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A facile synthesis, antibacterial, and antitubercular studies of some piperidin-4-one and tetrahydropyridine derivatives

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ABSTRACT

The raise in clinical significance of multidrug-resistant bacterial pathogens has directed us to synthesize 2,6-diarylpiperidin-4-one and Δ^3-tetrahydropyridin-4-ol based benzimidazole and *O*-arylsulfonyl derivatives. X-ray crystal structure of tetrahydropyridinol (**23**) confirmed a change in conformation and orientation of substituents upon amide formation. Antibacterial activities evaluated against a wide number of bacterial pathogens (both sensitive and multidrug-resistant) revealed that **19, 27** against *Staphylococcus aureus*, **27** against *Enterococcus faecalis*, and **19, 21, 23**, and **27** against *Enterococcus faecium* are significantly good at lowest MIC_{90} (16 μg/mL). Inhibitory power noticed by **23** against Vancomycin–Linezolid-resistant *E. faecalis* and **27** against Vancomycin-resistant *E. faecium* are onefold better than the standard Linezolid and Trovafloxacin drugs, respectively. Moreover, antitubercular activity for the selected compounds against *Mycobacterium tuberculosis* H37Rv revealed that compounds **23, 24**, and **27** expressed onefold improved potency compared to the standard Rifampicin drug.

During the past few decades, the alarming rate in the incidence of life threatening infections caused by multiple drug-resistant Gram-positive organisms particularly Methicillin-resistant *Staphylococcus aureus* (MRSA), Methicillin-resistant *Staphylococcus epidermidis* (MRSE) and recently found Vancomycin-resistant enterococci (VRE) are becoming significant health concern through out the world. As they do not respond to the current clinical drug therapy, the morbidity and mortality rate was raised among human population, which in turn pose a serious menace and gravely challenging the scientific community.[1] Among the several phenotypes for VRE, VanA (resistance to Vancomycin and Teicoplanin) is the most common[2] and particularly in USA, VanA accounts for about 60% of VRE isolates.[3] Recently, Linezolid-resistant enterococci (LRE) have also been identified as an outcome of intensive Linezolid therapy.[4] The therapeutic challenge of multidrug-resistant (MDR) enterococci (not only limited to Vancomycin) has brought their role as an important nosocomial pathogens into sharper focus.

Besides these pathogens, the most infectious *Mycobacterium tuberculosis* H37Rv, a slow-growing Gram-positive bacterium is also a life threatening pathogen and is the etiologic agent of contagious tuberculosis (TB). As per the estimated data from World Health Organization (WHO), Southeast Asia and Africa witness the alarming rise in TB cases where it develops at a rate of more than one per second.[5] Further, resurgence of TB is being provoked by the emergence of MDR-isolates of *M. tuberculosis* against the frontline drugs and the synergy of this disease with AIDS/HIV pandemic and mycotic infections in immunocompromised patients.[6] The hastily developing multidrug-resistant Gram-positive bacterial strains including *M. tuberculosis* to the currently prescribed pharmaceutical agents has fueled for the vigorous search for novel antibacterial agents in structural class distinct from the known antibiotic drugs.

2,6-Disubstitutedpiperidin-4-ones are regarded as an important framework and served as precursors for chiral biologically active natural alkaloids.[7] The biological activities of piperidones were found to be excellent if 2- and/or 6-positions are occupied by aryl groups.[8] Accordingly, antibacterial and antifungal activities of 2,6-diarylpiperidin-4-ones and their derivatives have been explored well.[8b,9] Similarly, the functionalized tetrahydropyridines[7,10] and hydroxyl substituted six-membered nitrogen heterocyclic scaffolds[8b,10] are the ubiquitous structural component of naturally occurring alkaloids and biologically active synthetic molecules. Sulfonates (sulfonyl esters) were also reported to exhibit moderate antibacterial activitiy[11a] and inhibitory activity for *Escherichia coli* aminopeptidase N[11b] in addition to varied marked pharmacological activities.[11] Generally, incorporation of benzimidazole nuclei is an important synthetic strategy in drug discovery program as it exerts broad-spectrum antibacterial[12] and antitubercular activities.[13] Particularly, against both sensitive and drug-resistant Gram-positive bacteria, they displayed excellent activities.[12a–e] Potential

