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PII: S0040-4020(15)30047-8

DOI: 10.1016/j.tet.2015.09.018

Reference: TET 27115

To appear in: *Tetrahedron*

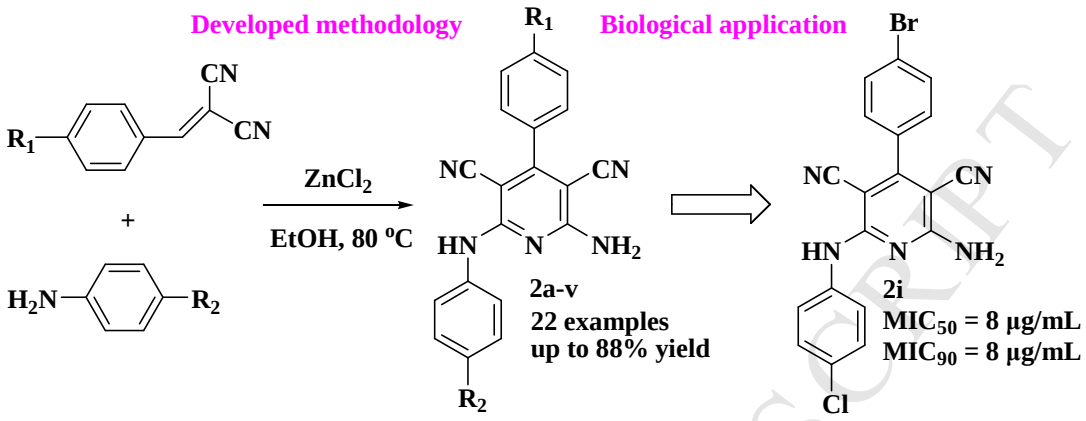
Received Date: 27 June 2015

Revised Date: 2 September 2015

Accepted Date: 7 September 2015

Please cite this article as: Huang J, Zhou J, Song S, Song H, Chen Z, Yi W, A new and efficient $ZnCl_2$-catalyzed synthesis and biological evaluation of novel 2-amino-3,5-dicyano-4-aryl-6-aryl-aminopyridines as potent antibacterial agents against Helicobacter Pylori (HP), *Tetrahedron* (2015), doi: 10.1016/j.tet.2015.09.018.

# Graphical Abstract




Herein a new and efficient method *via* $ZnCl_2$-catalyzed direct cyclization of diverse benzylidenemalononitriles and arylamines for one-pot synthesis of novel 2-amino-3,5-dicyano-4-aryl-6-aryl-aminopyridines as potent antibacterial agents is described.

# A new and efficient $ZnCl_2$-catalyzed synthesis and biological evaluation of novel 2-amino-3,5-dicyano-4-aryl-6-aryl-aminopyridines as potent antibacterial agents against Helicobacter Pylori (HP)

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**Abstract**

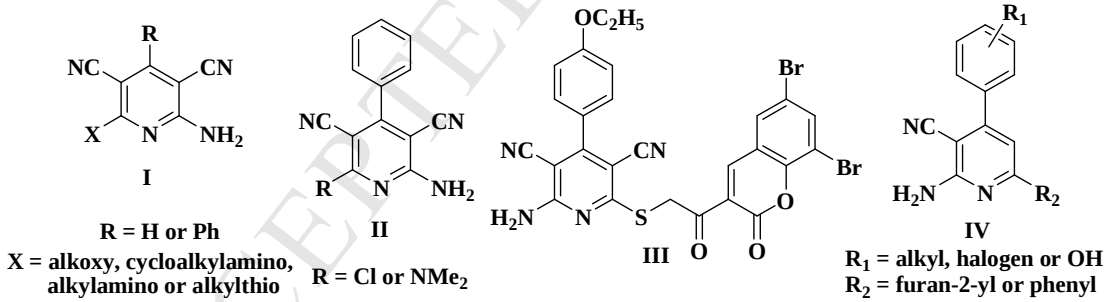
Here a new and efficient method *via* $ZnCl_2$-catalyzed direct cyclization of diverse benzylidenemalononitriles and arylamines has been developed. With this method, a variety of novel 2-amino-3,5-dicyano-4-aryl-6-aryl-aminopyridines (**2a-2v**) could be easily prepared under the mild conditions with board substrate/functional group tolerance and decent product yields. The biological activities of the selected compounds (**2c**, **2e**, **2g**, **2i**, **2k**, **2m**, **2n** and **2o**) has also been evaluated as new antibacterial agents. The results demonstrated that almost all of the compounds had more potent antibacterial activities against HP than that of clinically used drugs, Ornidazole, Metronidazole, Nitrimidazine and Clarithromycin, suggesting that further development of such compounds might be of great interest.

***Keywords*:** $ZnCl_2$-catalyzed cyclization; 2,6-diamino-3,5-dicyano-4-arylpyridines; antibacterial activity; Helicobacter Pylori (HP).

## 1. Introduction

Polysubstituted pyridine system has attracted considerable attentions since this class of compounds demonstrated many kinds of interesting biological activities. For example, 2-amino(or chloro)-3,5-dicyano-4-alkyl(or aryl)-6-substituted amino(or alkoxy, alkylthio)pyridine compounds could be used not only for the treatment of Alzheimer and neuronal vascular diseases (**I**, **II** in Fig. 1),[1,2] but also for the treatment of HIV-1 integrase (**III** in Fig. 1).[3,4] Besides, 2-Amino-3-cyano-4-substituted pyridines (**IV** in Fig. 1) were identified as potent adenosine receptor antagonists,[5] protection against edema and inhibition of plasma PGE2.[6] Moreover, they are key and useful synthons for rapid and efficient construction of other biologically important pharmacophores such as pyridopyrimidinone.[7-9] Driven by their potential in biological and chemical application, to date, a large number of polysubstituted pyridines have been successfully constructed by using a variety of developed methods.

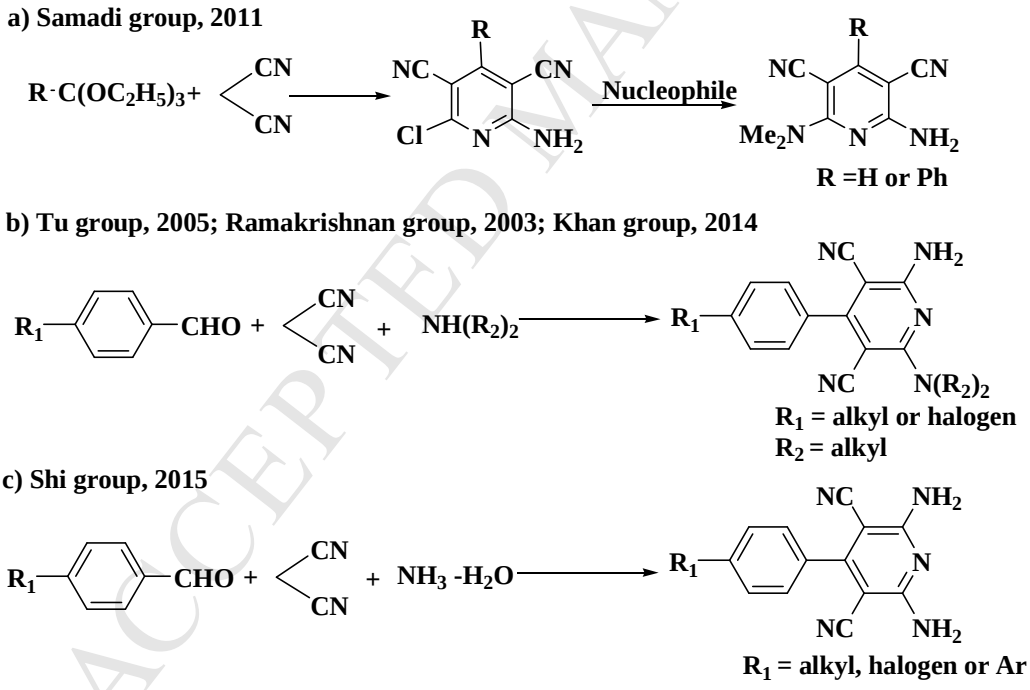
**Figure 1**. Chemical structures of representative polysubstituted pyridine compounds.




