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Investigations of regio- and stereoselectivities in the synthesis of cytotoxic isoxazolidines through 1,3-dipolar cycloadditions of nitrones to dipolarophiles bearing an allylic oxygen

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Abstract—Regio- and stereoselectivities in cycloadditions of nitrones to dipolarophiles bearing an allylic oxygen, which furnishes substituted-isoxazolidine analogs of the furanose ring of nucleosides, have been investigated. Although the obtained regioselectivities are anticipated, a rationalization of the preferred formation of *endo*-cycloadducts necessitates the involvement of an allylic oxygen in secondary interaction. The obtained isoxazolidines display cytotoxic activities against a number of human cancer cell lines.

1. Introduction

There has been an ever-increasing quest for modified nucleosides due to their potential applications in antiviral and anticancer therapies.[1] In a recent approach to modified nucleosides, the furanose ring has been replaced by other heterocyclic analogs.[2] Among these N and O containing five-membered heterocycles, isoxazolidines, and isoxazoline derivatives have emerged as important candidates, and have been shown to display useful anticancer and antiviral properties.[3] It is pertinent to mention here that substituted isoxazolidines have been known to display cytotoxicity as in the case of alkaloids such as pyrinodemin-A and isoxazolidinium salts employed in the therapy of malignant tumors (Fig. 1).[4]

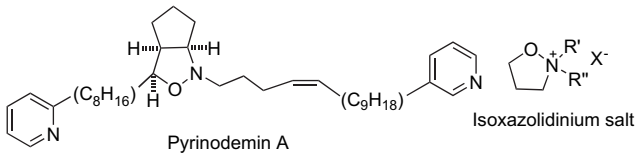
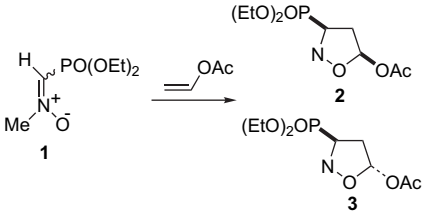


Figure 1.

Consequently, synthetic studies on isoxazolidines have drawn considerable attention and 1,3-dipolar cycloadditions of nitrones afford the most straightforward route to isoxazolidines. For instance, in one of the approaches, nitrophosphonate **1** has been reacted with vinyl acetate to obtain a mixture of epimeric isoxazolidines **2** and **3** (Scheme 1), which have been utilized as precursors to the synthesis of reverse-transcriptase inhibitors.[1e]



Scheme 1.

The formation of epimeric products is the outcome of two different approaches of the dipole to the dipolarophile. In the above example (Scheme 1), with the nitrone reacting in its most stable *Z*-form, the cis-product **2** arises from an *exo*-transition state and the trans-product **3** from an *endo*-transition state; the *exo*-adduct **2** was reported to be the major product.[1e] Similar predominance of an *exo*-adduct has also been reported in the addition of α-(2-pyridyl)-*N*-benzylnitrone to allyl alcohol.[2c] A variety of secondary factors have

Keywords: Cycloadditions; Nitrone; Stereoselectivities; Secondary interactions; Isoxazolidines; Anticancer activity.
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been invoked to explain stereoselectivities in 1,3-dipolar cycloadditions.[5] The predominant occurrence of *endo* selectivity in the cycloaddition reactions has generally been attributed to the role of secondary orbital interactions (SOI) or some secondary interactions (SI), however, contribution of such interactions is disputed and recently it has been contended that the existence of such SOI/SI is negated by closed-shell repulsions.[5a,c] However, more recent calculations favor the existence of such interactions in controlling stereoselectivity.[6] Consequently, the importance of secondary interactions in controlling stereoselectivities is far from settled. Recently, the involvement of oxygen atoms at allylic and homo-allylic positions in secondary interactions with LUMO-dipole has been reported to control the stereochemical outcome of nitrone addition to such dipolarophiles leading to the predominance of *endo*-adducts,[5d,e] which is in contradiction with the stereoselectivities reported in the nitrone cycloadditions discussed above.[1e,2c] We have investigated stereoselectivities in 1,3-dipolar cycloadditions of a variety of α-aryl-*N*-phenylnitrones with a number of dipolarophiles possessing oxygen at the allylic position so as to investigate the proposed involvement of allylic oxygen in secondary interactions with nitrogen of the nitrone and the obtained substituted isoxazolidines have also been evaluated for cytotoxic activity against a number of human cancer cells lines.

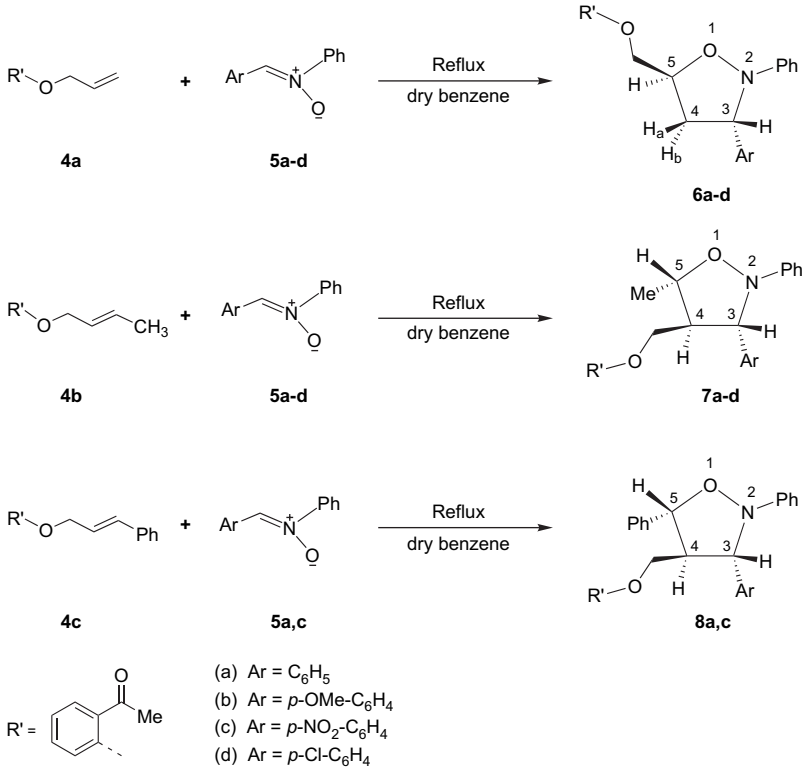
2. Results and discussion

Initially, cycloadditions of nitrones **5a–d** (prepared by the reaction of phenylhydroxylamine with the corresponding aldehydes and characterized spectroscopically), with *o*-allyloxy-/crotyloxy-/cinnamyloxy-acetophenones **4a–c** were carried out by refluxing (30–35 h) their equimolar solutions in dry benzene. After the completion of reactions (TLC), column chromatography afforded the isoxazolidines **6a–d**, **7a–d**, and **8a**,**c** (Scheme 2 and Table 1). The obtained isoxazolidines were characterized spectroscopically. The observed regio- and stereochemical outcomes of these cycloadditions were delineated by detailed NMR spectroscopic analyses involving extensive ^{1}H-decoupling experiments and establishing ^{1}H–^{1}H and ^{1}H–^{13}C connectivities by 2D NMR techniques.

The formation of the cycloadducts was established by the ^{1}H NMR and Mass spectra. The assigned regiochemistry of addition in the case of (**6a–d**) is based, besides ^{1}H NMR spectra, on the presence of two methine (*C*H–) resonances, one in the range of δ 69–70 (C3) and the other in the range

Table 1. Reaction times and yields of the products from cycloadditions of nitrones **5a–d** with dipolarophiles **4a–c**

Entry	Dipolarophile	Nitrone	Reaction time (h)	% Yields of adducts		
				6	**7**	**8**
1	**4a**	**5a**	30	65	—	—
2	**4a**	**5b**	32	63	—	—
3	**4a**	**5c**	30	70	—	—
4	**4a**	**5d**	35	60	—	—
5	**4b**	**5a**	32	—	64	—
6	**4b**	**5b**	33	—	62	—
7	**4b**	**5c**	31	—	68	—
8	**4b**	**5d**	35	—	60	—
9	**4c**	**5a**	33	—	—	65
10	**4c**	**5c**	31	—	—	67



Scheme 2.

