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Short communication

Synthesis of novel isoxazolidine derivatives and studies for their antifungal properties

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Abstract

A series of novel 5-substituted isoxazolidine derivatives **3a(i–viii)**, **3b(i–viii)** and **3c(i–viii)** have been prepared and their antifungal activity on *Aspergillus flavus*, *Fusarium moniliforme* and *Botrydiplodia theobromae* have been evaluated.

Keywords: Antifungal properties; Synthesis; Isoxazolidine derivatives; Cycloaddition

1. Introduction

Over the past two decades the frequency of systematic fungal infection in man has increased dramatically. Ketoconazole was the first orally active antifungal agent that was effective against a broad array of systematic and superficial fungal infections [1]. In addition to azole derivatives, a number of antifungal agents having chemical structures other than azoles have recently been introduced to the clinic.

In previous studies [2,3], we have described the application of 1,3-dipolar cycloaddition reaction to the synthesis of biologically active compounds. We recognized an opportunity to apply our knowledge of 1,3-dipolar species to the synthesis of a series of 5-substituted isoxazolidine compounds through the 1,3-dipolar cycloaddition reaction of α-substituted aldonitrones and monosubstituted alkenes. The resulting 5-substituted isoxazolidines were expected to differ in their chemical and antifungal properties from the known azole derivatives, thus providing valuable information of a new generation of antifungal agents.

2. Chemistry

Compounds **2(a–c)** were prepared by the reduction of nitro compounds and 4-biphenyl carboxaldehyde with zinc dust using histidine as catalyst as shown in Fig. 1 [4]. The nitrones were found to be light sensitive [5] and hygroscopic [6]. Hence, they were stored in the dark until further use. The nitrones are versatile synthetic intermediates in organic synthesis [7,8]. Recently, we reported that nitrones are convenient class of compounds used for synthesis of ultimate carcinogens [9–11] which are biologically interesting molecules. The novel isoxazolidines **3(a–c)** were obtained by refluxing the nitrones **2(a–c)** with equimolar amount of monosubstituted alkene in toluene–xylene. The cycloaddition of all monosubstituted olefins with nitrone showed high regioselectivity and gave 5-substituted derivatives predominantly major products [12] for both electron donating and electron withdrawing groups.

3. Results and discussion

The major products of 5-substituted isoxazolidine derivatives **3(a–c)** were separated on silica gel column using appropriate combination of chloroform, hexane, benzene and petroleum ether as eluent. The reaction condition and the physical data of cycloadducts are

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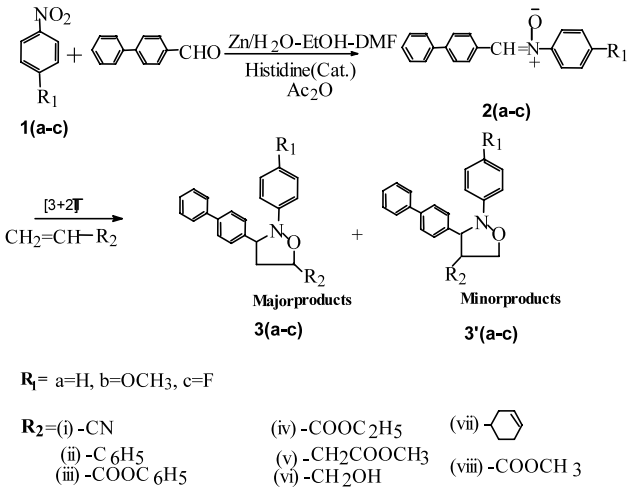

Fig. 1.

given in Table 1. All the synthesized isoxazolidines were structurally characterized by IR, ^{1}H-NMR and C, H, N analysis. The antifungal activity of these new compounds were evaluated in solid agar media, and their antifungal activity are summarized in Table 2. Some compounds **3b(ii)**, **3b(iv)**, **3b(vi)** **3c(ii)**, and **3c(vi)** were shown more potent than nystatin. In general, **3c(i–viii)** showed better activity than **3a(i–viii)** and **3b(i–viii)**. The introduction of fluorine to the phenyl ring enhanced the antifungal activity. However, introduction of one more phenyl ring to the isoxazolidine ring in **3b(ii)** and **3c(ii)** increasing the antifungal activity and the introduction of methylene hydroxy group in **3b(vi)** and **3c(vi)** of isoxazolidine enhancing the antifungal activity.

