominal cavity. Metronidazole and amikacin were used as reference drugs.

The susceptibility for anaerobic species was determined by means of plate dilution technique in Brucella agar supplemented with 5% lamb blood [16–18], whereas the data for aerobic ones was determined in Muller–Hinton agar. The incubation was performed at 37°C for 48 h under anaerobic and for 24 h under aerobic conditions. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of the respective derivative that inhibited growth of bacteria.

The tested derivatives exhibited differential activity against anaerobic bacteria, but all of them were much less active than reference drugs, metronidazole (MIC 0.4–100 μg/mL) and amikacin (6.2–25 μg/mL). At concentrations that ranged from ≤6.2 to 100 μg/mL, the anaerobes were the most susceptible to derivatives **1** (85%), **4** (77%), and **3** (73%) and the least susceptible to derivatives **6** and **12** (62%), **9** (46%), and **2** (42%) in the same concentration range.

The anaerobes were insensitive or almost insensitive to derivatives **8** and **11** (for 100% strains MIC ≥ 200 μg/mL), **7** (for 77% strains MIC ≥ 200 μg/mL), **5** (for 73% MIC ≥ 200 μg/mL), and **10** and **13** (for 62% strains MIC ≥ 200 μg/mL).

Derivative **7** showed the highest activity for the investigated strains of Gram-positive aerobic bacteria in the range from ≤6.2 to 100 μg/mL (15%). Most derivatives inhibited growth of only one to three strains of aerobic bacteria. Derivatives **8**, **9**, and **11** did not exhibit any activity on aerobic bacteria. Against the Gram-negative aerobic bacteria, no activity was observed.

EXPERIMENTAL

All melting points were determined with a Boetius apparatus and are uncorrected. The IR spectra were recorded with a Satellite spectrophotometer, and ^{1}H NMR spectra were obtained with a Varian Gemini 200-MHz apparatus (Varian, Palo Alto, CA). The results of elemental analyses (% C, H, and N) for all the compounds were in agreement with the calculated values within ±0.3% range. The reaction yields and physical constants of the compounds are given in Table 3.

2-(1,3-Bis(pyrrolidin-1-yl)allylidene)malononitrile (1). 1,1-Dicyano-4-(*N*,*N*-dimethyloamino)-2-methoxy-1,3-butadiene (0.01 mol, 1.77 g) was dissolved in pyrrolidine (0.06 mol, 5 mL), and the reaction mixture was refluxed for 2 h. After cooling down, the precipitate was filtered off and recrystallized from MeOH (20 mL). IR (KBr): 2984, 2875 (ν C-H), 2190, 2164 (ν C≡N), 1613, 1457 (ν C=C), 1390 (ν C-N), 1281 (ν C–O), 969, 775 (γ C–H), 554 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.96–3.57 (m, 16H, 8CH_2); 4.34 (d, J = 12.2 Hz, CH); 7.74 (d, J = 10.7 Hz, 1H, CH) ppm.

2-Bromo-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (2). Compound **1** (5 mmol, 1.21 g) was treated with 33% HBr/CH_3COOH

Table 2

In vitro antibacterial activity of compounds **1–13**.