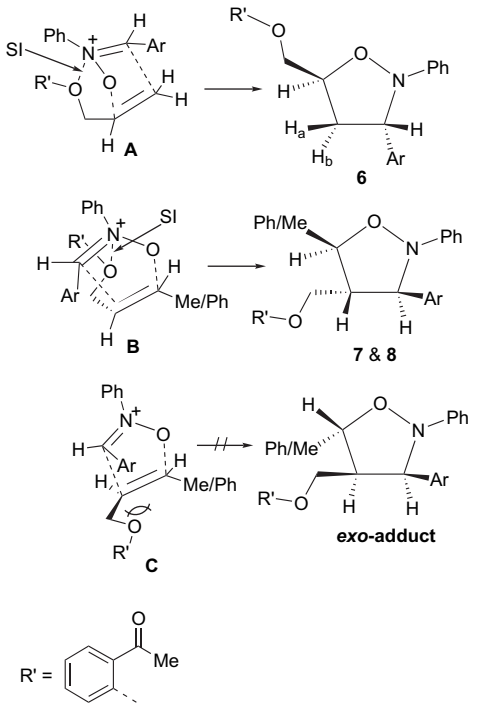


Figure 2.

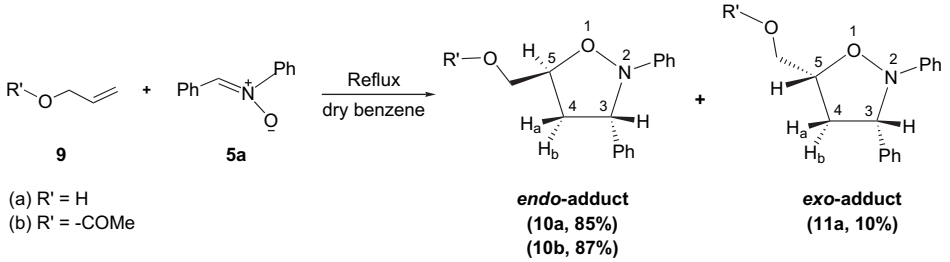
of δ 76–77 (C5). Another resonance of an oxygen-linked carbon (CH_2) appeared in the range of δ 68–70 (R′–O–*C*H_2–). The ^{1}H NMR spectrum of **6c** revealed the –C*H*$_2$–O– protons as double doublet at δ 4.28 (J=10.1, 6.4 Hz) and double doublet δ 4.11 (J=10.1, 4.5 Hz) and C3–H resonance as a dd at δ 4.97 (J=8.1, 6.5 Hz), and ^{1}H multiplet at δ 4.76 (C5–H). The C4–Hs of the isoxazolidine ring appeared as two separate ddds at δ 2.28 (J_{gem}=12.3 and J=8.2, 6.5 Hz, C4–H_b) and δ 3.05 (J_{gem}=12.3 and J=8.2, 7.3 Hz, C4–H_a). The assigned stereochemical dispositions are based on J values and ^{1}H-connectivities worked out from decoupling experiments, and derived from the basic premise that cis vicinal ^{1}H couplings are always higher than the trans in the case of isoxazolidines.[7] For instance, in **6c** the values of coupling constants $J_{5,4a}$=7.3 Hz, $J_{5,4b}$=8.2 Hz indicate that C5–H is cis to the C4–H_b and $J_{3,4a}$=8.1 Hz, $J_{3,4b}$=6.5 Hz allude to trans relationship between C3–H and C4–H_b, thereby, establishing that both C5–H and C3–H are trans to each other.

The regio- and stereochemical assignments in the case of **7a–d** and **8a**,**c** have been similarly achieved. Thus, the ^{1}H NMR spectrum of **7c** revealed, besides the resonances in the aromatic region, the presence of a doublet at δ 4.14 (2H, J=5.2 Hz, –OCH_2), a resonance δ 4.86 (d, J=6.5 Hz, C3–H), and a 1H doublet of quartet at δ 4.34 (J=8.6, 6.2 Hz, C5–H); the chemical shift value of C5–H was critical for the assigned regiochemistry of addition. A 1H multiplet at δ 2.70 was due to C4–H and the C5–Me was located as a 3H doublet at δ 1.51 (J=6.2 Hz). The characteristic features of its ^{13}C NMR were the presence of methine carbons of the isoxazolidine ring δ 77.0 (C5), δ 72.7 (C3), δ 61.1 (C4), besides, –O*C*H_2 at δ 66.8 and the carbonyl carbon resonance at δ 198.7. Stereochemically, the substituent at C4 and the methyl at C5 have to be trans because of the concerted nature of nitrone cycloaddition. Again, the obtained coupling constant value $J_{3,4}$=6.5 Hz is lower than the value of coupling constants $J_{5,4}$=8.6 Hz for a trans relationship between C5–H and C4–H, thereby, signifying that C3–H is also trans to C4–H.

The investigations have clearly established that the regiochemistry of addition of nitrones to *o*-allyloxyacetophenone, leading to isoxazolidines **6a–d**, is different from addition to *o*-crotyloxy/cinnamyloxy-acetophenones, the latter affording isoxazolidines **7a–d** and **8a**,**c** and these regiochemical variations are anticipated.[8] The stereochemical outcomes of the cycloadditions in all the cases are derived from an *endo*-mode of addition as far as the –CH_2–O–R′ moiety is concerned, involving the *Z*-isomers of nitrones (Fig. 2). Thus, addition of nitrone in its *Z*-form[8,9] to *o*-allyloxy-/crotyloxy-/cinnamyloxy-acetophenones involves an *endo*-transition state, possibly stabilized by recently proposed[5d,e] secondary interaction involving allylic oxygen (**A** and **B**, Fig. 2) and N of dipole and/or avoidance of steric encumbrance, particularly, in the case of addition to *o*-crotyloxy-/cinnamyloxy-acetophenones, with altered regiochemistry (**C**).

In order to further investigate the observation of complete *endo* selectivity in the above cycloadditions and to substantiate the possible role of the secondary orbital interactions and steric factors, the investigations were extended to the cycloadditions of nitrones to dipolarophiles such as allyl alcohol and allyl-acetate **9a**,**b**. Here, two stereoisomers i.e., *endo*- (**10a**, major product) and *exo*-adduct **11a** were isolated from α,*N*-diphenylnitrone addition to allyl alcohol and only *endo*-adduct **10b** was obtained in the case of nitrone addition to allyl-acetate (Scheme 3).

The assigned stereochemistry in the case of **10a**,**b** and **11a** are based on the determination of vicinal coupling constants (Table 2). Thus, in the case of **10a** the values of coupling constants $J_{5,4a}$=7.2 Hz, $J_{5,4b}$=7.8 Hz indicate that C5–H is cis to the C4–H_b and $J_{3,4a}$=7.8 Hz, $J_{3,4b}$=5.4 Hz allude to a trans relationship between C3–H, and C4–H_b, thereby, establishing that both C5–H and C3–H are trans to each other.



Scheme 3.

Table 2. Some critical coupling constant values in isoxazolidines **10a**,**b** and **11a**

Compound	Coupling constant values (Hz)			
	J_{3H-4Ha}	J_{3H-4Hb}	J_{5H-4Ha}	J_{5H-4Hb}
10a	7.8	5.4	7.2	7.8
10b	7.8	5.1	7.2	8.1
11a	8.7	6.1	6.9	6.5

But in case of **11a** the values of coupling constants $J_{5,4a}$=6.9 Hz, $J_{5,4b}$=6.5 Hz indicate that C5–H is cis to the C4–H_a and $J_{3,4a}$=8.7 Hz, $J_{3,4b}$=6.1 Hz establish that C3–H is also cis to the C4–H_a, thereby, both C5–H and C3–H are cis to each other. Critical ^{1}H couplings in the case of **10b** (Table 2) establish its structure as an *endo*-cycloadduct.

