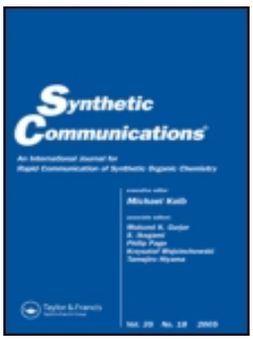

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Synthesis and Characterization of 5-Substituted Novel Isoxazolidines Derived from 1,3-Dipolar Cycloaddition of Nitrones with Olefins: Studies of Antibacterial and Antifungal Activities

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ABSTRACT

The synthesis, antibacterial and antifungal activities of a novel series of 5-substituted isoxazolidine derivatives **[3a,b(i–viii)]** were described. The synthesis of title compounds was achieved via a 1,3-dipolar cycloaddition of C-(4-biphenyl)-*N*-(4-methylphenyl)nitrone, C-(4-biphenyl)-*N*-(4-chlorophenyl) nitrone with monosubstituted alkenes.

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Key Words: Nitrones; Isoxazolidines; Cycloaddition; Antibacterial; Antifungal.

Nitrones are attractive class of 1,3-dipoles, because of their versatile synthetic applications in organic synthesis.[1–4] Recently, we showed that nitrones are convenient class of compounds used for the synthesis of ultimate carcinogens,[5,6] which are biologically interesting species. The nitrone addition to unsaturated substrate has been utilized to develop a synthesis of β-lactams,[7,8] natural products, versatile synthetic intermediates,[9] and biologically interesting compounds.[10]

In the interest of the above, we herein reported the synthesis and characterization of some novel aryl nitrones. The nitrones obtained were used to synthesize biologically interesting novel isoxazolidines, which were tested for antibacterial and antifungal activities.

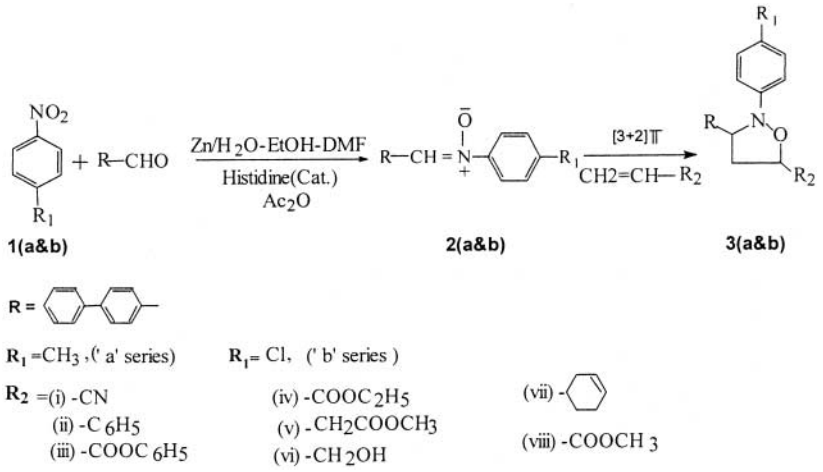
Nitrones were synthesized by the reduction of a mixture of nitro compounds and 4-biphenyl carboxaldehyde with zinc dust using histidine as catalyst.[11] The nitrones were found to be light sensitive and hygroscopic. Hence they were stored in the dark until further use, the obtained nitrones were structurally characterized by using ^{1}H NMR, IR, and C, H, N, analysis.

The novel 5-substituted isoxazolidines were obtained by refluxing the nitrones **2a** and **2b** with equimolar amount of monosubstituted alkenes in toluene/xylene. The cycloaddition of all monosubstituted olefins with nitrone showed high regioselectivity and gave 5-substituted derivatives predominantly (Sch. 1).[3]

The major products of 5-substituted isoxazolidine derivatives were separated on silica gel column using appropriate combination of chloroform, hexane, benzene, and petroleum ether as eluents. The reaction condition and the physical data of cycloadducts are given in Table 1. All synthesized isoxazolidines were structurally characterized by using IR, ^{1}H NMR, and C, H, N analysis.