		MIC (μg/mL)												
Tested strains	**Ref**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Anaerobic bacteria														
Gram positive														
Finegoldia magna	0.4	100	50	100	100	≥200	100	≥200	≥200	100	≥200	≥200	50	≤6.2
Micromonas micros	0.4	50	25	12.5	≤6.2	≤6.2	50	≤6.2	≥200	100	25	≥200	50	25
Actinomyces israeli	1.6	≤6.2	50	12.5	25	≤6.2	100	≤6.2	≥200	100	≥200	≥200	50	25
Actinomyces naesulundii	6.2	100	100	100	≥200	25	100	≥200	≥200	25	100	≥200	25	25
Propionibacterium acnes	50	100	100	100	≤6.2	≥200	100	≥200	≥200	100	≥200	≥200	50	100
Propionibacterium granulosum	100	100	≥200	≥200	≥200	≥200	≥200	≥200	≥200	100	100	≥200	50	≥200
Gram negative														
Prevotella bivia	0.4	100	50	100	25	≥200	100	≥200	≥200	50	50	≥200	≤6.2	25
Prevotella buccalis	0.4	100	≥200	≥200	25	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Prevotella intermedia	0.4	100	≥200	100	25	≥200	≥200	≥200	≥200	100	25	≥200	100	100
Porphyromonas saccharolytica	0.4	100	50	100	25	100	100	25	≥200	100	100	≥200	100	≥200
Fusobacterium nucleatum	0.4	100	50	100	25	≤6.2	100	25	≥200	≥200	≥200	≥200	≥200	≥200
Bacteroides forsythus	1.6	100	50	100	100	≥200	≥200	≥200	≥200	100	≥200	≥200	≥200	≥200
Bacteroides fragilis	0.4	50	50	100	25	12.5	100	50	≥200	100	100	≥200	25	100
Aerobic bacteria														
Gram positive														
Staphylococcus aureus	6.2	50	100	100	≥200	≥200	≥200	25	≥200	≥200	≥200	≥200	≥200	≥200
Enterococcus faecalis	–	≥200	≥200	≥200	≥200	50	≥200	50	≥200	≥200	100	≥200	≥200	50
Corynebacterium minutissimum	25	50	12.5	100	12.5	50	25	50	≥200	≥200	50	≥200	25	50
Gram negative														
Acinetobacter aumannii	6.2	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Escherichia coli	6.2	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Pseudomonas aeruginosa	6.2	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200

MIC values were determined by twofold plate dilution technique.
Ref, reference drug: metronidazole for anaerobic bacteria test and amikacin for aerobic bacteria test.

Table 3

Characteristics of newly synthesized compounds **1**, **3–6**, and **8–13**.

No	mp (°C) Solvent	Formula MW	Yield (%)	Calcd/Found					
				C		H		N	
1	179–180 MeOH	$C_{14}H_{18}N_4$ 242.32	80	69.39	69.25	7.49	7.48	23.12	23.16
3	170–171 MeOH	$C_{10}H_{10}ClN_3$ 207.66	31	57.84	57.78	4.85	4.86	20.24	20.28
4	111–113 MeOH/H_2O	$C_{11}H_{13}N_3O$ 203.24	43	65.01	65.11	6.45	6.45	20.68	20.72
5	167–169 MeOH	$C_{16}H_{15}N_3O$ 265.31	16	72.43	72.34	5.70	5.71	15.84	15.81
6	141–143 MeOH	$C_{16}H_{14}ClN_3O$ 299.76	38	64.11	64.23	4.71	4.72	14.02	14.05
8	128–130 MeOH	$C_{12}H_{16}N_4S$ 248.35	82	58.04	57.98	6.49	6.50	22.56	22.53
9	117–118 MeOH	$C_{11}H_{13}N_3S$ 219.31	85	60.24	60.33	5.97	5.96	19.16	19.20
10	93–94 MeOH/H_2O	$C_{12}H_{15}N_3S$ 233.34	71	61.77	61.68	6.48	6.47	18.01	18.04
11	63–64 MeOH	$C_{16}H_{24}N_4S$ 304.46	90	63.12	63.19	7.95	7.60	18.40	18.43
12	93–95 MeOH	$C_{16}H_{22}N_4S$ 302.44	76	63.54	63.63	7.33	7.34	18.53	18.51
13	120–124 MeOH	$C_{16}H_{22}N_4OS$ 318.44	46	60.35	60.42	6.96	6.97	17.59	17.56

(5 mL), the reaction mixture was left for 24 h at room temperature, and then poured into ice and alkalized by concentrated ammonia. The product was filtered off and recrystallized from MeOH (20 mL). Compound characteristic has been found to be identical with that recently described (mp 124–126°C) [15].

2-Chloro-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (3). Compound **1** (5 mmol, 1.21 g) was dissolved in 15 mL of concentrated HCl, the reaction mixture was left for 24 h at room temperature, and then poured into ice and alkalized by concentrated ammonia. The precipitate was filtered off and recrystallized from MeOH (20 mL). IR (KBr): 3086 (ν C–H), 2231 (ν C≡N), 1579, 1481 (ν C=C), 1036 (δ C–H), 842 (γ C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.94–2.01 (m, 4H, $2CH_2$); 3.61–3.67 (m, 4H, $2CH_2$); 6.96 (d, $J = 6.3$ Hz, 1H, pyridine); 7.87 (d, $J = 6.3$ Hz, 1H, pyridine) ppm.