4. Conclusion

We prepared a novel series of 5-substituted isoxazolidines. Some of these compounds possessed good antifungal activities against the fungus *Aspergillus flavus*, *Fusarium moniliforme* and *Botrydiplodia theobromae*.

5. Experimental

5.1. Chemistry

The 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 spectrophotometer by using CDCl3 as solvent and TMS as an internal standard (chemical shift in δ ppm). Elemental analyses (C, H, N) were obtained on a Vario-EL instrument. The results were within $\pm$0.4% of the theoretical values. Column and TLC were done with silica gel BDH 60–120 mesh and pre-coated silica gel plates.

Table 1
Reaction condition and physical data of isoxazolidines **3a(i–vii)**, **3b(i–vii)** and **3c(i-viii)** series

Isoxazolidines	Solvent used for reaction	Time taken to complete the reaction (h)	R_f value	Eluent used in separation	% Yield	M.p. (°C)
3a(i)	toluene	17	0.61	$CHCl_3$+hexane 1:2	57	oily
3a(ii)	toluene	17	0.63	$CHCl_3$+hexane 1:2	61	141
3a(iii)	toluene	18	0.58	$CHCl_3$+petroleum ether 2:1	54	oily
3a(iv)	toluene	18	0.54	$CHCl_3$+petroleum ether 2:1	84	oily
3a(v)	toluene	31	0.68	$CHCl_3$+petroleum ether 2:1	69	oily
3a(vi)	toluene	22	0.58	$CHCl_3$+petroleum ether 2:1	58.6	oily
3a(vii)	toluene	20	0.62	$CHCl_3$+petroleum ether 2:1	62	oily
3a(viii)	toluene	18	0.64	$CHCl_3$+hexane 1:2	68	oily
3b(i)	toluene	19	0.62	$CHCl_3$+hexane 1:2	69.5	oily
3b(ii)	toluene	24	0.64	$CHCl_3$+hexane 1:2	71.5	134
3b(iii)	toluene	19	0.61	$CHCl_3$+hexane 1:2	65	oily
3b(iv)	toluene	20	0.58	$CHCl_3$+petroleum ether 1:1	84	oily
3b(v)	toluene	24	0.67	$CHCl_3$+petroleum ether 2:1	80	oily
3b(vi)	toluene	17	0.69	$CHCl_3$+petroleum ether 2:1	65.5	oily
3b(vii)	toluene	22	0.62	$CHCl_3$+petroleum ether 2:1	61.5	oily
3b(viii)	toluene	18	0.66	$CHCl_3$+petroleum ether 2:1	64	oily
3c(i)	xylene	20	0.77	$CHCl_3$+benzene (2:1)	65	oily
3c(ii)	xylene	19	0.86	$CHCl_3$+benzene (2:1)	60	132
3c(iii)	xylene	20	0.63	$CHCl_3$+benzene (3:1)	59	oily
3c(iv)	xylene	22	0.71	$CHCl_3$+petroleum ether (3:1)	61	oily
3c(v)	xylene	24	0.69	$CHCl_3$+benzene (2:1)	62.8	oily
3c(vi)	xylene	24	0.68	$CHCl_3$+petroleum ether (2:1)	59.6	oily
3c(vii)	xylene	23	0.79	$CHCl_3$+benzene (1:1)	66.4	oily
3c(viii)	xylene	22	0.66	$CHCl_3$+benzene (3:1)	58	oily