The results of antibacterial and antifungal activities of the molecules are summarized in Tables 2 and 3. Introduction of chlorine substituent into phenyl ring proved to be very beneficial for activity, thus **3b(i–viii)** series showed better Minimum Inhibition Concentration (MIC) values against all tested fungi and bacteria compared to **3a(i–viii)** series.

Compounds **3a(iv)**, **3a(vii)**, **3b(iv)**, **3b(vi)**, and **3b(vii)** showed better antifungal activity compared to standard drug Nystatin against *Botrydiplodia theobromae*.



Scheme 1.

EXPERIMENTAL SECTION

Melting points were determined on SELACO-650 hot stage apparatus and are uncorrected. IR (nujol) spectra were measured on Shimadzu 8300 IR spectrophotometer, ^{1}H NMR were recorded on Shimadzu AMX 400-Bruker, 400 MHz spectrometer by using $CDCl_3$ as solvent and TMS as an internal standard (chemical shift in δ ppm). Elemental analyses were obtained on a Vario-EL instrument. Column and TLC were done with silica gel BDH 60–120 mesh and pre-coated silica gel plates.

Procedure for the Synthesis of C-(4-Biphenyl)-*N*-(4-methylphenyl) and C-(4-Biphenyl)-*N*-(4-chlorophenyl) Nitrones, 2a and 2b

Nitrones were synthesized according to the procedure we reported earlier.[11]

Synthesis of C-(4-biphenyl)-*N*-(4-methylphenyl) nitrone, 2a: This was obtained from 4-methyl nitrobenzene and 4-biphenyl carboxaldehyde as a white crystalline solid; yield 813 mg (91%), m.p. 225°C. ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.42 (s, 3H, Ar-CH_3); 7.25–7.29 (d, 2H, Ar-H); 7.38–7.51 (m, 3H, Ar-H); 7.64–7.74 (m, 6H, Ar-H); 7.95 (s, 1H, CH=N); 8.45–8.50 (d, 2H, Ar-H). Anal. calcd.

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Table 1. Reaction condition and physical data of isoxazolidines **3a** and **3b** series.

Isoxazolidines	Solvent used for refluxing	Time taken to complete the reaction	R_f value	Eluent used in separation	Yield in %	M.p. (°C)
3a(i)	Toluene	18 h	0.64	$CHCl_3$ + hexene (2:1)	68.2	Oily
3a(ii)	Toluene	24 h	0.63	$CHCl_3$ + pet. ether (2:1)	69.5	141.0
3a(iii)	Toluene	19 h	0.64	$CHCl_3$ + pet. ether (3:1)	71.5	Oily
3a(iv)	Toluene	20 h	0.61	$CHCl_3$ + pet. ether (2:1)	65.0	Oily
3a(v)	Toluene	24 h	0.58	$CHCl_3$ + hexene (3:1)	84.0	Oily
3a(vi)	Toluene	17 h	0.67	$CHCl_3$ + pet. ether (3:1)	80.0	Oily
3a(vii)	Toluene	22 h	0.69	$CHCl_3$ + hexene (3:2)	65.5	Oily
3a(viii)	Toluene	18 h	0.64	$CHCl_3$ + pet. ether (3:1)	61.5	Oily
3b(i)	Xylene	20 h	0.77	$CHCl_3$ + benzene (2:1)	65.0	134
3b(ii)	Xylene	19 h	0.86	$CHCl_3$ + benzene (3:1)	60.0	Oily
3b(iii)	Xylene	20 h	0.63	$CHCl_3$ + pet. ether (3:1)	59.0	Oily
3b(iv)	Xylene	22 h	0.71	$CHCl_3$ + benzene (2:1)	61.0	Oily
3b(v)	Xylene	24 h	0.69	$CHCl_3$ + pet. ether (2:1)	62.8	Oily
3b(vi)	Xylene	24 h	0.68	$CHCl_3$ + benzene (1:1)	59.6	Oily
3b(vii)	Xylene	23 h	0.79	$CHCl_3$ + benzene (3:1)	66.4	Oily
3b(viii)	Xylene	22 h	0.66	$CHCl_3$ + pet. ether (3:1)	58.0	Oily

Table 2. The minimum antibacterial and antifungal inhibitory concentrations (μgm/mL) of isoxazolidines **3a(i–viii)**.

