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Graphical Abstract

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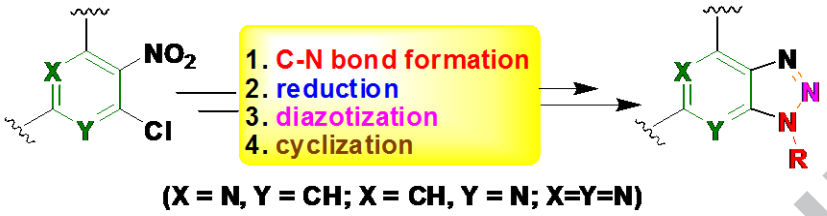

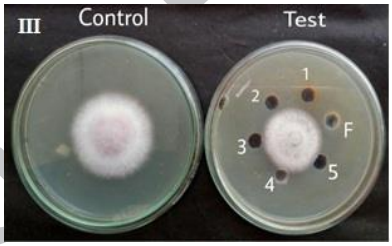

The 1,2,3-triazole fused pyridine / pyrimidine derivatives were synthesized and evaluated as new and potential antimicrobial agents.

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1,2,3-Triazole fused with pyridine / pyrimidine as new template for antimicrobial agents: Regioselective synthesis and identification of potent *N*-heteroarenes

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ABSTRACT

The 1,2,3-triazole ring fused with pyridine / pyrimidine was explored as new template for the identification of potential antimicrobial agents. The regioselective synthesis of these pre-designed *N*-heteroarenes was achieved via exploring the application of Buchwald's strategy (i.e. C-N bond formation / reduction / diazotization / cyclization sequence) to the *N*-heteroarene system. Two of them showed promising antibacterial (comparable to streptomycin) and several showed potent antifungal (comparable to mancozeb) activities.

The increasing bacterial resistance to the known and existing antibiotics is continuing to be a major threat to the public health worldwide.[1] Indeed the antimicrobial resistance (AMR) including the MDR (multidrug resistant) is the lead cause for increased morbidity and mortality among patients. This crisis has been attributed mainly to the overuse or misuse of antibiotics and lack of serious efforts in the development of new drugs (due to the reduced economic incentives and stringent regulatory requirements).[2] A number of bacteria has been classified as urgent and concerning threat by the Centers for Disease Control and Prevention (CDC) several of which are already causing substantial financial burden to the health care system, patients and their families.[3] Thus new research initiatives in addition to the coordinated efforts for implementing new policies and pursuing steps to manage crisis are need of the hour.[1] In this context the discovery and development of new or novel chemical class of molecules / agents is considered as one of the powerful approaches to overcome existing resistance mechanisms and combat life-threatening infections caused by these human pathogens. Recently the unmet clinical need of novel antifungal drugs has also been highlighted.[4]

The triazole moiety[5] fused with pyridine or pyrimidine ring (e.g. triazolopyridine or triazolopyrimidine) constitute an important *N*-heterocyclic class that has been explored for the identification / discovery of bioactive agents and drugs. This is exemplified by the early study of 1,2,3-triazolo[4,5-*d*]pyrimidines (8-azapurines) for the treatment of cancer and malignant tumors,[6a] development of trapidil (the most widely known triazolopyrimidine derivative) as an antiplatelet and vasodilator drug,[6b] clinical study of cevipabulin (a triazolo[1,5-*a*]pyrimidine) as potent anticancer agents,[7] isolation of essramycin as a first triazolopyrimidine antibiotic from nature[8] etc. Azoles (e.g. fluconazole) on the other hand represent one of the 3 classes of antifungal drugs developed for the treatment of life-threatening, invasive fungal infections.[4] However, the use of frameworks, especially the 1,2,3-triazole ring fused with pyridine / pyrimidine ring as represented by **A**-**C** (Fig. 1), for the identification of antimicrobial agents is not common in the literature. Due to our long term interest in the identification of new antibacterial agents[9] we decided to use templates **A**-**C** for the design and discovery of novel antimicrobial agents. Accordingly compounds **D**, **E** and **F** (Fig. 2) were aimed for the synthesis and evaluation of their potential antimicrobial properties. We anticipated that like other triazole based agents these fused triazolo derivatives might show the antibacterial activities following one or more of the usual mode of actions e.g. inhibition of the synthesis of cell wall, cell membrane, proteins

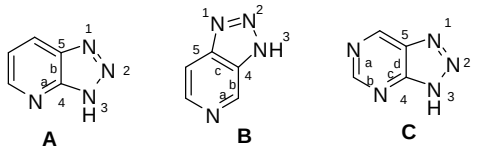

Fig. 1. 3*H*-[1,2,3]triazolo[4,5-*b*]pyridine (**A**), 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine (**B**) and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (**C**).

