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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of a series of aminocyanopyridines as antimicrobial agents

Aliye Altundas · Selcuk Ayvaz · Elif Logoglu

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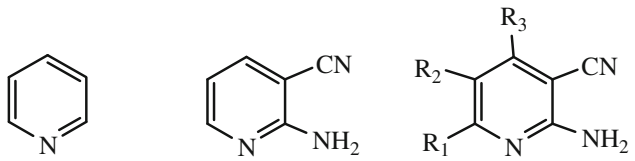
Abstract With the aim of developing potential antimicrobials, a series of 2-amino-3-cyanopyridines incorporating both sulfur and oxygen as part of the heteroaromatic ring (methyl thiophene, methyl furan) and fused cycloalkane groups were synthesized and characterized by FTIR, ^{1}H-NMR, ^{13}C-NMR, and bases of elemental analysis. All synthesized compounds were evaluated for their in vitro antibacterial and antifungal activity. Antibacterial and antifungal activities of aminocyanopyridines against *Pseudomonas aeruginosa* ATCC 29212, *Bacillus subtilis* RSKK 244, *Bacillus megaterium* (clinical isolate), the gram-positive bacterium *Micrococcus luteus* NRRLB 4375, and the fungus *Candida albicans* ATCC 90028 were studied. The relationship between the functional-group variation and the biological activity of the evaluated compounds is discussed.

Keywords 2-Amino-3-cyanopyridines · Thiophene · Furan · Antimicrobial agents

Introduction

The use of most antimicrobial agents is limited, not only by rapidly developing drug resistance, but also by the unsatisfactory results of present treatments of bacterial and fungal infections and side effects (Fidler, 1998). Therefore, the synthesis and investigation of new compounds which possess antimicrobial activity are very important.

A. Altundas (✉) · S. Ayvaz · E. Logoglu
Department of Chemistry, Faculty of Arts and Sciences, Gazi University, 06500 Ankara, Teknikokullar, Turkey
e-mail: aaltundas@gazi.edu.tr



1 **2** **3**

Many naturally occurring and synthetic compounds containing the pyridine (**1**) scaffold exhibit interesting pharmacological properties (Chang *et al.,* 2005). Pyridine is one of the most popular *N*-heteroaromatics incorporated into the structure of many pharmaceuticals. Among these, cyanopryridines and aminocycanopyridines (**2**) with different alkyl and aryl groups (**3**) were found to show antimicrobial (Moussa *et al.,* 1983), antihypertensive (Baldwin *et al.,* 1980), cardiovascular (Krauze *et al.,* 1985), anti-inflammatory, analgesic, and antipyretic (Manna *et al.,* 1999) properties as well as 1KK-β inhibitor properties (Murata *et al.,* 2004). They are also important as useful intermediates in preparing a variety of biologically active heterocyclic compounds (Deo *et al.,* 1991). The synthesis of 2-amino-3-cycanopyridines (**2**) has been extensively studied (Taylor and Crovetti, 1954). In the last few decades, a considerable amount of attention has been devoted to the synthesis of 2-amino-3-cycanopyridine derivatives (**3**) and the study of their biological activities such as antibacterial, antifungal, and inhibitor.

1,4-Dihydropyridines are calcium channel antagonists that produce vascular smooth muscle relaxation (Mayler, 1989). The nature and position of the C4-aryl ring substituent are responsible for the voltage-dependent calcium-channel antagonist activity. In general, the presence of an aryl group at C4, and of esters, acyl, sulfonyl, or nitrile groups at C3 and C5, of 1,4-dihydropyridine has proved to

be a fundamental requirement for pharmacological activity (Goldmann and Stoltefuss, 1991; Schramm *et al.,* 1983; Budriesi *et al.,* 2005). Elgemeie *et al.* (1989) reported the first synthesis of 4-(2-thienyl) and 4-(2-furyl)-3-cyano-2-amino pyridines. These compounds have 2-thienly or 2-furyl incorporated at the C4 position.