It appears that both steric factors and secondary interactions may be important in determining the sterochemical outcome. Thus, in the case of addition to allyl alcohol the involvement of proposed[5d,e] secondary interaction involving allylic oxygen leads to preferred formation of an *endo*-adduct **10a** with an *exo* isomer **11a** as the minor product. Secondary interaction coupled with steric encumbrance in the cycloadditions to allyl-acetate may be responsible for the preferred formation of *endo*-adduct **10b**. In these cycloadditions, the regiochemistry of addition of nitrone to dipolarophiles **9a**,**b** is similar to that obtained in the case of allyloxyacetophenone derived isoxazolidines **6a–d**. It is pertinent to mention here that in the reported formation of *exo*-adducts in the addition of α-(2-pyridyl)-*N*-butyl nitrone to allyl alcohol, no discussion of the NMR spectroscopic data was recorded and also the reported[2c] chemical shifts pattern for C3–H and C5–H is different i.e., C5–H is located downfield (δ 4.49 for *exo*-adduct and δ 4.28 for *endo*-adduct) than C3–H (δ 4.19 for *endo*- and δ 4.11 for *exo*-adduct),[2c] which is in reverse order as far as data recorded for various adducts in the present investigations. Even the theoretical calculations in the above report[2c] did not validate the experimental results. The present findings, on the other hand, are in consonance with the *endo* selectivity observed in the additions of nitrones, including some rigid ones, to dipolarophiles bearing allylic and homo-allylic oxygen.[5d,e]

3. Biological activity

The in vitro inhibitory potential of the obtained isoxazolidines **6–8** was evaluated using eight human cancer cell lines,[10] representing different organs/tissues, according to the method of Skehan et al.[10b] as reported previously.[11] The cytotoxicity was determined at 1×10^{-4}, 1×10^{-5}, and 1×10^{-6} M. Mitomycin C, Paclitaxel, and 5-Fluorouracil were used as the positive controls (1×10^{-5} M, Table 3). The isoxazolidines **6–8** exhibited a dose dependent cell

Table 3. In vitro cytotoxicity of isoxazolidines (**6a–d**, **7a**,**c**,**d**, and **8a**,**c**) against human cancer cell lines[10a]

Compounds/standard drugs	Concn (M)	% Growth inhibition against human cancer cell lines							
		HT-29 (colon)	SW-620 (colon)	DU-145 (prostate)	KB (oral)	Hep-2 (liver)	MCF-7 (breast)	A-549 (lung)	HOP-62 (lung)
6a	1×10^{-6}	0	0	22	15	12	9	4	0
	1×10^{-5}	0	2	39	21	19	22	18	0
	1×10^{-4}	33	21	43	*54*	44	45	43	0
6b	1×10^{-6}	32	—	19	1	—	—	0	—
	1×10^{-5}	30	—	30	12	—	—	0	—
	1×10^{-4}	*50*	—	42	0	—	—	0	—
6c	1×10^{-6}	1	0	9	5	9	13	19	0
	1×10^{-5}	19	0	14	7	22	28	27	0
	1×10^{-4}	22	0	19	2	32	38	18	1
6d	1×10^{-6}	0	0	22	22	8	10	0	0
	1×10^{-5}	14	0	22	35	21	28	1	0
	1×10^{-4}	34	4	36	*52*	41	42	*50*	5
7a	1×10^{-6}	44	0	22	0	11	11	28	1
	1×10^{-5}	*57*	0	25	0	29	26	30	0
	1×10^{-4}	*64*	10	32	0	*59*	*51*	33	7
7c	1×10^{-6}	5	0	0	0	17	9	25	2
	1×10^{-5}	18	0	5	5	30	26	32	2
	1×10^{-4}	39	22	0	4	46	38	34	6
7d	1×10^{-6}	10	—	19	10	—	—	26	—
	1×10^{-5}	42	—	21	8	—	—	30	—
	1×10^{-4}	*50*	—	*59*	4	—	—	*51*	—
8a	1×10^{-6}	0	0	*58*	11	14	9	8	0
	1×10^{-5}	20	8	*59*	0	28	29	7	0
	1×10^{-4}	36	17	*61*	0	40	37	40	0
8c	1×10^{-6}	3	0	13	0	14	9	28	0
	1×10^{-5}	8	0	18	36	23	20	35	0
	1×10^{-4}	*43*	32	19	0	*40*	*42*	38	0
Mitomycin C	1×10^{-5}	31	90	89	90	88	93	80	70
Paclitaxel	1×10^{-5}	—	—	85	86	—	—	63	—
5-Flourouracil	1×10^{-5}	34	8	—	—	12	31	—	3

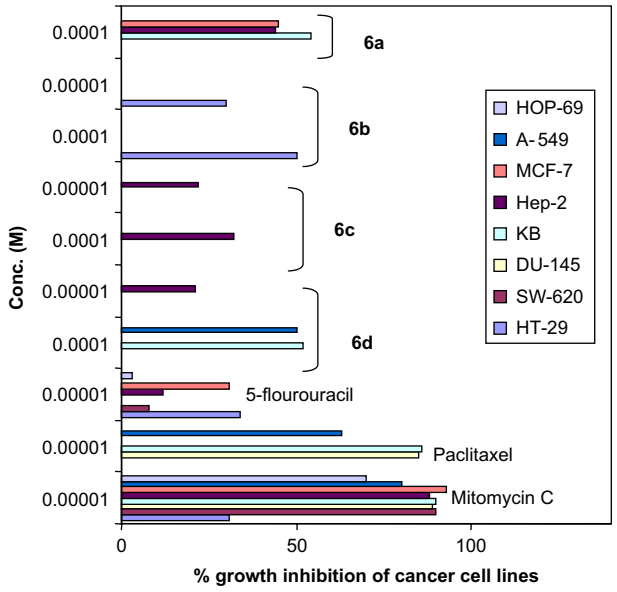


Figure 3. Cytotoxic activity of compounds **6a**–**d**.

line specific cytotoxic potential. The results of these investigations are shown in the Table 3 and in Figures 3–5. In the case of isoxazolidines **6a**–**d**, the maximum growth inhibition of 54% (**6a**, KB, 1×10^{-4} M) was followed by 52% (**6d**, KB, 1×10^{-4} M) and 50% (**6b**, HT-29 and **6d**, A-549, 1×10^{-4} M). The data indicate that **6a**,**b** and **d** are more active than **6c**. In case of isoxazolidines **7a**,**c** and **d**, at 1×10^{-5} M the maximum effect of 57% (**7a**, HT-29) was observed, whereas at 1×10^{-4} M the maximum effect of 64% (**7a**, HT-29) was followed by 59% (**7a**, Hep-2 and **7d**, DU-145), 51% (**7a**, MCF-7 and **7d**, A-549), and 50% (**7d**, HT-29) indicating that **7a** is most active among **7a**,**c** and **d**. In case of isoxazolidines **8a** and **c**, a maximum effect of 61% was observed with **8a** (DU-145) and the same compound also showed 59% and 58% growth inhibition at lower concentrations against the same cell line. It is worth mentioning here that the activities of some of the isoxazolidines were

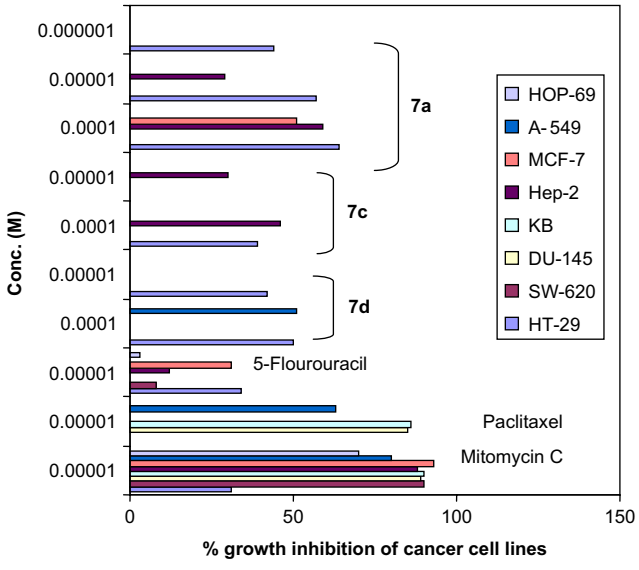


Figure 4. Cytotoxic activity of compounds **7a**,**c**,**d**.

