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Synthesis of 4-amino-2,6-diaryl-5-cyanopyrimidines as antimicrobial agents

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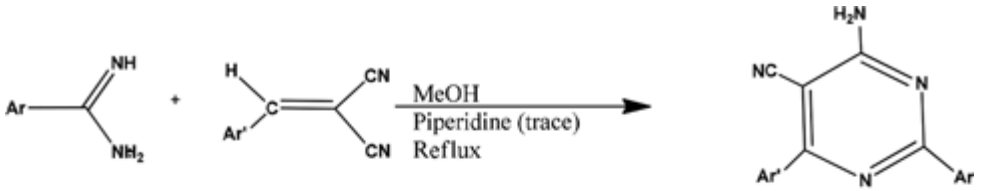
Abstract

This paper describes an efficient and facile synthesis of eleven 2,4,6-trisubstituted 5-cyanopyrimidines starting from *meta* and *para* substituted 2-cyanocinnamonitriles and arylamidines. The synthesized heterocycles, **3a-k,** were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. The probable mechanism of formation of the title compounds employing 2-cyanocinnamonitriles and arylamidines in the presence of a base was clarified.

A preliminary screening of the antibacterial tests clearly showed that four out of eleven pyrimidines, viz., **3a, 3e, 3f** and **3k** were effective against bacteria, *Staphyloccus aureus, Bacillus subtillis* and *Pseudomonas aeruginosa.* Further, the Minimum Inhibitory Concentration (MIC) against the bacteria has been determined.



1a-k **2a-k** **3a-k**

1-3	Ar	Ar'	m.p. (°C)
a:	Ph	*m*-NO_2Ph	221-222
b:	Ph	*p*-NO_2Ph	220-221
c:	*p*-CH_3 OPh	*m*-NO_2Ph	226-227
d:	*p*-CH_3OPh	*p*-NO_2Ph	221-222
e:	*p*-$(CH_3)_2$NPh	*m*-NO_2Ph	236-237
f:	*p*-$(CH_3)_2$NPh	*p*-NO_2Ph	222-223
g	*p*-CH_3Ph	*m*-NO_2Ph	241-243
h	*p*-CH_3Ph	*p*-NO_2Ph	289-291
i	*p*-NO_2Ph	*m*-NO_2Ph	260-262
j	*p*-NO_2Ph	*p*-NO_2Ph	237-239
k	*p*-NH_2Ph	*m*-NO_2Ph	243-245

KEYWORDS: arylpyrimidines, 2-cyanocinnamonitriles, 4-amino-2,6-diaryl-5-cyanopyrimidine, reaction mechanism, antimicrobial agents

1. INTRODUCTION

Extensive investigations of pyrimidines indicate that they are substructures of crucial building blocks of nucleotides with uracil and thymine, being the constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), respectively. Thymine is one of the nucleobases in the nucleic acid of DNA. In RNA, the thymine is replaced by the nucleobase uracil, a demethylated thymine. Pyrimidines containing compounds occur in nature and have biological properties [1]. These include nucleosides as well as alkaloids and antibiotics. Substituted pyrimidines prepared synthetically have been found to possess a variety of biological activities. For example, some are antiviral agents [2], others possess anti-parasitic, antimicrobial, anticancer and antibiotic activities[3-5]. In 2008, we

reported the synthesis and antiinflammatory activity of 4-amino-2,6-diaryl-5-cyanopyrimidines, where three compounds were found to posses antiinflammatory activity which are twice more effective than aspirin in reducing inflammation[6]. A recent review covers the significance and importance of pyrimidines in the Microbial World[7].

Considering observations in the recent literature, we prepared eleven 4-amino-2,4-diaryl-5-cyanopyrimidines with a view to verify their structures and evaluate their antibacterial properties. The present paper describes the synthesis, mechanism of formation and biological activity of title compounds., These compounds produced reasonable activity against bacteria.