Among these polysubstituted pyridine compounds, 2-amino-3,5-dicyano-4-aryl-6-substituted aminopyridine compounds occupied a prevalent position because of their broad ranges of fascinating biological properties.[1,2,10] However, to the best of our knowledge, there are only a few reported methods about their synthesis[2,11-14] (Scheme 1). The first method was the substitution reaction of 2-amino-6-chloro-4-phenyl-pyridine-3,5-dicarbonitrile with the

corresponding amine (Scheme 1a).[2] However, it needed harsh conditions and gave the desired product in low yields. The second method was one-pot three-component condensation reaction of substituted benzaldehydes, malononitrile and alkylamines[11-13] (Scheme 1b) or ammonia (Scheme 1c).[14] The latter is easier to implement in a more step-/atom- economic way than the former, while this reaction was not compatible for arylamines. Obviously, the development of a new and highly efficient procedure to improve the current limited scope of substrates and to obtain new analogues of 2-amino-3,5-dicyano-4-aryl-6-substituted aminopyridine for immediate drug screening is still high desired.

**Scheme 1.** The reported methods for synthesizing 2-amino-3,5-dicyano-4-aryl-6-substituted aminopyridine compounds




On the other hand, the increasing incidence of bacterial infection is a growing global health problem. Nowadays, infectious diseases caused by various bacteria especially constantly emerging antibiotic resistant bacteria are still a major concern and account for almost 13 50,000 deaths worldwide daily. Accordingly, to overcome

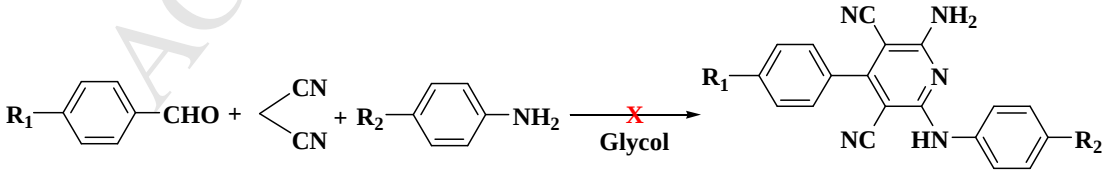
the threats, modern medicine has an eager quest for new antibacterial drugs. Based on these, so far many efforts have been spent in this field, and a large number of naturally occurring and synthetic antibiotics have been reported.[15-23] However, most of them are not potent enough to be put into practical use due to their weak individual activities or safety concerns. Undoubtedly, there is ongoing demand for developing novel antibacterial drugs with more promising potency including better activities and lower side effects.

Taking advantage of aforementioned information, here we report for the first time a mild and efficient $ZnCl_2$-catalyzed cyclization of diverse benzylidenemalononitriles and arylamines for direct construction of novel 2-amino-3,5-dicyano-4-aryl-6-aryl-aminopyridines. Moreover, in continuing our program aimed to search for potent drugs for bacterial infections,[24,25] the antibacterial activities against helicobacter pylori (HP) of the selected compounds were evaluated and the structure-activity relationships (SARs) were discussed. The nice data from biological evaluation suggested that further development of such compounds for antibacterial drug discovery might be of great interest.

## 2. Results and discussion

### 2.1. Chemistry

**Scheme 2**. The hoped **t**hree-component condensation reaction of substituted benzaldehyde, malononitrile and substituted phenylamine.

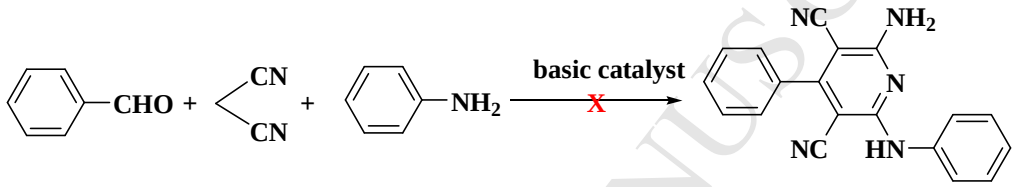



**$R_1$ = $R_2$ = H, methyl or methoxy**

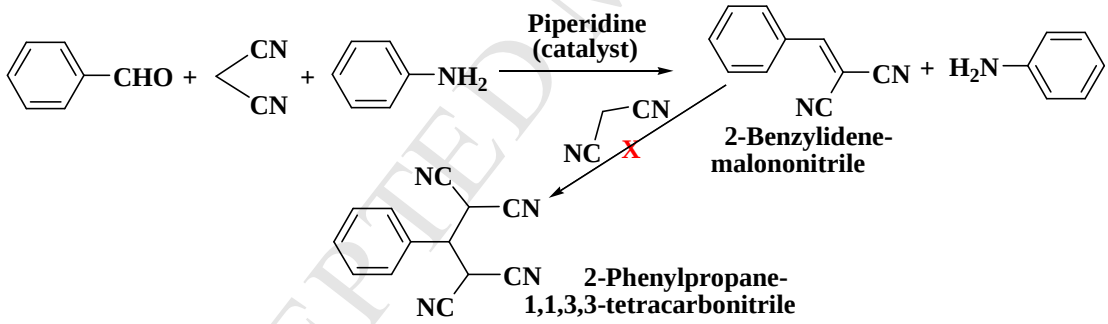
As reported (Scheme 1b), alkylamines were employed not only as the reagents, more importantly, but also as the basic catalysts to be involved in the

three-component condensation reaction. However, as illustrated in Scheme 2, we found that the weakly basic aniline could not catalyze this reaction. With this in mind, at the outset of this study, we chose benzaldehyde (1.0 eq.), malononitrile (2.1 eq.) and aniline (2.1 eq.) as a model reaction in the presence of catalyst amount of pyrrolidine at 75 $^{o}$C in glycol for 24 h. Unfortunately, no desired product was observed (Scheme 3). Inferior results were also obtained in other selected basic catalysts such as piperidine, triethylamine, morpholine or pyridine.

**Scheme 3.** Reaction of benzaldehyde, malononitrile and aniline with using pyrrolidine, piperidine, triethylamine, morpholine and pyridine as catalysts, respectively.

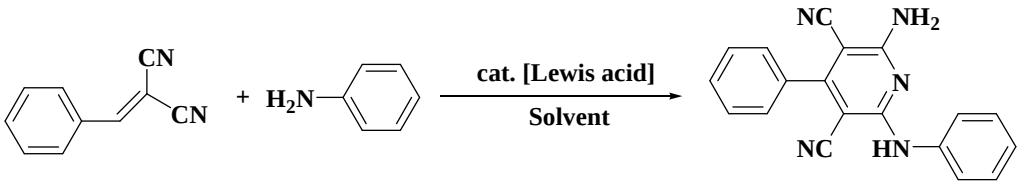



**Scheme 4.** Reaction of benzaldehyde, malononitrile and aniline with pyrrolidine as catalyst.




To our surprise, 2-benzylidenemalononitrile was detected as the main product in the above reaction system, although the molecular ratio of benzaldehyde and malononitrile in the reaction mixture was 1:2.1 (Scheme 4). This result revealed that the designed reaction might follow a quite different mechanism compared with the previously reported alkylamine-mediated reaction, which prompted us to explore an alternative reaction condition for starting this reaction, such as the well-known Lewis acid-catalyzed reaction system.