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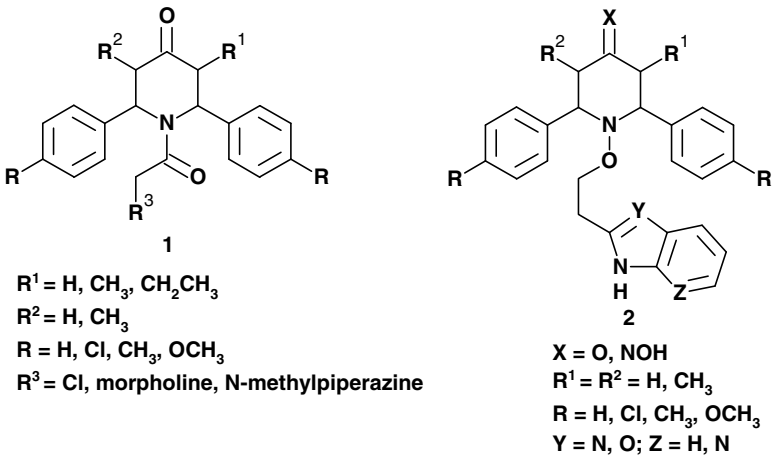
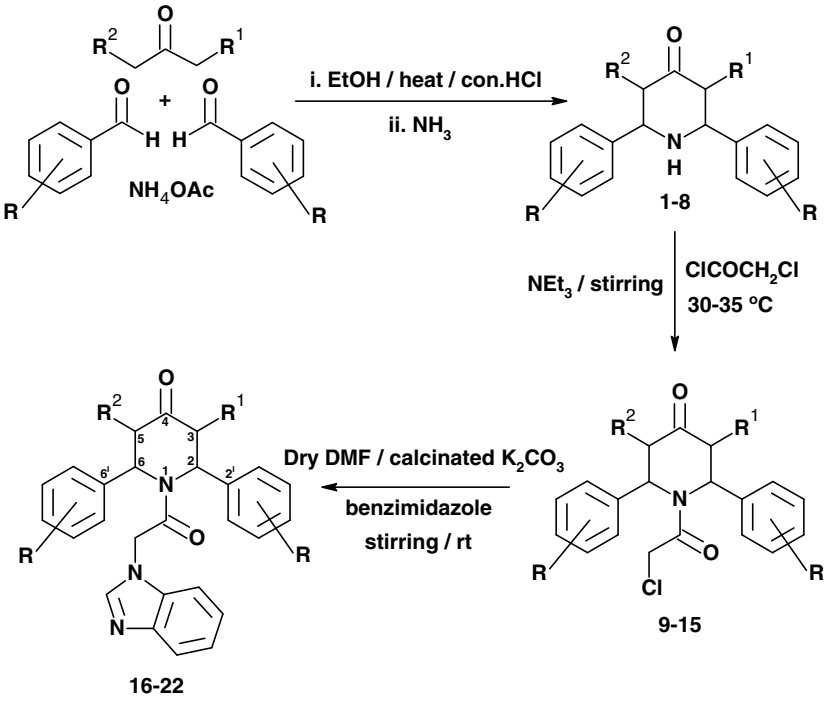


Figure 1. Some piperidone derivatives reported to exhibit antimicrobial activities.[14]

biological activities associated with benzimidazole derivatives are mainly pertaining to the fact that they are the structural isosteres of the naturally occurring nucleotides, which in turn permit them for the easy interaction with biopolymers of the living systems. Our recent investigations and SAR studies on compounds derived by using 2,6-diarylpiperidin-4-one as template have demonstrated that introduction of either chloroacetyl,[14a] morpholinoacetyl,[14b] *N*-methylpiperazino acetyl[14c] **1** or benzazolylethoxy[14d–f] moiety **2** (Fig. 1) at nitrogen exerted enhanced antibacterial and antifungal activities against a panel of pathogenic organisms. Traditionally,



Entry			R^1	R^2	R
1	**9**	**16**	CH_3	H	3,5-OCH_3
2	**10**	**17**	CH_3	H	4-OCH_3
3	**11**	**18**	CH_3	H	4-CH_3
4	**12**	**19**	CH_3	CH_3	4-OCH_3
5	**13**	**20**[14g]	CH_3	CH_3	4-CH_3
6	**14**	**21**	CH_3	CH_3	2-OCH_3
7	**15**	**22**	CH_3	CH_3	2-Cl