	Tested bacteria			Tested fungus		
Isoxazolidines	*E. coli*	*B. cereus*	*S. aureus*	*A. flavus*	*F. moniliforme*	*B. theobromae*
Ampicillin	5.0	3.0	2.5	Nystatin 12.0	14.0	21.0
3a(i)	70.0	70.0	100	40.0	60.0	60.0
3a(ii)	50.0	110	70.0	20.0	50.0	50.0
3a(iii)	70.0	100	60.0	30.0	20.0	40.0
3a(iv)	50.0	70.0	50.0	40.0	40.0	20.0
3a (v)	60.0	100	70.0	30.0	40.0	40.0
3a(vi)	70.0	50.0	70.0	40.0	60.0	40.0
3a(vii)	50.0	60.0	50.0	20.0	40.0	20.0
3a(viii)	70.0	50.0	50.0	40.0	20.0	40.0

Table 3. The minimum antibacterial and antifungal inhibitory concentrations (μgm/mL) of isoxazolidines **3b(i–viii)**.

	Tested bacteria			Tested fungus		
Isoxazolidines	*E. coli*	*B. cereus*	*S. aureus*	*A. flavus*	*F. moniliforme*	*B. theobromae*
Ampicillin	5.0	3.0	2.5	Nystatin 12.0	14.0	21.0
3b(i)	60.0	100	120	30.0	40.0	40.0
3b(ii)	50.0	120	100	20.0	30.0	30.0
3b(iii)	60.0	100	70.0	30.0	40.0	40.0
3b(iv)	70.0	50.0	50.0	40.0	30.0	20.0
3b(v)	70.0	110	80.0	20.0	40.0	40.0
3b(vi)	50.0	70.0	70.0	50.0	50.0	20.0
3b(vii)	60.0	60.0	50.0	40.0	30.0	20.0
3b(viii)	70.0	50.0	50.0	20.0	20.0	30.0

$C_{20}H_{17}NO$: C, 83.62; H, 5.92; N, 4.88. Found: C, 83.32; H, 5.48; N, 4.94. IR (Nujol): ν (cm^{-1}): 1548 (C=N); 1140 (NO).

Synthesis of C-(4-biphenyl)-*N*-(4-chlorophenyl) nitrone, 2b: This was obtained from 4-chloronitrobenzene and 4-biphenyl carboxaldehyde as a white crystalline solid; yield: 812 mg (96%), m.p. 307°C. ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 7.44–7.49 (m, 5H, Ar-H); 7.65–7.79 (m, 6H, Ar-H); 7.94 (s, 1H, CH=N); 8.44–8.48 (d, 2H, Ar-H). Anal. calcd. $C_{19}H_{14}NOCl$: C, 74.27; H, 4.56; N, 4.56. Found: C, 74.14; H, 4.72; N, 4.68. IR (Nujol): ν (cm^{-1}): 1572 (C=N); 1152 (NO).

General Procedure for the Synthesis of Novel Isoxazolidines, [3a,b (i–viii)]

Equimolar mixture of nitrones **2a** and **2b** and different alkenes were dissolved in 10 mL of toluene/xylene. The reaction mixture was refluxed till the reaction completes which was monitored by TLC. The pure products were separated by using silica gel column.

Synthesis of 2-(4-methylphenyl)-3-(4-biphenyl)-5-cyano isoxazolidines, 3a(i): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-methylphenyl) nitrone **2a** (500 mg) and acrylonitrile (0.31 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.28 (s, 3H, Ar-CH_3); 2.66–2.82 (q, 2H, H_4); 4.45 (t, 1H, H_5); 5.08 (t, 1H, H_3); 6.92 (d, 2H, Ar-H); 7.42 (d, 2H, Ar-H (BP); 7.52 (t, 1H, Ar-H (BP); 7.56 (d, 2H, Ar-H); 7.63 (t, 2H, Ar-H (BP); 7.69 (d, 4H, Ar-H (BP). Anal. calcd. for $C_{23}H_{20}N_2O$: C, 81.18; H, 5.88; N, 8.23. Found: C, 81.08; H, 5.92; N, 8.08. IR (Nujol): ν (cm^{-1}): 1748 (CO); 1278 (NO).