2. RESULTS AND DISCUSSION

The starting materials, arylamines, **1a-k**, and 2-cyanocimmonitriles, **2a-k**, were prepared according to the published procedure described earlier [6,8]. Compounds **1f-g** and **2f-g** were individually dissolved in methanol and a catalytic quantity of piperidine was added, followed by reflux for 6 hours. The work-up produced the desired products **3f** and **3g** in 92% and 95% yields, respectively. Similarly, **1a-e/1h-k** and **2a-e/2h-k** were allowed to react individually providing the desired compounds **3a-e** and **3h-k** in excellent yields (89-98%) as shown in Scheme S1. We were able to synthesize eleven 4-amino-2,6-diaryl-5-cyanopyrimidines **3a-k** in their crystalline states.

Eight of the title compounds, i.e., **3c, e-k** have not yet been reported in the literature. Compounds **3a, 3b and 3d**[6,9] have been described in the literature, but in smaller yields by using a different base and a longer reaction time (8 hours). Substances **3a**, **3b** and **3d** have been obtained in excellent yields in the present work. In fact, **3a** and **3b** gave almost quantitative yields (98%), while **3d** in 91% yield, respectively. Here the reaction time was 6 hours. Peter et al.[6] synthesized the compounds **3b** and **3d** with yields of 33% and 32%, respectively, using the reaction time of 8 hours. Compounds **3a** and **3b** were also obtained by Xavier et al.[9] with yields of, 40% and 67%, respectively, employing microwave radiation with reaction time of 40 minutes, in the presence of potassium carbonate as a base.

All compounds were characterized by their spectroscopic data, such as, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra. Considering that all compounds have three aromatic rings and eight quaternary carbons, ^{1}H and ^{13}C NMR assignments were made using 2D experiments: ^{1}H-^{1}H COSY (Correlation Spectroscopy), Heteronuclear Multi-Bond Correlation (HMBC) and Heteronuclear Single-Quantum Coherence (HSQC) spectroscopy. Supporting information of this paper, presents the ^{1}H and ^{13}C NMR spectra of compounds **3a, 3d**, **3f-g** and **3k.** By looking at ^{1}H and ^{13}C NMR spectra, it seemed quite difficult to attribute all signals. The ^{1}H-^{1}H COSY spectrum of compound **3d** made it possible to identify two *para*-substituted phenyl systems. The methoxy group was assigned easily at δ 3.81 ppm. From HSQC and HMBC spectra, it was possible to assign all hydrogen and carbon nuclei in the *p*-methoxyphenyl group. A similar strategy

was used to attribute the signals of the *p*-nitro- and *m*-nitrophenyl group of all compounds.

Here follows a description of the NMR assignments of **3f-g.** Initially, we examined the ^{1}H NMR spectrum of compound **3f**, which presented a singlet at δ 3.01 ppm, which is assigned as H1’’’, and four signals at δ 6.77, 7.64, 7.97 and 8.24 ppm. We observed two COSY correlations: δ 6.77 with δ 8.24 ppm; and δ 7.64 with δ 7.97. Therefore, there are two AA’BB’ systems, with all showing a coupling constant equal to 9.30 Hz. Also one band centered at δ 7.73 ppm was observed and assigned to the hydrogen nuclei of the amino group. The ^{13}C NMR spectrum presented 14 signals. The signal at δ_C 39.7 ppm was easily attributed to methyl groups. To assign all the others, it was necessary to obtain 2D spectra. In the HSQC spectrum, the following correlations to the AA’BB’ systems were observed: δ_H 6.77 ppm – δ_C 111.1 ppm; δ_H 7.64 ppm – δ_C 128.5 ppm; δ_H 7.97 ppm – δ_C 130.4 ppm; and δ_H 8.24 ppm – δ_C 130.1 ppm. But a complete assignment was only possible using the HMBC experiment. In this spectrum, correlations were observed from the signal attributed to methyl group (δ_H 3.01 ppm) with the following signals: δ_C 152.6 ppm, assigned to C4’ nucleus, and δ_C 39.7 ppm. Table S1 presents all HMBC correlations observed and the attributions made.

The signals at δ_C 164.3, 116.8 and 82.4 ppm were not yet attributed. Also the C4, C5 and C1’’’’ nuclei were not assigned. Considering the structure of compound **3f**, we attributed the signal at δ_C 82.4 to the C5 nucleus because its proximity to a *sp* hybridized carbon.

