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Synthesis, Spectral Analysis and Antibacterial Activity of Some new *N*-Substituted Sulfonamide Derivatives of 1,3-Benzodioxol-5-amine

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ABSTRACT
1,3-Benzodioxol-5-amine(**1**)was used as a precursor to synthesize*N*-alkyl/aralkyl-*N*-(1,3-benzodioxol-5-yl)arylsulfonamide derivatives, **7a-b** to **9a-b**. The molecule **1** was reacted with arylsulfonyl chlorides, **2a-b**,on stirring in a dilute aqueous sodium carbonate solution to synthesize *N*-(1,3-benzodioxol-5-yl)arylsulfonamide, **3a-b**. The molecules, **3a-b**, were further stirred with alkyl/aralkyl halides, **4-6**, in DMF at RT to get the desired final compounds, **7a-b**to **9a-b**.The synthesized molecules were structurally confirmed by IR, ^{1}H-NMR and EIMS spectral data.The antibacterial activity of these compounds rendered them moderately weak inhibitors relative to ciprofloxacin, the reference standard.

Keywords: 1,3-Benzodioxol-5-amine, antibacterial activity and arylsulfonyl chlorides.

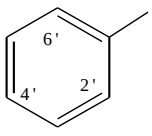
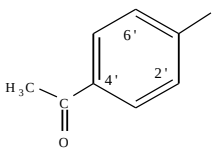
1. INTRODUCTION
The derivatives of sulfonamides are well known pharmaceutical agents.The stability and tolerance of sulfamoyl functional group rendered it a basic constituent of many pharmaceutical agentsemployed for treatment of many infections[1].The diversity of sulfonamide biological activities in agricultural[2]and pharmaceutical[3] fields gave them much importance in medicinal chemistry.These molecules have a diverse number of biological activities such as antibacterial[4], carbonic anhydrase inhibition[5], anti-inflammatory[6]and antitumor[7]activities.There are also many commercially available drugs containing sulfamoyl moiety such as bosentan[8], amprenavir[9]and sildenafil[10].

Such type of compounds have been synthesized and evaluated foranti-enzymaticactivities by our group[11-12] and the current projectwas an attempt to evaluate these molecules for their antibacterial potential and found them moderately low inhibitors.

2. EXPERIMENTAL
2.1*General*
The chemical reagents used including1,3-benzodioxol-5-amine,arylsulfonyl chlorides and alkyl/aralkyl halides were Merck and Alfa Aesar branded along with analytical grade solvents.The technique used to confirm the purity of the prepared compounds was thin layer chromatography run in solvent systems with varying ratios of EtOAc and *n*-hexane and visualized under UV at 254 nm. Melting points were determined by using Griffin George apparatus with open capillary tube. The IR spectra were obtained by adopting KBr pellet method on a Jasco-320-A spectrometer. ^{1}H-NMR spectra were recorded in $CHCl_3$-d_1 on Bruker spectrometers at 400 MHz. Mass spectra (EIMS) were recorded on a JMS-HX-110 spectrometer with data system.

2.2 *General procedure for synthesis of N-(1,3-Benzodioxol-5-yl)arylsulfonamide (3a-b)*
1,3-Benzodioxol-5-amine (**1**; 0.012 mol) was dispersed in 15 mL distilled water in a 100 mL round bottom flask. Then arylsulfonyl chlorides (**2a-b**; 0.012 mol) were added and set to stir for 2-4 hours. The solution was basified by aqueous Na_2CO_3 to maintain pH 8-9 during the whole reaction. The reaction was supervised by TLC till single spot. Cold distilled water was added and pH was turned to 4-5 by adding dilute HCl. The obtained precipitates were filtered, washed and dried for further use.