Table 2
The minimum inhibitory concentrations (MIC) [a] of isoxazolidines **3a(i–viii)**, **3b(i–viii)** and **3c**(i–**viii**) for antifungal activity

Isoxazolidines	Tested fungus		
	A. flavus (MIC in mM)	*F. moniliforme* (MIC in mM)	*B. theobromae* (MIC in mM)
Nystatin	3	5	2.5
3a(i)	12.0	12.0	11.5
3a(ii)	5.5	10.5	5.5
3a(iii)	7.0	5.0	9.5
3a(iv)	10.5	10.5	5.5
3a(v)	8.0	8.0	11.0
3a(vi)	12.0	3.5	12.0
3a(vii)	5.5	10.5	5.5
3a(viii)	11.5	5.5	11.5
3b(i)	8.5	8.5	7.5
3b(ii)	2.5	5.0	5.0
3b(iii)	4.5	6.5	7.0
3b(iv)	2.5	6.0	9.0
3b(v)	6.5	7.5	7.5
3b(vi)	3.0	3.0	5.5
3b(vii)	7.5	10.0	7.5
3b(viii)	5.5	9.0	6.5
3c(i)	9.0	7.5	8.5
3c(ii)	2.5	5.5	5.0
3c(iii)	5.5	7.0	6.0
3c(iv)	4.0	5.5	7.5
3c(v)	8.0	6.5	9.0
3c(vi)	3.0	3.0	6.0
3c(vii)	5.0	5.5	7.5
3c(viii)	8.0	6.5	8.0

[a] Average of atleast three determinations.

General procedure for the synthesis of isoxazolidines, **3a(i–viii)**, **3b(i–vii)** and **3c(i–viii)**: Equimolar mixture of nitrones **2a**, **2b** and **2c** and different alkenes were dissolved in 10 mL of toluene–xylene. The reaction mixture was refluxed for 18–20 h to complete the reaction, which was monitored by TLC. The pure products were separated by using appropriate mixture of chloroform, hexane, petroleum ether and benzene as eluent in silica gel column.

*5.1.1. Synthesis of C-biphenyl-N-phenyl nitrone (**2a**)*

This was obtained from the reduction of a mixture of nitrobenzene and 4-biphenyl carboxaldehyde with zinc dust using histidine as catalyst [4]. A white crystalline solid is obtained in ethanol; yield 748 mg (80%), m.p. 203 °C.

^{1}H-NMR δ (ppm): 7.39–7.51 (m, 6H, Ar–H), 7.65–7.48 (m, 6H, Ar–H), 7.97 (s, 1H, CH=N), 8.46–8.51 (dd, 2H, Ar–H).

IR (Nujol): ν (cm^{-1}): 1584 (C=N); 1168 (NO).

*5.1.2. Synthesis of C-biphenyl-N-(4-methoxyphenyl)nitrone (**2b**)*

This was obtained from the reduction of a mixture of 4-methoxynitrobenzene and 4-biphenyl carboxaldehyde with zinc dust using histidine as catalyst. A white crystalline solid is obtained in ethanol; yield 815 mg (95%), m.p. 178 °C.

^{1}H-NMR δ (ppm): 3.82 (s, 3H, Ar–OCH_3); 7.20–7.24 (d, 2H, Ar–H); 7.34–7.46 (m, 3H, Ar–H), 7.62–7.72 (m, 6H, Ar–H), 7.92 (s, 1H, CH=N), 8.24–8.28 (d, 2H, Ar–H).

IR (Nujol): ν (cm^{-1}): 1572 (C=N); 1152 (NO).

*5.1.3. Synthesis of C-biphenyl-N-(4-fluorophenyl)nitrone (**2c**)*

This was obtained from the reduction of a mixture of 4-fluoronitrobenzene and 4-biphenyl carboxaldehyde with zinc dust using histidine as catalyst [4]. A white crystalline solid is obtained in ethanol; yield 812 mg (96%), m.p. 307 °C.