**Table 1** Optimization of reaction conditions.




| Entry | Catalyst | Solvent | T ($^{o}$C) | T (h) | Yield[d] (%) |
|---|---|---|---|---|---|
| **1** | TsOH | EtOH | 75 | 12 | 0 |
| **2** | $AlCl_3$ | EtOH | 75 | 12 | 0 |
| **3** | $H_3BO_3$ | EtOH | 75 | 12 | 0 |
| **4** | $CF_3COOH$ | EtOH | 75 | 12 | 0 |
| **5** | $Zn(OCOCH_3)_2$ | EtOH | 75 | 12 | 0 |
| **6** | $FeCl_3$ | EtOH | 75 | 12 | 0 |
| **7** | $ZnCl_2$ | EtOH | 75 | 12 | 81 |
| **8** | $ZnCl_2$ | DMF | 75 | 12 | 10 |
| **9** | $ZnCl_2$ | DCE | 75 | 12 | 0 |
| **10** | $ZnCl_2$ | DMSO | 75 | 12 | 0 |
| **11** | $ZnCl_2$ | THF | 75 | 12 | 21 |
| **12** | $ZnCl_2$ | Toluene | 75 | 12 | 0 |
| **13** | $ZnCl_2$ | EtOH | 60 | 12 | 77 |
| **14** | $ZnCl_2$ | EtOH | 50 | 12 | 65 |
| **15** | $ZnCl_2$ | EtOH | 80 | 2.0 | 63 |
| **16** | $ZnCl_2$ | EtOH | 80 | 3.5 | 79 |
| **17** | $ZnCl_2$ | EtOH | 80 | 5.0 | 86 |
| **18**[a] | $ZnCl_2$ | EtOH | 80 | 5.0 | 52 |
| **19**[b] | $ZnCl_2$ | EtOH | 80 | 5.0 | 38 |
| **20**[c] | $ZnCl_2$ | EtOH | 80 | 5.0 | 83 |

Reaction conditions: benzylidenemalononitrile (6.0 mmol), aniline (6.9 mmol), Lewis acid-catalyst (9.0 mmol), solvent (20 mL). [a] 6.0 mmol $ZnCl_2$ was used. [b] 3.0 mmol $ZnCl_2$ was used. [c] Performed on a gram-scale. [d] Isolated yields.

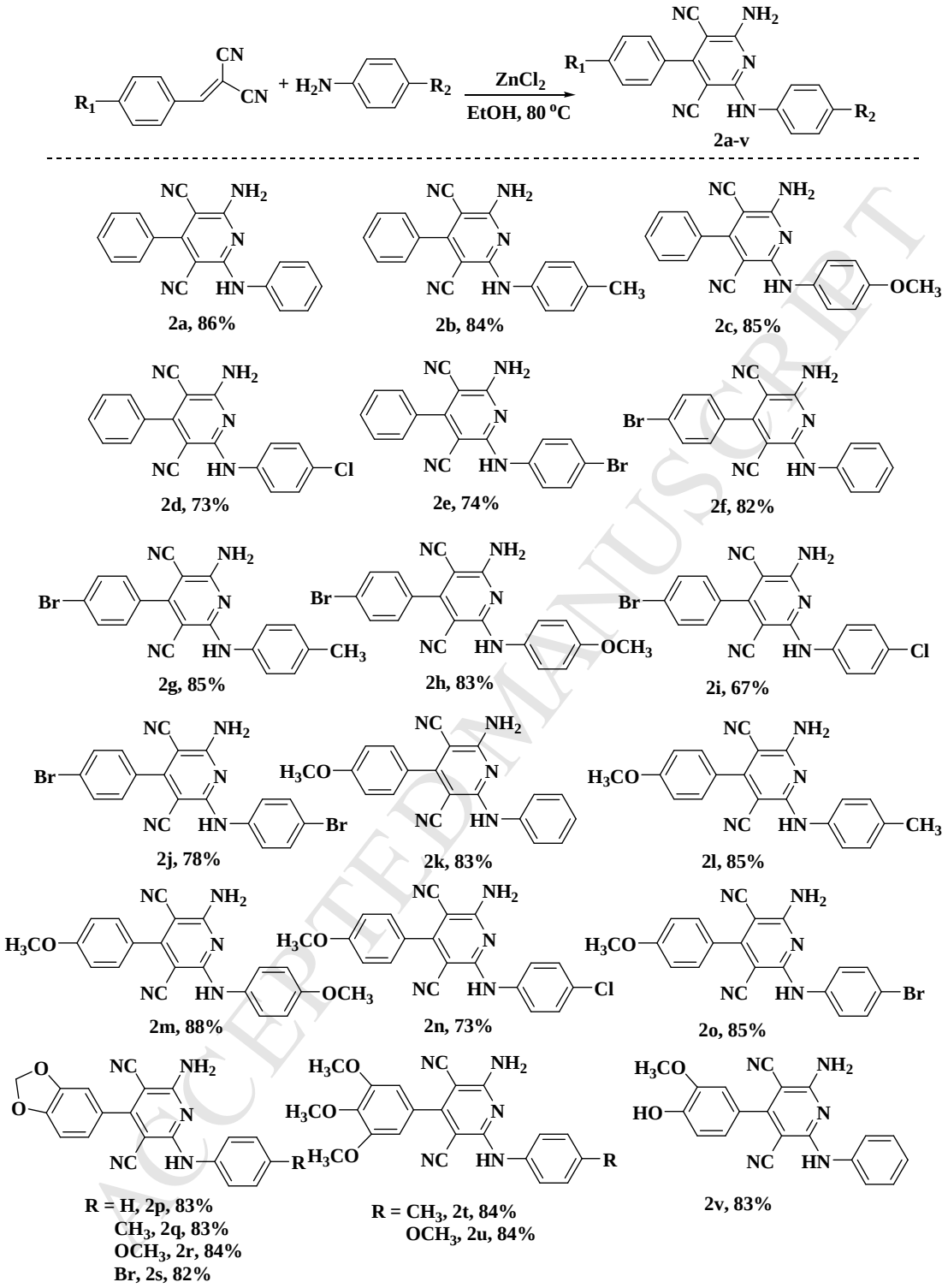
In order to confirm above conjecture, next we selected the benzylidenemalononitrile and aniline as the model substrates for the optimization of Lewis acid-catalyzed reaction system (Table 1). After extensive screening the common Lewis acids as catalysts (Table 1, entries 1-7), we were pleased to find that the reaction of benzylidenemalononitrile with aniline at 75 $^{o}$C in EtOH using $ZnCl_2$ as the catalyst gave the desired product **2a** in good yield (81%) along with the formation of *N*-benzylideneaniline as the by-porduct[26] (Table 1, entry 7). Changing EtOH to other solvents obviously inhibited the process (Table 1, entries 7-12). Further

investigation showed that the reaction time and temperature also obviously influenced the reaction efficiencies (Table 1, entries 13-17). The yield was raised to 86% with a shorter reaction time (5.0 h *vs* 12 h) when the reaction temperature was increased to 80 $^{o}$C (Table 1, entry 17). Moreover, an attempt to decrease the catalyst loading cut down the yield sharply (Table 1, entries 18-19). Finally, we were pleased to find that the reaction could conveniently be scaled up to a gram level without a decrease in isolated yield (Table 1, entry 20). In summary, the optimal conditions in ethanol included $ZnCl_2$ (150 mol %) at 80 $^{o}$C for 5.0 h under air.

With the optimized conditions in hand, we next examined the influence exerted by substituents at the benzylidenemalononitrile moiety. The results were shown in Scheme 5. In general, the reaction proceeded smoothly to give the desired products in high yields and also showed good compatibility with many valuable functional groups such as methoxy and bromo substituents. It was noteworthy that the hydroxyl group remains intact after reaction, providing easy handles for further synthetic elaborations.

Subsequently, we also explored the versatility of the optimized system by testing a representative set of arylamines. As shown in Scheme 5, both electro-donating and -withdrawing groups on 4-position of arylamine are all well tolerated affording the expected products in good yields. Tolerance to the chloro and bromo functional groups was especially noteworthy since they are useful for subsequent cross-coupling reactions.