Synthesis of 2-(4-methylphenyl)-3-(4-biphenyl)-5-phenyl isoxazolidines, 3a(ii): It was obtained from equimolar mixture of C-(4-biphenyl-*N*-(4-methylphenyl) nitrone **2a** (500 mg) and styrene (0.25 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.28 (s, 3H, Ar-CH_3); 2.69–2.85 (q, 2H, H_4); 5.03 (t, 1H, H_5); 5.12 (t, 1H, H_3); 6.92 (d, 2H, Ar-H); 7.29–7.41 (m, 5H, Ar-H); 7.42 (d, 2H, Ar-H (BP)); 7.52 (t, 1H, Ar-H (BP); 7.55 (d, 2H, Ar-H); 7.64 (t, 2H, Ar-H (BP)); 7.69 (d, 4H, Ar-H (BP)). Anal. calcd. for $C_{28}H_{25}NO$: C, 85.93; H, 6.39; N, 3.58. Found: C, 85.68; H, 6.26; N, 3.72. IR (Nujol): ν (cm^{-1}): 1712 (CO); 1246 (NO).

Synthesis of 2-(4-methylphenyl)-3-(4-biphenyl)-5-benzoate isoxazolidines, 3a(iii): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-methylphenyl) nitrone **2a** (500 mg) and vinyl benzoate (0.26 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.29 (s, 3H, Ar-CH_3); 2.65–2.84 (q, 2H, H_4); 4.72 (t, 1H, H_5); 5.12 (t, 1H, H_3); 6.93 (d, 2H, Ar-H); 7.28–7.50 (m, 3H, Ar-H); 7.42 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H, BP); 7.55 (d, 2H, Ar-H); 7.64 (t, 2H, Ar-H, BP); 7.79 (d, 4H, Ar-H, BP). 7.81 (d, 2H, Ar-H). Anal. calcd. for $C_{29}H_{25}NO_3$: C, 80; H, 5.75; N, 3.22. Found: C, 80.08; H, 5.62; N, 3.14. IR (Nujol): ν (cm^{-1}): 1752 (C=O); 1732 (CO); 1270 (NO).

Synthesis of 2-(4-methylphenyl)-3-(4-biphenyl)-5-ethylate isoxazolidines, 3a(iv): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-methylphenyl) nitrone **2a** (500 mg) and ethyl acrylate (0.17 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 0.93 (t, 3H, CH_3); 2.28 (s, 3H, Ar-CH_3); 2.66–2.84 (q, 2H, H_4); 3.62 (q, 2H, CH_2); 4.46 (t, 1H, H_5); 5.12 (t, 1H, H_3); 6.92 (d, 2H, Ar-H); 7.42 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H, BP); 7.55 (d, 2H, Ar-H);

7.64 (t, 2H, Ar-H, BP); 7.79 (d, 4H, Ar-H, BP). Anal. calcd. for $C_{25}H_{25}NO_3$: C, 77.52; H, 6.46; N, 3.62. Found: C, 77.46; H, 6.36; N, 3.44. IR (Nujol): ν (cm^{-1}): 1726 (C=O); 1708 (CO); 1240 (NO).

Synthesis of 2-(4-methylphenyl)-3-(4-biphenyl)-5-methylene acetate isoxazolidine, 3a(v): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-methylphenyl) nitrone **2a** (500 mg) and allyl acetate (0.23 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.28 (s, 3H, Ar-CH_3); 2.42 (d, 2H, CH_2); 2.64–2.82 (q, 2H, H_4); 3.42 (s, 3H, OCH_3); 4.25 (t, 1H, H_5); 5.12 (t, 1H, H_3); 6.92 (d, 2H, Ar-H); 7.42 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H, BP); 7.53 (d, 2H, Ar-H); 7.64 (t, 2H, Ar-H, BP); 7.79 (d, 4H, Ar-H, BP). Anal. calcd. for $C_{25}H_{25}NO_3$: C, 77.72; H, 6.22; N, 3.62. Found: C, 77.58; H, 6.16; N, 3.58. IR (Nujol): ν (cm^{-1}): 1720 (CO); 1250 (NO).