The C1'''' nuclei are shifted downfield from the C4 nucleus, making the signal at δ_C 164.30 ppm which can be attributed to the C4 nucleus.

Next, attribution to compound **3g** was performed. In the ^{1}H NMR spectrum, the singlet at δ 2.38 ppm was attributed to the methyl group. There is one band, centered at δ 8.06 ppm, assigned to hydrogen nuclei of amino group. The ^{1}H-^{1}H COSY spectrum shows two spin systems, which are constituted by signals centered at δ 8.75, 8.42 and 7.89 ppm, for the first system; and δ 8.29 and 7.34 ppm, for the second system. The signal at δ 8.75 ppm (t, 2.1 Hz, 1H) was attributed to the H2'' nucleus, while the peak at δ 7.89 ppm (t, 8.1 Hz, 1H) was assigned to H5'' nucleus. The assignment made to H2'' nucleus is explained by as follows: first, the downfield shift appears due to its structure where the just-mentioned proton has a nitro group in its *ortho* position and the pyrimidine ring is also linked at *ortho* to this hydrogen (Linkage 1" → 6, see Figure S1). Since the aromatic proton H2" has two electro-withdrawing groups – the pyrimidine ring on one side and the nitro group on the other side, this aromatic hydrogen will have a strong deshielding effect. Further, assuming the planar structure of the molecule, the lone pair of electron on N1 plays an additional influence on H2" causing a further downfield shift.

Another observation is about the smaller peak area is assigned to H2" nucleus. Since there is no proton in its vicinity, its relaxation process is quite slow. This explains the lower integrated area as well for this proton.

The multiplet among δ 8.47 – 8.39 ppm (2H) was assigned to the H4'' and H6'' nuclei. The two duplets at δ 8.29 ppm and δ 7.34 ppm were attributed to AA'BB' system, but they were not assigned. In the ^{13}C spectrum, the signal at δ 21.2 ppm was attributed to the methyl group, while the signal at δ 84.7 ppm was attributed to the C5 nucleus. In the HMBC spectrum, the signal at δ 21.2 ppm is correlated to the duplet at δ 7.34 ppm. So, the signal at δ 7.34 ppm was attributed to the H3'and H5' nuclei, and the signal at δ 8.29 ppm was attributed to the H2' and H6' nuclei. Since the hydrogen nuclei of the AA'BB' system were already attributed, it is possible assign the carbon nuclei in this system, using HMBC and HSQC spectra. The signals at δ 129.3 and 128.5 ppm were attributed to the C3'/C5' and C2'/C6' nuclei, respectively. The signal attributed to the H3'/H5' nuclei shows an HMBC correlation with the signals attributed to the methyl group, C3'/C5' and the C1' nuclei. Therefore, the signal at δ 133.6 ppm was attributed to C1' nucleus. The peak assigned to the H2'/H6' nuclei presents an HMBC correlation with the signals attributed to C2, C2'/C6' and C4'. Then, the signals at δ 164.3 and 141.9 ppm were attributed to the C2 and C4' nuclei, respectively.

The first spin system, observed in COSY spectrum, was attributed to the *m*-NO_2 substituted ring. HMBC and HSQC correlations were used to attribute the carbon nuclei to this system. The signals at δ 123.4 and 130.4 ppm were attributed to the C2'' and C5'' nuclei, respectively. To attribute the H4'', H6'', C4'' and C6'' nuclei, we use HMBC correlations. H4'' nuclei shows the HMBC correlation with the signals attributed to the C6'' and C2'' nuclei, while the H6'' nuclei presents an HMBC correlation with the C6, C2'' and C4'' nuclei. Therefore, the signals at δ 8.47 – 8.39 ppm were attributed to H6''

and H4'', respectively. The signals at δ 125.5 and 135.1 ppm were attributed to C6'' and C4'', respectively. The signal at δ 166.0 ppm was attributed to the C6 nucleus. The peak attributed to H5'' presents HMBC correlations with the C3'' and C1'' nuclei. On the other hand, the C3'' nucleus shows a weak HMBC correlation with the H4''and H2'' nuclei. Then, the signals at δ 147.8 and 138.1 ppm were attributed to the C3'' and C1'' nuclei, respectively. Finally, the signals at δ 164.4 and 116.1 ppm were attributed to the CN group and the C4 nucleus, respectively.