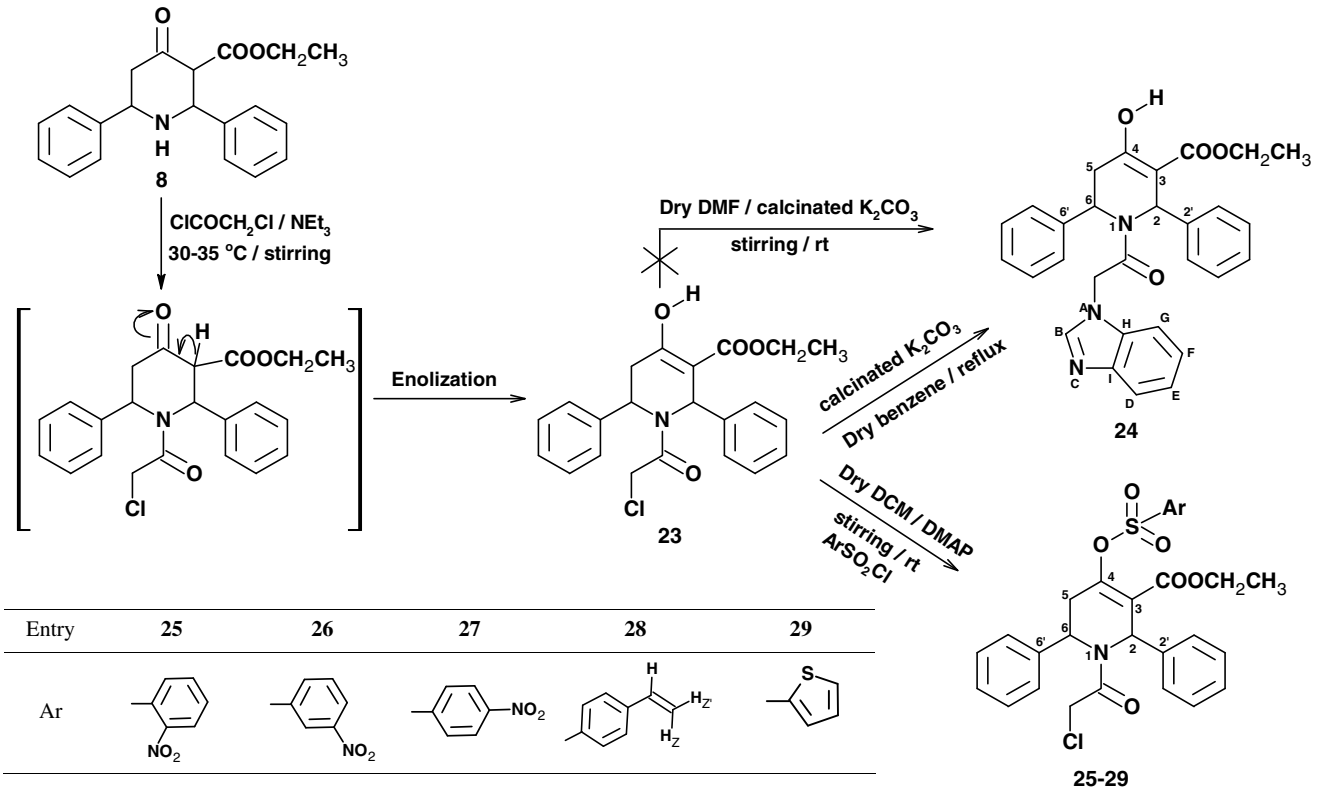
Scheme 1. Synthesis of target compounds **16**–**22**.

small molecules have been a reliable source for discovering novel biologically active agents.

Encouraged by the earlier reports and in continuation of our recent research program to find out novel antimicrobials,[14] we have designed and synthesized acetyl derivative of few 2,6-diarlypiperidin-4-ones framework coupled with benzimidazole system. Further, to study the impact of biological activity upon double bond incorporation into the piperidine nucleus, we have also synthesized Δ^3-tetrahydropyridin-4-ol and their sulfonates. The synthesized compounds (**16–29**) were evaluated for their antibacterial and antitubercular activities besides establishing the effect of aromatic phenyl substituents with regard to the substituent position on antibacterial and antitubercular efficacies.

The facile synthetic routes which furnished the target compounds are shown in Schemes 1 and 2. Chloroacetylation[15] of variously substituted 2,6-diarylpiperidin-4-ones followed by condensation with benzimidazole in dry DMF using calcinated K_2CO_3 to about 2–4 h (in room temperature) afforded the desired products in good yields. Facile synthesis of *N-chloroacetyl*-3-carboxyethyl-2,6-diphenyl-4-hydroxy-Δ^3-tetrahydropyridine (**23**) was achieved exclusively from 3-carboxyethyl-2,6-diphenylpiperidin-4-one (**8**) by simple amide formation. To furnish compound **24**, benzene was used as a solvent in place of DMF under refluxed condition. Likewise, nucleophilic substitution of OH at C-4 in **23** was accomplished with diversely substituted arylsulfonyl chlorides using DMAP as base in dry DCM at room temperature. The synthesized compounds were analyzed by IR, mass, and one and two-dimensional NMR techniques.