Table-1: Different *N*-substituted aryl groups

Compd.	R	Compd.	R
3a,7a-9a		**3b,7b-9b**	

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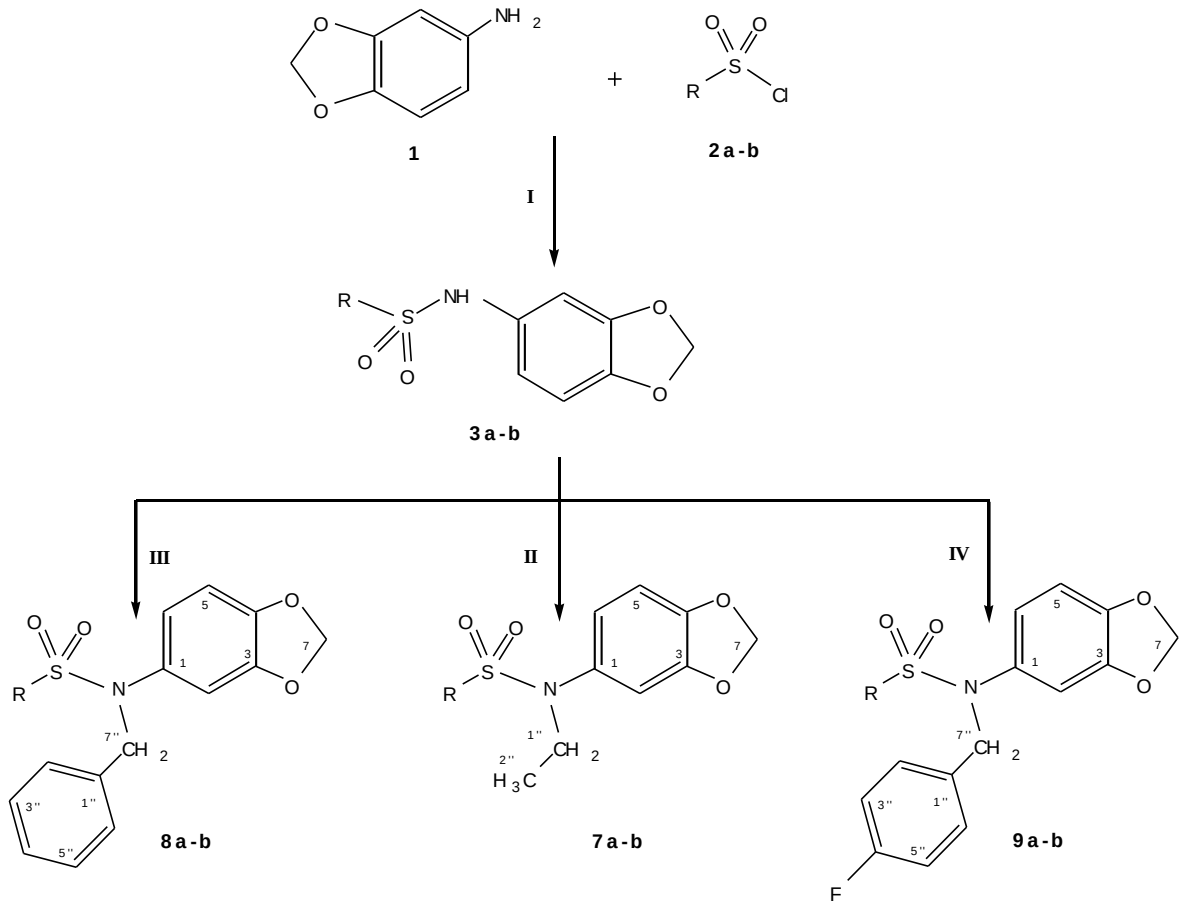

Scheme-1: Protocol for the synthesis of sulfonamide derivatives of 1,3-Benzodioxol-5-amine **(1)**. **Reagents and conditions:** (I) Aq. Na_2CO_3, stir 2-4 hr, pH = 9-10 (II) C_2H_5I (**4**), LiH, DMF, stir 3-5 hr(III) $C_6H_5CH_2Cl$ (**5**), LiH, DMF, stir 3-5 hr (IV) 4-$FC_6H_5CH_2Cl$ (**6**), LiH, DMF, stir 3-5 hr.