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and nucleic acids of bacteria. To the best of our knowledge the (triazolo)pyridines / pyrimidines based on **D-F** has not been explored as potential antimicrobial agents earlier.

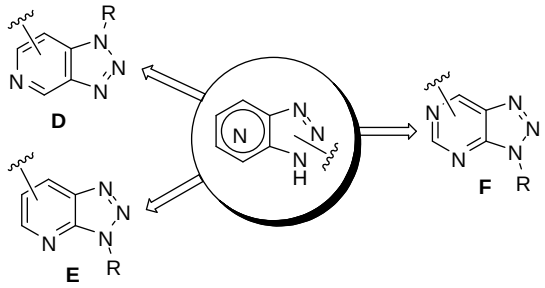
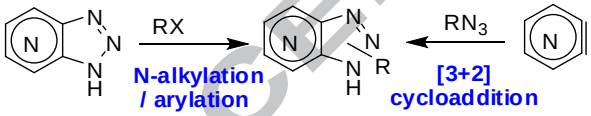


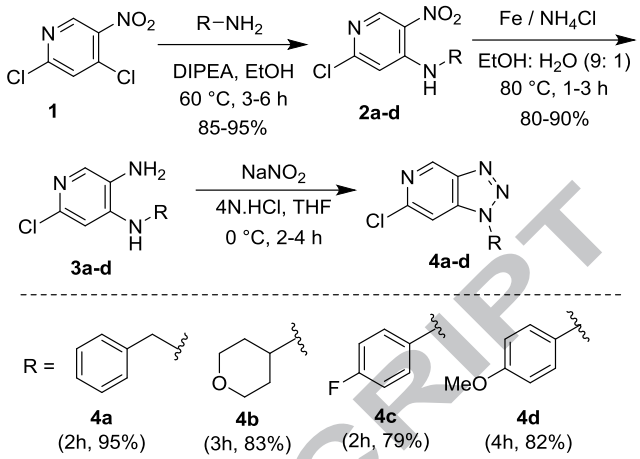
Fig. 2. (Triazolo)pyridines/pyrimidines (**D-F**) as potential antimicrobial agents.

In order to fulfil our project goal we were in need of a straightforward, convenient and efficient method for the regioselective synthesis of our target molecules. A literature search revealed that only a handful number of methods[10,11] are known for the synthesis of 1,2,3-triazolo fused pyridines / pyrimidines. Moreover, the existing methods though appeared to be effective for the construction of the central core ring were found to be inappropriate for the direct synthesis of **D-F**. While the traditional methods for the preparation of *N*-substituted benzotriazoles (e.g. via *N*-alkylation / arylation strategy or [3+2] cycloaddition of azides and benzynes) could be extended to our synthesis (Scheme 1) however lack of regioselectivities, handling of unstable reactants (e.g. benzynes, azides etc), separation of products etc are the major concerns reported in these cases.[12] More importantly accessing or generating the required starting materials as shown in Scheme 1 could be a bigger concern. It was also evident that establishing a common route to **D-F** could be problematic if not impossible because of significant dissimilarities in their chemical structures.



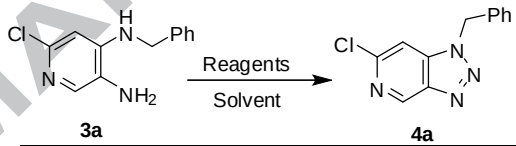
Scheme 1. Extending traditional approaches to the target triazolo derivatives.