Furan derivatives, obtained from both synthetic and natural sources, have been attracting much interest due to their wide range of pharmaceutical applications (Shevchenko, 1999). Drugs containing sulfur are antibacterial agents, because they are competitive inhibitors in enzyme-catalyzed reactions which require *p*-aminobenzoic acid in the synthesis of folic acid (Bermingham and Derrick, 2002).

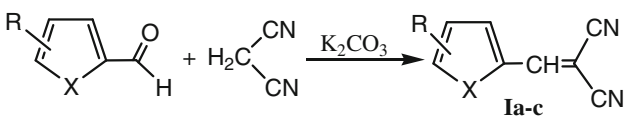
We synthesized cycloalkane fused with aminothiophenes, followed by formation of their Schiff bases and metal complexes, to study their antimicrobial and antifungal effects in previous work (Altundas *et al.,* 2009). The results above indicate that the seven-membered cycloalkanethiophenes, their Schiff bases, and their metal complexes showed more activity against *Br. abortus* than the other cycloalkane-fused compounds.

Based on good biological activity in novel heterocyclic systems, we undertook the synthesis of a new series of compounds incorporating the above-mentioned biologically active moieties (cycloalkane, furan, and thiophene derivatives) to 2-amino-3-cyanopyridine (Schemes 1 and 2). Synthesized compounds were characterized on the basis of their analytical and spectral data (Table 1). Antibacterial and antifungal activities were also evaluated (Tables 2 and 3).

Materials and methods

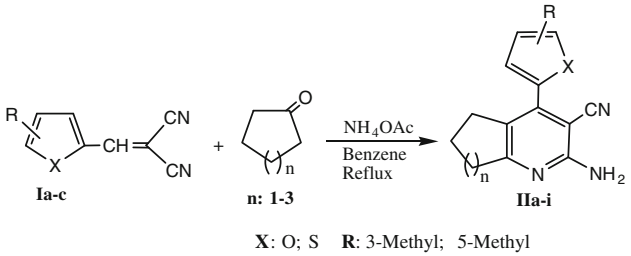
Chemistry

All chemicals used in the study were reagent grade and were purified when necessary. All organic solvents were purified according to standard methods. Elemental analyses were carried out with a LECO-CHNSO-932 instrument. ^{1}H- and ^{13}C-NMR spectra were recorded with a 200- and 50-MHz Varian using TMS as an internal standard. IR spectra were recorded on a Mattson-5000 FT-IR instrument in KBr pellets. Melting points were determined with a Gallenkamp apparatus.



X: O; S
R:3-Methyl; 5-Methyl

Scheme 1 Synthesis of ylidenemalononitriles (**Ia–c**)



X: O; S **R**: 3-Methyl; 5-Methyl

Scheme 2 Synthesis of aminocyanopyridines (**IIa–i**)

General procedure for synthesis of ylidenemalononitrile compounds (**Ia–c**)

Aromatic aldehyde (10 mmol), malononitrile (11 mmol), and potassium carbonate were added to a mortar and ground rapidly with a pestle at room temperature for a specified period of time. The mixture was dissolved in chloroform (150 ml) and then washed with water (2 × 50 ml). The organic phase was dried with $MgSO_4$, filtered off, and recrystallized from ethanol. All ylidenemalononitriles (**Ia–c**) were prepared in high yields using the same procedure (Scheme 1).

*2-((3-Methylthiophen-2-yl)methylene)malononitrile (**Ia**)*

M.p., 198–199°C. ^{1}H-NMR (acetone-d_6, δ, ppm): 2.50 (s, 3H, CH_3), 7.10–7.9 (d, J: 2.6 Hz, 2H, Ar–H), 8.3 (s, 1H, CH). ^{13}C-NMR (acetone-d_6): 156, 151, 142, 132, 128, 115, 114, 75, 14.