2-Methoxy-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (4). Metallic sodium (5 mmol, 0.115 g) was dissolved in 10 mL of MeOH. To this solution, compound **2** (4 mmol, 1.00 g) was added and the reaction mixture was refluxed for 1 h. The solution was cooled down to ambient temperature, and the precipitate was filtered off and recrystallized from MeOH/H_2O (1:3) (10 mL). IR (KBr): 2947, 2874 (ν C–H), 2210 (ν C≡N), 1603, 1536 (ν C=C), 1380 (ν C–N), 1295, 1108 (ν C–O), 798 (γ C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.96–2.02 (m, 4H, $2CH_2$); 3.64–3.70 (m, 4H, $2CH_2$); 3.95 (s, 3H, CH_3); 6.11 (d, $J = 6.3$ Hz, 1H, pyridine); 7.76 (d, $J = 6.3$ Hz, 1H, pyridine) ppm.

General method for the synthesis of 2-phenoxy-4-(pyrrolidin-1-yl)pyridine-3-carbonitriles (5, 6). KOH (9 mmol, 0.504 g) was dissolved in 10 mL of EtOH and treated with phenol (5 mmol, 0.47 g) or *p*-chlorophenol (5 mmol, 0.642 g). The solvent was evaporated, and then compound **2** (5 mmol, 1.26 g) and 3 mL of DMF were added. The solution was refluxed for 5 h. Then ice was added, and the precipitate was filtered off and recrystallized from MeOH (15 mL).

2-Phenoxy-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (5). IR (KBr): 2922, 2853 (ν C–H), 2213 (ν C≡N), 1596, 1532 (ν C=C), 1208, 1091 (ν C–O), 780, 722 (γ C–H) cm^{-1}. ^1H NMR ($CDCl_3$): 2.02–2.08 (m, 4H, $2CH_2$); 3.71–3.77 (m, 4H, $2CH_2$); 6.19 (d, $J = 6.3$ Hz, 1H, pyridine); 7.22–7.42 (m, 5H, Ph); 7.76 (d, $J = 6.3$ Hz, 1H, pyridine) ppm.

2-(4-Chlorophenoxy)-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (6). IR (KBr): 3094, 2964, 2877 (ν C–H), 2215(ν C≡N), 1597, 1533 (ν C=C), 1385 (ν C–N), 1212, 1087 (ν C–O), 859, 801 (ν C–H) cm^{-1}. ^1H NMR ($CDCl_3$): 2.01–2.07 (s, 4H, $2CH_2$); 3.70–3.76 (s, 4H, $2CH_2$); 6.20 (d, $J = 6.3$ Hz, 1H, pyridine); 7.10 (d, $J = 8.8$ Hz, 2H, Ph); 7.35 (d, 2H, $J = 8.8$ Hz, Ph); 7.74 (d, $J = 6.3$ Hz, 1H, pyridine) ppm.

4-(Pyrrolidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (7). Compound **2** (4 mmol, 1.00 g) was dissolved in 15 mL of MeOH. To the solution, thiourea (12 mmol, 0.912 g) was added. Then the reaction mixture was shaken well for 2 min to obtain a suspension, which was refluxed for 40 min. The precipitate was filtered off, then dissolved in 20 mL of 10% NaOH, and the solution was refluxed for 15 min. After this time, the mixture was cooled down and acidified with acetic acid. The solid formed was filtered off and recrystallized from MeOH (20 mL). The compounds' characteristic (mp and elemental analysis) and reaction yield have been found to be identical with that recently described [15]. IR (KBr): 3127 (ν N–H), 2960 (ν C–H), 2208 (ν C≡N), 1633 (δ N–H), 1526, 1456 (ν C=C), 1244 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.92–1.98 (m, 4H, $2CH_2$); 3.67 (m, 4H, $2CH_2$); 6.28 (d, $J = 7.0$ Hz, 1H, pyridine); 7.40 (d, $J = 7.0$ Hz, 1H, pyridine); 12.60 (s, 1H, NH) ppm.

