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Investigations on synthesis of indole based constrained mimetic scaffolds through 1,3-dipolar cycloadditions of the *C*-(3-indolyl)-*N*-phenylnitrone with a variety of olefinic and allenic dipolarophiles under microwave irradiation

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ABSTRACT

Monomode microwave assisted regio- and stereo-selective 1,3-dipolar cycloadditions of *C*-(3-indolyl)-*N*-phenylnitrone (**19**) with a number of olefinic dipolarophiles (**20a–f**) afford isoxazolidines (**21–26**) in high yields, which are conformationally constrained mimetics of indole-3-propionic acid of biological significance. Similar cycloadducts derived from addition of nitrone (**19**) to allenic esters (**27a–c**) undergo domino reorganization to afford potentially biologically active bis-indole derivatives (**28**, **29**). The observed regio- and stereo-selectivities are analysed, inter alia, in terms of HOMO-dipole–LUMO-dipolarophile and involved secondary orbital/steric interactions in the transition states intervening these cycloadditions.

1. Introduction

In nature, the indole (**1**) derivatives bearing heterocyclic functionalities at C3 are represented by a small number of the natural products such as martefragin A (**2**), a potent inhibitor of lipid peroxidation[1] and various forms of the natural pimprinine alkaloids (**3–7**), which have been shown to be potent inhibitors of HIV-1 integrase.[2] Consequently, efforts for the synthesis of indole derivatives having bio-isosteric heterocyclic functionalities at C3 is drawing considerable attention and recently, 3-substituted indoles (**8**, **9**) have been synthesized, and found to posses interesting biological activities.[3] For instance, compounds related to **8** and **9** were found to act as aromatase inhibitors, and have been used to treat breast cancer.[3] On the other hand, the di-indolyl or bis-indole natural product, staurosporine (**10**), is one of the best ATP competitive kinase inhibitors.[4] Inspired by such considerations, the 3-[2-indol-1-yl-ethyl]-1*H*-indole scaffold (**11**) and β,β-bisindolyl ketone (**12**) have been designed as selective inhibitors of cyclin-dependant-kinases (CDK4) and synthesized by substitution at C3 position of the indole.[5] A linear dimer of indole (**13**) is an important anticancer agent[6] and its analog (**14**) displays potent oral anticancer activity against various cancers, and is shown to be devoid of significant toxicity.[7] Another natural C3 substituted indole derivative is the 3-(1*H*-indol-3-yl)propanoic acid (**15**), which is extracted from the root nodules of intact pea plant (*Pisum sativum*)[8] and is a potent neuroprotective agent.[9] Recently, a three-component, one-pot procedure involving substitution at C3 of indole has been developed for synthesis of 3-indolepropionic acid derivatives (**16**) in good yields.[10]

1,3-Dipolar cycloaddition is a versatile tool in the hands of synthetic organic chemists to generate various biologically important target molecules.[11] In continuation of our investigations on application of 1,3-dipolar cycloadditions of a variety of nitrones with olefinic and allenic dipolariphiles[12] to obtain biologically active molecules/molecular scaffolds, we have recently investigated the regio- and stereoselectivities in 1,3-dipolar cycloadditions of nitrones to dipolarophiles bearing an allylic oxygen leading to cytotoxic isoxazolidines.[12c] Here in we report investigations on 1,3-dipolar cycloadditions of *C*-(3-indolyl)-*N*-phenylnitrone, derived from 3-formylindole, with a variety of olefinic and allenic dipolarophiles under microwave irradiation. Synthetically the cycloadditions were aimed to obtain the conformationally constrained mimetics of the indole 3-propionic acid (**15**), by

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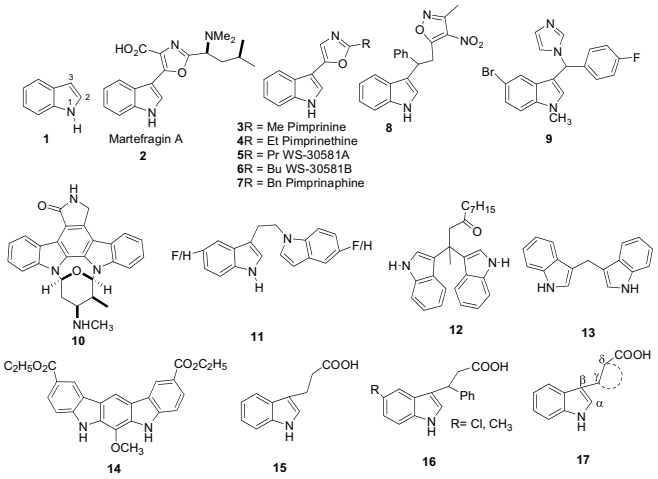