2.2.1 *N-(1,3-Benzodioxol-5-yl)benzenesulfonamide (3a)*

Grey amorphous solid; Yield: 78%; M. P.: 143-144 ^oC; Mol. Formula: $C_{13}H_{11}NO_4S$; Mol. Weight: 277; IR (KBr, cm^{-1})υ_{max}: 3028 (Ar C-H), 2906 (R C-H), 1596 (Ar C=C), 1430 (S=O), 1167 (C-O);^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.85 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.57 (t, J = 8.4 Hz, 1H, H-4'), 7.50 (t, J = 8.0 Hz, 2H, H-3', H-5'), 6.64 (d, J = 2.0 Hz, 1H, H-2), 6.60 (d, J = 8.0 Hz, 1H, H-5), 6.38 (dd, J = 8.4, 2.4 Hz, 1H, H-6), 5.91 (s, 2H, H-7); EIMS (*m/z*): 277 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 121 $[C_7H_5O_2]^+$, 77 $[C_6H_5]^+$, 75 $[C_6H_3]^+$, 51 $[C_4H_3]^+$.

2.2.2 *N-(1,3-Benzodioxol-5-yl)-4-acetylbenzenesulfonamide (3b)*

Creamy white amorphous solid; Yield: 85%; M. P.: 133-135 ^oC; Mol. Formula: $C_{15}H_{13}NO_5S$; Mol. Weight: 319; IR (KBr, cm^{-1})υ_{max}: 3025 (Ar C-H), 2900 (R C- H), 1716 (Ketone C=O) 1566 (Ar C=C), 1460 (S=O), 1197 (C-O);^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 8.08 (d, J = 8.0 Hz, 2H, H-2', H-6'), 7.96 (d, J = 8.8 Hz, 2H, H-3', H-5'), 6.69 (d, J = 2.4 Hz, 1H, H-2), 6.63 (d, J = 8.8 Hz, 1H, H-5), 6.33 (dd, J = 8.8, 2.0 Hz, 1H, H-6), 5.94 (s, 2H, H-7), 2.62 (s, 3H, CH_3CO-4'); EIMS (*m/z*): 319 $[M]^+$, 183 $[C_8H_7SO_3]^+$, 121 $[C_7H_5O_2]^+$, 119 $[C_8H_7O]^+$, 75 $[C_6H_3]^+$, 51 $[C_4H_3]^+$.

2.3*General procedure for synthesis of N-Alkyl/aralkyl-N-(1,3-benzodioxol-5-yl)arylsulfonamide(7a-bto 9a-b)*

The molecules**3a-b**(0.002mol) and lithium hydride (0.002 mol)were dissolved in 13 mL*N*,*N*-dimethyl formamide (DMF)in a 50 mL RB flaskbyone hour stirring. The electrophiles, alkyl/aralkyl halides (**4-6**; 0.002mol) were added to the reaction mixture and further stirred for 3-5hours. After single spot on TLC plate, ice cold distilled water was added with hand shaking and left for 15-20 min. The precipitated products,**7a-b**to**9a-b**, were filtered, washed with distilled water and dried for further analysis.

2.3.1 *N-Ethyl-N-(1,3-benzodioxol-5-yl)benzenesulfonamide (7a)*

Dark pink amorphous solid; Yield: 74%; M. P.: 77-78 ^oC; Mol. Formula: $C_{15}H_{15}NO_4S$; Mol. Weight: 305; IR (KBr, cm^{-1})υ_{max}: 3032 (Ar C-H), 2940 (R C-H), 1598 (Ar C=C), 1450 (S=O), 1157 (C-O);^{1}H–NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.87 (d, J = 7.6 Hz, 2H, H-2', H-6'), 7.55 (t, J = 7.6 Hz, 1H, H-4'), 7.52 (t, J = 8.4 Hz, 2H, H-3', H-5'), 6.68 (d, J = 2.4 Hz, 1H, H-2), 6.66 (d, J = 8.4 Hz, 1H, H-5), 6.35 (dd, J = 8.0, 2.4 Hz, 1H, H-6), 5.94 (s, 2H, H-7), 3.27 (q, J = 7.6 Hz, 2H, H-1"), 0.92 (t, J = 7.6 Hz, 3H, CH_3-2"); EIMS (*m/z*): 305 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 121 $[C_7H_5O_2]^+$, 77 $[C_6H_5]^+$, 75 $[C_6H_3]^+$, 51 $[C_4H_3]^+$, 29 $[C_2H_5]$.