Synthesis of 2-(4-methylphenyl)-3-(4-biphenyl)-5-methylene hydroxy isoxazolidines, 3a(vi): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-methylphenyl) nitrone **2a** (500 mg) and allyl alcohol (0.24 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.28 (s, 3H, Ar-CH_3); 2.66–2.85 (q, 2H, H_4); 3.64 (d, 2H, CH_2); 4.76 (t, 1H, H_5); 5.15 (t, 1H, H_3); 5.25 (s, 1H, OH); 6.92 (d, 2H, Ar-H); 7.42 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H, BP); 7.55 (d, 2H, Ar-H); 7.63 (t, 2H, Ar-H, BP); 7.79 (d, 4H, Ar-H, BP). Anal. calcd. for $C_{23}H_{23}NO_2$: C, 80; H, 6.66; N, 4.06. Found: C, 80.04; H, 6.52; N, 4.12. IR (Nujol): ν (cm^{-1}): 1728 (CO); 1262 (NO).

Synthesis of 2-(4-methylphenyl)-3-(4-biphenyl)-5-(3-cyclohexene) isoxazolidines, 3a(vii): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-methylphenyl) nitrone **2a** (500 mg) and 4-vinyl-1-cyclohexene (0.21 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 1.38–1.42 (m, 2H, CH_2, cyclohexene); 1.52 (s, 1H, cyclohexene); 2.26 (s, 3H, Ar-H); 2.28–2.31 (m, 2H, cyclohexene); 2.33–2.38 (m, 2H, cyclohexene); 2.65–2.83 (q, 2H, H_4); 4.82 (m, 1H, CH); 5.12 (t, 1H, CH); 5.6–5.66 (m, 2H, cyclohexene); 6.92 (d, 2H, Ar-H); 7.42 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H, BP); 7.55 (d, 2H, Ar-H); 7.63 (t, 2H, Ar-H, BP); 7.74 (d, 4H, Ar-H, BP). Anal. calcd. for $C_{28}H_{29}NO$: C, 85.06; H, 7.34; N, 3.54. Found: C, 85.12; H, 7.18; N, 3.48. IR (Nujol): ν (cm^{-1}): 1744 (CO); 1270 (NO).

Synthesis of 2-(4-methylphenyl)-3-(4-biphenyl)-5-methylate isoxazolidines, 3a(viii): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-methylphenyl) nitrone **2a** (500 mg) and methyl acrylate (0.17 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.28 (s, 3H, Ar-CH_3); 2.67–2.85 (q, 2H, H_4); 3.41 (s, 3H, OCH_3); 4.44 (t, 1H, CH); 5.14 (t, 1H, CH); 6.92 (d, 2H, Ar-H); 7.43 (d, 2H, Ar-H, BP); 7.53 (t, 1H, Ar-H, BP); 7.55 (d, 2H, Ar-H); 7.64 (t, 2H, Ar-H, BP); 7.73

(d, 4H, Ar-H, BP). Anal. calcd. for $C_{24}H_{23}NO_3$: C, 77.2; H, 6.17; N, 3.75. Found: C, 77.12; H, 6.12; N, 3.58. IR (Nujol): ν (cm^{-1}): 1726 (C=O); 1708 (CO); 1240 (NO).

Synthesis of 2-(4-chlorophenyl)-3-(4-biphenyl)-5-cyano isoxazolidines, 3b(i): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-chlorophenyl) nitrone **2b** (500 mg) and acrylonitrile (0.30 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.83–3.01 (q, 2H, H_4); 4.46 (t, 1H, H_5); 5.10 (t, 1H, H_3); 7.28 (d, 2H, Ar-H); 7.41 (d, 2H, Ar-H (BP)); 7.52 (t, 1H, Ar-H (BP)); 7.64 (t, 2H, Ar-H (BP)); 7.77 (d, 2H, Ar-H); 7.69 (d, 4H, Ar-H (BP)). Anal. calcd. $C_{22}H_{17}N_2OCl$: C, 73.3; H, 4.72; N, 7.28. Found: C, 73.08; H, 4.88; N, 7.64. IR (Nujol): ν (cm^{-1}): 1734 (CO); 1274 (NO).