2-(2-Aminoethylthio)-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (8). KOH (12 mmol, 0.672 g) was dissolved in 10 mL of EtOH and 5 mL of water. Then compound **2** (5 mmol, 1.26 g) and cysteamine (5 mmol, 0.385 g) were added. The solution was refluxed for 2 h, cooled down to ambient temperature, and the precipitated product was filtered off and recrystallized from MeOH (10 mL). IR (KBr): 2976, 2871 (ν C–H), 2200 (ν C≡N), 1581 (ν C=C), 1335 (ν C–N), 1006 (δ C–H), 805 (γ C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.41 (s, 2H, NH_2); 1.99–2.05 (m, 4H, $2CH_2$); 2.97 (t, $J = 6.3$ Hz, 2H, CH_2); 3.39 (t, $J = 6.3$ Hz, 2H, CH_2); 3.61–3.67 (m, 4H, $2CH_2$); 6.17 (d, $J = 6.2$ Hz, 1H, pyridine); 7.95 (d, $J = 6.2$ Hz, 1H, pyridine) ppm.

2-(Methylthio)-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (9). KOH (3 mmol, 0.168 g) was dissolved in 10 mL of EtOH and 5 mL of water. To the solution, compound **7** (1.5 mmol, 0.307 g) was added. After it had dissolved, methyl iodide (2 mmol, 0.124 mL) was added dropwise. Then the reaction

mixture was refluxed for 30 min. After cooling to ambient temperature, the precipitated solid was filtered off and recrystallized from MeOH (10 mL). IR (KBr): 2973, 2872 (ν C–H), 2194 (ν C≡N), 1573 (ν C═C), 1334 (ν C–N), 1008 (δ C–H), 787 (δ C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.95–2.01 (m, 4H, $2CH_2$); 2.54 (s, 3H, CH_3); 3.62–3.68 (m, 4H, $2CH_2$); 6.18 (d, $J = 6.2$ Hz, 1H, pyridine); 7.99 (d, $J = 6.2$ Hz, 1H, pyridine) ppm.

2-(Ethylthio)-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (10). KOH (1.5 mmol, 0.084 g) was dissolved in 10 mL of EtOH. To the solution, compound **7** (2 mmol, 0.41 g) was added. After it had dissolved, ethyl iodide (2 mmol, 0.159 mL) was added dropwise. Then the reaction mixture was refluxed for 30 min. The solvent was evaporated, and ice was added. The crude solid was filtered off and recrystallized from MeOH/H_2O (1:1) (10 mL). IR (KBr): 2959, 2863 (ν C–H), 2200 (ν C≡N), 1576 (ν C═C), 1330 (ν C–N), 1004 (δ C–H), 792 (γ C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.36 (t, $J = 7.3$ Hz, 3H, CH_3); 1.99–2.05 (m, 4H, $2CH_2$); 3.20 (q, $J_1 = 14.7$ Hz, $J_2 = 7.3$ Hz, 2H, CH_2); 3.62–3.68 (m, 4H, $2CH_2$); 6.18 (d, $J = 6.3$ Hz, 1H, pyridine); 8.01 (d, $J = 6.3$ Hz, 1H, pyridine) ppm.

2-[2-(Diethylamino)ethylthio]-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (11). KOH (10 mmol, 0.56 g) was dissolved in 10 mL of EtOH, and compound **7** (5 mmol, 1.02 g) was added. To the solution, 2-(*N*,*N*-diethyl)-1-chloroethane hydrochloride (5 mmol, 0.86 g) was added. The reaction mixture was refluxed with stirring for 3 h. The solution was treated with water (40 mL), and the precipitated product was filtered off and recrystallized from MeOH/H_2O (1:1) (20 mL). IR (KBr): 2967, 2858 (ν C–H), 2200 (ν C≡N), 1582, 1497(ν C═C), 1334 (ν C–N), 1005 (δ C–H), 805 (γ C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.07 (t, $J = 7.2$ Hz, 6H, $2CH_3$); 1.98–2.04 (m, 4H, $2CH_2$); 2.57 (q, $J_1 = 14.6$ Hz $J_2 = 7.2$ Hz, 4H, $2NCH_2$); 2.75 (t, $J = 5.0$ Hz, 2H CH_2); 3.25 (t, $J = 4.8$ Hz, 2H, CH_2); 3.61–3.67 (m, 4H, $2CH_2$); 6.45 (d, $J = 6.2$ Hz, 1H, pyridine); 7.95 (d, $J = 6.2$ Hz, 1H, pyridine) ppm.