Table 2: MIC values for antibacterial activity of *N*-Substituted sulfonamide derivatives

Compound	MIC				
	B. subtilis (+)	***S. aureus (+)***	***S. typhi (-)***	***E. coli (-)***	***P. aeruginosa (-)***
3a	10.25±0.44	13.76±0.51	12.50±0.13	15.77±1.76	14.43±0.44
3b	19.21±0.56	12.33±0.89	14.42±0.15	-	18.06±0.89
7a	12.36±0.77	15.24±0.51	11.28±0.90	13.42±0.20	14.13±0.11
7b	14.32±0.45	-	14.27±0.92	-	18.07±0.78
8a	-	17.17±0.14	12.08±0.54	-	-
8b	12.92±0.54	13.00±0.03	11.55±0.54	-	-
9a	-	-	17.63±0.45	-	-
9b	17.79±0.44	-	18.91±0.22	-	-
Ciprofloxacin	7.22±0.67	7.00±1.54	7.83±0.78	8.01±0.12	7.98±0.89

2.3.2 *N-Ethyl-N-(1,3-benzodioxol-5-yl)-4-acetylbenzenesulfonamide (7b)*

Light orange amorphous solid; Yield: 78%; M. P.: 124-125 ^{o}C; Mol. Formula: $C_{17}H_{17}NO_5S$; Mol. Weight: 347; IR (KBr, cm^{-1})υ_{max}: 3026 (Ar C-H), 2910 (R C-H), 1717 (Ketone C=O), 1556 (Ar C=C), 1461 (S=O), 1198 (C-O);^{1}H–NMR ($CDCl_3$, 400 MHz, δ/ppm): 8.04 (d, *J* = 8.0 Hz, 2H, H-2', H-6'), 7.92 (d, *J* = 7.6 Hz, 2H, H-3', H-5'), 6.61 (d, *J* = 2.4 Hz, 1H, H-2), 6.65 (d, *J* = 8.0 Hz, 1H, H-5), 6.30 (dd, *J* = 8.8, 2.4 Hz, 1H, H-6), 5.97 (s, 2H, H-7), 3.26 (q, *J* = 7.6 Hz, 2H, H-1"), 2.64 (s, 3H, CH_3CO-4'), 0.96 (t, *J* = 7.6 Hz, 3H, CH_3-2"); EIMS (*m/z*): 347 $[M]^+$, 183 $[C_8H_7SO_3]^+$, 121 $[C_7H_5O_2]^+$, 119 $[C_8H_7O]^+$, 75 $[C_6H_3]^+$, 51 $[C_4H_3]^+$, 29 $[C_2H_5]^+$.

2.3.3 *N-Benzyl-N-(1,3-benzodioxol-5-yl)benzenesulfonamide (8a)*

Light pink amorphous solid; Yield: 85%; M. P.: 83-84 ^{o}C; Mol. Formula: $C_{20}H_{17}NO_4S$; Mol. Weight: 367; IR (KBr, cm^{-1})υ_{max}: 3038 (Ar C-H), 2936 (R C-H), 1586 (Ar C=C), 1440 (S=O), 1157 (C-O);^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.88 (d, *J* = 7.6 Hz, 2H, H-2', H-6'), 7.52 (t, *J* = 8.0 Hz, 1H, H-4'), 7.52 (t, *J* = 8.4 Hz, 2H, H-3', H-5'), 7.17-7.07 (m, 5H, H-2" to H-6"), 6.68 (d, *J* = 2.4 Hz, 1H, H-2), 6.70 (d, *J* = 8.4 Hz, 1H, H-5), 6.48 (dd, *J* = 8.8, 2.4 Hz, 1H, H-6), 5.93 (s, 2H, H-7), 3.46 (s, 2H, H-7"); EIMS (*m/z*): 367 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 121 $[C_7H_5O_2]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 75 $[C_6H_3]^+$, 51 $[C_4H_3]^+$.