Structure of the compound **23** was elucidated without ambiguity by $^1H/^{13}C$ NMR, HOMOCOSY, NOESY, HSQC, SEFT, and DEPT analysis. Proton NMR spectrum of this compound indicates the presence of a new sharp singlet for C(4)–OH at 12.43 ppm and the absence of a signal at 3.68 ppm due to C-3 methine proton of its precedent piperidone. This confirms the enolization along C(3)–C(4) bond owing to the more acidic nature of the axial hydrogen at C-3 which is alpha to the $-COOCH_2CH_3$ group. Further, the signal due to benzylic protons (refer spectrum in Supplementary files) at C-2 and C-6 are broadened and deshielded as a result of restricted rotation about N–C=O bond. Thus, the more deshielded broad singlet at 5.28 ppm is assigned to H-6 proton while the other at 4.00 ppm is due to H-2 proton as they correspond to each one proton integral. Similarly, on the basis of integral value, the multiplet in the region 4.12–4.18 ppm is characteristic for acetyl methylene (N–COCH_2) and –COOCH_2CH$_3$ protons whereas a doublet and a triplet centered at 2.84 and 1.09 ppm are pertinent to H-5a/H-5e and –COOCH$_2$$CH_3$ protons. The above made assignments were further confirmed by the observed correlations in its HOMOCOSY and NOESY spectra (refer Supplementary files). These unambiguous characterizations of protons in **23** paved a way for the precise assignment of its carbon signals in ^{13}C NMR through the observed ^1H–^{13}C correlations. SEFT and DEPT spectra proved the quaternary nature of the signal at 99.2 ppm and thus could be assigned to C-3 carbon by keeping in view the β-effect[15] of *N*-acyl group while C-4 carbon is merged with aromatic carbons. All these noticed facts demonstrate clearly the existence of double bond about C(3)–C(4) bond and presence of enolic OH at C-4. Structure and change in conformation is also confirmed beyond doubt by its X-ray crystallographic study. The ORTEP diagram (The asymmetric unit of the compound **23** contains two crystallographically independent molecules.) of **23** is displayed in Figure 2 with important bond lengths and bond angles. These observed bond parameters confirm the coplanarity of N–COCH$_2$ group. Further, distinct from its parent piperidone **8** (where phenyl groups are in equatorial disposition),[16] phenyl groups [at C(1) and C(5) in Fig. 2] in **23** are oriented axially in order to avoid steric repulsion ($A^{1,3}$ strain)[17] with coplanar –COCH$_2$ group. As well, shortening of C(3)–C(4) bond length (1.34 Å) compared to other bonds (≈1.48 Å) in the heterocyclic ring clearly confirms its double bond character. Similarly, existence of



Scheme 2. Synthesis of target compounds **23–29**.