General method for the synthesis of 2-(2-aminoethylthio)-4-(pyrrolidin-1-yl)pyridine-3-carbonitriles (12, 13). KOH (6 mmol, 0.336 g) was dissolved in a 2:1 EtOH/H_2O mixture. Compound **7** (2 mmol, 0.41 g) and 1-(2-chloroethyl)pyrrolidine hydrochloride (2 mmol, 0.34 g) or 4-(2-chloroethyl)morpholine hydrochloride (2 mmol, 0.372 g) were added. The mixture was stirred at room temperature for 3 h. After this time, the solvent was evaporated and ice was added. The precipitated product was filtered off and recrystallized from MeOH (15 mL).

2-[2-(Pyrrolidin-1-yl)ethyltio]-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (12). IR (KBr): 2961, 2872 (ν C–H), 2201 (ν C≡N), 1581, 1498 (ν C═C), 1334 (ν C–N), 1006 (δ C–H), 806 (γ C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.75–1.99 (m, 8H, $4CH_2$); 2.56–2.62 (m, 4H, $2CH_2$); 2.88 (t, $J = 7.2$ Hz, 2H, CH_2); 3.34 (t, $J = 7.2$ Hz, 2H, CH_2); 3.60–3.66 (m, 4H, $2CH_2$); 6.15 (d, $J = 6.2$ Hz, 1H, pyridine); 7.98 (d, $J = 6.2$ Hz, 1H, pyridine) ppm.

2-(2-Morpholinoethylthio)-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (13). IR (KBr): 2977, 2861, 2816 (ν C–H), 2201 (ν C≡N), 1579, 1497 (ν C═C), 1334 (ν C–N), 1113, 1006 (δ C–H), 807 (γ C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.98–2.54 (m, 8H, $4CH_2$); 2.68 (t, $J = 7.6$ Hz, 2H, CH_2); 3.30 (t, $J = 7.6$ Hz, 2H, CH_2); 3.64–3.74 (m, 8H, CH_2); 6.15 (d, $J = 6.2$ Hz, 1H, pyridine); 7.95 (d, $J = 6.2$ Hz, 1H, pyridine) ppm.

X-ray crystallography. Single crystals suitable for an X-ray diffraction study were obtained by slow evaporation of a methanolic solution of compound **1**. The diffraction data were collected with a Bruker SMART CCD diffractometer (Bruker, Madison, WI) operating with Mo radiation at room temperature (ω scan) and corrected for absorption [19]. The structure was solved by direct methods [20] and refined by full-matrix least squares [21]. Hydrogen atoms, although clearly visible on Fourier maps, were refined in riding positions with free isotropic thermal parameters. Details of data collection and refinement are summarized in Table 4.

Table 4

Crystal data and refinement parameters for compound **1**.

Empirical formula	$C_{14}H_{18}N_4$
Formula weight	1938.6
Crystal system, space group, and Z	Orthorhombic, $P2_12_12_1$, /8/
Unit cell dimensions (Å)	$a = 11.002(1)$
	$b = 14.693(1)$
	$c = 16.505(1)$
Volume ($Å^3$)	2668.2(1)
Density (calculated) (mg/mm^3)	1.206
Absorption coefficient (mm^{-1})	0.08
$F(000)$	1040
Crystal size (mm)	$0.15 \times 0.06 \times 0.04$
Theta range (°)	3.7–54.97
Index ranges	$-14 \le h \le 14$
	$-19 \le k \le 19$
	$-21 \le l \le 21$
Reflections collected	46453
Unique reflections	3055 [R(int) = 0.033]
Data completeness	0.99
Data/restraints/parameters	3055/0/235
Goodness-of-fit on F^2	1.05
*Final R indices [$I > 2$sigma(I)]	$R_1 = 0.048$ [2334]
R indices (all data)	$R_1 = 0.064$, $wR_2 = 0.1326$
w^{-1} [where $P = (F_o^2 + 2F_c^2)/3$]	$\sigma^2(F_o^2) + (0.0700P)^2 + 0.3546P$
Largest diff. peak and hole ($eÅ^3$)	0.22, −0.12