restricting the side chain across the γ and δ carbon atoms as indicated (**17**), through bio-isosteric heterocyclic and double bond (bis-indole) functionalities, because conformational restriction of the side chain has been shown to be an effective tool to optimize potency and selectivity in a number of useful precursors for non-peptide peptidomimetic molecules based on indole scaffolds.[13] These investigation are also of interest for understanding the complete regio- and stereoselectivity of 1,3-dipolar cycloaddition on the periphery of indole nucleus under microwave irradiation conditions.

2. Results and discussion

The *C*-(3-indolyl)-*N*-phenylnitrone (**19**) was obtained in quantitative yield by reacting 3-formylindole (**18**) with *N*-phenylhydroxylamine in dry ethanol (Scheme 1) and characterized spectroscopically.

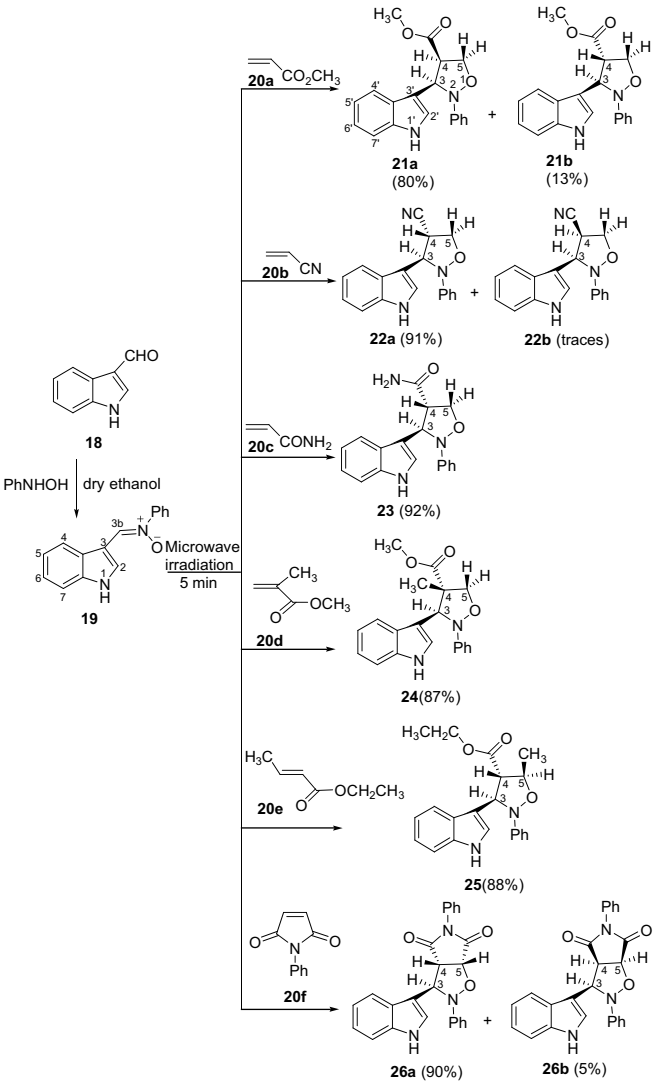
2.1. Reactions of the *C*-(3-indolyl)-*N*-phenylnitrone (19) with various olefinic dioplarophiles (20a–f)

The cycloaddition reactions of nitrone (**19**) with monosubstituted, di-substituted and cyclic dipolarophiles were carried out by irradiating equimolar amount of the addends (neat) in a focused monomode microwave reactor.

Initially, the reaction of nitrone (**19**) with methyl acrylate (**20a**) was carried out by microwave irradiations under solvent free condition. After completion of the reaction (TLC) the residues obtained were resolved by column chromatography over silica gel to obtain the cycloadduct (**21a**, 80%) as major adduct along with (**21b**, 13%) as minor adduct (Scheme 1).