**Scheme 5.** Substrate scope.

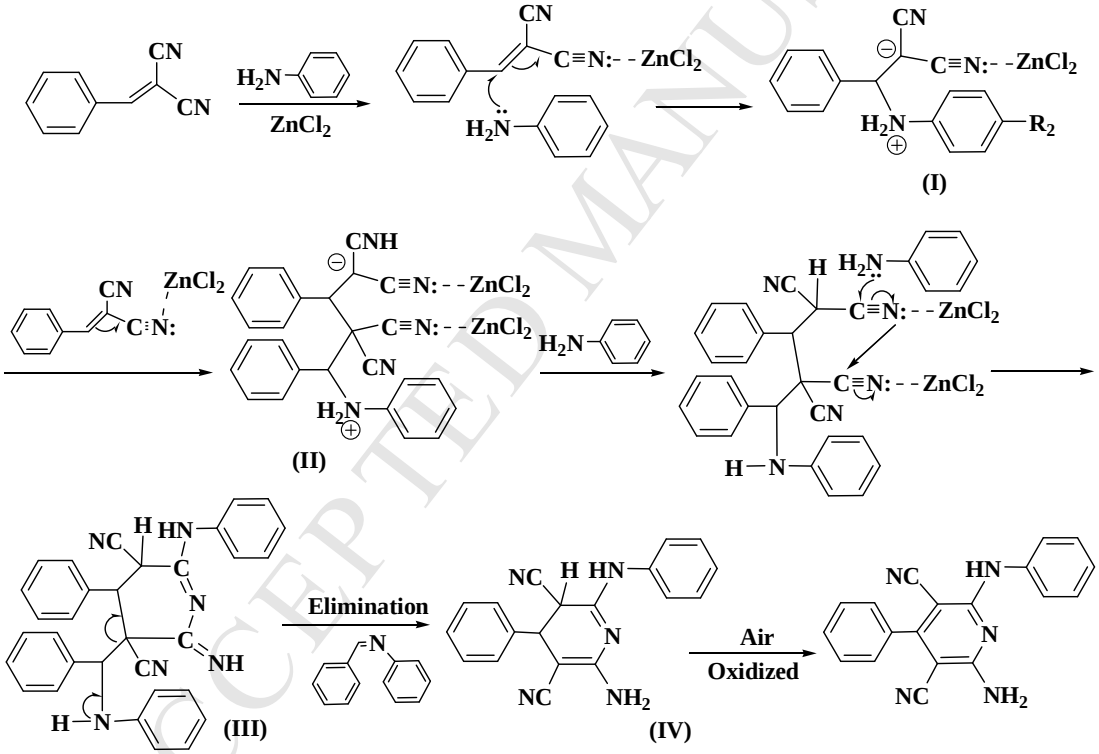



Reaction conditions: Cat. $ZnCl_2$ (9.0 mmol), the corresponding benzylidenemalononitriles (6.0 mmol) and anilines (6.9 mmol) in EtOH (20 mL) at 80 °C for 5.0 h under air. Isolated yields.

Encouraged by the above results, we finally expanded the scope of functional groups attached at both benzylidenemalononitrile and arylamine moieties. Thus, several typical substituents such as methoxy, bromo, methyl and chloro were selected

as the effectors for the investigation (Scheme 5). As expected, the corresponding double-substituted or poly-substituted products were obtained in good yields. Furthermore, we were pleased to find that benzylidenemalononitrile moiety, bearing a bulkier substituent at benzene ring such as 3,4-methylenedioxy or 3,4,5-trimethoxy, also smoothly reacted with 4-functionized arylamines to deliver the corresponding products under the optimized conditions without significant decrease in the product yields, which further illustrated the remarkable robustness of our developed $ZnCl_2$ catalytic system.

**Scheme 6**. Proposed mechanism.




Based on these observations and literature precedents, we used 2-benzylidene-malononitrile and aniline as model reaction to propose a possible mechanism illustrated in Scheme 6. First, 2-benzylidenemalononitrile reacted with aniline in the presence of $ZnCl_2$ forming intermediate **I** which reacted further with 2-benzylidenemalononitrile generating intermediate **II**. Catalyzing by $ZnCl_2$ again, **II**

reacted with aniline and followed by an intramolecular ring-closing reaction forming intermediate **III**. Sequentially, **III** was changed into **IV** by eliminating *N*-benzylidenebenzenamine, and finally, **IV** was oxidized by air and aromatized into 2-amino-3,5-dicyano-4-phenyl-6-phenylaminopyridine.

In addition, from Scheme 6 we found that $ZnCl_2$ took part in four reaction steps: (1) the addition reaction of 2-benzylidenemalononitrile and aniline, (2) the addition reaction of 2-benzylidenemalononitrile and **I**, (3) the addition reaction of **II** and aniline, and (4) the intramolecular ring-closing reaction forming **III**. Taken together, $ZnCl_2$ played a vital role in the outcome of this reaction.

**2.2. Biology**

With these synthesized 2-amino-3,5-dicyano-4-aryl-6-arylaminopyridines in hand, their biological activities of selected samples against eleven HP strains (ATCC Hp11637 and clinically separated HP strains, Hp05-5, Hp05-6, Hp05-7, Hp05-8, Hp05-9, Hp05-10, Hp05-11, Hp05-12, Hp05-13, Hp05-14) were evaluated by usual procedure,[27-31] and the results were presented in Tables 2-4. Here clinically used antibacterial drugs, Ornidazole ($D_1$), Metronidazole ($D_2$), Nitrimidazine ($D_3$) and Clarithromycin ($D_4$), were employed as standard references.

**Table 2** The MIC values of synthesized compounds against HP-strains in comparison with four drug references, $D_1$, $D_2$, $D_3$ and $D_4$ respectively in $10^6$ and $10^4$ of colony forming units of HP strains.

| Bacterial strains | Colony forming units /cfu/mL | MIC(μg/mL) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **2c** | **2e** | **2g** | **2i** | **2k** | **2m** | **2n** | **2o** | $D_1$ | $D_2$ | $D_3$ | $D_4$ |
| 11637 | $10^6$ | 32 | 16 | 16 | 8 | 16 | 16 | 4 | 32 | 64 | 64 | 64 | 64 |
| HP05-5 | | 32 | 16 | 16 | 8 | 32 | 32 | 8 | 32 | 128 | 64 | 64 | 128 |
| HP05-6 | | 32 | 16 | 16 | 8 | 16 | 16 | 4 | 128 | 128 | 32 | 64 | 128 |
| HP05-7 | | 64 | 128 | 128 | 64 | 64 | 64 | 64 | 64 | 128 | 128 | 64 | 128 |
| HP05-8 | | 32 | 16 | 16 | 8 | 16 | 16 | 4 | 32 | 128 | 16 | 64 | 128 |
| HP05-9 | | 32 | 16 | 16 | 8 | 16 | 16 | 4 | 32 | 128 | 64 | 64 | 128 |
| HP05-10 | | 64 | 32 | 16 | 8 | 32 | 32 | 8 | 64 | 128 | 64 | 64 | 128 |
| HP05-11 | | 64 | 32 | 16 | 8 | 32 | 32 | 32 | 64 | 128 | 64 | 64 | 128 |
| HP05-12 | | 32 | 16 | 16 | 8 | 16 | 32 | 4 | 32 | 128 | 64 | 64 | 128 |
| HP05-13 | | 32 | 16 | 16 | 8 | 16 | 16 | 8 | 32 | 128 | 64 | 64 | 128 |
| HP05-14 | | 32 | 16 | 16 | 8 | 16 | 16 | 8 | 32 | 128 | 64 | 64 | 128 |
| 11637 | $10^4$ | 32 | 16 | 16 | 8 | 16 | 16 | 4 | 32 | 64 | 64 | 64 | 64 |
| HP05-5 | | 32 | 16 | 16 | 8 | 32 | 32 | 8 | 32 | 128 | 64 | 64 | 128 |
| HP05-6 | | 32 | 16 | 16 | 8 | 16 | 16 | 4 | 128 | 128 | 32 | 64 | 128 |
| HP05-7 | | 64 | 128 | 128 | 64 | 64 | 64 | 64 | 64 | 128 | 128 | 64 | 128 |
| HP05-8 | | 32 | 16 | 16 | 8 | 16 | 16 | 4 | 32 | 128 | 16 | 64 | 128 |
| HP05-9 | | 32 | 16 | 16 | 8 | 16 | 16 | 4 | 32 | 128 | 64 | 64 | 128 |
| HP05-10 | | 64 | 32 | 16 | 8 | 32 | 32 | 8 | 64 | 128 | 64 | 64 | 128 |
| HP05-11 | | 64 | 32 | 16 | 8 | 32 | 32 | 32 | 64 | 128 | 64 | 64 | 128 |
| HP05-12 | | 32 | 16 | 16 | 8 | 16 | 32 | 4 | 32 | 128 | 64 | 64 | 128 |

First, in order to evaluate the anti-HP activities of the target compounds and investigate the effects of the concentrations of colony forming units of bacteria on the activity, two concentrations ($10^6$ and $10^4$ units /cfu/mL) of colony forming units of HP strains was used to determine the MIC values of samples (Table 2). As shown in Table 2, the results showed that the similar MIC value for each sample were obtained in two different concentrations, suggesting that the antibacterial activity against HP of the tested sample was not related with the concentration of colony forming units of bacteria in the inoculums.