^{1}H-NMR 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).

IR (Nujol): ν (cm^{-1}): 1572 (C=N); 1152 (NO).

*5.1.4. Synthesis of 2-phenyl-3-biphenyl-5-cyano isoxazolidine (**3a(i)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-phenylnitrone (**2a**) (500 mg) and acrylonitrile (0.10 mL).

^{1}H-NMR δ (ppm): 2.65–2.81 (dd, 2H, H_4); 4.45 (t, 1H, H_5); 5.08 (t, 1H, H_3); 6.91 (t, 1H, Ar–H); 7.2 (t, 2H,

Ar–H); 7.41 (d, 2H, Ar–H(BP); 7.52 (t, 1H, Ar–H(BP); 7.64 (t, 2H, Ar–H(BP); 7.72 (d, 2H, Ar–H); 7.69 (d, 4H, Ar–H(BP).

IR (Nujol): ν (cm^{-1}): 1742 (CO); 1280 (NO).

*5.1.5. Synthesis of 2-phenyl-3-biphenyl-5-phenyl isoxazolidine (**3a(ii)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-phenylnitrone (**2a**) (500 mg) and styrene (0.25 mL).

^{1}H-NMR δ (ppm): 2.72–2.88 (dd, 2H, H_4); 5.05 (t, 1H, H_5); 5.12 (t, 1H, H_3); 6.91 (t, 1H, Ar–H); 7.2 (t, 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); 7.72 (d, 2H, Ar–H); 7.69 (d, 4H, Ar–H(BP).

IR (Nujol): ν (cm^{-1}): 1712 (CO); 1240 (NO).

*5.1.6. Synthesis of 2-phenyl-3-biphenyl-5-benzoate isoxazolidine (**3a(iii)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-phenylnitrone (**2a**) (500 mg) and vinyl benzoate (0.25 mL).

^{1}H-NMR δ (ppm): 2.70–2.86 (dd, 2H, H_4); 4.72 (t, 1H, H_5); 5.13 (t, 1H, H_3); 6.91 (t, 1H, Ar–H); 7.20 (t, 2H, Ar–H); 7.28–7.50 (m, 3H, Ar–H); 7.41 (d, 2H, Ar–H(BP); 7.52 (t, 1H, Ar–H(BP); 7.72 (d, 2H, Ar–H); 7.64 (t, 2H, Ar–H(BP); 7.79 (d, 4H, Ar–H(BP); 7.81 (d, 2H, Ar–H).

IR (Nujol): ν (cm^{-1}): 1748 (C=O); 1730 (CO); 1260 (NO).

*5.1.7. Synthesis of 2-phenyl-3-biphenyl-5-ethylate isoxazolidine (**3a(iv)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-phenylnitrone (**2a**) (500 mg) and ethyl acrylate (0.20 mL).

^{1}H-NMR δ (ppm): 0.94 (t, 3H, CH_3); 2.68–2.86 (dd, 2H, H_4); 3.62 (q, 2H, CH_2); 4.43 (t, 1H, H_5); 5.12 (t, 1H, H_3); 6.91 (t, 1H, Ar–H); 7.2 (t, 2H, Ar–H); 7.41 (d, 2H, Ar–H, BP); 7.52 (t, 1H, Ar–H, BP); 7.64 (t, 2H, Ar–H, BP); 7.72 (d, 2H, Ar–H); 7.79 (d, 4H, Ar–H, BP).

IR (Nujol): ν (cm^{-1}): 1720 (C=O); 1722 (CO); 1234 (NO).

*5.1.8. Synthesis of 2-phenyl-3-biphenyl-5-methylene acetate isoxazolidine (**3a(v)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-phenylnitrone (**2a**) (500 mg) and allyl acetate (0.2 mL).