The products were characterized by detailed spectroscopic analysis. A comparison of the spectroscopic, in particular, NMR spectral data with the data reported for isoxazolidines obtained by 1,3-dipolar cycloadditions of nitrones to a variety of dipolarophiles,[12d,14] clearly indicated that the presently obtained cycloadducts are also derived from 1,3-dipolar cycloadditions. The assigned regiochemistry of addition in (**21a**) and (**21b**) is based on ^{1}H NMR chemical shift of methylene-Hs (C5–Hs) located at δ 4.57–4.41 and this downfield shifted position is indicative of the attachment of methylene carbon to oxygen in **21a** & **21b**.

These conclusions are corroborated by the observed proton connectivities (couplings), which clearly indicated that C4–H is vicinal to both C3–H and C5–Hs, and ^{13}C NMR chemical shift assignments.[12d,15,16] The *syn*/*anti*-stereochemistry in **21a**/**21b** respectively, involving indole group at C3 and the ester functionality at C4 of isoxazolidine ring is based on ^{1}H NMR couplings involving C3–H and C4–H, and follows from the premise that the cis-vicinal ^{1}H coupling constants are always higher than trans in case of isoxazolidines and related heterocycles.[12d,14,15] Thus, in case of **21a**, C3–H appeared as a doublet at δ 5.46 (J=8.1 Hz) and in case of **21b**, C3–H appeared as a doublet at δ 5.28 (J=5.4 Hz); the high value of $J_{3,4}$ in the case of **21a** compared to **21b**, alluded to cis arrangement in former and trans in the latter.[12d,14,15]



Scheme 1.

Further, the reactions of nitrone (**19**) with the acrylonitrile (**20b**) and acrylamide (**20c**) were investigated under similar conditions (Scheme 1). The reaction of the nitrone with **20b** afforded **22a** (91%) as major and **22b** as minor (traces) cycloadducts. In the case of **20c**, single cycloadduct (**23**, 92%) was obtained. The assigned regio- and stereochemistry chemistry of addition in **22a**,**b** and **23** is based on similar ^{1}H NMR and ^{13}C NMR spectroscopic analysis. For instance the assigned trans-arrangement of substituents at C3 and C4 in **22a** and **23** is based on similar lower values of coupling constant $J_{3,4}$ 5.7 Hz and $J_{3,4}$ 5.6 Hz, respectively.

The regiochemistry of addition leading to adducts (**21**–**23**) can be rationalized in terms of the frontier molecular orbital controlled cycloaddition involving HOMO (dipole)–LUMO (dipolarophiles) interaction.[16] Thus, the nitrone (**19**) is a relatively electron rich 1,3-dipole, which is a consequence of involvement of C3 of indole, therefore, the obtained regiochemistry of the addition is the one which is otherwise anticipated in reactions of nitrones with highly electron deficient dipolarophiles such as nitro-alkenes.[16a–d]

To further substantiate the above conclusions, regarding involvement of HOMO-dipole, theoretical calculations were performed on nitrone (**19**) and α,*N*-diphenyl nitrone (**19a**) at B3LYP/6-31G* level. The results of calculation on the energy minimized structure of these nitrones (*Z*-form) are given in Table 1, which clearly indicate that nitrone **19** has a high lying HOMO with highest AO coefficient at oxygen of nitrone moiety, hence the observed regioselectivity is in keeping with the HOMO-dipole controlled cyclaoadditions.[16]

Table 1
Frontier orbital energies (HOMO and LUMO) and atomic orbital (AO) coefficients of atoms of nitrone moiety for nitrones **19** and **19a** obtained at B3LYP/6-31G* level

Parameters		19	19a
Energy of HOMO, eV		−4.917	−5.481
Energy of LUMO, eV		−1.240	−1.656
AO coefficients in HOMO	αC	0.224	0.278
	N	0.219	0.116
	O	0.343	0.396
AO coefficients in LUMO	αC	0.259	0.272
	N	0.274	0.273
	O	0.241	0.231