*2-((5-Methylthiophen-2-yl)methylene)malononitrile (**Ib**)*

M.p., 136–138°C. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.6 (s, 3H, CH_3), 6.9–7.5 (d, J: 3.95 Hz, 2H, Ar–H), 7.7 (s, 1H, CH). ^{13}C-NMR ($CDCl_3$): 155, 152, 141, 135, 129, 116, 115, 78, 18.

*2-((5-Methylfuran-2-yl)methylene)malononitrile (**Ic**)*

M.p., 93–95°C. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.4 (s, 3H, CH_3), 6.3–7.2 (d, J:3.58 Hz, 2H, Ar–H), 7.3 (s, 1H, CH). ^{13}C-NMR ($CDCl_3$, ppm) 163, 149, 144, 127, 116, 115, 113, 76, 16.

General procedure for synthesis of aminocyanopyridine compounds (**IIa–i**)

To a suspension of compounds **Ia–c** (5 mmol) in benzene (10 ml) was added ammonium acetate (7.50 mmol) and the

Table 1 Analytical and physical data for **IIa–i**

Compound	X	R	*N*	m.p. (°C)	Yield (%)	IR (cm^{-1})	Analysis (%), found (calc.): C; H; N; S
2a	S	3-Methyl	1	192–195	30	3475–3370(NH_2), 2210(CN), 1630(C=N)	65.91 (65.88); 5.14 (5.09); 16.55 (16.47); 12.75 (12.54)
2b	S	3-Methyl	2	204–207	39	3419–3307(NH_2), 2210(CN), 1644(C=N)	66.70 (66.91); 5.54 (5.57); 15.33 (15.61); 12.43 (11.89)
2c	S	3-Methyl	3	212–215	42	3405–3321(NH_2), 2210(CN), 1651(C=N)	67.90 (67.84); 6.09 (6.0);14.66 (14.84); 11.03 (11.30)
2d	S	5-Methyl	1	237–239	38	3433–3286(NH_2), 2210(CN), 1630(C=N)	65.34 (65.88); 5.06 (5.09); 15.56 (16.47); 12.84 (12.54)
2e	S	5-Methyl	2	245–248	59	3461–3300(NH_2), 2210(CN), 1636(C=N)	66.64 (66.91); 5.51 (5.57); 15.28 (15.61); 12.18 (11.89)
2f	S	5-Methyl	3	217–218	71	3400–3321(NH_2), 2210(CN), 1651(C=N)	68.75 (67.84); 6.75 (6.0); 15.07 (14.84); 10.62 (11.30)
2g	O	5-Methyl	1	214–215	50	3412–3300(NH_2), 2196(CN), 1644(C=N)	71.0 (70.29); 5.07 (5.43); 15.01 (17.57)
2h	O	5-Methyl	2	191–192	54	3433–3300(NH_2), 2210(CN), 1637(C=N)	70.77 (71.14); 5.74 (5.92); 16.14 (16.60)
2i	O	5-Methyl	3	164–166	66	3412–3314(NH_2), 2210(CN), 1644(C=N)	70.67 (71.91); 6.41 (6.36); 15.30 (15.73)

cycloalkanone (5 mmol). The flask was fitted with a reflux condenser and a Dean-Stark apparatus. The mixture was refluxed for 6 h, then the solvent was evaporated. The mixture was solved in chloroform (150 ml) and then washed with water (2 × 50 ml). The organic phase was dried over $MgSO_4$, filtered off, and recrystallized from ethyl acetate. All aminocyanopyridines (**IIa–i**) were prepared using the same procedure (Scheme 2).

*2-Amino-6,7-dihydro-4-(3-methylthiophen-2-yl)-5H-cyclopenta[b]pyridine-3-carbonitrile (**IIa**)*

^{1}H-NMR (acetone-d_6, δ, ppm): 1.8 (m, 2H, CH_2), 2.0 (s, 3H, CH_3), 2.5–2.8 (t, J: 2.8 Hz, 4H, $2CH_2$), 5.9 (s, 2H, NH_2), 6.9–7.4 (d, J: 2.6 Hz, 2H, Ar–H). ^{13}C-NMR (acetone-d_6, ppm): 14, 23, 26, 35, 91, 116, 126,128, 130, 131, 137,143, 161, 170.