$^*R_1 = \sum| |F_o| - |F_c| | / \sum |F_o|$ and $wR_2 = \left[\sum w\left(F_o^2 - F_c^2\right)^2 / \sum w\left(F_o^2\right)^2\right]^{1/2}$

$\text{Goof} = \left[\sum w\left(F_o^2 - F_c^2\right)^2 / \left(N_d - N_p\right)\right]^{1/2}$

$R\text{int} = \sum \left| F_o^2 - F_c^2(\text{mean}) \right| / \sum w F_o^2$

Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 626184. Copies of the data can be obtained free of charge by quoting the respective CCDC code number on application to Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; (fax: +44(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk; website: http://www.ccdc.cam.ac.uk).

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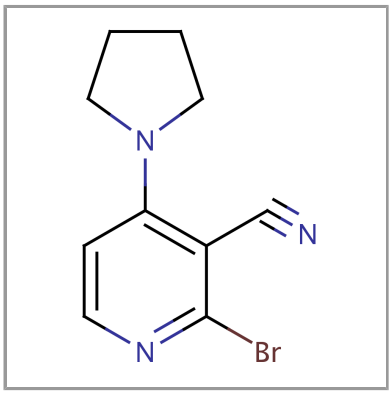
2



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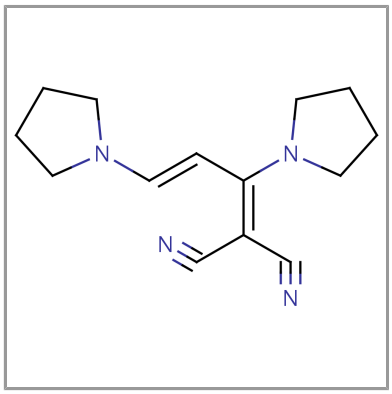

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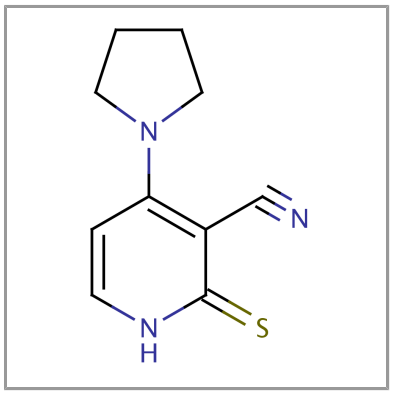

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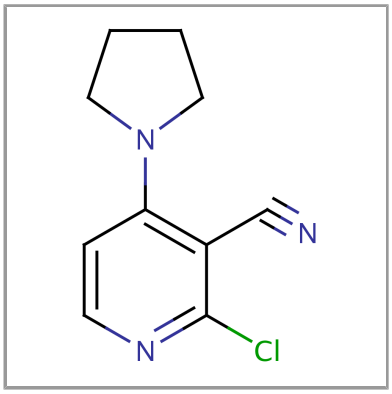

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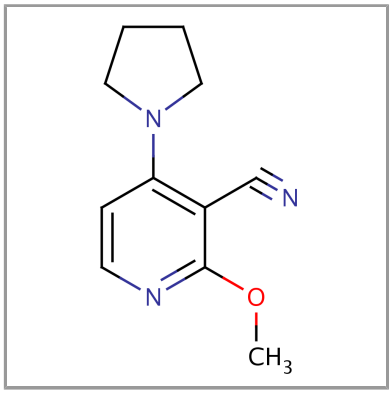