Synthesis of 2-(4-chlorophenyl)-3-(4-biphenyl)-5-phenyl isoxazolidines, 3b(ii): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-chlorophenyl) nitrone **2b** (500 mg) and styrene (0.25 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.88–3.06 (q, 2H, H_4); 5.05 (t, 1H, H_5); 5.14 (t, 1H, H_3); 7.29 (d, 2H, Ar-H); 7.29–7.41 (m, 5H, Ar-H); 7.42 (d, 2H, Ar-H (BP)); 7.52 (t, 1H, Ar-H (BP)); 7.64 (t, 2H, Ar-H (BP)); 7.77 (d, 2H, Ar-H); 7.79 (d, 4H, Ar-H (BP)). Anal. calcd. $C_{27}H_{22}NOCl$: C, 78.83; H, 5.35; N, 3.41. Found: C, 78.68; H, 5.52; N, 3.28. IR (Nujol): ν (cm^{-1}): 1700 (CO); 1240 (NO).

Synthesis of 2-(4-chlorophenyl)-3-(4-biphenyl)-5-benzoate isoxazolidines, 3b(iii): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-chlorophenyl) nitrone **2b** (500 mg) and vinyl benzoate (0.15 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.85–3.03 (q, 2H, H_4); 4.72 (t, 1H, H_5); 5.15 (t, 1H, H_3); 7.28 (d, 2H, Ar-H); 7.29–7.50 (m, 3H, Ar-H); 7.42 (d, 2H, Ar-H, BP); 7.53 (t, 1H, Ar-H, BP); 7.64 (t, 2H, Ar-H, BP); 7.78 (d, 2H, Ar-H); 7.79 (d, 4H, Ar-H, BP). 7.81 (d, 2H, Ar-H). Anal. calcd. $C_{28}H_{22}NO_3Cl$: C, 73.85; H, 4.86; N, 3.1. Found: C, 73.58; H, 4.58; N, 3.08. IR (Nujol): ν (cm^{-1}): 1738 (C=O); 1730 (CO); 1268 (NO).

Synthesis of 2-(4-chlorophenyl)-3-(4-biphenyl)-5-ethylate isoxazolidines, 3b(iv): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-chlorophenyl) nitrone **2b** (500 mg) and ethyl acrylate (0.21 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 0.93 (t, 3H, CH_3); 2.84–3.02 (q, 2H, H_4); 3.62 (q, 2H, CH_2); 4.44 (t, 1H, H_5); 5.13 (t, 1H, H_3); 7.28 (d, 2H, Ar-H); 7.41 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H, BP); 7.64 (t, 2H, Ar-H, BP); 7.77 (d, 2H, Ar-H); 7.79 (d, 4H, Ar-H, BP). Anal. calcd. $C_{24}H_{22}NO_3Cl$: C, 70.76; H, 5.41; N, 3.44. Found: C, 70.62; H, 5.36; N, 3.38. IR (Nujol): ν (cm^{-1}): 1722 (C=O); 1700 (CO); 1232 (NO).

Synthesis of 2-(4-chlorophenyl)-3-(4-biphenyl)-5-methylene acetate isoxazolidines, 3b(v): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-chlorophenyl) nitrone **2b** (500 mg) and allyl acetate (0.1 mL).

^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.42 (d, 2H, CH_2); 2.84–3.02 (q, 2H, H_4); 3.42 (s, 3H, OCH_3); 4.26 (t, 1H, H_5); 5.12 (t, 1H, H_3); 7.26 (d, 2H, Ar-H); 7.41 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H, BP); 7.64 (t, 2H, Ar-H, BP); 7.77 (d, 2H, Ar-H); 7.79 (d, 4H, Ar-H, BP). Anal. calcd. $C_{24}H_{22}NO_3Cl$: C, 70.76; H, 5.40; N, 3.44. Found: C, 70.58; H, 5.38; N, 3.38. IR (Nujol): ν (cm^{-1}): 1740 (CO); 1266 (NO).