*2-Amino-5,6,7,8-tetrahydro-4-(3-methylthiophen-2-yl)quinoline-3-carbonitrile (**IIb**)*

^{1}H-NMR ($CDCl_3$ δ, ppm): 1.6 (m, 4H, $2CH_2$), 2.0 (s, 3H, CH_3), 2.2–2.8 (t, J: 1.1 Hz, 4H, $2CH_2$), 5.2 (s, 2H, NH_2), 6.9–7.3 (d, J:5.13 Hz, 2H, Ar–H). ^{13}C-NMR ($CDCl_3$, ppm): 14, 22, 23, 26, 33, 91, 116, 123, 126, 130, 131, 136, 147, 157, 161.

*2-Amino-6,7,8,9-tetrahydro-4-(3-methylthiophen-2-yl)-5H-cyclohepta[b]pyridine-3-carbonitrile (**IIc**)*

^{1}H-NMR ($CDCl_3$ δ, ppm): 1.4–1.6 (m, 6H, $3CH_2$), 2.0 (s, 3H, methyl), 2.5–2.9 (t, J: 5.12 Hz, 4H, $2CH_2$), 5.2 (s, 2H, NH_2), 6.9–7.1 (d, J:5.12 Hz, 2H, Ar–H). ^{13}C-NMR ($CDCl_3$, ppm): 14, 26, 28, 29, 32, 39, 91, 116, 125, 128, 130, 131, 136, 146, 157, 168.

*2-Amino-6,7-dihydro-4-(5-methylthiophen-2-yl)-5H-cyclopenta[b]pyridine-3-carbonitrile (**IId**)*

^{1}H-NMR ($CDCl_3$, δ, ppm): 2.0 (m, 2H, CH_2), 2.5 (s, 3H, CH_3), 2.9–3.0 (t, J: 3.57 Hz, 4H, $2CH_2$), 5.1(s, 2H, NH_2), 6.8–7.3 (d, J:3.58 Hz, 2H, Ar–H). ^{13}C-NMR ($CDCl_3$, ppm): 17, 24, 32, 37, 91, 116, 126, 127, 130, 132, 137, 145, 162, 172.

*2-Amino-5,6,7,8-tetrahydro-4-(5-methylthiophen-2-yl)quinoline-3-carbonitrile (**IIe**)*

^{1}H-NMR ($CDCl_3$, δ, ppm): 1.6 (m, 4H, $2CH_2$), 2.5 (s, 3H, CH_3), 2.6–2.8 (t, J: 5.23 Hz, 4H, $2CH_2$), 5.0 (s, 2H, NH_2), 6.7–6.9 (d, J:3.50 Hz, 2H, Ar–H). ^{13}C-NMR ($CDCl_3$, ppm): 17, 24, 25, 28, 35, 92, 118, 123, 127, 130, 135, 144, 149, 159, 163.

Table 2 Disc diffusion method results of the aminocyanopyridines and standard reagents (diameter of the zone of inhibition (mm))

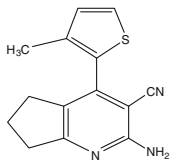
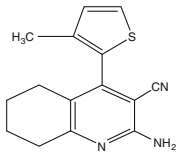
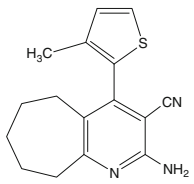
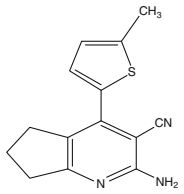
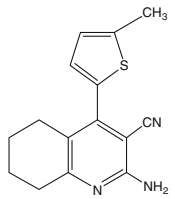
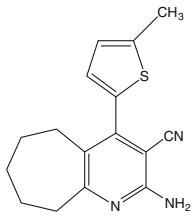
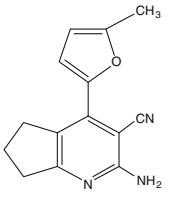
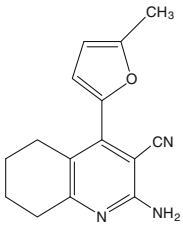
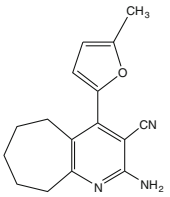
Compound	*B. subtilis*	*M. luteus*	*P. aeruginosa*	*B. megaterium*	*C. albicans*
 **2a**	13	11	–	–	–
 **2b**	–	9	9	–	–
 **2c**	10	–	17	–	–
 **2d**	15	12	15	–	–
 **2e**	–	12	20	–	–
 **2f**	10	20	19	–	–