2.3.4 *N-Benzyl-N-(1,3-benzodioxol-5-yl)-4-acetylbenzenesulfonamide (8b)*

Creamy white amorphous solid; Yield: 85%; M. P.: 130-131 ^{o}C; Mol. Formula: $C_{22}H_{19}NO_5S$; Mol. Weight: 409; IR (KBr, cm^{-1})υ_{max}: 3029 (Ar C-H), 2910 (R C-H), 1717 (Ketone C=O), 1546 (Ar C=C), 1450 (S=O), 1196 (C-O);^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 8.01 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.89 (d, *J* = 8.4 Hz, 2H, H-3', H-5'), 7.16-7.06 (m, 5H, H-2" to H-6"), 6.64 (d, *J* = 2.8 Hz, 1H, H-2), 6.61 (d, *J* = 8.4 Hz, 1H, H-5), 6.32 (dd, *J* = 8.0, 2.4 Hz, 1H, H-6), 5.95 (s, 2H, H-7), 3.44 (s, 2H, H-7"), 2.65 (s, 3H, CH_3CO-4'); EIMS (*m/z*): 409 $[M]^+$, 183 $[C_8H_7SO_3]^+$, 121 $[C_7H_5O_2]^+$, 91 $[C_7H_7]^+$, 119 $[C_8H_7O]^+$, 75 $[C_6H_3]^+$, 51 $[C_4H_3]^+$.

2.3.5 *N-(4-Fluorobenzyl)-N-(1,3-benzodioxol-5-yl)benzenesulfonamide (9a)*

Dark pink amorphous solid; Yield: 82%; M. P.: 84-85 ^{o}C; Mol. Formula: $C_{20}H_{16}FNO_4S$; Mol. Weight: 385; IR (KBr, cm^{-1})υ_{max}: 3045 (Ar C-H), 2936 (R C-H), 1600 (Ar C=C), 1450 (S=O), 1177 (C-O), 1050 (C-F);^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.80 (d, *J* = 7.8 Hz, 2H, H-2', H-6'), 7.65 (d, *J* = 7.6 Hz, 2H, H-2", H-6"), 7.60 (t, *J* = 8.0 Hz, 1H, H-4'), 7.55 (t, *J* = 8.4 Hz, 2H, H-3', H-5'), 6.89 (d, *J* = 8.0 Hz, 2H, H-3", H-5"), 6.72 (d, *J* = 2.4 Hz, 1H, H-2), 6.59 (d, *J* = 8.8 Hz, 1H, H-5), 6.48 (dd, *J* = 8.8, 2.8 Hz, 1H, H-6), 5.97 (s, 2H, H-7), 3.95 (s, 2H, H-7"); EIMS (*m/z*): 385 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 121 $[C_7H_5O_2]^+$, 110 $[C_7H_7F]^+$, 77 $[C_6H_5]^+$, 75 $[C_6H_3]^+$, 51 $[C_4H_3]^+$.

2.3.6 *N-(4-Fluorobenzyl)-N-(1,3-benzodioxol-5-yl)-4-acetylbenzenesulfonamide (9b)*

Light brown amorphous solid;Yield: 95%; M. P.: 133-135 ^{o}C; Mol. Formula: $C_{22}H_{18}FNO_5S$; Mol. Weight: 427; IR (KBr, cm^{-1})υ_{max}: 3015 (Ar C-H), 2920 (R C-H), 1718 (Ketone C=O), 1536 (Ar C=C), 1455 (S=O), 1167 (C-O), 1050 (C-F);^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.93 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.89 (d, *J* = 8.4 Hz, 2H, H-3', H-5'), 7.71 (d, *J* = 7.6 Hz, 2H, H-2", H-6"), 6.84 (d, *J* = 7.6 Hz, 2H, H-3", H-5"), 6.69 (d, *J* = 2.8 Hz, 1H, H-2), 6.64 (d, *J* = 8.8 Hz, 1H, H-5), 6.32 (dd, *J* = 8.8, 2.4 Hz, 1H, H-6), 5.98 (s, 2H, H-7), 3.95 (s, 2H, H-7"), 2.64 (s, 3H, CH_3CO-4'); EIMS (*m/z*): 427 $[M]^+$, 183 $[C_8H_7SO_3]^+$, 121 $[C_7H_5O_2]^+$, 110 $[C_7H_7F]^+$, 119 $[C_8H_7O]^+$, 75 $[C_6H_3]^+$, 51 $[C_4H_3]^+$.