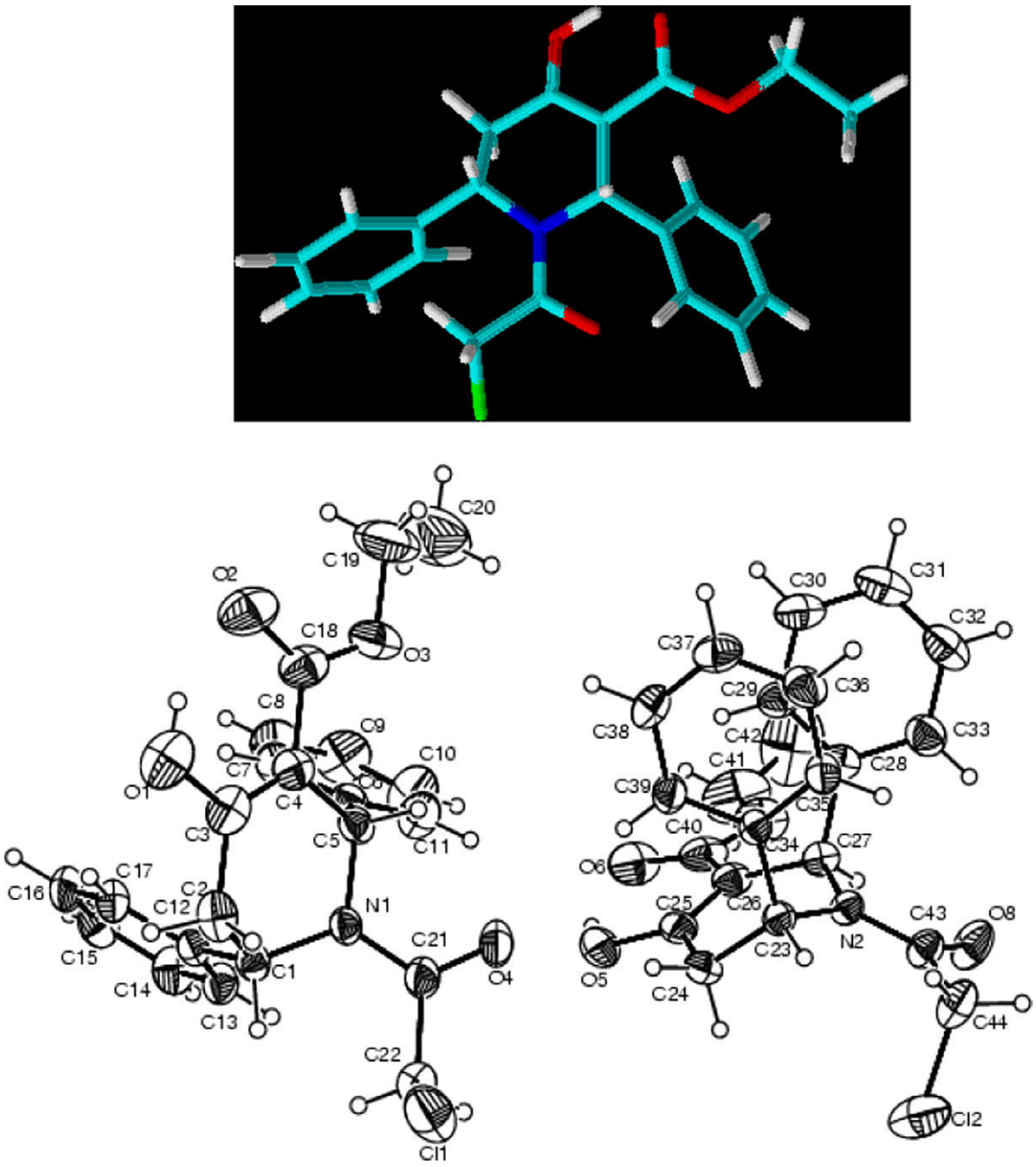


Figure 2. Stick model and ORTEP diagram of **23**. The important bond lengths (Å): C(1)–N(1) = 1.48; C(5)–N(1) = 1.48; C(21)–N(1) = 1.36; C(21)–O(4) = 1.21; C(21)–C(22) = 1.53; C(2)–C(3) = 1.49; C(3)–C(4) = 1.34; C(4)–C(5) = 1.50. The important bond angles (°): C(21)–C(22)–Cl(1) = 107.70; O(4)–C(21)–N(1) = 122.50; N(1)–C(21)–C(22) = 119.80; N(1)–C(5)–C(6) = 111.05; C(5)–N(1)–C(1) = 117.46; C(21)–N(1)–C(5) = 117.03; C(21)–N(1)–C(1) = 125.30.

partial double bond character about N–C═O bond is revealed from their decreased bond lengths [C(21)–N(1) = 1.36 Å and C(21)–O(4) = 1.21 Å]. Therefore, the change in chair conformation of the parent compound upon chloroacetylation into energetically favorable non-chair conformation is revealed from its ORTEP. Furthermore, introduction of arylsulfonyl groups at C(4)–OH deshielded H(2), C(2) and C(3) resonances due to the electronic interaction with O═S═O group in the assumed conformation. Assignments of the deshielded signals were also confirmed by NOESY and HSQC correlations (refer Supplementary files).

All the synthesized compounds were screened for their antibacterial efficacy in vitro against a spectrum of Gram-positive pathogenic bacteria including resistant strains viz. Methicillin-resistant and -sensitive *Staphylococcus aureus, Staphylococcus epidermidis*, Methicillin-resistant *Staphylococcus epidermidis, Enterococcus faecalis, Enterococcus faecium*, Vancomycin-resistant *Enterococcus faecalis/Enterococcus faecium* and Vancomycin, and Linezolid-resistant *Enterococcus faecalis*. Minimum inhibitory concentrations (MIC_{90}) were determined by broth micro dilution in accordance with the methods of the National Committee for Clinical Laboratory Standards (NCCLS)[18] and are furnished in Table 1. Linezolid and Trovafloxacin drugs were used as positive controls while DMSO served as negative control. Test compounds were prepared up to a concentration of 128 μg/mL.

A glance at the MIC_{90} values in Table 1 indicates that among the benzimidazole derivatives **16–22**, *ortho*-methoxyphenyl bearing compound (**21**) with C-3/C-5 methyl groups showed moderate activity (32 μg/mL) against *S. aureus* and better activity (16 μg/

Table 1
In vitro antibacterial activities (MIC_{90} in μg/mL) of compounds **16–29** against selected sensitive and resistant Gram-positive bacterial strains