Table 2 continued

Compound	*B. subtilis*	*M. luteus*	*P. aeruginosa*	*B. megaterium*	*C. albicans*
 **2g**	22.5	15	17	–	–
 **2h**	–	11	–	–	–
 **2i**	–	9	14	–	–
Penicillin		31			
Tetracycline		9			
Ampicillin	15	28		10	
Gentamicin			16		
Ketoconazole					16

*2-Amino-6,7,8,9-tetrahydro-4-(5-methylthiophen-2-yl)-5H-cyclohepta[b]pyridine-3-carbonitrile (**IIf**)*

^{1}H-NMR ($CDCl_3$, δ, ppm): 1.5–1.8 (m, 6H, $3CH_2$), 2.5 (s, 3H, $1CH_3$), 2.6–2.9 (t, J: 5.23 Hz, 4H, $2CH_2$), 5.1 (s, 2H, NH_2), 6.7–6.8 (d, J:3.46 Hz, 2H, Ar–H). ^{13}C-NMR ($CDCl_3$, ppm) 17, 28, 30, 31, 33, 41, 92, 118, 127, 128, 130, 135, 144, 147, 159, 169.

*2-Amino-6,7-dihydro-4-(5-methylfuran-2-yl)-5H-cyclopenta[b]pyridine-3-carbonitrile (**IIg**)*

^{1}H-NMR ($CDCl_3$, δ, ppm): 2.1 (m, 2H, CH_2), 2.4 (s, 3H, CH_3), 2.9–3.1 (t, J: 8.0 Hz, 4H, $2CH_2$), 5.1 (s, 2H, NH_2), 7.1–7.2 (d, J:2.4 Hz, 2H, Ar–H). ^{13}C-NMR ($CDCl_3$, ppm): 14, 22, 28, 34, 80, 109, 116, 118, 120, 136, 147, 154, 162, 170.

*2-Amino-5,6,7,8-tetrahydro-4-(5-methylfuran-2-yl)quinoline-3-carbonitrile (**IIh**)*

^{1}H-NMR ($CDCl_3$, δ, ppm): 1.7 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3), 2.6–2.7 (t, J: 6.51 Hz, 4H, $2CH_2$), 5.2 (s, 2H, NH_2), 6.1–6.7 (d, J:3.27 Hz, 2H, Ar–H). ^{13}C-NMR ($CDCl_3$, ppm): 15, 24, 25, 28, 35, 99, 109, 117, 119, 121, 143, 149, 156, 159, 163.

*2-Amino-6,7,8,9-tetrahydro-4-(5-methylfuran-2-yl)-5H-cyclohepta[b]pyridine-3-carbonitrile (**IIi**)*

^{1}H-NMR: 1.6–1.8 (m, 6H, $3CH_2$), 2.3 (s, 3H, $1CH_3$), 2.7–2.9 (t, J: 5.78 Hz, 4H, $2CH_2$), 5.2 (s, 2H, NH_2), 6.1–6.6 (d, J:3.3 Hz, 2H, Ar–H). ^{13}C-NMR ($CDCl_3$, ppm): 15, 28,

Table 3 MIC results for aminocyanopyridines and standard reagents against various bacteria and an alga: μg/ml