The stereochemistry of the addition depends on the interaction of dipolarophiles in the transition state (*exo*/*endo*) as well as the geometry of the dipole (*Z* or *E*). Four plausible mode of addition are shown in Figure 1. The approach (**A**) and (**B**) can be described as *Z*-*exo*, and *Z*-*endo*, whereas (**C**) and (**D**) are the alternative *E*-*endo*, and *E*-*exo* approaches. The cis adduct (**21a**) may result from the approach (**A**) or (**C**). Approach (**A**) shall be, apparently, disfavoured for the steric reason and approach (**D**) should be favoured due to possible involvement of the secondary orbital interactions.[16d] It is pertinent to mention here that existence of the nitrone as mixture of more stable *Z*-form and less stable *E*-form, and involvement of nitrone in its more reactive, i.e., less stable *E*-form in cycloaddition leading to major reaction products is precedented.[16d]

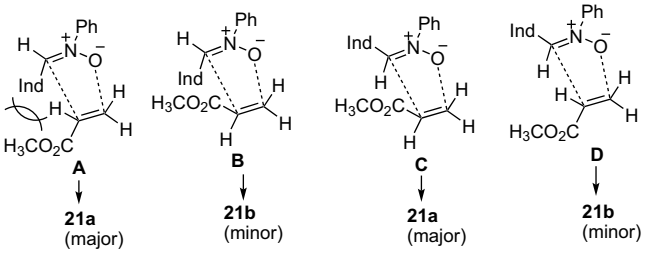


Figure 1.

The stereo-selectivity of addition leading to higher relative proportions of trans-cycloadducts (**22a** and **23**) than the corresponding cis-cycloadduct (**22b**) can be rationalized in terms of preference of *endo*-orientation (**E**) of the substituent on the dipolarophiles with nitrone reacting in its *Z*-form, over the *exo*-mode of addition (**F**, Fig. 2);[16d,17] such *endo*-selectivity has been observed earlier in the case of substituents capable of undergoing secondary interaction.[12d,17] However, it may be mentioned here that a variety of interactions have been invoked to explain stereoselectivities in 1,3-dipolar cycloadditions, and cycloadditions generally,[17d] though, the question of secondary orbital or secondary interaction is still far from settled and steric factors appear to play an overwhelming role.

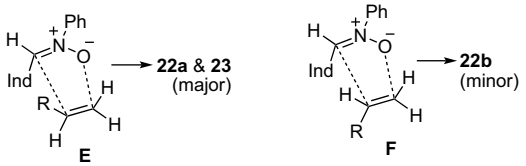


Figure 2.

Recently, preferred endo-orientation[17b,c] of alkoxy groups, even in the presence of an ester function, has been reported.[17c]

Further, the investigations were extended to disubstituted and cyclic dipolarophiles such as methyl methacrylate, ethyl crotonate and *N*-phenylmaleimide. The reaction of nitrone (**19**) with methyl methacrylate (**20d**) under similar conditions afforded the cycloadduct (**24**, 87%, Scheme 1). Structure of **24** has been similarly assigned by detailed spectroscopic analysis. The methylene-Hs (C5–Hs) showed up, in the ^{1}H NMR spectrum of **24**, as doublets (1H each) at δ 4.61 and δ 3.97, and their downfield shifted position was indicative of the attachment of methylene carbon (C5) to oxygen. C3–H appeared as a singlet at δ 5.43. The absence of observable NOE between the C4–CH_3 and C3–H (C4–CH_3 irradiated) alluded to a trans-relationship between indole moiety and ester function in **24**. The assigned stereochemistry can be rationalized as *endo* mode (**G**) of the addition as far as ester function is concerned, with nitrone reacting in *Z*-form (**G**, Fig. 3).

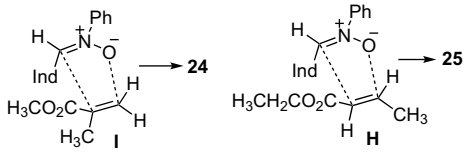


Figure 3.