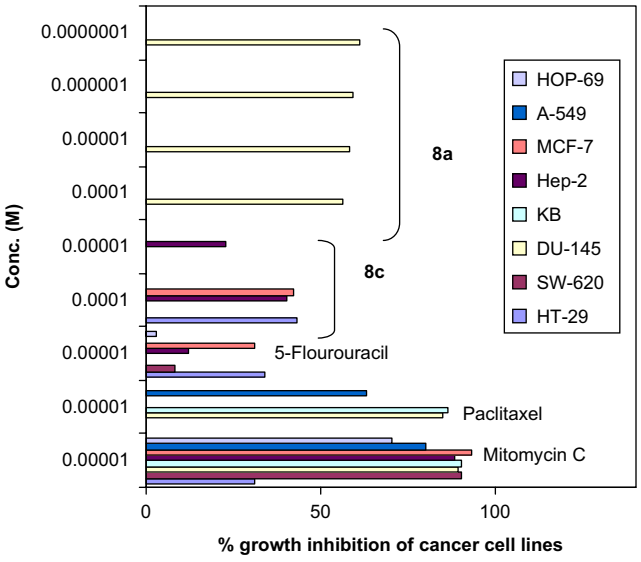


Figure 5. Cytotoxic activity of compounds **8a**,**c**.

well comparable to the known anticancer drugs used as positive controls. These isoxazolidines have been found to be inactive against lung cell line (HOP-62) at all the concentrations employed.

4. Experimental

4.1. General information

Starting materials and reagents were purchased from commercial suppliers and used after further purification (crystallization/distillation). Bruker AC-200FT (200 MHz) and JEOL AL-300FT (300 MHz) spectrometers were used to record ^{1}H NMR and ^{13}C NMR (50 and 75 MHz) spectra. Chemical shifts (δ) are reported as downfield displacements from TMS used as an internal standard and coupling constants (J) are reported in Hertz. IR spectra were recorded with Shimadzu DR-2001 FT-IR spectrophotometer on KBr pellets. Mass spectra, EI and ESI-methods, were recorded on Shimadzu GCMS-QP-2000A and Bruker Daltonics Esquire 300 mass spectrometers, respectively. The high-resolution mass spectra (HRMS) were measured on a Finnigan MAT 8200 spectrometer. Elemental analyses were carried out on a Perkin–Elmer 240C elemental analyzer and are reported in percent atomic abundance. All melting points are uncorrected and measured in open glass-capillaries on a Veego MP-D digital melting point apparatus.

4.2. General procedure for cycloaddition of nitrones (5a–d) with dipolarophiles (4a–c)

Solution of nitrones (**5a**–**d**, 200 mg, prepared by the reaction of phenylhydroxylamine with the corresponding aldehydes and characterized spectroscopically), and *o*-allyloxy-/crotyloxy-/cinnamyloxy-acetophenones (**4a**–**c**, 1.0 molar equivalent, respectively) in dry benzene (20 mL) was refluxed with stirring for 30–35 h. After the completion of the reactions (TLC), solvent was distilled off and the traces of solvent were removed under vacuum. The obtained crude product mixtures were subjected to column chromatographic resolution

over silica gel (Acme Synthetic Chemicals Mumbai, India, 60–120 mesh, 20 g, column packed in hexane) using hexane–chloroform (gradient) as an eluant to obtain pure isoxazolidines (**6a–d**, **7a–d**, and **8a**,**c**), whose physical and spectroscopic data are as follows.

4.2.1. *o*-(2,3-Diphenyl-isoxazolidin-5-yl)methoxy-acetophenone, 6a. White crystals (260 mg, 65%; benzene–chloroform 4:1), mp 56–57 °C; ν_{max} (KBr) 1673, 1597, 1487, 1451, 1360, 1296 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.78 (dd, 1H, *J*=8.6, 1.4 Hz, arom.–*H*), 7.53–7.22 (m, 8H, arom.–*H*s), 7.04–6.90 (m, 5H, arom.–*H*s), 4.98–4.69 (dd at δ 4.82, *J*=6.5, 8.2 Hz, C3–H, overlapping a 1H multiplet, C5–*H*), 4.20 (dd, 1H, J_{gem}=10.1, 6.4 Hz, –OC*H*H), 4.10 (dd, 1H, J_{gem}=10.1, 4.5 Hz, –OCH*H*), 3.03 (ddd, 1H, *J*=7.3, 8.2, 12.3 Hz, C4–H_a), 2.71 (s, 3H, –COCH_3), 2.34 (ddd, 1H, *J*=6.5, 8.3, 12.3 Hz, C4–H_b); δ_C ($CDCl_3$, 50 MHz) 198.9 (C=O), 157.8 (q), 151.4 (q), 142.0 (q), 133.5 (CH), 130.7 (CH), 128.9 (CH), 128.6 (q), 127.6 (CH), 126.3 (CH), 122.1 (CH), 121.2 (CH), 114.8 (CH), 112.4 (CH), 76.3 (C3), 70.1 (C5), 69.3 (OCH_2), 42.7 (C4), 32.1 (–COCH_3); MS *m*/*z* (%): 373 (M^+, 20), 181 (33), 77 (100); Anal. Calcd for $C_{24}H_{23}NO_3$ requires: C, 77.19; H, 6.21; N, 3.75 and found: C, 77.08; H, 6.40; N, 3.89.

4.2.2. *o*-(2-Phenyl-3-*p*-anisyl-isoxazolidin-5-yl)methoxy-acetophenone, 6b. White crystals (252 mg, 63%; benzene–chloroform 4:1), mp 68–69 °C; ν_{max} (KBr) 1668, 1594, 1512, 1486, 1449, 1364, 1297 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.75 (dd, 1H, *J*=7.7, 1.8 Hz, arom.–*H*s), 7.46–7.35 (m, 4H, arom.–*H*s), 7.32–7.09 (m, 4H, arom.–*H*s), 7.04–6.85 (m, 4H, arom.–*H*s), 4.78–4.66 [overlapping dd (at δ 4.70, 1H, *J*=6.5, 8.2 Hz, C3–*H*) and multiplet, 1H, C5–*H*], 4.34 (dd, 1H, J_{gem}=10.1 and *J*=6.4 Hz, –OC*H*H), 4.14 (dd, 1H, J_{gem}=10.1, 4.5 Hz, –OCH*H*), 3.81 (s, 3H, –OCH_3), 2.91 (ddd, 1H, *J*=7.3, 8.2, 12.3 Hz, C4–H_a), 2.68 (s, 3H, –COCH_3), 2.31 (ddd, 1H, *J*=6.5, 8.2, 12.3 Hz, C4–H_b); δ_C ($CDCl_3$, 50 MHz) 198.8 (*C*=O), 158.9 (q), 157.8 (q), 151.5 (q), 133.8 (q), 133.6 (CH), 130.6 (CH), 128.8 (CH), 128.3 (q), 127.4 (CH), 122.0 (CH), 121.0 (CH), 114.9 (CH), 114.2 (CH), 112.4 (CH), 76.2 (C3), 69.7 (C5), 69.2 (–OCH_2), 55.1 (–OCH_3), 42.6 (C4), 32.1 (–COCH_3); MS *m*/*z* (%): 404 (M^++1, 16), 403 (M^+, 42), 211 (33), 77 (47), 70 (49), 58 (100); Anal. Calcd for $C_{25}H_{25}NO_4$ requires: C, 74.42; H, 6.25; N, 3.47 and found: C, 74.29; H, 6.34; N, 3.61.