	B. subtilis	*M. luteus*	*P. aeruginosa*	*B. megaterium*	*C. albicans*
2a	37.5	37.5	–	–	–
2b	–	37.5	25	–	–
2c	37.5	–	12.5	–	–
2d	25	37.5	25	–	–
2e	–	25	12.5	–	–
2f	37.5	25	25	–	–
2g	12.5	25	12.5	–	–
2h	–	37.5	–	–	–
2i	–	25	25	–	–
Ampicillin		8	–	–	–
Fluconazole		8	–	–	128

29, 31, 33, 41, 99, 109, 116, 119, 128, 142, 149, 155, 159, 170.

Biological activities

Test microorganisms and medium

In this study, gram-negative bacteria, i.e., *Pseudomonas aeruginosa* ATCC 29212, *Bacillus subtilis* RSKK 244, and *Bacillus megaterium* (clinical isolate), the gram-positive bacterium *Micrococcus luteus* NRRLB 4375, and the fungus *Candida albicans* ATCC 90028 were used. Bacterial strains were cultured overnight at 37°C in Mueller–Hinton broth and the yeast was cultured overnight at 30°C in YEPDE agar for antibacterial and antifungal activity tests. Test strains were suspended in nutrient agar to give a final density of 5×10^5 cfu/ml.

Screening of antimicrobial activity

The antimicrobial activity of compounds was determined by the disc diffusion method and minimum inhibitory concentrations (MICs). MICs were determined by the macrodilution broth method following the procedures recommended by the National Committee for Clinical Laboratory Standards for testing purposes (NCCLS, 1997a, b). MICs were defined as the lowest concentrations of the antimicrobial. The antimicrobial activity of compounds was determined by the disc diffusion method (NCCLS, 1997a; Arslan *et al.,* 2006). *Candida albicans* ATCC 90028 was used for antifungal activity testing (NCCLS, 1997b).

Nutrient agar (20 ml) was poured into each sterile petri dish after injecting cultures (100 μl) of microorganisms and distributing a medium in the petri dish homogeneously. Compounds were filtered with a pore size of 0.45 μm. All of the compounds were dissolved in 100 μg/ml DMSO. Empty sterilized discs of 6 mm (No. 2668; Schleicher and Schuell, Germany) were impregnated with 50 μl of the compounds. Discs were placed on agar plates, and the plates were incubated at 37°C for 24 h for bacteria. Culture suspensions were prepared and adjusted by comparison against 0.3 McFarland turbidity standard tubes. Inhibition zones formed on the medium were evaluated (millimeters). The solvent control (DMSO) did not show any antimicrobial activity. Studies were performed in duplicate and the inhibition zones were compared with those of the reference discs. Reference discs used for control were as follows: ketoconazole, ampicillin, tetracycline, penicillin, and gentamicin.

Results and discussion

In this study, we synthesized a series of 5,6-cycloalkane condensed 2-amino-3-cyanopyridine derivatives (**IIa–i**) which bear a substituent at the 4-position such as 3-methyl and 5-methyl furan and thiophene from ylidenemalononitriles (**Ia–c**). Activated nitriles are versatile reagents in developing synthetic approaches for polyfunctionally substituted heterocycles (Fathy and Elgemeie, 1988). Ylidenemalononitrile (**Ia–c**) can be easily prepared through a Knoevenagel condensation between furan and thiophene-2-carbaldehyde derivatives with malononitrile (Scheme 1). The cyclization of cycloalkylketones with ylidenemalononitriles (**Ia–c**) in the presence of amonium acetate gave 2-amino-3-cyano-4,5,6-trisubstituted pyridine derivatives (**IIa–i**) (Scheme 2) through the Michael reaction with the elimination of 1 mol water and hydrogen (Sakurai and Midorikawa, 1968).