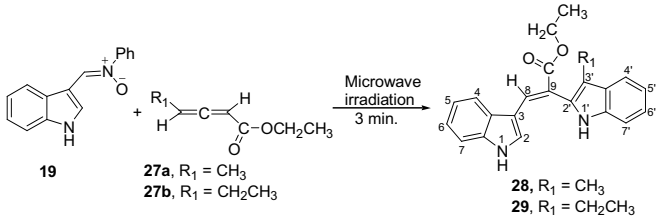
A similar reaction of nitrone (**19**) with ethyl crotonate (**20e**) afforded a single product, which has been characterized as cycloadduct (**25**, 88%, Scheme 1) by comparison of the spectroscopic data with the data reported for cycloadducts derived from addition of some nitrones to crotonates.[12d,15f,g] Here the assigned regiochemistry of addition is easily discerned from chemical shift value of C5–H (δ 4.38); the C5–H resonance could be easily identified from its multiplicity (dq). Here, the trans-relationship between C3–H and C4–H is based on lower coupling constant value, i.e., $J_{3,4}$=5.9 Hz. The coupling constant value between C5–H and C4–H $J_{5,4}$ value is 8.9 Hz; the latter hydrogens are anticipated to be trans as a consequence of concerted cycloaddition to *trans*-crotonate.[15f,g] Though, the regiochemistry of addition to **20d**,**e** was anticipated in the light of literature reports,[12d,16] however, the important aspect of the present results is the obtained complete stereo-selectivity, which can be rationalized in terms of addition of nitrone in *Z*-form with ester moiety being *endo*-oriented in the transition state (approach **H**, Fig. 3) for steric reasons and/or secondary interaction.

Reaction of nitrone (**19**) with *N*-phenylmaleimide (**20f**) under identical conditions afforded two compounds (**26a**, 90%) and (**26b**, 5%, Scheme 1). The major compound (**26a**) displayed, *interalia*, a 1H singlet at δ 6.05 which was attributed to C3–H and lack of any observable vicinal coupling signified its trans-relationship with C4–H; such lack of any observable coupling between *trans*-vicinal-hydrogens in the case of isoxazolidines, particularly, for rigid systems derived from addition of nitrones to cyclic-dipolarophiles is precedented.[12d] Both C4–H and C5–H were present as 1H doublets at δ 4.15 and δ 5.12, respectively, displaying a mutual splitting of 7.5 Hz. The minor cycloadduct (**26b**) on the other hand displayed C3–H resonance as a doublet 5.95 (*J*=8.7 Hz), C5–H as a doublet at δ 4.98 (*J*=9.9 Hz) and C4–H as a unresolved double doublet at δ 4.13 (*J*∼9.4 Hz). Mechanistically, the compound **26a** can be described as the *endo*-cycloadduct and **26b** as the corresponding *exo*-cycloadduct derived from addition of nitrone in the *Z*-form.

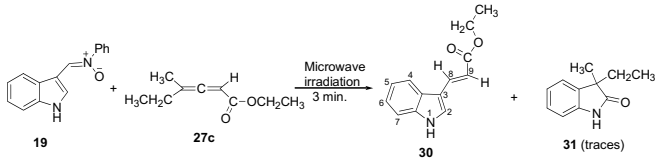
2.2. Reactions of the *C*-(3-indolyl)-*N*-phenylnitrone (19) with allenic esters (27a–c)

The investigations on 1,3-dipolar cycloadditions of nitrone (**19**) were extended to allenic esters (**27a**–**c**) under microwave

irradiation in solvent free conditions using focused monomode microwave reactor. The reactions of the *C*-(3-indolyl)-*N*-phenylnitrone (**19**) with allenic esters (**24a**–**c**) were investigated, which furnished the 2-(3-methyl-1*H*-indol-2-yl)-3-(1*H*-indol-3-yl)-acrylic acid ethyl ester (**28**, 84%) and 2-(3-ethyl-1*H*-indol-2-yl)-3-(1*H*-indol-3-yl)-acrylic acid ethyl ester (**29**, 90%) and the 3-(1*H*-indol-3-yl)-acrylic acid ethyl ester (**30**, 90%) as major products, respectively (Schemes 2 and 3).



Scheme 2.



Scheme 3.

The structures of the compounds (**28**, **29** and **30**, **31**) were established through rigorous spectroscopic analysis. For instance in the case of **29** the molecular ion peak in the mass spectrum (ESI) appeared at 358.0, indicating that it is derived from addition of elements of nitrone (**19**) to allenic ester (**27b**). In its ^{1}H NMR spectrum, two broad singlets at δ 8.13 and δ 7.74 (amenable to deuterium exchange) were attributed to two NH protons. The 1H doublet at δ 6.36 (J=3.0 Hz) is assigned to C2–H and 1H singlet at δ 8.35 is assigned to C8–H. The resonances due to protons of the ester moiety appeared as a quartet (2H) at δ 4.28 (−OC*H*$_2$) and a triplet (3H) at δ 1.30. The quartet (2H) at δ 2.62 was attributed to the C3′–C*H*$_2$ and the corresponding methyl resonance appeared as a triplet at δ1.15. The IR spectrum and critical ^{13}C NMR assignments corroborated the assigned structure, which was finally established X-ray crystallographically (Fig. 4).[18a] The structure of compound (**30**) was established by similar rigorous spectroscopic analysis and by X-ray crystallography (Fig. 5)[18b] and the compound **31** was detected (^{1}H NMR) only in some mixture column chromatographic fractions.