S. No.	Strain	Minimum inhibitory concentration (MIC_{90})* in μg/mL															
		Linezolid	Trovafloxacin	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
LCB0001	*S. aureus*	1	<0.0625	NA	NA	NA	16	64	32	64	32	32	64	NA	16	NA	32
LCB0002	*S. aureus*^{MR}	2	1	NA	NA	NA	128	64	NA	NA	64	NA	NA	128	64	NA	64
LCB0003	*S. epidermidis*	1	<0.0625	NA	NA	NA	NA	NA	NA	NA	64	128	NA	NA	64	NA	64
LCB0004	*S. epidermidis*^{MR}	2	<0.0625	NA	NA	NA	NA	NA	NA	128	128	NA	NA	NA	64	NA	128
LCB0005	*E. faecalis*	2	0.128	NA	NA	NA	64	128	64	NA	32	64	128	128	16	NA	NA
LCB0006	*E. faecalis*^{VanA} (VR)	2	8	NA	NA	NA	NA	128	NA	NA	64	NA	NA	NA	32	NA	NA
LCB0007	*E. faecalis*^{VanA} (VLR)	64	16	NA	NA	NA	NA	NA	NA	NA	32	128	NA	NA	64	NA	NA
LCB0008	*E. faecium*^{VanA} (VR)	2	64	NA	NA	NA	NA	NA	NA	NA	64	NA	NA	NA	32	NA	NA
LCB0009	*E. faecium*	2	8	NA	128	64	16	32	16	NA	16	64	128	NA	16	NA	32

LCB, M/s LegoChem Biosciences, Inc., Deajeon, South Korea (where the activity test was carried out).
MR, Methicillin-resistant; *VanA*, phenotype; VR, Vancomycin-resistant; VLR, Vancomycin, and Linezolid-resistant.
NA – no activity even at highest concentration (i.e., 128 μg/mL) tested in this study.
* MIC_{90} is the minimum concentration of an antibacterial agent that will significantly inhibits the growth of 90% of organisms after a period of incubation.

mL) against *E. faecium* whereas its *para*-methoxy analogue (**19**) exerted onefold improved activity (16 μg/mL) against *S. aureus* but retains the same activity against *E. faecium*. However, the *para*-methyl analogue of **19** (compound **20**) registered two and onefold decreased activities against the above said strains, respectively. But, *meta*-dimethoxy (**16**), *para*-methoxy (**17**), and *para*-methyl (**18**) analogues with C-3 methyl group and *ortho*-chloro (**22**) counterpart of **21** are almost inactive up to 128 μg/mL against all the tested organisms except **18** and **22** against *E. faecium* and *S. aureus*, respectively (MIC_{90} = 64 μg/mL). Among tetrahydropyridinol **23** and its derivatives **24–29**, compound **23** with carbethoxy group at C-3 and unsubstituted phenyl moieties at C-2 and C-6 exhibited moderate to good activities (MIC_{90} between 16 and 64 μg/mL) against all the tested Gram-positive organisms. In particular, its inhibitory activity was doubled against VLR *E. faecalis* compared to that of the standard Linezolid drug whereas against VR *E. faecium*, potency is at par with Trovafloxacin drug tested at the same laboratory condition. Similarly, against *S. aureus*/*E. faecalis* and *E. faecium*, growth inhibition was noticed at 32 and 16 μg/mL, respectively. Nucleophilic substitution of benzimidazole to **23** (i.e., compound **24**) suppressed the activities against all the organisms except against *S. aureus* for which the same activity was retained. Therefore, to explore the impact of arylsulfonylation on antibacterial activities through nucleophilic substitution of OH in **23**, compounds **25–26** were synthesized and assessed. Some of these sulfonates showed marginal enhancement in activity. Like **24**, compounds **25** and **26** with *ortho*- and *meta*-nitro substituents, respectively, in the benzenesulfonyl moiety are also profoundly decreased in their antibacterial activities against all the tested Gram-positive organisms. However, their *para*-nitro derivative **27** produced significant inhibitory profiles against both sensitive and resistant organisms. Compared to **23**, compound **27** registered onefold elevated efficacies against *S. aureus*, MR *S. epidermidis, E. faecalis*, VR *E. faecalis*, and VR *E. faecium*, while against rest of the strains the same activity was restored except against VLR *E. faecalis* – for which onefold decreased activity was noted. A surprising observation here is that, potency of compound **27** was doubled against VR *E. faecium* compared to standard Trovafloxacin drug but an equi-potency was noticed with standard Linezolid drug against VLR *E. faecalis* tested at the same laboratory condition. Though thiophen-2-sulfonyl analogue of **27** (compound **29**) produced moderate activty against four *Staphylococcus* species, 4-vinylbenzenesulfonyl counter part (**28**) did not display activity even at highest concentration tested in this study, that is, 128 μg/mL. Therefore, the inhibitory potencies of compound **23** and few of its arylsulfonyl derivatives are relatively better than the benzimidazole series and falls in the order **27 > 23 > 29 > 19 > 21**.

In order to extend the evaluation of antibacterial activities, they were also tested against Gram-negative bacterial strains such as three different *E. coli* strains, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*. The noticed MIC_{90}'s are reproduced in Table 2.