**Table 3** The $MIC_{50}$, $MIC_{90}$ and MIC range values of compounds **2a-2h** against HP-strains in comparison with four drug references, $D_1$, $D_2$, $D_3$ and $D_4$.

| Sample | MIC value (μg/mL) | | | Samples | MIC value (μg/mL) | | |
|---|---|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | MIC-range | | $MIC_{50}$ | $MIC_{90}$ | MIC-range |
| **2c** | 32 | 64 | 32-64 | **2n** | 8 | 32 | 4-64 |
| **2e** | 16 | 32 | 16-128 | **2o** | 32 | 64 | 32-128 |
| **2g** | 16 | 16 | 16-128 | **$D_1$** | 128 | 128 | 64-128 |
| **2i** | 8 | 8 | 8-64 | **$D_2$** | 64 | 64 | 16-128 |
| **2k** | 16 | 32 | 16-64 | **$D_3$** | 128 | 128 | 64-128 |
| **2m** | 16 | 32 | 16-64 | **$D_4$** | 64 | 64 | 64 |

Therefore, next the minimum inhibitory concentrations at the inhibitory percentages of 50%, 90% (named $MIC_{50}$ and $MIC_{90}$, respectively) and minimum inhibitory concentration range (MIC-range) of samples against HP-strains were determined under the condition of single concentration (Table 3). The results demonstrated that most of target compounds performed more potent antibacterial activities against eleven HP-strains than $D_1$, $D_2$, $D_3$ and $D_4$. Especially, compound **2i** was found to be the most potent antibacterial agent with the same $MIC_{50}$ and $MIC_{90}$ value (8 μg/mL).

From the antibacterial activities of the synthesized 2-amino-3,5-dicyano-4-aryl-6-arylaminopyridine compounds, the following SAR results could be derived:

(1) Compared with the reference drugs, all the selected compounds showed potent anti-HP activities, suggesting that 2-amino-3,5-dicyano-4-aryl-6-arylaminopyridine moiety could serve as a privileged structural core motif for new and potent antibacterial drug discovery.

(2) In general, at 4-position of phenyl rings, the compounds bearing electro-withdrawing halogen groups showed better antibacterial activities than that bearing electro-donating methyl or methoxy group (**2e** *vs* **2c**, **2i** *vs* **2g**, and **2n** *vs* **2m**). The results suggested that the antibacterial activities of

2-amino-3,5-dicyano-4-aryl-6-arylaminopyridines might be associated with the electronic character of the substituent on the 4-position of benzene. In the present investigation, the halogen substitution for improving the antibacterial activity strength followed the order: Cl >Br (**2n** *vs* **2o**).

(3) Double-substituted compounds **2g**, **2i** and **2m-n** (except **2o**) have more potent anti-HP activities than that bearing mono-substituted group (**2c** and **2e**), suggesting that the introduction of an additional functional group might be efficacious for the anti-HP activity. Furthermore, compared with the most active compounds **2i** and **2n**, it showed that bromo group was more favorable than methoxy group for improving the potent antibacterial activities.

**Table 4** The statistical data of anti-HP activity of synthesized compounds in comparison with four drug references.

| Sample | N[a] | Mean | Standard deviation | Standard error | 5%confidence interval for mean | | Min-imum | Max-imum |
|---|---|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound | | |
| **2c** | 11 | 1.587249 | 0.1406109 | 0.0423958 | 1.492785 | 1.681713 | 1.5051 | 1.8062 |
| **2e** | 11 | 1.340952 | 0.2812218 | 0.0847916 | 1.152024 | 1.529879 | 1.2041 | 2.1072 |
| **2g** | 11 | 1.286219 | 0.2722919 | 0.0820991 | 1.103291 | 1.469147 | 1.2041 | 2.1072 |
| **2i** | 11 | 0.985189 | 0.2722919 | 0.0820991 | 0.802261 | 1.168117 | 0.9031 | 1.8062 |
| **2k** | 11 | 1.340952 | 0.2069737 | 0.0624049 | 1.201905 | 1.479999 | 1.2041 | 1.8062 |
| **2m** | 11 | 1.368318 | 0.2069737 | 0.0624049 | 1.229271 | 1.507365 | 1.2041 | 1.8062 |
| **2n** | 11 | 0.903090 | 0.4038741 | 0.1217726 | 0.631764 | 1.174416 | 0.6021 | 1.8062 |
| **2o** | 11 | 1.641982 | 0.2069737 | 0.0624049 | 1.502935 | 1.781029 | 1.5051 | 2.1072 |
| **$D_1$** | 11 | 2.079844 | 0.0907640 | 0.0273664 | 2.018868 | 2.140820 | 1.8062 | 2.1072 |
| **$D_2$** | 11 | 1.751447 | 0.2260004 | 0.0681417 | 1.599618 | 1.903276 | 1.2041 | 2.1072 |
| **$D_3$** | 11 | 2.079844 | 0.0907640 | 0.0273664 | 2.018868 | 2.140820 | 1.8062 | 2.1072 |
| **$D_4$** | 11 | 1.806180 | 0.0000000 | 0.0000000 | 1.806180 | 1.806180 | 1.8062 | 1.8062 |
| Total | 132 | 1.513199 | 0.4474078 | 0.0327177 | 1.448653 | 1.577744 | 0.3010 | 2.1072 |

[a] number of strains used in this test

Finally, The proceeded MIC test data were treated by using SPSS statistical software, and the results including mean, standard deviation, standard error, 5% confidence interval for mean, minimum and maximum values were listed in Table 4. As shown in Table 4, we found that **2i** and **2n** had the highest anti-HP activities in a

similar order of magnitude ($P > 0.05$), which was significantly better than that of the other tested compounds and selected four drug references ($P < 0.05$). This further confirmed our obtained results shown as above.

## 3. Conclusion

In summary, we have developed for the first time a $ZnCl_2$-catalyzed direct cyclization of diverse benzylidenemalononitriles and arylamines. With this method, a wide range of novel 2-amino-3,5-dicyano-4-aryl-6-aryl-aminopyridines were conveniently synthesized in high yields with board substrate/functional group tolerance. Moreover, the application of the synthesized compounds was demonstrated, the results showed that most of target compounds have more potent antibacterial activities against HP strains (including ATCC Hp11637 and eleven kinds of clinically separated HP strains) than currently used four antibacterial drugs $D_1$, $D_2$, $D_3$ and $D_4$. In particular, compound **2i** was found to be the most potent antibacterial agent with the same $MIC_{50}$ and $MIC_{90}$ value (8 μg/mL). SAR analysis showed: (1) 2-amino-3,5-dicyano-4-aryl-6-aryl-aminopyridine moiety could serve as a privileged structural core motif for new and potent antibacterial drug discovery; and (2) the electronic character and number of the substituent on the 4-position of benzene played a key role in determining the antibacterial activity, suggesting that further development of such compounds might be of great interest.

## 4. Experimental section

### 4.1. General

Melting points were determined on a WRS-1B digital instrument without correction. NMR spectra were recorded on a Varian Mercury-Plus 300 spectrometer in DMSO-$d_6$. All chemical shifts ($\delta$) were quoted in parts per million and coupling constants ($J$) were given in Hertz. Mass spectra were obtained from VG ZAB-HS,

LCMS-2010A or LCQ DECA XP spectrometer. All commercially available reagents and solvents were used without further purification. Ornidazole ($D_1$, lot number 10336-0001) and Metronidazole ($D_2$, 100191-200305) were purchased from National Institutes for Food and Drug Control; Nitrimidazine ($D_3$,) was provided by the Industry of Sichuan antibiotics; Clarithromycin ($D_4$, lot number 040908) was purchased from Zhejiang Huayi Medicines Co. Dimethyl sulfoxide was used as solvent to dissolve all the reference drugs. HP strains (including ATCC Hp11637 and eleven kinds of clinically separated HP strains, Hp05-5, Hp05-6, Hp05-7, Hp05-8, Hp05-9, Hp05-10, Hp05-11, Hp05-12, Hp05-13, Hp05-14) used in these studies were provided by professor Fulian Hu (Peking University).