^{1}H-NMR δ (ppm): 2.42 (d, 2H, CH_2) 2.62–2.78 (dd, 2H, H_4); 3.42 (s, 3H, OCH_3); 2.70–4.25 (m, 1H, H_5); 5.06 (t, 1H, H_3) 6.91 (t, 1H, Ar–H); 7.2 (t, 2H, Ar–H); 7.41 (d, 2H, Ar–H, BP); 7.52 (t, 1H, Ar–H, BP); 7.64 (t, 2H, Ar–H, BP); 7.72 (d, 2H, Ar–H); 7.69 (d, 4H, Ar–H, BP).

IR (Nujol): ν (cm^{-1}): 1745 (CO); 1270 (NO).

*5.1.9. Synthesis of 2-phenyl-3-biphenyl-5-methelene hydroxy isoxazolidine (**3a(vi)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-phenylnitrone (**2a**) (500 mg) and allyl alcohol (0.12 mL).

^{1}H-NMR δ (ppm): 2.65–2.80 (dd, 2H, H_4); 3.64 (d, 2H, CH_2); 4.76 (m, 1H, H_5); 5.14 (t, 1H, H_3); 5.25 (s, 1H, OH); 6.92 (t, 1H, Ar–H); 7.2 (t, 2H, Ar–H); 7.41 (d, 2H, Ar–H, BP); 7.52 (t, 1H, Ar–H, BP); 7.64 (t, 2H, Ar–H, BP); 7.72 (d, 2H, Ar–H); 7.69 (d, 4H, Ar–H, BP).

IR (Nujol): ν (cm^{-1}): 1710 (CO); 1242 (NO).

*5.1.10. Synthesis of 2-phenyl-3-biphenyl-5-(3-cyclohexene) isoxazolidine (**3a(vii)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-phenylnitrone (**3a**) (500 mg) and 4-vinyl-1-cyclohexene (0.25 mL).

^{1}H-NMR δ (ppm): 1.38–1.42 (m, 2H, CH_2, cyclohexene); 1.52 (s, 1H, cyclohexene); 2.27–2.31 (m, 2H, cyclohexene); 2.33–2.38 (m, 2H, cyclohexene); 2.6–2.65–2.80 (dd, 2H, H_4); 3.64 (d, 2H, CH_2); 4.76 (t, 1H, H_5); 5.14 (t, 1H, H_3); 4.82 (m, 1H, CH); 5.12 (t, 1H, CH); 5.6–5.66 (m, 2H, cyclohexene); 6.92 (t, 1H, Ar–H); 7.2 (t, 2H, Ar–H); 7.41 (d, 2H, Ar–H, BP); 7.52 (t, 1H, Ar–H, BP); 7.64 (t, 2H, Ar–H, BP); 7.72 (d, 2H, Ar–H); 7.79 (d, 4H, Ar–H, BP).

IR (Nujol): ν (cm^{-1}): 1730 (CO); 1262 (NO).

*5.1.11. Synthesis of 2-phenyl-3-biphenyl-5-methylate isoxazolidine (**3a(viii)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-phenylnitrone (**3a**) (500 mg) and methyl acrylate (0.17 mL).

^{1}H-NMR δ (ppm): 2.6–2.9 (dd, 2H, CH_2); 3.41 (s, 3H, OCH_3); 4.45 (t, 1H, CH); 5.12 (t, 1H, CH); 6.92 (t, 1H, Ar–H); 7.2 (t, 2H, Ar–H); 7.41 (d, 2H, Ar–H, BP); 7.52 (t, 1H, Ar–H, BP); 7.64 (t, 2H, Ar–H, BP); 7.72 (d, 2H, Ar–H); 7.79 (d, 4H, Ar–H, BP).

IR (Nujol): ν (cm^{-1}): 1742 (CO); 1280 (NO).

*5.1.12. Synthesis of 2-(4-methoxyphenyl)-3-biphenyl-5-cyano isoxazolidine (**3b(i)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-methoxyphenyl)nitrone (**2b**) (500 mg) and acrylonitrile (0.31 mL).