2.4*Antibacterial activity*

The rule for antibacterial activity is thatthe microbial cell number depends on the logarithmof growth rate which depends on absorbance of broth medium.As the absorbance of the broth medium increases the logarithm of growth also increases.And as a result microbial cell number increases[13].

2.5*Statistical analysis*

All the calculations and measurements were done in triplicate and statistical analysiswas performed by Microsoft Excel 2010. Results are mean of triplicate (n=3, ± SEM). Reference standard taken was ciprofloxacin. Minimum inhibitory concentration (MIC) was computed with suitable dilutions (5-30 µg/well) for each sample and results were measured using EZ-Fit Perrella Scientific Inc. Amherst USA software.

3. RESULTS AND DISCUSSION

A comprehensive outline for the synthesis of a series of sulfonamides is given in Scheme 1 along with necessary conditions and reagents required. All the molecules were screened for the antibacterial activity against the bacterial strains of Gram-positive and Gram-negative bacteria taking ciprofloxacin as reference standard.

3.1 *Chemistry*

The synthesized molecule **3a** showed the $[M]^+$ peak at *m/z* 277 along with other significant peaks at *m/z* 141 for benzenesulfonylcation, at *m/z* 121 for the 1,3-benzodioxol-5-yl cation and at *m/z* 77 for the phenyl cation in EIMS spectrum. The definite absorption bands obtained from IR spectrum supporting the major functionalities in the molecule were 3028 (Ar C-H), 2906 (R C-H), 1596 (Ar C=C), 1430 (S=O) and 1167 (C-O). The signals of ^{1}H-NMRresonated at δ 7.85 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.57 (t, J = 8.4 Hz, 1H, H-4'), 7.50 (t, J = 8.0 Hz, 2H, H-3', H-5') for the phenyl group attached to sulfur of sulfamoyl moiety while the signals confirming the 1,3-benzodioxol group appeared at δ 6.64 (d, J = 2.0 Hz, 1H, H-2), 6.60 (d, J = 8.0 Hz, 1H, H-5), 6.38 (dd, J = 8.4, 2.4 Hz, 1H, H-6) and 5.91 (s, 2H, H-7). All the spectral data obtained confirmed the molecular structure of **3a** named, *N*-(1,3-Benzodioxol-5-yl)benzenesulfonamide. By the same way, all the structures of prepared molecules were affirmed by ^{1}H-NMR, IR and mass spectral data.

3.2. *Antibacterial activity (in vitro)*

Only two compounds, **9a** and **8a** were inactive against *B. subtilis*. The most active one against this strain was **3a** with MIC of 10.25 ± 0.44 µmol/L relative to the reference. *S. aureus* was moderately inhibited by all the compounds except **7b**, **9a** and **9b**. The molecules, **3a** and **7a** showed inhibition against all the bacterial strains while **9a** remained the least active showing MIC only against *S. typhi*. Among all the bacterial strains, *S.typhi* was inhibited by all the synthesized molecules. The molecules, **7a** and **8b** showed the best inhibition results with MIC of 11.28 ± 0.90 µmol/L and 11.55 ± 0.54 µmol/L with reference of 7.83 ± 0.78 µmol/L, the MIC of ciprofloxacin. Against *E. coli*only **7a** and **3a** remained active with moderate MIC values relative to ciprofloxacin. Half of the synthesised compounds remained inactive and half were moderately active against *P.aeruginosa*.

4. CONCLUSION

The synthesized molecules were obtained inreasonable yields and were structurallycorroborated by spectral analysis. The antibacterial activity evaluation rendered them moderate inhibitors.

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