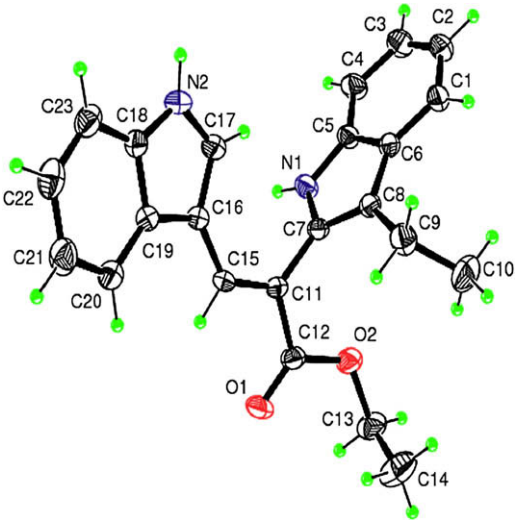


Figure 4. ORTEP diagram of compound **29**.

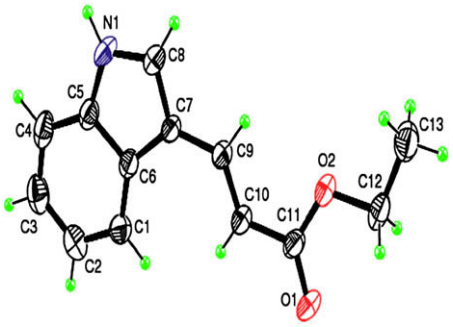


Figure 5. ORTEP diagram of compound **30**.

The crystal structures of compound **29** and **30** were solved.[18] Figures 6 and 7 show the ORTEP diagrams and labeling scheme used in structure analysis. In both the compounds the crystal packing diagrams show intermolecular H-bonding networks. In case of compound **29** the N2–H12···O1^{ii} (2.002 Å, where *ii*=*x*−1, +*y*, +*z*) hydrogen bonded chains are held together by the C–H···π interactions leading to the formation of sheets parallel to *ab* plane (Fig. 6). Similarly in case of compound **30** the carbonyl oxygen O1 is an acceptor to the N1–H1···O1^{i} (2.042(2) Å, where *i*=*x*, +*y*, +*z*+1) hydrogen bond leading to the formation of parallel chains which are held together by C–H···π interactions (Fig. 7). The distance between H13 and the centre of the π electron cloud of pyrazole ring is 3.051(2) Å.

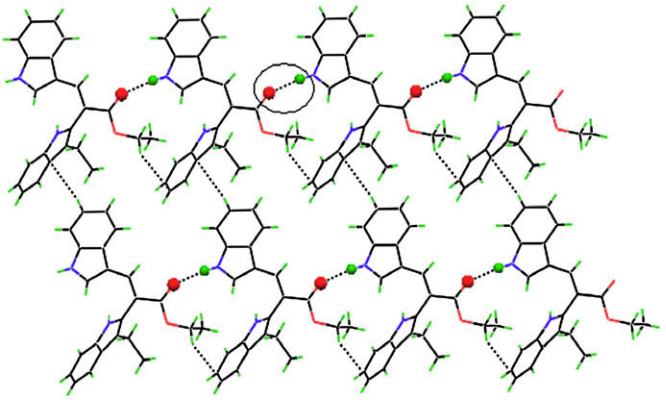


Figure 6. Crystal packing diagram of compound **29**.