4.2.3. *o*-(2-Phenyl-3-*p*-nitrophenyl-isoxazolidin-5-yl)-methoxy-acetophenone, 6c. White crystals (280 mg, 70%; benzene–chloroform 4:1), mp 117–118 °C; ν_{max} (KBr) 1673, 1596, 1511, 1487, 1450, 1384, 1346, 1297 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 8.22 (d, 2H, *J*=8.6 Hz, arom.–*H*s), 7.73–7.64 (m, 3H, arom.–*H*s), 7.37 (t, 1H, *J*=7.8 Hz, arom.–*H*), 7.29–7.17 (m, 2H, arom.–*H*s), 7.05–6.87 (m, 5H, arom.–*H*s), 4.97 (dd, 1H, *J*=6.5, 8.1 Hz, C3–*H*), 4.80–4.72 (m, 1H, *J*=4.5, 7.3, 8.2 Hz, C5–*H*), 4.28 (dd, 1H, J_{gem}=10.1, 6.4 Hz, –OC*H*H), 4.11 (dd, 1H, J_{gem}=10.1, 4.5 Hz, –OCH*H*), 3.08 (ddd, 1H, *J*=7.3, 8.1, 12.3 Hz, C4–H_a), 2.63 (s, 3H, –COCH_3), 2.28 (ddd, 1H, *J*=6.5, 8.2, 12.3 Hz, C4–H_b); δ_C ($CDCl_3$, 50 MHz) 198.9 (C=O), 157.5 (q), 150.7 (q), 149.6 (q), 147.3 (q), 133.5 (CH), 130.4 (CH), 129.1 (CH), 128.5 (q), 127.1 (CH), 124.0 (CH), 122.5 (CH), 121.2 (CH), 114.5 (CH), 112.5 (CH), 76.6 (C3), 69.2 (C5), 68.8 (–OCH_2), 41.9 (C4), 31.9 (–COCH_3); MS *m*/*z* (%): 418 (M^+, 30), 70 (44), 58 (100); Anal. Calcd for $C_{24}H_{22}N_2O_5$ requires: C, 68.89; H, 5.30; N, 6.69 and found: C, 68.71; H, 5.45; N, 6.81.

4.2.4. *o*-(2-Phenyl-3-*p*-chlorophenyl-5-methyl-isoxazolidin-5-yl)methoxy-acetophenone, 6d. White crystals (240 mg, 60%), mp 122–123 °C; ν_{max} (KBr) 1663, 1595, 1486, 1449, 1409, 1365, 1296, 1241 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.75 (dd, 1H, *J*=7.7, 1.8 Hz, arom.–*H*), 7.73–7.20 (m, 7H, arom.–*H*s), 7.06–6.90 (m, 5H, arom.–*H*s), 4.82–4.67 (overlapping dd at δ 4.78, *J*=6.5, 8.2 Hz, C3–H and multiplet, 1H, C5–*H*), 4.23 (dd, 1H, *J*=10.1, 6.4 Hz, –OC*H*H), 4.15 (dd, 1H, *J*=10.1, 4.5 Hz, –OCH*H*), 3.05–2.92 (ddd, 1H, *J*=7.3, 8.2, 12.3 Hz, C4–H_a), 2.71 (s, 3H, –COCH_3), 2.33–2.19 (ddd, 1H, *J*=6.5, 8.8, 12.3 Hz, C4–H_b); δ_C ($CDCl_3$, 50 MHz) 198.9 (C=O), 157.6 (q), 151.1 (q), 140.6 (q), 133.5 (CH), 133.3 (q), 130.5 (CH), 128.9 (CH), 128.5 (q), 127.8 (CH), 122.2 (CH), 121.2 (CH), 114.9 (CH), 112.4 (CH), 76.3 (C3), 69.4 (C5), 69.0 (–OCH_2), 42.3 (C4), 31.9 (–COCH_3); MS *m*/*z* (%): 407 (M^+, 25), 307 (37), 267 (27), 253 (28), 252 (68), 251 (62), 171 (52), 112 (17), 105 (26), 84 (18), 83 (29), 77 (24), 71 (43), 70 (47), 69 (37), 58 (94), 57 (84), 56 (100). HRMS (FAB) *m*/*z*: Calcd mass for $C_{24}H_{22}ClNO_3$: 407.1288; found 407.1302 $(M)^+$.

4.2.5. *o*-(2,3-Diphenyl-5-methyl-isoxazolidin-4-yl)-methoxy-acetophenone, 7a. White crystals (256 mg, 64%), mp 99–100 °C; ν_{max} (KBr) 1674, 1597, 1487, 1467, 1450, 1387, 1356, 1295, 1236 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.54 (dd, 1H, *J*=7.7, 1.8 Hz, arom.–*H*), 7.46–7.09 (m, 7H, arom.–*H*s), 6.92–6.75 (m, 5H, arom.–*H*s), 4.51 (d, 1H, *J*=7.4 Hz, C3–*H*), 4.31–4.17 (dq, 1H, *J*=6.0, 8.8 Hz, C5–*H*), 4.07 (d, 2H, *J*=5.1 Hz, –OCH_2), 2.67–2.59 (m, 2H, *J*=7.4, 8.8 Hz, C4–*H*), 2.16 (s, 3H, –COCH_3), 1.46 (d, *J*=6.0 Hz, C5–CH_3); δ_C ($CDCl_3$, 50 MHz) 199.1 (C=O), 157.2 (q), 152.1 (q), 141.9 (q), 133.3 (CH), 130.4 (CH), 128.9 (q), 128.9 (CH), 128.5 (q), 127.7 (CH), 126.6 (CH), 121.5 (CH), 121.2 (CH), 114.0 (CH), 112.1 (CH), 76.9 (C5), 73.8 (C3), 66.6 (–OCH_2), 61.1 (C4), 31.2 (–COCH_3), 17.6 (C5–CH_3); MS *m*/*z* (%): 388 (M^++1, 35), 387 (M^+, 60), 182 (18), 181 (54), 180 (74), 171 (18), 136 (23), 121 (59), 104 (19), 93 (20), 91 (21), 78 (18), 77 (100), 71 (24), 70 (25), 65 (22), 58 (46), 52 (57). HRMS (FAB) *m*/*z*: Calcd mass for $C_{25}H_{25}NO_3$: 387.1834; found 387.1808 $(M)^+$.