2.1 Mechanism Of Formation Of 4-Amino-2,6-Diaryl-5-Cyanopyrimidines

In 2000, Dos Santos[10] proposed the mechanism of formation of 4-amino-2,6-diaryl-5-cyanopyrimidines briefly, but did not publish it . Since then, two more articles have appeared in the literature dealing with the mechanism of formation of 4-oxo-5-cyanopyrimidines[10,11]. In this present publication, we are trying to give more details and clarification concerning the mechanism of formation of the title pyrimidines. These are given below:

Initially, we tried to see if the reaction could be completed without the use of a base. For this, we used reagents **1a** and **2a** in methanol and refluxed the contents for 6 hours. Examination of the contents by thin-layer chromatography clearly showed the absence of any product formation. Only the starting reagents were observed. However, when a catalytic quantity of piperidine was added to the reagents **1a** and **2a** in methanol followed by reflux, product formation was clearly observed. Thus, it is clear that a base is important to affect the reaction. The piperidine abstracts a proton from arylamidine to

produce a stable anion **1'**, which then attacks the carbon-3 of 2-cyanocinnamonitrile **2,** as shown in scheme S2. The anion **6** abstracts a proton from **4** to give **7** where the imidine nitrogen is properly set up to attack the carbon atom of one of the —CtbndN group to provide **8** which goes to **9**. This intermediate then tautomerizes to **10,** which is the 3,6-dihydro-pyrimidine. This in the presence of air reacts with atmospheric oxygen to furnish the final product **3a.** Similarly, **3b-k** are also formed.

We tried to isolate **10** by performing the reaction under nitrogen atmosphere, where the thin-layer chromatogram had shown a slow-moving spot with R_f = 0.2 and another spot at R_f = 0.4 (n-hexane-ethyl acetate, 7:3). This last spot was attributed to pyrimidine **3** and not dihydropyrimidine **10**. This slow moving spot is assumed to be due to **10.** When the contents were heated again without nitrogen, this slow moving spot disappeared as indicated by TLC and the spot with R_f value 0.4 intensified. This is indicative of the aromatization of **10** in the presence of air. It therefore appears that biradical oxygen is responsible for the aromatization of **10** to **3**.

2.2. Antibacteria Activity

Compounds **3a-k** were screened for antibacterial activity. (Mueller Hinton Broth – Difco) 3.2 to 0.00125 mg/mL was used as nutrient, with DMSO as solvent and a blank. The compounds were tested for their activities against Gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtillis*) and Gram Negative bacteria (*Pseudomonas aeruginosa*). The results revealed that most of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the

inhibitory activity against the tested Gram Positive bacteria was higher than that of the Gram Negative bacteria. In short, all pyrimidines **3a, e**, **f**, **g** and **k** have bacterial growth inhibitions, as shown in Table S2. Compounds **3a, e, f,** and **k** displayed broad spectrum antibacterial property. These were the best of the series, and presented activity against all three organisms, at lower concentrations, varying between 1.6 to 0.1 mg /mL. Compound **3c** was only moderately active against Gram Negative bacteria (Pseudomonas aeruginosa) at a concentration of 3.2 mg /mL.