^{1}H-NMR δ (ppm): 2.82–3.0 (dd, 2H, H_4); 3.76 (s, 3H, Ar–OCH_3); 4.44 (t, 1H, H_5); 5.06 (t, 1H, H_3); 7.28 (d, 2H, Ar–H); 7.42 (d, 2H, Ar–H(BP); 7.52 (t, 1H, Ar–H(BP); 7.63 (t, 2H, Ar–H(BP); 7.68 (d, 2H, Ar–H); 7.74 (d, 4H, Ar–H(BP).

IR (Nujol): ν (cm^{-1}): 1748 (CO); 1278 (NO).

*5.1.13. Synthesis of 2-(4-methoxyphenyl)-3-biphenyl-5-phenyl isoxazolidine (**3b(ii)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl-*N*-(4-methoxyphenyl)nitrone (**2b**) (500 mg) and styrene (0.25 mL).

^{1}H-NMR δ (ppm): 2.74–2.92 (dd, 2H, H_4); 3.80 (s, 3H, Ar–OCH_3); 5.04 (t, 1H, H_5); 5.13 (t, 1H, H_3); 7.28–7.40 (m, 5H, Ar–H); 7.28 (d, 2H, Ar–H); 7.68 (d, 2H, Ar–H); 7.42 (d, 2H, Ar–H(BP); 7.54 (t, 1H, Ar–H(BP); 7.64 (t, 2H, Ar–H(BP); 7.72 (d, 4H, Ar–H(BP).

IR (Nujol): ν (cm^{-1}): 1712 (CO); 1246 (NO).

*5.1.14. Synthesis of 2-(4-methoxyphenyl)-3-biphenyl-5-benzoate isoxazolidine (**3b(iii)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-methoxyphenyl)nitrone (**2b**) (500 mg) and vinyl benzoate (0.26 mL).

^{1}H-NMR δ (ppm): 2.74–2.92 (dd, 2H, H_4); 3.78 (s, 3H, Ar–OCH_3); 4.74 (t, 1H, H_5); 5.14 (t, 1H, H_3); 7.26–7.50 (m, 3H, Ar–H); 7.28 (d, 2H, Ar–H); 7.63 (t, 2H, Ar–H(BP) 7.70 (d, 2H, Ar–H); 7.42 (d, 2H, Ar–H(BP); 7.52 (t, 1H, Ar–H(BP); 7.68 (d, 2H, Ar–H); 7.74 (d, 4H, Ar–H(BP).

IR (Nujol): ν (cm^{-1}): 1752 (C=O); 1732 (CO); 1270 (NO).

*5.1.15. Synthesis of 2-(4-methoxyphenyl)-3-biphenyl-5-ethylate isoxazolidine (**3b(iv)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl-*N*-(4-methoxyphenyl)nitrone (**2b**) (500 mg) and ethyl acrylate (0.17 mL).

^{1}H-NMR δ (ppm): 0.94 (t, 3H, CH_3); 2.68–2.85 (dd, 2H, H_4); 3.62 (q, 2H, CH_2); 3.78 (s, 3H, Ar–OCH_3); 4.45 (t, 1H, H_5); 5.13 (t, 1H, H_3); 7.28 (d, 2H, Ar–H); 7.42 (d, 2H, Ar–H(BP); 7.52 (t, 1H, Ar–H(BP); 7.63 (t, 2H, Ar–H(BP); 7.68 (d, 2H, Ar–H); 7.74 (d, 4H, Ar–H(BP).

IR (Nujol): ν (cm^{-1}): 1726 (C=O); 1708 (CO); 1240 (NO).

*5.1.16. Synthesis of 2-(4-methoxyphenyl)-3-biphenyl-5-methylene acetate isoxazolidine (**3b(v)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-methoxyphenyl)nitrone (**2b**) (500 mg) and allyl acetate (0.23 mL).