**4.2. Chemistry**

General procedure for the synthesis of 2-amino-3,5-dicyano-4-aryl-6-arylamino-pyridines **2a-2v**: Substituted benzylidenemalononitrile compounds were prepared by the condensation reaction of appropriate substituted benzaldehydes and malononitrile in the presence of piperidine or pyrrolidine in ethanol.

To the solution of substituted benzylidenemalononitrile (6.0 mmol) in anhydrous ethanol (20 mL) were added appropriate substituted aniline (6.9 mmol), cat. $ZnCl_2$ (9.0 mmol), the mixture was stirred at 80 $^{o}$C for 5.0 h. Then, the mixture was cooled to room temperature and slowly poured into 150 mL of ice-water by stirring. The precipitate solid was filtered, washed, recrystallized in the mixture of acetone and methanol to afford pure target compounds **2a-2v**.

**4.2.1.** 2-Phenylamino-6-amino-4-phenylpyridine-3,5-dicarbonitrile (**2a**)

Colorless powder solid, m.p. 255-256 $^{o}$C. $^{1}$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 7.10 (t, $J$ = 7.4 Hz, 1H), 7.32 (t, $J$ = 7.8 Hz, 2H), 7.52-7.55 (m, 7H, ArH + $NH_2$), 7.66 (d, $J$ = 9.0 Hz, 2H), 9.12 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75MHz) $\delta$: 81.9, 82.7, 116.3,

116.6, 123.2, 124.4, 128.9, 129.2, 130.6, 135.6, 139.4, 149.1, 157.9, 161.2. IR (KBr) *v*: 3621, 3328, 3220, 3127, 3032, 2218, 1623, 1575, 1551, 1491, 822, 751, 680, 616. FAB-MS *m/z* (%): 312 [$(M + H)^+$, 10].

**4.2.2.** 2-(*p*-Tolylamino)-6-amino-4-phenylpyridine-3, 5-dicarbonitrile (**2b**)

Colorless powder solid, m.p. 275 °C (dec.). $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 2.26 (s, 3H), 7.09 (d, $J$ = 8.1 Hz, 2H), 7.45-7.51 (m, 9H, ArH + $NH_2$), 9.01 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75MHz) $\delta$: 21.4, 81.8, 82.6, 112.8, 116.8, 123.6, 129.0, 129.3, 129.5, 130.6, 133.6, 135.7, 136.8, 158.0, 161.2. IR (KBr) *v*: 3325, 3225, 2211, 1627, 1551, 1514, 822, 779. FAB-MS *m/z* (%):326 [$(M + H)^+$, 25]. Anal. calcd. for $C_{20}H_{15}N_5$: C 73.83, H 4.65, N 21.52; found C 73.26, H 4.84, N 21.35.

**4.2.3.** 2-(4-Methoxyphenylamino)-6-amino-4-phenylpyridine-3,5-dicarbonitrile (**2c**)

Colorless powder solid, m.p. 241 °C (dec.). $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 3.75 (s, 3H), 6.87 (d, $J$ = 9.0 Hz, 2H), 7.33-7.42 (br s, 2H, $NH_2$), 7.45-7.57 (m, 7H), 8.98 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75MHz) $\delta$: 56.1, 81.6, 82.4, 114.4, 116.9, 117.0, 125.7, 129.2, 129.5, 130.8, 132.5, 136.0, 156.9, 158.4, 161.5. IR (KBr) v: 3483, 3314, 3223, 2211, 1636, 1558, 1509, 1420, 1242, 822, 696. FAB-MS m/z: 342[$(M + H)^+$, 4]. Anal. calcd. for $C_{20}H_{15}N_5$: C 70.37, H 4.43, N 20.52; found C 69.92, H 4.50, N 20.46.

**4.2.4.** 2-(4-Chlorophenylamino)-6-amino-4-phenylpyridine-3, 5-dicarbonitrile (**2d**)

Colorless powder solid, m.p. 255 °C (dec.). $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 7.34 (d, $J$ = 8.7 Hz, 2H), 7.50-7.54 (m, 7H, ArH + $NH_2$), 7.69 (d, $J$ = 8.7 Hz, 2H), 9.27 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75MHz) $\delta$: 82.2, 82.8, 116.6, 124.8, 128.1, 128.7, 128.9, 129.2, 130.6, 135.5, 138.4, 157.6, 160.9, 161.1. IR(KBr) *v*: 3478, 3326, 3218, 2210, 1632, 1590, 1550, 1490, 818, 740, 697, 602. FAB-MS *m/z* (%): 345 [(M

+ H)$^+$, 5]. Anal. calcd. for $C_{19}H_{12}ClN_5$: C 66.00, H 3.50, N 20.25; found C 65.97, H 3.58, N 20.23.

**4.2.5.** 2-(4-Bromophenylamino)-6-amino-4-phenylpyridine-3, 5-dicarbonitrile (**2e**)

Colorless powder solid, m.p. 275 $^o$C (dec.). $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 7.44-7.54 (m, 9H), 7.64 (d, $J$ = 9.0Hz, 2H), 9.25 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75MHz) $\delta$: 82.2, 82.8, 116.2, 116.5, 125.2, 128.9, 129.2, 130.6, 131.7, 135.5, 138.9, 157.6, 160.9, 161.1. IR (KBr) $v$: 3469, 3337, 3225, 2212, 1643, 1591, 1549, 1489, 816, 737, 696, 601. FAB-MS $m/z$ (%): 391 [(M + H)$^+$, 8]. Anal. calcd. for $C_{19}H_{12}BrN_5$: C 58.48, H 3.10, N 17.95; found C 58.34, H 3.21, N 17.81.

**4.2.6.** 2-Phenylamino-6-amino-4-(4-bromophenyl)pyridine-3,5-dicarbonitrile (**2f**)

Colorless powder solid, m.p. 271 $^o$C (dec.). $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 7.08 (t, $J$ = 7.4 Hz, 1H), 7.30 (t, $J$ = 7.8 Hz, 2H), 7.45 (d, $J$ = 8.4 Hz, 2H), 7.55 (br s, 2H, $NH_2$), 7.63 (d, $J$ = 7.8 Hz, 2H), 7.76 (d, $J$ = 8.4 Hz, 2H), 9.15 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75MHz) $\delta$: 81.7, 82.5, 116.5, 123.3, 124.2, 124.5, 129.0, 131.1, 132.3, 134.8, 139.3, 157.7, 159.7, 161.0. IR (KBr) $v$: 3335, 3225, 2210, 1652, 1506, 1303, 1137, 1020, 810. FAB-MS $m/z$ (%): 389 [(M + H)$^+$, 10].

**4.2.7.** 2-(*p*-Tolylamino)-6-amino-4-(4-bromophenyl)pyridine-3,5-dicarbonitrile (**2g**)

Colorless powder solid, m.p. 270 $^o$C (dec.). $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 2.30 (s, 3H), 7.13 (d, $J$ = 8.4 Hz, 2H), 7.47-7.52 (m, 6H, ArH + $NH_2$), 7.78 (d, $J$ = 8.4 Hz, 2H), 9.09 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75MHz) $\delta$: 21.1, 81.4, 82.3, 116.6, 123.6, 124.2, 129.4, 131.1, 132.3, 133.7, 134.9, 136.7, 157.9, 159.6, 161.1. IR (KBr) ν: 3500, 3324, 3225, 2211, 1628, 1531, 1513, 1425, 822, 779, 669. FAB-MS $m/z$: 404 [(M + H)$^+$, 20]. Anal. calcd. for $C_{20}H_{14}BrN_5$: C 59.42, H 3.49, N 17.32; found C 58.99, H 3.68, N 17.88.