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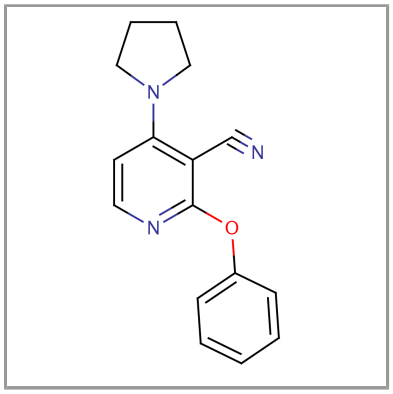

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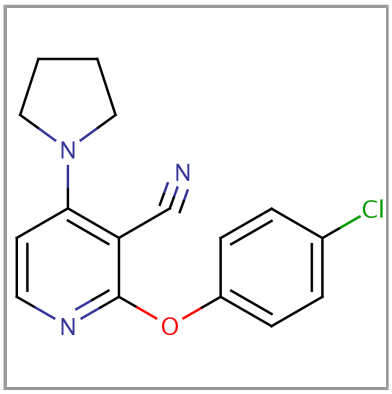

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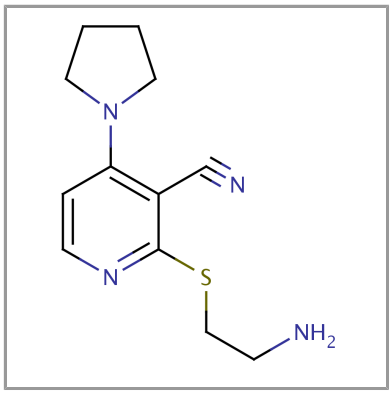

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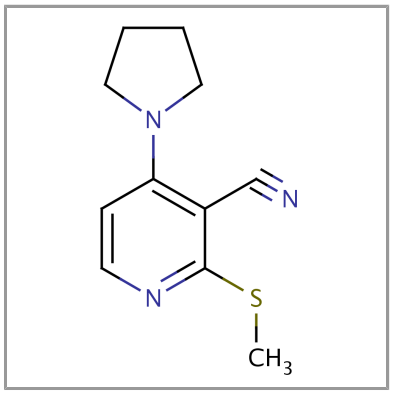

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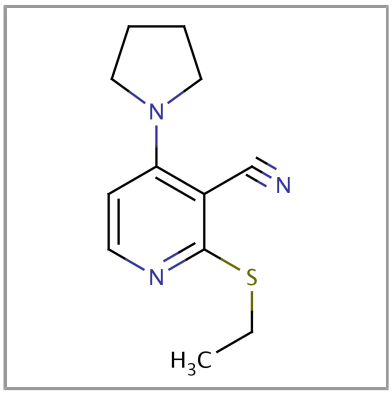

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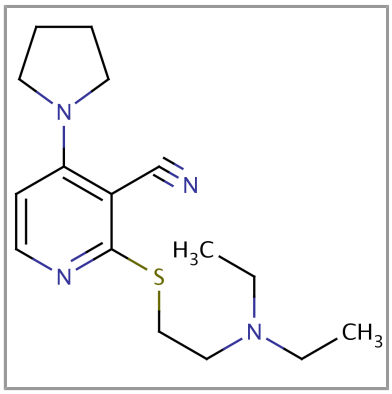

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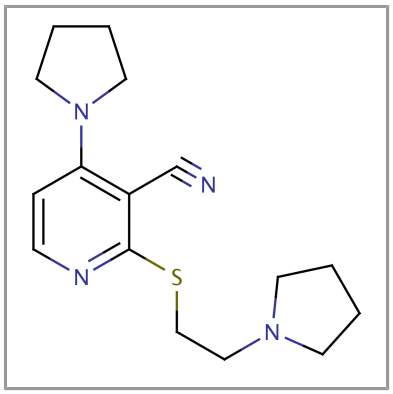

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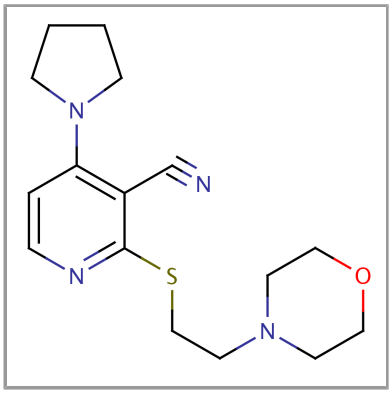

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