At this stage a strategy similar to that of Chen and Buchwald[12] i.e. the multistep sequence involving a C-N bond formation / reduction / diazotization / cyclization appeared to be promising for the synthesis of **4** (Scheme 2) derived from **D** (Fig. 1). Since application of this strategy to *N*-heteroarene system was not explored earlier hence it was necessary to test feasibility and scope of this strategy in our case. Nevertheless, the readily available 2,4-dichloro-5-nitropyridine (**1**) was used as the starting material for this purpose. While Pd-catalyzed C-N cross-coupling[12] could be utilized as the first step in this case we preferred nucleophilic aromatic substitution (S_NAr) approach to avoid the use of expensive Pd-catalyst. Thus the regioselective displacement of chloro group of **1** by aliphatic / aromatic amines was examined in the presence of a range of bases including Et_3N, DIPEA (diisopropyl ethylamine), Na_2CO_3 and K_2CO_3 in EtOH. The best result however was obtained using DIPEA in EtOH to afford the product **2** in good yield. The reduction of NO_2 group of **2** was attempted under various conditions. The



Scheme 2. Synthesis of 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivatives (**4**) derived from **D** (Fig.1).

Table 1. Optimization of diazotization / cyclization leading to **4a**.[a]



3a **4a**

Entry	Reagents (equiv)	Solvent (mL)	Time (h)	Yield[b] (%)
1	$^tBuNO_2$ (1.5) Cu(II)Br (1.2)	MeCN (10)	4	55
2	$^tBuNO_2$ (3)	MeCN (10)	4	61
3	$NaNO_2$ (3) 4N HCl (5)	MeCN (10)	6	16
4	$NaNO_2$ (1.5) 4N HCl (5)	H_2O (5)	3	65
5	$NaNO_2$ (3) 4N HCl (5)	H_2O: MeCN (5 : 1), (5)	3	72
6	$NaNO_2$ (3) 4N HCl (5)	H_2O: THF (5 : 1), (5)	3	95

[a]Reactions were performed using **3a** (1 equiv) and appropriate reagent(s) in a solvent at 25-28 °C.

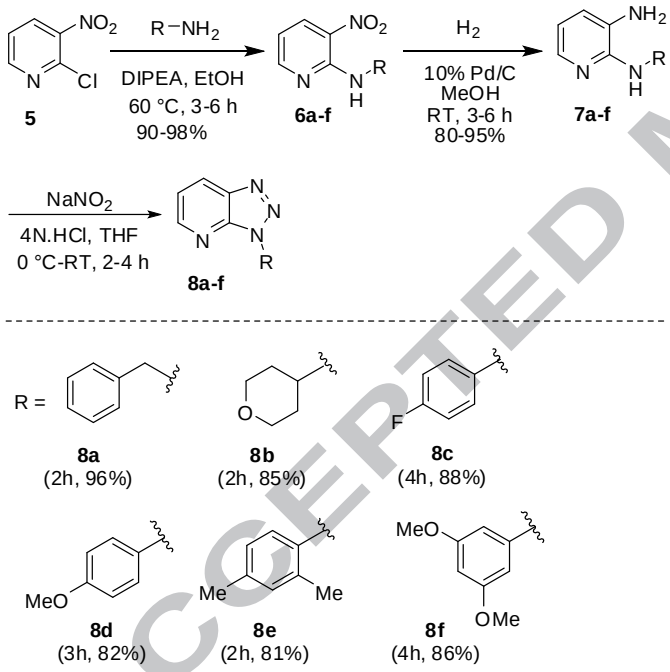
[b]Isolated yield.

hydrogenation in the presence of Pd/C in MeOH or EtOAc afforded the corresponding amine but that was a dechlorinated product. The dechlorination was avoided when the reduction was performed using $SnCl_2$ in EtOAc-H_2O though the desired amine **3** was obtained in poor yield. Finally, the use of Fe/NH_4Cl afforded **3** in good yields. The construction of fused triazole ring via diazotization / cyclization was also examined under a number of conditions using the conversion of **3a** to **4a** as a model reaction (Table 1). Initially, the use of $^tBuNO_2$ in the presence or absence of Cu(II)Br in MeCN afforded the product **4a** in moderate yield (entry 1 and 2, Table 1). The product yield was decreased when a combination of $NaNO_2$ and HCl was used in MeCN (entry 3, Table 1). However, significant improvement was observed when MeCN was replaced by H_2O or aqueous MeCN (entry 4 and 5, Table 1). Finally, the best yield of **4a** was achieved when aqueous THF was used as the solvent (entry 6,