^{1}H-NMR δ (ppm): 2.42 (d, 2H, CH_2); 2.67–2.85 (dd, 2H, H_4); 3.42 (s, 3H, OCH_3); 3.76 (s, 3H, Ar–OCH_3); 4.26 (t, 1H, H_5); 5.12 (t, 1H, H_3); 7.26 (d, 2H, Ar–H); 7.42 (d, 2H, Ar–H(BP); 7.50 (t, 1H, Ar–H(BP); 7.62 (t, 2H, Ar–H(BP); 7.68 (d, 2H, Ar–H); 7.70 (d, 4H, Ar–H(BP).

IR (Nujol): ν (cm^{-1}): 1720 (CO); 1250 (NO).

*5.1.17. Synthesis of 2-(4-methoxyphenyl)-3-biphenyl-5metylene hydroxy isoxazolidine (**3b(vi)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-methoxyphenyl)nitrone (**2b**) (500 mg) and allyl alcohol (0.24 mL).

^{1}H-NMR δ (ppm): 2.66–2.84 (dd, 2H, H_4); 3.63 (d, 2H, CH_2); 3.78 (s, 3H, Ar–OCH_3); 4.74 (t, 1H, H_5); 5.12 (t, 1H, H_3); 5.25 (s, 1H, OH); 7.26 (d, 2H, Ar–H); 7.42 (d, 2H, Ar–H(BP); 7.52 (t, 1H, Ar–H(BP); 7.63 (t, 2H, Ar–H(BP); 7.68 (d, 2H, Ar–H); 7.74 (d, 4H, Ar–H(BP).

IR (Nujol): ν (cm^{-1}): 1728 (CO); 1262 (NO).

*5.1.18. Synthesis of 2-(4-methoxyphenyl)-3-biphenyl-5-(3-cyclohexene) isoxazolidine (**3b(vii)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-methoxyphenyl)nitrone (**2b**) (500 mg) and 4-vinyl-1-cyclohexene (0.21 mL).

^{1}H-NMR δ (ppm): 1.37–1.41 (m, 2H, CH_2, cyclohexene); 1.52 (s, 1H, cyclohexene); 2.26–2.30 (m, 2H, cyclohexene); 2.32–2.36 (m, 2H, cyclohexene); 2.68–2.86 (dd, 2H, H_4); 3.76 (s, 3H, Ar–OCH_3) 4.82 (m, 1H, H_5); 5.12 (t, 1H, H_3); 5.60–5.68 (m, 2H, cyclohexene); 7.28 (d, 2H, Ar–H); 7.42 (d, 2H, Ar–H, BP); 7.52 (t, 1H, Ar–H, BP); 7.63 (t, 2H, Ar–H, BP); 7.68 (d, 2H, Ar–H); 7.79 (d, 4H, Ar–H, BP).

IR (Nujol): ν (cm^{-1}):1744 (CO); 1270 (NO).

*5.1.19. Synthesis of 2-(4-methoxyphenyl)-3-biphenyl-5-methylate isoxazolidine (**3b(viii)**)*

This was obtained from equimolar mixture of *C*-(4-biphenyl-*N*-(4-methoxyphenyl)nitrone (**2b**) (500 mg) and methyl acrylate (0.17 mL).

^{1}H-NMR δ (ppm): 2.66–2.84 (dd, 2H, H_4); 3.42 (s, 3H, OCH_3); 3.80 (s, 3H, Ar–OCH_3); 4.44 (t, 1H, H_5); 5.14 (t, 1H, H_3); 7.28 (d, 2H, Ar–H); 7.42 (d, 2H, Ar–H, BP); 7.52 (t, 1H, Ar–H, BP); 7.63 (t, 2H, Ar–H, BP); 7.68 (d, 2H, Ar–H); 7.79 (d, 4H, Ar–H, BP).

IR (Nujol): ν (cm^{-1}): 1726 (C=O); 1708 (CO); 1240 (NO).