4.2.6. *o*-(2-Phenyl-3-*p*-anisyl-5-methyl-isoxazolidin-4-yl)methoxy-acetophenone, 7b. Light brown oil (248 mg, 62%); ν_{max} (KBr) 1674, 1597, 1512, 1487, 1467, 1450, 1385, 1357, 1295, 1247 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.62 (dd, 1H, *J*=7.7, 1.8 Hz, arom.–*H*), 7.42–7.37 (overlapping doublet at δ 7.39, *J*=10.4 Hz and multiplet, 4H, arom.–*H*s), 7.23–7.14 (m, 2H, arom.–*H*s), 7.01–6.81 (m, 6H, arom.–*H*s), 4.50 (d, 1H, *J*=7.5 Hz, C3–*H*), 4.31–4.24 (dq, 1H, *J*=6.0, 8.7 Hz, C5–*H*), 4.10 (d, 2H, *J*=5.1 Hz, –OCH_2), 3.79 (s, 3H, –OCH_3), 2.70–2.62 (m, 1H, *J*=7.3, 8.7 Hz, C4–*H*), 2.22 (s, 3H, –COCH_3), 1.50 (d, *J*=6.0 Hz, C5–CH_3); δ_C ($CDCl_3$, 50 MHz) 199.1 (C=O), 159.2 (q), 157.3 (q), 152.2 (q), 133.8 (q), 133.3 (CH), 130.4 (CH), 128.8 (q), 128.9 (CH), 127.8 (CH), 121.5 (CH), 121.1 (CH), 114.4 (CH), 114.1 (CH), 112.1 (CH), 76.8 (C5), 73.6 (C3), 66.6 (–OCH_2), 61.0 (C4), 55.1 (–OCH_3), 31.3 (–COCH_3), 17.7 (C5–CH_3); MS *m*/*z* (%): 417 (M^+, 60), 211 (78), 210 (100),

136 (24), 121 (72), 93 (20), 77 (97), 71 (26), 70 (32), 66 (37), 65 (38), 58 (56), 56 (80), 53 (58). HRMS (FAB) *m/z*: Calcd mass for $C_{26}H_{27}NO_4$: 416.186; found 416.263 $(M)^+$.

4.2.7. *o*-(2-Phenyl-3-*p*-nitrophenyl-5-methyl-isoxazolidin-4-yl)methoxy-acetophenone, 7c. White crystals (272 mg, 68%), mp 86–87 °C; ν_{max} (KBr) 1688, 1674, 1597, 1516, 1487, 1470, 1448, 1383, 1348, 1292, 1231 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 8.25 (d, 2H, *J*=8.7 Hz, arom.–*H*s), 7.74 (d, 2H, *J*=8.8 Hz, arom.–*H*s), 7.62 (dd, 1H, *J*=7.7, 1.7 Hz, arom.–*H*), 7.41 (split triplet, 1H, *J*=8.5, 1.7 Hz, arom.–*H*), 7.27–7.20 (m, 2H, arom.–*H*s), 7.05 (t, 4H, *J*=7.7 Hz), 6.98–6.93 (m, 4H, arom.–*H*s), 6.87 (d, 1H, *J*=8.3 Hz, arom.–*H*s), 4.86 (d, 1H, *J*=6.5 Hz, C3–*H*), 4.34 (dq, 1H, *J*=6.1, 8.6 Hz, C5–*H*), 4.14 (d, 2H, *J*=5.2 Hz, –O*C*H_2), 2.74–2.65 (m, 1H, *J*=8.6, 6.5, 5.2 Hz, C4–*H*), 2.27 (s, 3H, –CO*C*H_3), 1.51 (d, 3H, *J*=6.2 Hz, C5–*C*H_3); δ_C ($CDCl_3$, 50 MHz) 198.7 (C=O), 156.9 (q), 151.2 (q), 149.8 (q), 147.3 (q), 133.2 (CH), 130.2 (CH), 129.1 (CH), 128.5 (q), 127.5 (CH), 124.0 (CH), 121.8 (CH), 121.3 (CH), 113.8 (CH), 112.5 (CH), 77.0 (C5), 72.7 (C3), 66.8 (–OCH_2), 61.1 (C4), 30.9 (–CO*C*H_3), 17.5 (C5–CH_3); MS *m/z* (%): 432 (M^+, 42), 195 (27), 194 (33), 169 (48), 120 (46), 111 (21), 93 (24), 83 (26), 77 (30), 71 (57), 70 (54), 69 (30), 58 (100), 56 (91); HRMS (FAB) *m/z*: Calcd mass for $C_{25}H_{24}N_2O_5$: 432.1685; found 432.1684 $(M)^+$.

4.2.8. *o*-(2-Phenyl-3-*p*-chlorophenyl-5-methyl-isoxazolidin-4-yl)methoxy-acetophenone, 7d. White crystals (240 mg, 60%), mp 83–84 °C; ν_{max} (KBr) 1671, 1597, 1520, 1486, 1450, 1397, 1350, 1294, 1228 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.86 (d, 2H, *J*=8.7 Hz, arom.–*H*s), 7.65 (dd, 1H, *J*=1.7, 6.8 Hz, arom.–*H*), 7.50–7.42 (m, 4H, arom.–*H*s), 7.33 (dd, 2H, *J*=1.2, 7.7 Hz, arom.–*H*s), 7.06 (dd, 2H, *J*=1.2, 7.4 Hz, arom.–*H*s), 6.91 (d, 2H, *J*=8.3 Hz, arom.–*H*), 4.84 (d, 1H, *J*=6.6 Hz, C3–*H*), 4.38–4.29 (dq, 1H, *J*=6.2, 8.5 Hz, –O*CH*), 4.17 (d, 2H, *J*=5.1 Hz, –O*C*H_2), 2.77–2.65 (m, 1H, *J*=6.6, 8.5 Hz, C4–*H*), 2.17 (s, 3H, –CO*C*H_3), 1.52 (d, 3H, *J*=6.2 Hz, C5–*C*H_3); δ_C ($CDCl_3$, 50 MHz) 199.2 (C=O), 158.3 (q), 151.9 (q), 149.9 (q), 147.9 (q), 134.1 (CH), 131.0 (CH), 129.5 (CH), 128.2 (q), 127.3 (CH), 124.9 (CH), 123.0 (CH), 122.1 (CH), 114.8 (CH), 112.5 (CH), 77.5 (C5), 73.0 (C3), 66.8 (–OCH_2), 61.2 (C4), 31.0 (–CO*C*H_3), 17.6 (C5–*C*H_3); MS *m/z* (%): 423 (M^++2, 10), 421 (M^+, 35), 302 (26), 274 (35), 161 (45), 131 (43), 77 (20), 58 (100), 56 (70). HRMS (FAB) *m/z*: Calcd mass for $C_{25}H_{24}ClNO_3$: 421.1445; found 421.1440 $(M)^+$.

4.2.9. *o*-(2,3,5-Triphenyl-isoxazolidin-4-yl)methoxy-acetophenone, 8a. Pale yellow crystals (260 mg, 65%), mp 98–99 °C; ν_{max} (KBr) 1715, 1653, 1598, 1559, 1541, 1490, 1455, 1361 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 7.69–7.58 (m, 2H, arom.–*H*s), 7.50–7.26 (m, 8H, arom.–*H*s), 7.05–6.96 (m, 3H, arom.–*H*s), 6.84 (d, 1H, *J*=8.4 Hz, arom.–*H*), 5.18 (d, 1H, *J*=9.1 Hz, C3–*H*), 4.81 (d, 1H, *J*=7.8 Hz, C5–*H*), 4.22–4.11 (split AB quartet, 2H, δ_A=4.20, J_{AB}=9.6, 6.5 Hz; δ_B=4.09, *J*=9.6, 4.8 Hz, –O*C*H_2), 3.16–3.08 (m, 1H, *J*=4.3, 7.8, 9.1 Hz, C4–*H*); δ_C ($CDCl_3$, 75 MHz) 199.8 (C=O), 157.2 (q), 152.1 (q), 141.7 (q), 136.9 (q), 133.4 (CH), 130.4 (CH), 129.1 (CH), 129.1 (CH), 128.8 (q), 127.9 (CH), 121.8 (CH), 121.2 (CH), 114.3 (CH), 111.9 (CH), 82.8 (C5), 74.3 (C3), 65.6 (–OCH_2), 62.5 (C4), 31.1 (–$COCH_3$); MS *m/z* (%): 450 (M^++1, 15), 449 (M^+, 35), 406 (22), 458 (51), 330 (100), 327 (29), 258 (38), 223 (41), 103 (35). HRMS (FAB) *m/z*: Calcd mass for $C_{30}H_{27}NO_3$: 449.1991; found 449.1971 $(M)^+$.