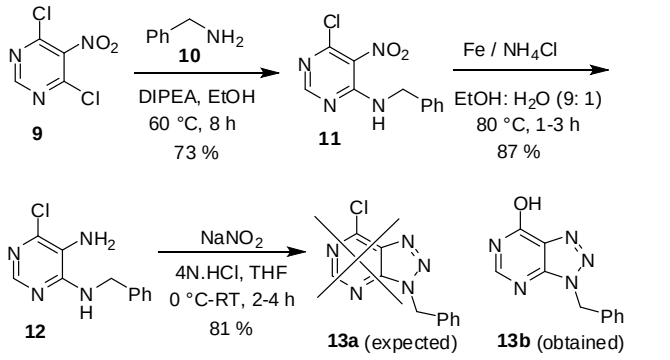
Table 1). Thus other analogues of **4a** i.e. **4b-d** were also prepared using this strategy in good yields.

A similar strategy was used for the preparation of triazolopyridines (**8**) derived from **E** (Fig. 1). The 2-chloro-3-nitropyridine (**5**) being the starting compound in this case (Scheme 3) afforded the amine derivative (**6**) after the first step that on reduction (hydrogenation) gave the di-amino derivative **7**. The diazotization / cyclization of compound **7** afforded the target compound **8**.[13]

Having prepared the two types of triazolopyridine derivatives successfully we then focused on the synthesis of triazolopyrimidines derived from **F** (Fig. 1). Initially, the 4,6-dichloro-5-nitropyrimidine (**9**) (Scheme 4) was treated with benzylamine (**10**) to give the amine **11** that on reduction afforded **12**. The diazotization / cyclization of compound **12** afforded the compound **13b** instead of expected product **13a**. It appeared that the chloro compound **13a** was hydrolysed to **13b** under the condition employed. Notably, the reaction of **9** with other aromatic amines e.g. $PhNH_2$ under the condition of step 1 of Scheme 4 was not successful even after several trials. Thus the synthesis of other analogues of **13a/b** became a major challenge for us. However, from the view point of Med Chem strategy the need for other such analogues/derivatives was dependent on biological activity of **13b** that was found to be unimpressive



Scheme 3. Synthesis of 3*H*-[1,2,3]triazolo[4,5-*b*]pyridine derivatives (**8**) derived from **E** (Fig. 1).



Scheme 4. Synthesis of 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidines (**13**) derived from **F** (Fig. 1)

particularly in terms of antibacterial activities (see the next paragraph). Therefore further chemistry effort towards this direction was halted at this stage.

All the synthesized compounds were then tested[14] for their potential antimicrobial properties. Accordingly, gram-positive bacteria, *Bacillus subtilis* (*B. subtilis)* and gram-negative *Escherichia coli (E. coli)* were used for this purpose. Initially, the zone inhibition was recorded for all the compounds at a concentration of 10 µg along with positive controls streptomycin and mancozeb. The results are presented in Fig. 3 and Table 2. It is evident that the compound **4a** (sample 1) showed a zone of inhibition 13 and 10 mm against *B. subtilis* and *E. coli* in compared to streptomycin's 16 and 13 mm, respectively. Similarly, the compound **8c** (sample C) showed a zone of inhibition 12 and 11 mm against *B. subtilis* and *E. coli*, respectively. Notably, no other samples showed any visible zone

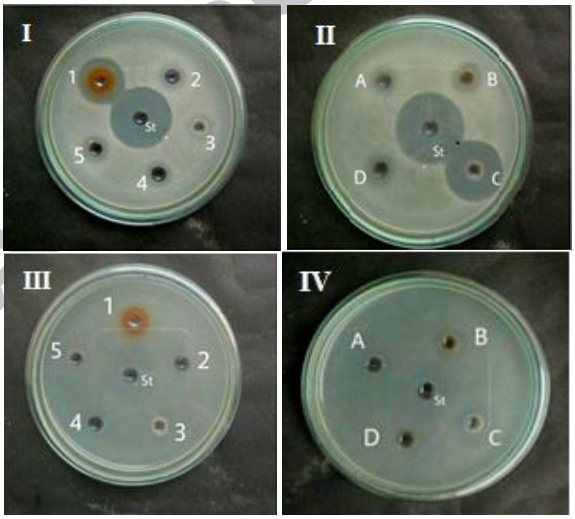


Fig. 3. Zone of inhibition assay in bacteria culture plates: 10µg of each compound was loaded onto the corresponding microbial culture plate. Zone of inhibition was recorded after 24 hrs of incubation. (I) and (II): Gram Positive *B. subtilis*, (III) and (IV): Gram Negative *E. coli*.