3. EXPERIMENTAL

3.1. General Experimental Procedures

All reagents were obtained from commercial sources and used without further purification. All melting points were recorded on a BUCHI B-540 apparatus and are not corrected. The IR spectra were recorded on a Perkin Elmer Spectrum400, using the KBr wafer technique. The spectra of compound **3b-d** and **3f-k** were acquired using VARIAN VNMRS400 spectrometer operating at 400 MHz and 100 MHz for ^{1}H and ^{13}C nuclei, respectively. The spectra of compounds **3a**, **3e** and **3g** were performed using VARIAN Unity Plus 300 spectrometer operating at 300 MHz and 75 MHz for ^{1}H and ^{13}C nuclei, respectively. HSQC and HMBC experiments were optimized to observe coupling constants equal to 140 Hz ($^{1}J_{C\text{-}H}$) and 8 Hz ($^{3}J_{C\text{-}H}$). The mass spectra were recorded on a MALDI-TOF mass spectrometer (Bruker Daltonics, Autoflex III). Monitoring the reactions and checking the purity of the final products were carried out by thin layer chromatography (TLC) using precoated silica gel on aluminum sheets (60 mesh

containing fluorescent indicator F_{254}, Merck) and visualization of the spots was carried out under ultraviolet light (UV) at 365 and 254 nm.

3.2. Typical Experimental Procedures

Preparation of 4-amino-2,6-diaryl-5-cyanopyrimidines, **3a-k**: An appropriate bisnitrile **2a-k**[8,11] and arylamidine **1a-k**[6,10] in equimolar quantity (3.46 mmol) were dissolved in methanol (10 mL) and refluxed for 6h in the presence of piperidine as a base. The contents were cooled to room temperature and solvent evaporated to give a solid mass which was crystallized and recrystallized with an appropriate solvent.

4-Amino-5-Cyano-2-(*P*-Diethylaminophenyl)-6-(*P*-Nitrophenyl)-Pyrimidine (3f)

This compound was obtained as colorless crystals from MeOH in 92% yield, m.p. 222-223, R_f = 0.75(n-hexane-ethyl acetate 6:4); IR, KBr, γ_{max} cm^{-1}: 3117 ($NH_{2asymm.}$), 3039 ($NH_{2symm.}$), 2230 ($C\equiv N$), 1602 ($C=N$); ^{1}H-NMR (DMSO-d_6 300 MHz), δ: 8.24 (d, 2H, *J* 9.3 Hz, H2' and H6'); 7.97 (d, 2H, *J* 9.3 Hz, H2" and H6"); 7.73 (b, 2H, C2-NH_2); 7.64 (d, 2H, *J* 9.3 Hz, H3" and H5"); 6.77 (d, 2H, *J* 9.3 Hz, H3' and H5') and δ 3.10 (s, 6H). ^{13}C-NMR (DMSO-d_6 300 MHz), the assignment of all ^{13}C atoms are given in the text above MS (MALDI TOF MS: m/z (molecular mass found = 360.3219; calculated for $C_{19}H_{16}N_6O_3$ M^+, mass = 360.1335).

4-Amino-5-Cyano-2-(*P*-Methylphenyl)-6-(*M*-Nitrophenyl)-Pyrimidine (3g)

This compound was obtained as colorless crystals from MeOH in 95% yield, m.p. 241-243, R_f = 0.55 (n-hexane-ethyl acetate-methanol 6:3:1); IR, KBr, γ_{max} cm^{-1}: 3443

($NH_{2asymm.}$), 3352 ($NH_{2symm.}$), 2167(C≡N), 1606 (C=N); ^{1}H-NMR (DMSO-d_6 300 MHz) δ: 8.75 (t, *J* 2.10 Hz, 1H, H2"); 8.47-8.39 (m, 2H, H4" and H6"); 8.29 (d, *J* 8.10 Hz, 2H, H2' and H6'); 8.06 (b , 2H, C2-NH_2); 7.89 (t, *J* 8.10 Hz,1H, H5") 7.34 (d, *J* 8.10 Hz, 2H, H3' and H5'); and 2.38 (s, 3H). ^{13}C-NMR (DMSO-d_6 300 MHz), he assignment of all ^{13}C atoms are given in the text above MS (MALDI TOF MS: m/z (molecular mass found = 332.3184; calculated for $C_{18}H_{14}N_5O_2$ $[M^+1]^+$, mass = 332.1069).