4.2.10. *o*-(2,5-Diphenyl-3-nitrophenyl-isoxazolidin-4-yl)-methoxy-acetophenone, 8c. White crystals (268 mg, 67%), mp 99–100 °C; ν_{max} (KBr) 1715, 1687.6, 1674, 1597, 1516, 1487, 1470, 1448, 1383, 1348, 1292, 1231 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 8.37 (d, 2H, *J*=8.6 Hz, arom.–*H*s), 7.90 (d, 2H, *J*=8.6 Hz, arom.–*H*s), 7.71 (dd, 1H, *J*=7.6, 1.3 Hz, arom.–*H*), 7.48–7.32 (m, 7H, arom.–Hs), 6.92 (d, 1H, *J*=8.3 Hz, arom.–*H*), 6.84 (d, 1H, *J*=8.4 Hz, arom.–*H*), 5.18 (d, 1H, *J*=9.1 Hz, C3–*H*), 4.81 (d, 1H, *J*=7.8 Hz, C5–*H*), 4.19–4.16 (split AB quartet, 2H, δ_A=4.19, J_{AB}=10.0, 6.4 Hz; δ_B=4.15, *J*=10.0, 4.9 Hz, –O*C*H_2), 5.25 (d, 1H, *J*=8.7 Hz, C3–*H*), 5.13 (d, 1H, *J*=6.6 Hz, C5–*H*), 4.29–4.17 (split AB quartet, 2H, *J*=9.2, 4.3 Hz), 3.18–3.10 (m, 1H, C4–*H*), 2.23 (s, 3H, –CO*C*H_3); δ_C ($CDCl_3$, 75 MHz) 199.5 (C=O), 156.8 (q), 151.2 (q), 149.4 (q), 147.5 (q), 136.3 (q), 133.3 (CH), 130.3 (CH), 129.3 (CH), 129.1 (CH), 128.9 (q), 127.5 (CH), 126.9 (CH), 124.3 (CH), 122.2 (CH), 121.5 (CH), 113.9 (CH), 112.4 (CH), 82.8 (C5), 74.9 (C3), 66.1 (–OCH_2), 62.4 (C4), 30.9 (–CO*C*H_3); MS *m/z* (%): 495 (M^++1, 15), 494 (M^+, 35), 451 (22), 403 (51), 375 (100), 372 (29), 297 (38), 268 (41), 149 (35). HRMS (FAB) *m/z*: Calcd mass for $C_{30}H_{26}N_2O_5$: 494.1842; found 494.1818 $(M)^+$.

4.3. General procedure for cycloaddition of nitrone (5a) with dipolarophiles, 9a,b

Solution of nitrone (**5a**, 200 mg) and allyl alcohol/allyl-acetate (**9a**,**b**, 1.0 molar equivalent, respectively) in dry benzene (20 mL) was refluxed with stirring for 30–35 h. After the completion of the reactions (TLC), solvent was distilled off and the traces of solvent were removed under vacuum. The obtained crude product mixtures were subjected to column chromatographic resolution over silica gel (Acme Synthetic Chemicals Mumbai, India, 60–120 mesh, 20 g, column packed in hexane) using hexane–chloroform (gradient) as an eluant to obtain pure isoxazolidines (**10a**,**b** and **11a**), whose physical and spectroscopic data are as follows.

4.3.1. (2,3-Diphenyl-isoxazolidin-5-yl)-methanol, 10a. Yellow liquid (340 mg, 85%); ν_{max} ($CHCl_3$) 1678, 1597, 1487, 1450, 1358, 1248, 1061, 1028 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 7.45 (d, 2H, *J*=7.2 Hz, arom.–*H*s), 7.35 (t, 1H, *J*=7.2 Hz, arom.–*H*), 7.326–7.147 (m, 4H, arom.–*H*s), 6.97 (d, 2H, *J*=8.1 Hz, arom.–*H*s), 6.93 (t, 1H, *J*=7.5 Hz, arom.–*H*), 4.68 (dd, 1H, *J*=5.4, 7.8 Hz, C3*H*), 4.43 (ddd, 1H, *J*=3.0, 7.5, and 12.8 Hz, C5*H*), 3.84 (dd, 1H, *J*=3.0, 12.15 Hz, –OC*H*H), 3.71 (dd, 1H, *J*=5.4, 12.0 Hz, –OCH*H*), 2.87–2.76 (ddd, 1H, $J_{3,4Ha}$=7.8 Hz and *J*=7.2, 12.7 Hz, C4*H*a), 2.35–2.26 (ddd, 1H, $J_{3,4Hb}$=5.4 Hz and *J*=7.8 and 12.6 Hz, C4*H*b), 1.99 (s, broad singlet of O*H*); δ_C ($CDCl_3$, 300 MHz) 151.5 (q), 141.9 (q), 128.9 (CH), 128.8 (CH), 127.5 (CH), 126.4 (CH), 122.2 (CH), 115.2 (CH), 78.7 (C3), 70.8 (C5), 63.4 (OCH_2), 40.9 (C4); MS (ESI) *m/z* (%): 294 $(M+Ca)^+$. HRMS (FAB) *m/z*: Calcd mass for $C_{16}H_{17}NO_2$: 255.1278; found 255.1432 $(M)^+$.

4.3.2. (2,3-Diphenyl-isoxazolidin-5-yl)-methyl ester, 10b. Yellow liquid (348 mg, 87%); ν_{max} ($CHCl_3$) 1742, 1597, 1487, 1450, 1369, 1234, 1076, 1042 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 7.44 (d, 2H, J=7.5 Hz, arom.–*H*s), 7.32 (t, 1H, J=7.8 Hz, arom.–*H*s), 7.29–7.11 (m, 4H, arom.–*H*s), 6.98 (d, 2H, J=7.8 Hz, arom.–*H*s), 6.82 (t, 1H, J=7.5 Hz, arom.–*H*), 6.99–6.85 (m, 3H, arom.–*H*s), 4.73–4.65 (dd, tending to be triplet, 1H, J=5.1 and 7.8 Hz, C3*H*), 4.49–4.40 (m, 1H, J=3.3, 7.0, 14.1 Hz, C5*H*), 4.26 (dd, 1H, J=3.3, 12.0 Hz, –OC*H*H), 4.18 (dd, 1H, J=6.6, 11.9 Hz, –OCH*H*), 2.83 (ddd, 1H, $J_{3,4Ha}$=7.8 Hz and J=7.2 and 12.5 Hz, C4*H*a), 2.16 (ddd, 1H, $J_{3,4Hb}$=5.1 Hz and J=8.1, 13.1 Hz, C4*H*b), 2.08 (s, 3H, CH_3); δ_C ($CDCl_3$, 300 MHz) 170.2 (–O–C=O), 151.3 (q), 141.9 (q), 128.7 (CH), 128.7 (CH), 127.5 (CH), 126.4 (CH), 121.6 (CH), 115.1 (CH), 75.7 (C3), 69.8 (C5), 64.04 (OCH_2), 41.6 (C4), 20.5 ($COCH_3$). MS (ESI) m/z (%): 320 $(M+Na)^+$. HRMS (FAB) m/z: Calcd mass for $C_{18}H_{19}NO_3$: 297.1386; found 297.1538 $(M)^+$.