**4.2.8.** 2-(4-Methoxyphenylamino)-6-amino-4-(4-bromophenyl)pyridine-

3,5-dicarbonitrile (**2h**)

Colorless powder solid, m.p. 260 °C (dec.). $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 3.73 (s, 3H), 6.87 (d, $J$ = 9.0 Hz, 2H), 7.44-7.49 (m, 6H, ArH + $NH_2$), 7.75 (d, $J$ = 8.4 Hz, 2H), 9.04 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75MHz) $\delta$: 55.8, 81.2, 81.9, 114.1, 115.5, 116.6, 124.2, 125.5, 131.1, 132.1, 132.3, 134.9, 156.6, 159.6, 161.1. IR (KBr) $v$: 3500, 3369, 3297, 3168, 2214, 1655, 1552, 1509, 1421, 827, 775, 666, 617. EI-MS $m/z$ (%): 420 [$M^+$, 100], 405 [$M^+$ -$CH_2$, 30], 324 [$M^+$ -$CH_3$-Br-H, 30], 296 [$M^+$ -$CH_3$OPhNH, 12]. Anal. calcd. for $C_{20}H_{14}BrN_5O$: C 57.16, H 3.36, N 16.66; found C 57.34, H 3.59, N 16.35.

**4.2.9.** 2-(4-Chlorophenylamino)-6-amino-4-(4-bromophenyl)pyridine-

3,5- dicarbonitrile (**2i**)

Colorless powder solid, m.p. 260-261 °C. $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 7.33 (d, $J$ = 8.7 Hz, 2H), 7.46 (d, $J$ = 8.4 Hz, 2H), 7.60 (br s, 2H, $NH_2$), 7.68 (d, $J$ = 9.0 Hz, 2H), 7.76 (d, $J$ = 8.4 Hz, 2H), 9.29 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75MHz) $\delta$: 82.0, 82.6, 116.4, 124.3 124.9, 128.1, 128.7, 131.1, 132.3, 134.7, 138.4, 157.6, 159.8, 161.0. IR (KBr) $v$: 3383, 3285, 3239, 2212, 1581, 1489, 1424, 1072, 881, 820, 667. FAB-MS m/z: 426 [$(M + H)^+$, 6].

**4.2.10.** 2-(4-Bromophenylamino)-6-amino-4-(4-bromophenyl)pyridine-

3,5-dicarbonitrile (**2j**)

Colorless powder solid, m.p. 285 °C (dec.). $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 7.44 (d, $J$ = 7.5 Hz, 4H), 7.61 (d, $J$ = 8.7 Hz, 4H, 2ArH + $NH_2$), 7.74 (d, $J$ = 8.4 Hz, 2H), 9.27 (s, 1H, NH). IR (KBr) $v$: 3449, 3331, 3230, 2912, 2216, 1638, 1572, 1505, 1445, 1034, 816, 742, 607. FAB-MS $m/z$ (%): 470 [$(M + H)^+$, 5].

**4.2.11.** 2-Phenylamino-6-amino-4-(4-methxoyphenyl)pyridine-3,5-dicarbonitrile (**2k**)

Colorless powder solid, m.p. 235-237 °C. $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 3.83

(s, 3H), 7.04-7.10 (m, 3H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 4H, ArH + $NH_2$), 7.63 (d, *J* = 7.8 Hz, 2H), 9.00 (s, 1H, NH). IR(KBr) *v*: 3838, 3760, 3320, 2981, 2213, 1581, 1420, 1240, 1162, 825, 743, 694. ESI-MS *m/z*: 340 $[M - H]^-$.

**4.2.12.** 2-(*p*-Tolylamino)-6-amino-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (**2l**)

Colorless powder solid, m.p. 270-272 °C. $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 2.27 (s, 3H), 3.83 (s, 3H), 7.07-711 (m, 4H), 7.39 (br s, 2H, $NH_2$), 7.43-7.49 (m, 4H), 8.96 (s, 1H, NH). IR (KBr) *v*: 3435, 3370, 3210, 2200, 1640, 1546, 1458, 1256, 1175, 846, 780, 650. EI-MS *m/z* (%): 355 [$M^+$, 100].

**4.2.13.** 2-(4-Methoxyphenylamino)-6-amino-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile(**2m**)

Colorless powder solid, m.p. 248-249 °C. $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 3.75 (s, 3H), 3.84 (s, 3H), 6.89 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 7.34 (br s, 2H, $NH_2$), 7.46 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 9.0 Hz, 2H), 8.93 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75MHz) $\delta$: 55.2, 55.3, 80.7, 81.5, 113.5, 113.9, 116.4, 124.7, 127.0, 130.0, 131.6, 156.0, 157.6, 160.0, 160.5, 160.6. IR (KBr) ν: 3478, 3431, 3372, 3211, 2198, 1638, 1544, 1459, 1225, 1180, 840, 779, 651. EI-MS *m/z*: 370 $[M-H]^-$. Anal. calcd. for $C_{21}H_{17}N_5O_2$: C 67.91, H 4.61, N 18.86; found C 65.04, H 5.19, N 18.94.

**4.2.14.** 2-(4-Cholorophenylamino)-6-amino-4-(4-methoxyphenyl)pyridine-3,5- dicarbonitrile (**2n**)

Colorless powder solid, m.p. 256-257 °C. $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 3.85 (s, 3H), 7.10 (d, *J* = 8.4, Hz 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.51 (br s, 2H, $NH_2$), 7.69 (d, *J* = 8.7 Hz, 2H), 9.21 (s, 1H, NH). IR (KBr) ν: 3469, 3348, 3210, 2212, 1624, 1548, 1502, 1243, 1151, 1014, 887, 816. ESI-MS *m/z*: 374 $[M-H]^-$.

**4.2.15.** 2-(4-Bromophenylamino)-6-amino-4-(4-methoxyphenyl)pyridine-3,5- dicarbonitrile (**2o**)

Colorless powder solid, m.p. 260-261 $^{o}$C. $^{1}$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 3.83 (s, 3H), 7.09 (d, $J$ = 8.7 Hz, 2H), 7.43- 7.50 (m, 6H, 4ArH + $NH_2$), 7.62 (d, $J$ = 9.0 Hz, 2H), 9.19 (s, 1H, NH). IR (KBr) ν: 3478, 3376, 3312, 3194, 2926, 2205, 1616, 1558, 1507, 1260, 1179, 1027, 889, 824,772. ESI-MS *m/z*: 418 $[M-H]^-$.

**4.2.16.** 2-Phenylamino-6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)pyridine-3,5- dicarbonitrile (**2p**)

Colorless powder solid, m.p. 266 $^{o}$C (dec.). $^{1}$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 6.13 (s, 2H), 6.97 (dd, $J$ = 8.1, 1.5Hz, 1H), 7.04-7.09 (m, 3H), 7.29 (m, 2H), 7.46 (br s, 2H, $NH_2$), 7.63 (d, $J$ = 7.5Hz, 2H), 9.05 (s, 1H, NH). IR (KBr)*v*: 3446, 3337, 3227, 2913, 2212, 1624, 1559, 1497, 1451, 1277, 1032, 926, 853, 814, 739. ESI-MS *m/z*: 354 $[M - H]^-$.

**4.2.17.** 2-(*p*-Tolylamino)-6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)pyridine-3,5- dicarbonitrile (**2q**)

Colorless powder solid, m.p. >300 $^{o}$C. $^{1}$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 2.27 (s, 3H), 6.12 (s, 2H), 6.97 (dd, $J$ = 8.1, 1.5Hz, 1H), 7.08 (m, 4H), 7.41(br s, 2H, $NH_2$), 7.47 (d, $J$ = 8.4Hz, 2H), 8.98 (s, 1H, NH). IR (KBr) *v*: 3856, 3745, 3613, 2929, 2208, 1646, 1560, 1418, 1246, 1032, 881, 668. ESI-MS (*m/z*): 368 $[M - H]^-$.