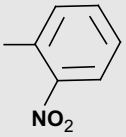
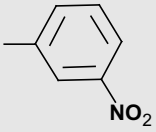
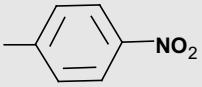
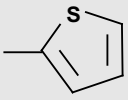
According to the observed results from Table 2, unexpectedly, an appreciable drop in the antibacterial potencies against Gram-negative organisms has been noted. Even though a few of the compounds showed the sign of inhibitory potencies at 64 and 128 μg/mL against *P. aeruginosa, K. pneumoniae, H. influenzae*, and three different *E. coli* (LCB0010, 0011, and 0012) strains, most of them failed to exert activities up to the maximum concentration tested (i.e., 128 μg/mL). Additionally, the noticed potencies of **23** against *P. aeruginosa* and **27** against *K. pneumoniae* are superior to the standard Linezolid drug (which is not active up to 128 μg/mL) as they recorded better activity at 64 μg/mL. Interestingly, compounds **19,**

Table 2
In vitro antibacterial activities (MIC_{90} in μg/mL) of compounds **16–29** against selected Gram-negative bacterial strains

S. No.	Strain	Minimum inhibitory concentration (MIC_{90})* in μg/mL															
		Linezolid	Trovafloxacin	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
LCB0010	*E. coli*	NA	<0.0625	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LCB0011	*E. coli*	16	<0.0625	NA	NA	NA	NA	128	NA	NA	NA	NA	128	NA	128	128	128
LCB0012	*E. coli*	64	<0.0625	NA	128	128	128	128	NA	NA	NA	NA	NA	NA	NA	128	NA
LCB0013	*P. aeruginosa*	NA	0.125	NA	NA	NA	NA	NA	NA	NA	64	NA	NA	NA	NA	NA	NA
LCB0014	*K. pneumoniae*	NA	0.125	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	64	NA	NA
LCB0015	*H. influenzae*	16	<0.0625	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	128	NA
LCB0016	*M. catarrhalis*	8	<0.0625	NA	NA	NA	16	NA	NA	NA	32	64	NA	NA	32	NA	32

LCB, M/s LegoChem Biosciences, Inc., Deajeon, South Korea (where the activity test was carried out).
NA – no activity even at highest concentration (i.e., 128 μg/mL) tested in this study.
* MIC_{90} is the lowest concentration of an antibacterial agent that will significantly inhibits the visible growth of a bacterial organism after a period of incubation.

Table 3
Antitubercular activity of selected compounds against *M. tuberculosis* H37Rv (ATCC 27294)

Entry[a]	Substituent			MIC[b](AP[c])
	R/Ar	R^1	R^2	
19	4-OCH_3	CH_3	CH_3	64 ($0.39^{S1}/50^{S2}$)
21	2-OCH_3	CH_3	CH_3	128 ($0.19^{S1}/25^{S2}$)
23	–	–	–	16 ($1.56^{S1}/200^{S2}$)
24	–	–	–	16 ($1.56^{S1}/200^{S2}$)
25		–	–	NA
26		–	–	NA
27		–	–	16 ($1.56^{S1}/200^{S2}$)
29		–	–	32 ($0.78^{S1}/100^{S2}$)
Isoniazid	–	–	–	0.25
Rifampicin	–	–	–	32

S1 and S2 – AP compared to Isoniazid and Rifampicin standards, respectively.
NA – no activity even at highest concentration (i.e., 256 μg/mL) tested in this study.
[a] Only selected compounds were screened for antitubercular activity.
[b] MIC, minimum inhibitory concentration represented in μg/mL.
[c] Antitubercular potency (AP in%) = MIC of Rifampicin/MIC of test compound × 100.

23, 24, 27, and **29** prominently inhibited the growth of *M. catarrhalis* with the MIC_{90} ranging from 16 to 64 μg/mL, in which **19** ranks at the top on the basis of effectiveness (i.e., MIC_{90} at 16 μg/mL).

Antibacterial activity tests for the compounds under study evidently demonstrate that compounds **19, 21, 23–27**, and **29** expressed moderate to elevated potency thereby render them to assess further for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv (ATCC 27294). Antitubercular activity test was done by radiometric respiratory technique using the BACTEC system as described earlier[19] and MIC's are given in Table 3. Isoniazid and Rifampicin drugs were used as positive controls whereas DMSO was used as solvent. Test compounds were prepared up to a concentration of 256 μg/mL.