Structures of synthesized compounds were characterized spectroscopically by IR, ^{1}H-NMR, ^{13}C-NMR, and CHN analysis. IR spectra of **IIa–i** showed some characteristic peaks indicating the presence of particular functional

groups. The absorption at 3476–3286, 2210, and 1630–1651 cm^{-1} are characteristic of $\nu(NH_2)$, $\nu(CN)$, and $\nu(CH=N)$, respectively (Table 1).

Structures of 2-amino-3-cyanopyridines were identified primarily with ^{1}H- and ^{13}C-HMR spectra. While aliphatic proton and aromatic proton signals showed δ 1.40–3.00 ppm and δ 6.10–7.40 ppm, respectively, the ^{1}H-NMR spectra of amine protons appeared at a characteristic signal of δ 5.00 ppm. The ^{13}C-NMR spectral data on synthesized compounds are also in accordance with the proposed structures.

Synthesized compounds were evaluated for their in vitro antibacterial and antifungal activity (Table 2). Compounds **2a**, **2c**, **2d**, **2f**, and **2g** showed antimicrobial activity against *Bacillus subtilis* RSKK 244. 2-Amino-6,7-dihydro-4-(5-methylfuran-2-yl)-5H-cyclopenta[*b*]pyridine-3-carbonitrile (**2g**) has more activity than ampicillin against *Bacillus subtilis* RSKK 244.

Compounds **2c**, **2f**, and **2g**, and especially 2-amino-5,6,7,8-tetrahydro-4-(5-methylthiophen-2-yl)quinoline-3-carbonitrile (**2e**), show more activity than gentamicin against *Pseudomonas aeruginosa* ATCC 29212. All of the compounds, except **2c**, have average antimicrobial activity against *Micrococcus luteus* NRRLB 4375. 2-Amino-6,7,8,9-tetrahydro-4-(5-methylthiophen-2-yl)-5H-cyclohepta-[*b*]pyridine-3-carbonitrile (**2f**) possesses the best activity against *Micrococcus luteus* NRRLB 4375 compared with the other compounds. Unfortunately, none of the synthesized 2-amino-3-cyanopyridines derivatives showed any activity against *Bacillus megaterium* or *Candida albicans* (ATCC 90028). The MICs of ketoconazole, ampicillin, tetracycline, penicillin, and gentamicin were determined individually in parallel experiments in order to control the sensitivity of the test organisms. MIC values of the compounds and the standards are presented in Table 3.

As reported in Table 2, the six-membered cycloalkane fused with 2-amino-3-cyanopyridenes (**2b**, **2e**, **2h**), regardless of the nature of the heterocyclic and methyl substituent at the 3- or 5-position, did not show any biological activity against *B. subtilis*. In the seven-membered fused system (**2f**, **2c**), we observed the same activity against *B. subtilis*. The position of the methyl group at the thiophene ring was not significant. Moreover, the furan derivative (**2i**) did not show any activiy. The best result was obtained in the case of the five-membered cycloalkane (**2g**) along with 5-methyl furan. As shown above, the biological activity against *B. subtilis* is dependent on the ring size and substituent.

In the activity study against *M. luteus* (Table 2), the ring size of the cycloalkanes and features of furan and thiophene at the C4-position of pyridine was not crucial. However, 5-methyl thiophene at C4 (**2f**) gave the best result in antimicrobial activity. As reported in Table 2, most synthesized compounds, except for **2a** and **2h**, show biological activity against *P. aeruginosa.*

The ring size of cycloalkanes and nature of the substituent at the C4-position of pyridine do not present clear information about the SAR. However, 5-methyl thiophene at C4 exhibits respectable antimicrobial activity against *P. aeruginosa* ATCC 29212 (Table 2).

Conclusion

In this study, nine new aminocycanoprydine derivatives were synthesized and characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and CHN analysis. Their antibiogram tests showed better results than some known antibiotics. In general, 2-amino-3-cyanaopyridines substituted at C4 with 5-methyl furan and thiophene show better activity than 3-methyl thiophene-substituted compounds. However, except against *P. aeruginosa*, six-member cycloalkane-fused compounds did not show good results compared to five- and seven-member compounds.

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