*5.1.20. Synthesis of 2-(4-fluorophenyl)-3-biphenyl-5-cyano isoxazolidines (**3c(i)**)*

It was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-fluorophenyl)nitrone (**2c**) (500 mg) and acrylonitrile (0.30 mL).

^{1}H-NMR 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).

IR (Nujol): ν (cm^{-1}): 1734 (CO); 1274 (NO).

*5.1.21. Synthesis of 2-(4-fluorophenyl)-3-biphenyl-5-phenyl isoxazolidines (**3c(ii)**)*

It was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-fluorophenyl)nitrone (**2c**) (500 mg) and styrene (0.25 mL).

^{1}H-NMR 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).

IR (Nujol): ν (cm^{-1}): 1700 (CO); 1240 (NO).

*5.1.22. Synthesis of 2-(4-fluorophenyl)-3-biphenyl-5-benzoate isoxazolidines (**3c(iii)**)*

It was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-fluorophenyl)nitrone (**2c**) (500 mg) and vinyl benzoate (0.15 mL).

^{1}H-NMR 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).

IR (Nujol): ν (cm^{-1}): 1738 (C=O); 1730 (CO); 1268 (NO).

*5.1.23. Synthesis of 2-(4-fluorophenyl)-3-biphenyl-5-ethylate isoxazolidines (**3c(iv)**)*

It was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-fluorophenyl)nitrone (**2c**) (500 mg) and ethyl acrylate (0.21 mL).

^{1}H-NMR 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).

IR (Nujol): ν (cm^{-1}): 1722 (C=O); 1700 (CO); 1232 (NO).

*5.1.24. Synthesis of 2-(4-fluorophenyl)-3-biphenyl-5-methylene acetate isoxazolidines (**3c(v)**)*

It was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-fluorophenyl)nitrone (**2c**) (500 mg) and allyl acetate (0.1 mL).

^{1}H-NMR 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).

IR (Nujol): ν (cm^{-1}): 1740 (CO); 1266 (NO).

*5.1.25. Synthesis of 2-(4-fluorophenyl)-3-biphenyl-5-methylene hydroxy isxazolidine (**3c(vi)**)*

It was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-fluorophenyl)nitrone (**2c**) (500 mg) and allyl alcohol (0.15 mL).

^{1}H-NMR 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).

IR (Nujol): ν (cm^{-1}): 1720 (CO); 1248 (NO).

*5.1.26. Synthesis of 2-(4-fluorophenyl)-3-biphenyl-5-(3-cyclohexene) isoxazolidines (**3c(vii)**)*

It was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-fluorophenyl)nitrone (**2c**) (500 mg) and 4-vinyl-1-cyclohexene (0.25 mL).

^{1}H-NMR 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).

IR (Nujol): ν (cm^{-1}): 1730 (CO); 1260 (NO).

*5.1.27. Synthesis of 2-(4-fluorophenyl)-3-biphenyl-5-ethyl isoxazolidines (**3c(viii)**)*

It was obtained from equimolar mixture of *C*-(4-biphenyl)-*N*-(4-fluorophenyl)nitrone (**2c**) (500 mg) and methyl acrylate (0.35 mL).

^{1}H-NMR 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).

IR (Nujol): ν (cm^{-1}): 1745 (CO); 1278 (NO).

5.2. Determination of antifungal activity

Fungus used for the antifungal activity: *Aspergillus flavus* (ATCC76087) *Fusarium moniliforme* (ATCC5342) *Botrydiplodia theobromae* (ATCC76087)

The isoxazolidines were tested for antifungal activity by serial tube dilution technique [13,14] at different concentrations (0.5, 1, 1.5, ..., 12 mM) against *A. flavus*, *F. moniliforme* and *B. theobromae*. Nystatin 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 0.001 mL. After incubating all the tubes at 37 °C for 24 h, their absorbance was recorded at 640 nm along with Nystatin. Percentage of inhibition was calculated as by the following equation,

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

where P = absorbance without the test sample and Q = absorbance with test sample.

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