3.3. Sensibility Test Of The Drugs (Minimum Inhibitory Concentration - MIC)

For determining the MIC, the compounds were dissolved individually in a solution containing 20% dimethyl-sulfoxide (DMSO) and 80% Tween-80. The culture medium employed was Mueller Hinton Broth (Difco). The microorganisms used in the present test were: *Staphylococcus aureus* UFPEDA 02; *Bacillus subtilis* UFPEDA 86 and *Pseudomonas aeruginosas* UFPEDA 416 from the culture collection of the Department of Antibiotics, Federal University of Pernambuco, all maintained in Mueller Hinton agar. The MIC test was carried out using the micro dilution method in micro 96-well plates containing 100 mL Mueller Hinton Broth, according to the procedure recommended by Standard Clinical Laboratory Institute SCLI[12] The bacterial suspensions were taken in the sterilized distilled water and the turbidity adjusted to 0.5 on the McFarland scale ($1.5x10^8$ UFC/mL). The concentrations of all eleven compounds tested were from 3.2 to 0.0125 mg/mL. Oxacillin and ciprofloxacine antibiotics were employed as standards, having the same concentrations as recommended by CLSI[13] *Overall, 12 wells (columns) were used:* In the first one, the broth; in the second, solvent

and the broth. From columns 3 through 11, in 1.0 mL of the solvent, the broth was employed as follows : 3.2 mg/mL, 1.6 mg/mL, 0.8mg/mL, 0.4/mL, 0.2mg/mL, 0.1mg/mL, 0.05 mg/mL, 0.025 mg/mL, and 0.0125mg/mL. In the 12th well, both broth and bacteria were added. In the second to eleventh wells, 20mL of bacteria were added. The plates were incubated at 35^{o}C for 24 hours. When the plate cultivation period ended, a reading was taken with naked eyes and afterwards a sterilized aqueous solution of resazurine (0.1%) was added. After 4 hours of incubation, the reading was taken again. Resazurine facilitates the verification of microbial proliferation, and a blue color indicates that there is no bacterial proliferation, while a red color indicates the presence of living cells in the process of proliferation. Thus it was possible to determine the minimum concentration responsible for the inhibition of the micro-organisms.

Supporting Information: Full experimental details and spectroscopic data (IR spectra, ^{1}H-NMR , ^{13}C-NMR , and MALDI-TOF MS) for compounds **3a-k** including HSQC and HMBC spectra for compounds **3a,** and HSQC, HMBC and COSY spectra for compounds **3d**, **3f-g** and **3k** can be found in the ‘‘Supplementary Content’’ section of this article’s webpage.

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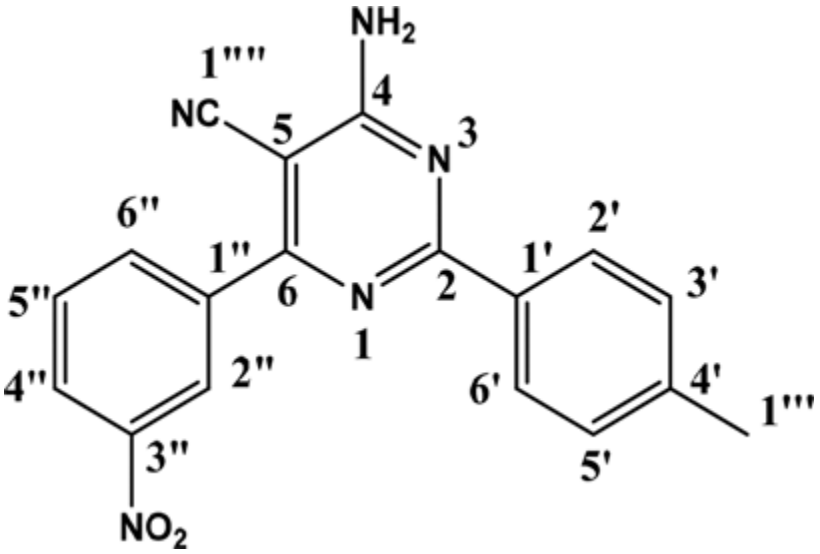
Table S1. HMBC correlations of compound of 4-Amino-5-cyano-2-(*p*-diethylaminophenyl)-6-(*p*-nitrophenyl)-pyrimidine **(3f)**