Table 2. Antibacterial activities of compounds **4**, **8**, and **13**

Sample No.	Compounds	Zone of inhibition (diameter in mm) at 10 µg	
		B. subtilis	*E. coli*
1	**4a**	13	10
2	**4d**	--	--
3	**4b**	--	--
4	**4c**	--	--
5	**8b**	--	--
A	**8e**	--	--
B	**13b**	--	--
C	**8c**	12	11
D	**8d**	--	--
	streptomycin	16	13

of inhibition against any of these bacterial species (Table 2). Thus MIC values were estimated for compound **4a** and **8c** (Fig. 4 and Table 3) via loading them in a concentration dependent manner (i.e. 0, 25, 50, 75 and 100 µg) in the corresponding microbial culture plates. Compound **4a** demonstrated antibacterial activity at a concentration as low as 25 µg, similar to that of standard drug streptomycin, both against *B. subtilis* and *E. coli*. The compound **8c** also showed antibacterial activity

equivalent to that of streptomycin against *B. subtilis*. However, **8c** did not show such a potent antibacterial activity against *E. coli* (Table 3). Overall, the triazolopyridine **4a** and **8c** demonstrated MIC similar to streptomycin against the gram-positive bacteria tested whereas the triazolopyrimidine **13b** was found to be inactive.

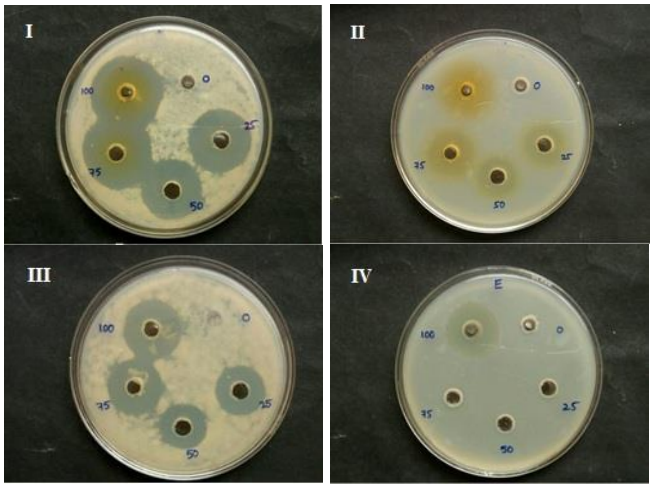


Fig. 4. Estimation of MIC of the compounds in bacterial cultures: ompounds were loaded in increasing volumes of 0, 25, 50, 75 and 100 µg in the corresponding microbial culture plates. (I) compound **4a** against *B. subtilis*; (II) compound **4a** against *E. coli*; (III) compound **8c** against *B. subtilis*; (IV) compound **8c** against *E. coli*.

Table 3. MIC value (µg) of compounds against bacterial species

Compounds	*B. subtilis*	*E. coli*
4a	25	25
8c	25	100
streptomycin	25	25

We then screened all the (triazolo)pyridines / pyrimidines for their potential antifungal activities using *Fusarium oxysporum* f. sp. *Lycopersici*[15a] and *Fusarium ricini*[15b] as the fungal species. Interestingly, unlike their antibacterial activities majority of these compounds showed visible zone of inhibition regions when tested on fungal cultures (Fig. 5 and Table 4). For instance, compounds **4a**, **4d, 4b, 8e** and **8c** showed good response either against one or both the fungal species. Indeed, several of our compounds were comparable to the positive control mancozeb. Estimation of MIC of these compounds was carried out using fungal culture plates (compounds were loaded in 0, 25, 50 75 and 100 µg in the corresponding microbial culture plates). The MIC value of each compound is presented in Table 5. The antifungal activities of **4a**, **4b** and **4d** were promising and similar to the standard control in case of *Fusarium recini*. However, in case of *Fusarium oxysporum lycopersici*, compounds **4a, 4b** and **4d** were less effective than the reference standard. Compound **4c** showed similar MIC against both the fungi, but reduced activity (i.e. 50 µg) than **4a** and **4b**, in case of *Fusarium recini.* Similarly, **8b, 8c, 8d** and **13b** showed reduced activities against *Fusarium recini* and were less effective against *Fusarium oxysporum lycopersici*. Nevertheless, in view of their promising activities **4a**, **4b** and **4d** were identified as initial hit molecules that deserve further pharmacological profiling.