4.3.3. (2,3-Diphenyl-isoxazolidin-5-yl)-methanol, 11a. Yellow liquid (40 mg, 10%); ν_{max} ($CHCl_3$) 1678, 1597, 1487, 1450, 1358, 1248, 1061, 1028 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 7.43 (d, 2H, J=8.2 Hz, arom.–*H*s), 7.37 (t, 1H, J=8.6 Hz, arom.–*H*), 7.32–7.07 (m, 4H, arom.–*H*s), 6.92 (d, 2H, J=7.8 Hz, arom.–*H*s), 6.84 (t, 1H, J=7.6 Hz, arom.–*H*), 4.51 (dd, 1H, J=6.1, 8.7 Hz, C3*H*), 4.45–4.37 (m, 1H, C5*H*), 3.79 (dd, 1H, J=5.1, 11.4 Hz, –OC*H*H), 3.56 (dd, 1H, J=5.4, 12.1 Hz, –OCH*H*), 2.64 (ddd, 1H, $J_{3,4Ha}$=8.7 Hz and J=6.9, 13.8 Hz, C4*H*a), 2.26 (ddd, 1H, $J_{3,4Hb}$=6.1 Hz and J=6.5, 12.8 Hz, C4*H*b), 1.96 (s, broad singlet of O*H*); δ_C ($CDCl_3$, 300 MHz) 151.4 (q), 141.8 (q), 128.8 (CH), 128.7 (CH), 127.5 (CH), 126.3 (CH), 122.1 (CH), 114.9 (CH), 76.6 (C3), 70.6 (C5), 63.4 (OCH_2), 37.1 (C4); MS (ESI) m/z (%): 294 $(M+Ca)^+$. HRMS (FAB) m/z: Calcd mass for $C_{16}H_{17}NO_2$: 255.1379; found 255.1457 $(M)^+$.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.12.076.

References and notes

1. (a) Richman, D. D. *Nature* **2001**, *410*, 995; (b) De Clercq, E. *Biochim. Biophys. Acta* **2002**, *1507*, 258; (c) De Clercq, E. *Med. Res. Rev.* **2002**, *22*, 531; (d) Macchi, B.; Balestreri, E.; Mastino, A. *J. Antimicrob. Chemother.* **2003**, *51*, 1327; (e) Chiacchio, U.; Balestrieri, E.; Macchi, B.; Iannazzo, D.; Piperno, A.; Rescifina, A.; Romeo, R.; Saglimbeni, M.; Sciortino, T.; Vincenza, V.; Mastino, A.; Romeo, G. *J. Med. Chem.* **2005**, *48*, 1389; (f) De Clercq, E. *Nat. Rev. Drug Discov.* **2002**, *1*, 13; (g) Donadas, H. A.; Fishwick, C. W. G.; Grigg, R.; Kilner, C. *Tetrahedron* **2004**, *60*, 3473.
2. (a) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistara, V.; Rescifina, A.; Romeo, R.; Valveri, V.; Mastino, A.; Romeo, G. *J. Med. Chem.* **2003**, *46*, 3696; (b) Coutouli-Argropoulou, E.; Pilanidou, P. *Tetrahedron Lett.* **2003**, *44*, 3755; (c) Merino, P.; Tejero, T.; Laguna, M.; Cerrada, E.; Moreno, A.; Lopez, J. A. *Org. Biomol. Chem.* **2003**, *1*, 2336.
3. (a) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistara, V.; Rescifina, A.; Romeo, R.; Sindona, G.; Romeo, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2717; (b) Chiacchio, U.; Borrello, L.; Iannazzo, D.; Merino, P.; Piperno, A.; Rescifina, A.; Richichi, B.; Romeo, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2419; (c) Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 9321; (d) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Procopio, A.; Rescifina, A.; Romeo, G.; Romeo, R. *Eur. J. Org. Chem.* **2001**, 1893; (e) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Rescifina, A.; Romeo, R.; Romeo, G. *Tetrahedron Lett.* **2001**, *42*, 1777; (f) Iannazzo, D.; Piperno, A.; Pistara, V.; Rescifina, A.; Romeo, R. *Tetrahedron* **2002**, *58*, 581.
4. (a) Tsuda, M.; Hirano, K.; Kubota, T.; Kobayashi, J. *Tetrahedron Lett.* **1999**, *40*, 4819; (b) Imamura, H. *Chem. Pharm. Bull.* **1960**, *8*, 449.
5. (a) Gracia, J. I.; Mayoral, J. A.; Salvatella, L. *Eur. J. Org. Chem.* **2005**, 85; (b) Houk, K. N.; Luskus, L. J. *J. Am. Chem. Soc.* **1993**, *93*, 4606; (c) Buridisso, M.; Gandolfi, R.; Grunanger, P.; Rostelli, A. *J. Org. Chem.* **1990**, *55*, 3427; (d) Ali, A. sK.; Wazeer, M. I. M.; Haque, U. M. *Tetrahedron* **1990**, *46*, 7207; (e) Bernardi, L.; Bonini, B. F.; Franchini, M. C.; Fochi, M.; Folegatti, M.; Grilli, S.; Mazzanti, A.; Ricci, A. *Tetrahedron: Asymmetry* **2004**, *15*, 245.
6. (a) Silva, M. A.; Goodman, J. M. *Tetrahedron* **2002**, *58*, 3667; (b) Arrieta, A.; Cossio, F. P. *J. Org. Chem.* **2001**, *66*, 6178.
7. (a) Huisge, R.; Garshey, R.; Hauck, H.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2548; (b) Huisge, R.; Garshey, R.; Seidl, H.; Hauck, H. *Chem. Ber.* **1968**, *101*, 2559; (c) Huisge, R.; Hauck, H.; Garshey, R.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2568; (d) Joucla, D.; Gre, D.; Hamelin, J. *Tetrahedron* **1973**, *29*, 2315; (e) Gree, R.; Tonnard, F.; Carrie, R. *Tetrahedron Lett.* **1973**, 453; (f) Huisgen, R.; Hauck, H.; Seidel, H.; Burger, M. *Chem. Ber.* **1969**, *102*, 1117; (g) Sustmann, R.; Huisgen, R.; Huber, H. *Chem. Ber.* **1967**, *100*, 1802; (h) Bened, A.; Durand, R.; Pioh, D.; Geneste, P.; Guimon, C.; Guillouzo, G. P.; Declercq, J.-P.; Germain, G.; Briard, P.; Rambaud, J.; Roques, R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1.
8. (a) Gilchrist, T. L.; Storr, R. C. *Organic Reaction and Orbital Symmetry*; Cambridge University: Cambridge, 1972; pp 132–166; (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976; pp 148–161; (c) Padwa, A.; Fisera, L.; Koehler, K. F.; Rodriguea, A.; Wong, G. S. K. *J. Org. Chem.* **1984**, *49*, 276.
9. (a) Structures of α-aryl-*N*-phenyl and related nitrones have been established by various spectroscopic techniques (UV, IR, NMR, and X-ray) and their preferred existence in *Z*-form has been repeatedly emphasized in literature. A large number of stereoselective/enantioselective cycloadditions of these nitrones has been rationalized in terms of their involvement in *Z*-form; (b) Inouye, Y.; Takaya, K.; Kakisawa, H. *Magn. Reson. Chem.* **1985**, *23*, 101; (c) Thesing, J.; Sirrenberg, W.

Chem. Ber. **1958**, *91*, 1978; (d) Folting, K.; Lipscomb, W. N.; Jerslev, B. *Acta Chem. Scand.* **1963**, *17*, 2138; (e) Gree, R.; Tonnard, F.; Carrie, R. *Tetrahedron* **1976**, *32*, 675; (f) Gree, R.; Carrie, R. *Tetrahedron* **1976**, *32*, 683; (g) Viton, F.; Bernardinelli, G.; Kundig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968; (h) Iwasa, S.; Maeda, H.; Nishiyama, K.; Tsushima, S.; Tsukamoto, Y.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 8281; (i) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457; (j) Minakata, S.; Ezoe, T.; Nakamura, K.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 5205; (k) Saito, T.; Yamada, T.; Miyazaki, S.; Otani, T. *Tetrahedron Lett.* **2004**, *45*, 9581; (l) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. *J. Am. Chem. Soc.* **2004**, *126*, 2716.

10. (a) Cytotoxic evaluation of compounds has been carried out at Pharmacology Division, Regional Research Laboratory, Jammu, India; (b) Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMohan, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107.
11. Samanta, S.; Pain, A.; Dutta, S.; Saxena, A. K.; Shanmugavel, M.; Pandita, R. M.; Qazi, G. N.; Sanyal, U. *J. Exp. Ther. Oncol.* **2005**, *5*, 15.