^{1}H NMR signals	^{13}C NMR signals
δ_H 8.24 ppm (H2' and H6' nuclei)	δ_C 164.2 ppm (C2 nucleus)
	δ_C 152.6 ppm (C4' nucleus)
	δ_C 130.1 ppm (C2' and C6' nuclei)
δ_H 7.97 ppm (H2'' and H6'' nuclei)	δ_C 166.5 ppm (C6 nucleus)
	δ_C 135.5 ppm (C4'' nucleus)
	δ_C 130.4 ppm (C2'' and C6'' nuclei)
	δ_C 128.5 ppm (C3'' and C5'' nuclei)
δ_H 7.64 ppm (H3'' and H5'' nuclei)	δ_C 135.7 ppm (C1'' nucleus)
	δ_C 130.4 ppm (C2'' and C6'' nuclei)
	δ_C 128.5 ppm (C3'' and C5'' nuclei)
δ_H 6.77 ppm (H3' and H5' nuclei)	δ_C 123.1 ppm (C1' nucleus)
	δ_C 111.1 ppm (C3' an C5' nuclei)

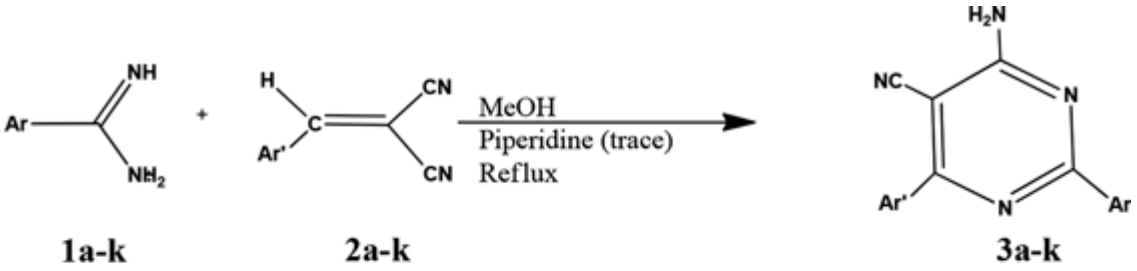
Table S2. Antibacterial property of compounds **3a-k**, MIC = 3.2 a 0.2 mg/mL

Sample	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**
Control (DMSO)	0	0	0	0	0	0	0	0	0	0	0
Staphylococcus aureus	0.8	>3.2	>3.2	>3.2	0.2	0.2	0.4	>3.2	>3.2	>3.2	0.1
Bacillus subtillis	0.8	>3.2	>3.2	>3.2	1.6	0.4	0.2	>3.2	>3.2	>3.2	0.2
Pseudomonas aeruginosa	0.8	>3.2	3.2	>3.2	0.8	0.4	>3.2	>3.2	>3.2	>3.2	0.4

Figure S1. 4-Amino-5-cyano-2-(*p*-methylphenyl)-6-(*m*-nitrophenyl)-pyrimidine (**3g**)



Scheme S1. Synthesis of compounds **3a-k** from **1a-k** and **2a-k**.



1a-k **2a-k** **3a-k**

1-3	Ar	Ar'	m.p. (°C)
a:	Ph	*m*-NO_2Ph	221-222
b:	Ph	*p*-NO_2Ph	220-221
c:	*p*-CH_3 OPh	*m*-NO_2Ph	226-227
d:	*p*-CH_3OPh	*p*-NO_2Ph	221-222
e:	*p*-$(CH_3)_2$NPh	*m*-NO_2Ph	236-237
f:	*p*-$(CH_3)_2$NPh	*p*-NO_2Ph	222-223
g	*p*-CH_3Ph	*m*-NO_2Ph	241-243
h	*p*-CH_3Ph	*p*-NO_2Ph	289-291
i	*p*-NO_2Ph	*m*-NO_2Ph	260-262
j	*p*-NO_2Ph	*p*-NO_2Ph	237-239
k	*p*-NH_2Ph	*m*-NO_2Ph	243-245

Scheme S2. Mechanism of formation of 4-amino-2,6-diaryl-5-cyanopyrimidines from arylamidine and 2-cyanocinnamonitrille