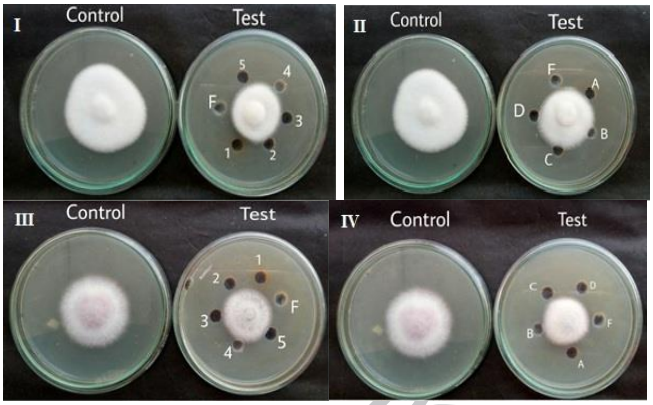


Fig. 5. Zone of inhibition assay in fungal culture plates: 10µg of each compound was loaded onto the corresponding microbial culture plate. Zone of inhibition was recorded after 48hrs of incubation. (I) and (II): *Fusarium oxysoprum lycopersici*. (III) and (IV): *Fusarium recini*.

Table 4. Antifungal activities of compounds **4**, **8**, and **13**

Sample No.	Compounds	Zone of inhibition (diameter in mm) at 10 µg	
		Fusarium oxysporum lycopersici	*Fusarium recini*
1	**4a**	1	7
2	**4d**	6	7
3	**4b**	6	6
4	**4c**	3	7
5	**8b**	3	5
A	**8e**	6	6
B	**13b**	5	6
C	**8c**	6	5
D	**8d**	2	3
	mancozeb	6.5	7

Table 5. MIC value (µg) of compounds against fungal species

Compounds	*Fusarium oxysporum lycopersici*	*Fusarium recini*
4a	100	25
4b	50	25
4c	50	50
4d	50	25
8b	75	50
8c	75	50
8d	100	50
8e	75	100
13b	100	50
mancozeb	25	25

In conclusion, for the first time the 1,2,3-triazole ring fused with pyridine / pyrimidine was explored as new templates for the identification of potential antimicrobial agents. Accordingly, a series of related compounds were designed and synthesized. Indeed, our efforts have resulted in the application of Buchwald's strategy i.e. C-N bond formation / reduction / diazotization / cyclization sequence to the *N*-heteroarene system and the target compounds were synthesized in a regioselective manner. The strategy however showed some limitations when applied to the triazolopyrimidine system and needs further exploration. Two of the synthesized compounds e.g. **4a** and **8c** showed promising antibacterial activities comparable to the broad-spectrum antibiotic streptomycin when tested against multi-drug resistant

bacteria like *B. subtilis* and *Escherichia coli*. Several of them e.g. **4a**, **4b** and **4d** also showed potent antifungal activities against *Fusarium recini* comparable to the broad spectrum protectant fungicide mancozeb. Overall, this research highlighted not only the usefulness of Buchwald's strategy to *N*-heteroarene system but also the utility of (triazolo)pyridine / pyrimidine framework for the discovery and development of new and potent antimicrobial agents.

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Supplementary data

Supplementary data associated with this article can be found, in the on line version, at xxxxxxxxx

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Highlights

- Explored 1,2,3-triazolo pyridine/pyrimidine as new template for antimicrobial agents.
- Demonstrated the application of Buchwald's strategy to *N*-heteroarene system.
- Two compounds were comparable to streptomycin and several were comparable to mancozeb.