**4.2.18.** 2-(4-Methoxyphenylamino)-6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)pyridine-3,5-dicarbonitrile (**2r**)

Colorless powder solid, m.p. 250-251 $^{o}$C. $^{1}$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 3.73 (s, 3H), 6.12 (s, 2H), 6.87 (d, $J$ = 9.0 Hz, 2H), 6.95 (dd, $J$ = 7.8, 1.5Hz, 1H), 7.07 (d, $J$ = 7.8 Hz, 2H), 7.35 (brs, 2H, $NH_2$), 7.45 (d, $J$ = 8.7 Hz, 2H), 8.95 (s, 1H, NH). IR

(KBr) *v*: 3445, 3336, 3225, 2915, 2213, 1626, 1559, 1495, 1450, 1347, 1283, 1259, 1032, 926, 856, 815, 735. ESI-MS *m/z*: 384 $[M - H]^-$.

**4.2.19.** 2-(4-Bromophenylamino)-6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)pyridine-3,5-dicarbonitrile (**2s**)

Colorless powder solid, m.p. 258-260 °C. $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 6.13 (s, 2H), 6.98 (d, *J* = 8.1, 1H), 7.08 (d, *J* = 7.5, 2H), 7.44 (d, *J* = 8.7, 2H), 7.52 (br s, 2H, $NH_2$), 7.63 (d, *J* = 9.0Hz, 2H), 8.98 (s, 1H, NH). IR (KBr) *v*: 3484, 3324, 3225, 2937, 2834, 2208, 1624, 1561, 1246, 1125, 1030, 883, 826, 721. ESI-MS *m/z*: 433 $[M - H]^-$.

**4.2.20.** 2-(*p*-Tolylamino)-6-amino-4-(3,4,5-trimethoxyphenyl)pyridine-3,5- dicarbonitrile (**2t**)

Colorless powder solid, m.p. 214 °C (dec.). $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 2.20 (s, 3H), 3.66 (s, 3H), 3.73 (s, 6H), 6.76 (s, 2H), 7.02 (d, *J* = 8.1, 2H), 7.34 (brs, 2H, $NH_2$), 7.39 (d, *J* = 8.4, 2H), 8.91 (s, 1H, NH). IR (KBr) *v*: 3336, 2930, 2209, 1613, 1555, 1511, 1427, 1246, 1179, 1034, 880, 832. ESI-MS *m/z*: 414 $[M - H]^-$.

**4.2.21.** 2-(4-Methoxyphenylamino)-6-amino-4-(3,4,5-trimethoxyphenyl) pyridine-3,5-dicarbonitrile (**2u**)

Colorless powder solid, m.p. 212-213 °C. $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 3.74 (s, 6H), 3.82 (s, 6H), 6.85-6.89 (m, 4H), 7.38 (brs, 2H, $NH_2$), 7.48 (d, *J* = 8.7, 2H), 8.98 (s, 1H, NH). IR (KBr) *v*: 3325, 2937, 2834, 2208, 1624, 1561, 1513, 1314, 1246, 1125, 1031, 826. ESI-MS (*m/z*): 430 $[M - H]^-$.

**4.2.22.** 2-Phenylamino-6-amino-4-(3-hydroxy-4-methoxyphenyl)pyridine-3,5-dicarbonitrile (**2v**)

Colorless powder solid, m.p. 274 °C (dec.). $^1$H NMR (DMSO-$d_6$, 300MHz) $\delta$: 3.72 (s, 3H), 6.80-6.88 (m, 2H), 6.96-7.01 (m, 2H), 7.21 (t, *J* = 7.8, 2H), 7.34 (brs, 2H,

$NH_2$), 7.55 (d, *J* = 7.5, 2H), 8.93 (s, 1H, NH), 9.46 (s, 1H, OH). IR (KBr) *v*: 3438, 3266, 3221, 3128, 3044, 2927, 2209, 1605, 1571, 1495, 1322, 1106, 896, 752, 687. ESI-MS *m/z*: 356 $[M - H]^-$.

**4.3. Biology**

The antibacterial activities *in vitro* of all the target compounds were tested against HP strains (including ATCC Hp11637 and eleven kinds of clinically separated HP strains, Hp05-5, Hp05-6, Hp05-7, Hp05-8, Hp05-9, Hp05-10, Hp05-11, Hp05-12, Hp05-13, Hp05-14), using Ornidazole ($D_1$), Metronidazole ($D_2$), Nitrimidazine ($D_3$) and Clarithromycin ($D_4$) as references, according to the method reported by other[27-31] and our[24,25] groups with some slight modifications. Briefly, all of the selected compounds were evaluated for their antibacterial activity using conventional agar-dilution method. Twofold serial dilutions of the compounds and reference drugs were prepared in Mueller–Hinton agar. Drugs were dissolved in dimethylsulfoxide (DMSO, 1 mL) and the solution was diluted with water (9 mL) without precipitation. Further progressive double dilution with melted Mueller–Hinton agar was performed to obtain the required concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2, 1 μg/mL. Petri dishes were incubated with $1x10^4$ or $1x10^6$ colony forming units (cfu) and incubated at 37 °C for 18 h. The minimal inhibitory concentration (MIC) was the lowest concentration of the test compound, which resulted in no visible growth on the plate. $MIC_{50}$ and $MIC_{90}$ values represents a concentration giving 50% and 90% inhibition of the corresponding HP activity, respectively. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment.

**Acknowledgements**

We thank the Chinese Postdoctoral Science Foundation (2012M511158 and

2013T60477) and National Natural Science Foundation of China (81125023) for financial support on this study. We also thank Professor Fulian Hu (Peking University) for providing HP strains (including ATCC Hp11637 and clinically separated HP strains, Hp05-5, Hp05-6, Hp05-7, Hp05-8, Hp05-9, Hp05-10, Hp05-11, Hp05-12, Hp05-13, Hp05-14) used in these studies.

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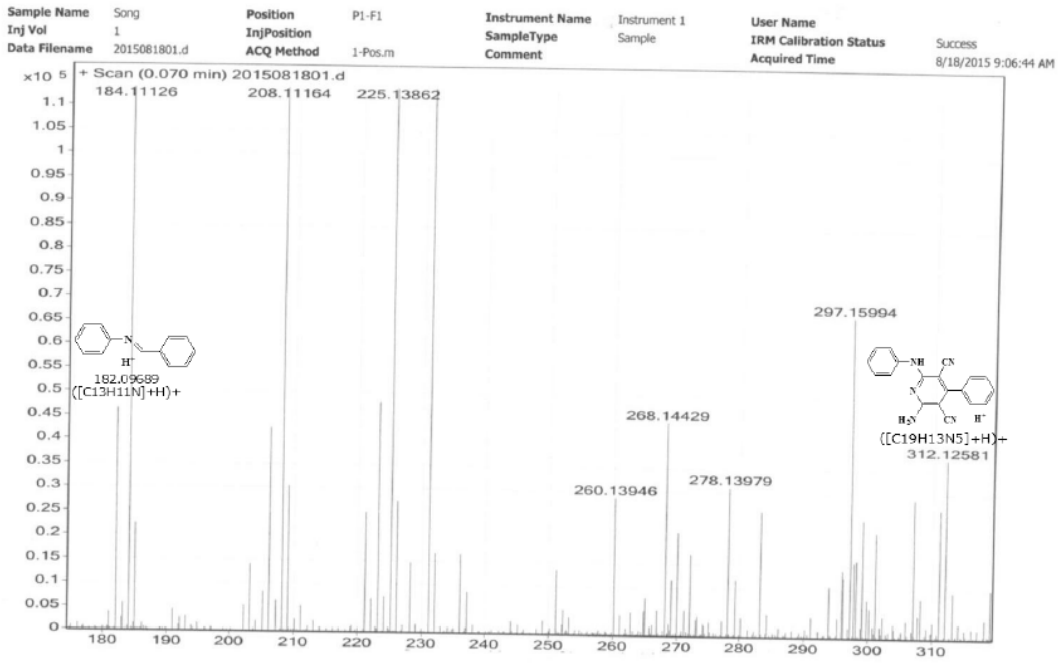
26. The reaction was carried out for 5 h under the conditions of table 1-entry 7, and the obtained mixture was monitored by ESI-HRMS analysis (see below). The results showed that the desired product **2a** and the compound *N*-benzylideneaniline were generated.

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