Synthesis of 2-(4-chlorophenyl)-3-(4-biphenyl)-5-methylene hydroxy isoxazolidine, 3b(vi): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-chlorophenyl)nitrone **2b** (500 mg) and allyl alcohol (0.15 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$; δ (ppm): 2.74–2.92 (q, 2H, H_4); 3.64 (d, 2H, CH_2); 4.76 (t, 1H, H_5); 5.12 (t, 1H, H_3); 5.25 (s, 1H, OH); 7.28 (d, 2H, Ar-H); 7.41 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H, BP); 7.64 (t, 2H, Ar-H, BP); 7.77 (d, 2H, Ar-H); 7.79 (d, 4H, Ar-H, BP). Anal. calcd. $C_{22}H_{20}NO_2Cl$: C, 72.33; H, 5.48; N, 3.84. Found: C, 72.18; H, 5.38; N, 3.72. IR (Nujol): ν (cm^{-1}): 1720 (CO); 1248 (NO).

Synthesis of 2-(4-chlorophenyl)-3-(4-biphenyl)-5-(3-cyclohexene) isoxazolidines, 3b(vii): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-chlorophenyl) nitrone **2b** (500 mg) and 4-vinyl-1-cyclohexene (0.25 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 1.38–1.42 (m, 2H, CH_2, cyclohexene); 1.52 (s, 1H, cyclohexene); 2.28–2.31 (m, 2H, cyclohexene); 2.33–2.38 (m, 2H, cyclohexene); 2.85–3.03 (q, 2H, H_4); 4.82 (m, 1H, CH); 5.14 (t, 1H, H_3); 5.6–5.66 (m, 2H, cyclohexene); 7.28 (d, 2H, Ar-H); 7.41 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H, BP); 7.63 (t, 2H, Ar-H, BP); 7.77 (d, 2H, Ar-H); 7.79 (d, 4H, Ar-H, BP). Anal. calcd. $C_{27}H_{26}NOCl$: C, 78.07; H, 6.26; N, 3.37. Found: C, 78.14; H, 6.18; N, 3.18. IR (Nujol): ν (cm^{-1}): 1730 (CO); 1260 (NO).

Synthesis of 2-(4-chlorophenyl)-3-(4-biphenyl)-5-methyl isoxazolidines, 3b(viii): It was obtained from equimolar mixture of C-(4-biphenyl)-*N*-(4-chlorophenyl) nitrone **2b** (500 mg) and methyl acrylate (0.35 mL). ^{1}H NMR (Bruker-AMX-400, 400 MHz, $CDCl_3$); δ (ppm): 2.87–3.05 (q, 2H, H_4); 3.41 (s, 3H, OCH_3); 4.45 (t, 1H, H_5); 5.12 (t, 1H, H_3); 7.28 (d, 2H, Ar-H); 7.41 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H, BP); 7.64 (t, 2H, Ar-H, BP); 7.77 (d, 2H, Ar-H); 7.79 (d, 4H, Ar-H, BP). Anal. calcd. $C_{23}H_{20}NO_3Cl$: C, 70.23; H, 5.09; N, 3.56. Found: C, 70.14; H, 5.12; N, 3.42. IR (Nujol): ν (cm^{-1}): 1745 (CO); 1278 (NO).

Microorganisms Used for the Antimicrobial Activity

Bacteria: *Escherichia coli*, *Bacillus cereus*, and *Staphylococcus aureus*.

Fungus: *Aspergillus flavus*, *Fusarium moniliforme* and *Botrydiplodia theobromae*.

Determination of Antibacterial Activity

The isoxazolidines were tested for antibacterial activity by serial tube dilution technique[12,13] at different concentrations (10, 20..... 150 μg/mL) against *E. coli* (Gram-negative), *B. cereus* (Gram-positive) and *S. aureus* (Gram-positive) microbes. Ampicillin was used as reference standard and $CHCl_3$ as control. To the culture tubes containing 1.9 mL of media, 0.1 mL of test solution was added at sterile conditions. To all the tubes including standard and controls, the fresh inoculum was added using Himedia flexiloop 4 calibrated to 0.1 mL. After incubating all the tubes at 37°C for 24 h, their absorbance was recorded at 640 nm along with ampicillin. Percentage of inhibition was calculated as follows,

$$\% \text{ Inhibition} = \frac{100(P - Q)}{P}$$

where P = absorbance without the test sample and Q = absorbance with test sample. Then the minimum inhibitor concentration (MIC) was recorded in μg/mL.

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