The Table 3 clearly illustrates that the benzimidazole derivatives of piperidin-4-one **19** bearing methoxy functionality at the *para*-position of the phenyl groups besides methyl groups at C-3/C-5 produced inhibition potency at 64 μg/mL but its *ortho*-methoxy analogue (compound **21**) showed onefold decline in activity. Virtually, tetrahydropyridinol **23** and its benzimidazole **24** and arylsulfonyl derivatives **25, 26, 27, and 29** exhibited promising antitubercular activity. Due to the substitution of benzimidazole moiety in place of chlorine in **23** (compound **24**) retain the activity without any alteration. But, introduction of *ortho*- (**25**) and *meta*-nitro (**26**) benzenesulfonyl moieties at C(4)–OH in **23** makes the compound impotent up to 256 μg/mL. However, excellent inhibition power of *para*-nitro analogue (**27**) noticed at 16 μg/mL reveals that impotency of **25** and **26** can be significantly alleviated by simple structural amendment. A comparison of antitubercular potency (%) of tested compounds with Rifampicin drug was made by employing the formula: antitubercular potency (AP in %) = MIC of Rifampicin/MIC of test compound × 100 and is displayed as bar graph in Figure 3. From this figure, it is apparent that the compounds **23/24/27** and **29**, respectively, displayed 200% and 100% antitubercular potency compared to the standard Rifampicin drug.

In conclusion, a three steps synthetic practice furnished 1-[2-(1*H*-benzimidazol-1-yl)acetyl]-2,6-diarylpiperidin-4-ones (**16–22**) in good yields. Similarly, tetrahydropyridinol (**23**) and their sulfonates (**24–29**) were achieved by simple synthetic strategy and structurally identified by X-ray crystallography, one and two-dimensional NMR techniques. The surprising level of activity seen with tetrahydropyridinol **23** and one of its sulfonate derivatives **27** against susceptible and resistant organisms of several Gram-positive strains including *M. tuberculosis* suggests that enolization across C(3)–C(4) bond upon chloroacetylation seems to be more important than the keto analogues (**16–22**) even though the later analogues bear biologically accepted benzimidazole pharmacophore. As well, C(2) and C(6) aryl groups in chloroacetyl intermediates of **16–22** are oriented in axial and equatorial directions,[20] respectively, whereas in **23**, both the phenyl groups are dispositioned axially. From this it is well conceived that enolization about C(3)–C(4) bond, orientation of aryl groups at C(2)/C(6) and the conformational preferences play a crucial role in exhibiting better biological response as they presumed to execute different mode of action. The marked activity associated with sulfonate **27**, as well as the apparent ability of the nitro group in the *para*-position to permit the restoration of activity from the otherwise inactive

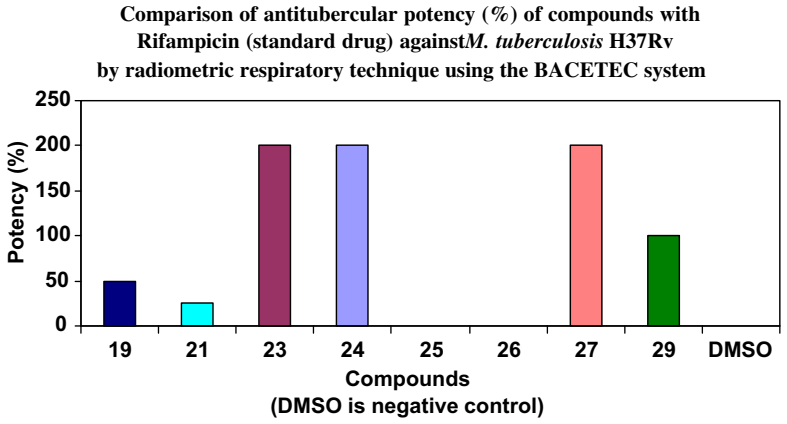


Figure 3. Comparison of antitubercular potency (%) of compounds with standard Rifampicin drug (antitubercular potency (AP in%) = MIC of Rifampicin/MIC of test compound × 100).

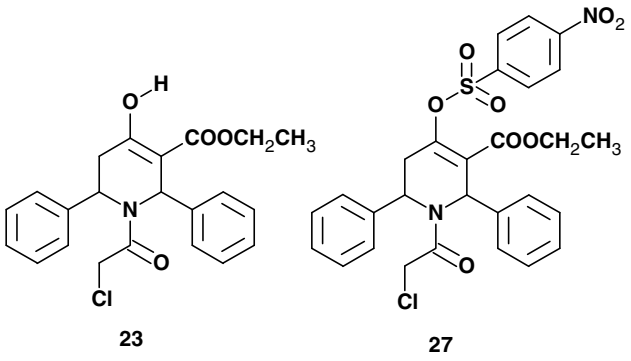


Figure 4. Structures of potential lead compounds **23** and **27**.

ortho- (compound **25**) and *meta*-nitro (compound **26**) analogues points quite specific substituent effect possibly related to the enhanced interaction with the target. Therefore, the noticed promising antibacterial and antitubercular activities associated to compounds **23** and **27** (Fig. 4) render them as an attractive leads for further structural optimization.

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Supplementary data

Complete experimental details and characterization data for all the compounds along with NMR, NOE and HSQC spectra for the representative compounds are furnished. The crystallographic data of **23** have been deposited at Cambridge Crystallography Data Center (CCDC No. 686632). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.10.045.

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