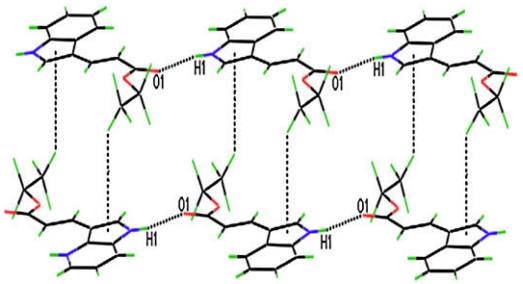
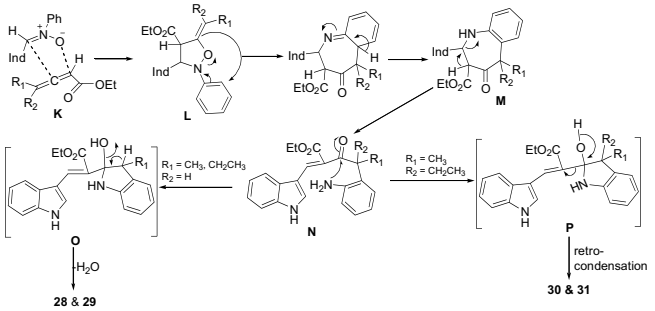


Figure 7. Crystal packing diagram of compound **30**.

Mechanistically, the plausible routes to the formation of the di-indole acrylic acid ethyl ester derivatives (**28** & **29**) and the 3-(1*H*-indol-3-yl)-acrylic acid ethyl ester (**30**) involve hetero-cope rearrangement of the initially formed 5-*exo*-alkylidene-

isoxazolidines (**L**), derived from regioselective addition of nitrone to the C_2–C_3 π-bond of the allenic esters (approach **K**), to tetrahydrobenzazepinones (**M**),[12b,19a] followed by retro-Michael-addition ring opening of the azepinone, leading to the intermediate (**N**), and the latter cyclizes by condensation to yields (through O) the di-indole acrylic acid ethyl ester derivatives (**28**, **29**, Scheme 4). Alternatively, in the case of allenic ester **27c**, the intermediate **N** cyclizes to **P** and the latter, instead of dehydration, undergoes a retro-condensation to furnish **30** (Scheme 4). Apparently, the *gem*-dialkyl moiety in P precludes its aromatization and possibly also destabilizes **O** sterically. Related domino-reorganizations of cycloadducts derived from addition of *N*-phenynitrones to allenic systems have precedents.[19b]



Scheme 4.

The restrictions imposed by five-membered heterocycles, isoxazolidines, in the case of **21**–**26** and by double bond in **28**, **29** and **30** make these compounds valuable conformationally constrained mimetics of the 3-(1*H*-indol-3-yl)propanoic acid (**15**). Recently, some indole derivatives in their minimum energy conformation, having structure similar to **21**–**26** (possessing hetrocyclic functionalities) and **28**, **29** (bis-indoles) and **30** were found to act as aromatase inhibitors and have been used to treat breast cancer.[3] In the reported structure–activity relationship studies,[7] the anticancer activity profile of compounds related to **28** and **29** is shown to be depending on the distance between *N*, *N*′ in their minimum energy conformation. The total energy and dipole moment for compounds **21**–**26** and **28**–**31** were computed at B3LYP/6-31G* level. In the preliminary investigation of the **28** and **29**, on their minimum energy conformation as measured at B3LYP/6-31G* level (Fig. 8), it was observed that the distance between N1, N1′ is 5.6 Å for **28** and 5.4 Å for **29**, as compared to the structurally similar compounds, such as **13** and **14**, wherein *N*, *N*′ distance lies in the range of 4.7–5.9 Å in their minimum energy conformations.[7] Good polarity (dipole moment) of compounds is known to influence their membrane permeability and thus improve their oral bioavailability. For compounds **21**–**26** the calculated dipole moment are in the range of 2.15–4.14 Debye, and for **28**, **29**, **30** and **31** the calculated values are 3.39, 3.46, 3.89 and 2.63 Debye, respectively. Compounds with these ranges of dipole moment values are known to exhibit high oral bioavailability for potent antitumor effect.[7]

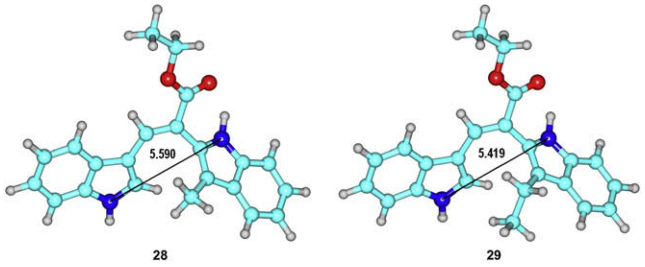


Figure 8. Optimized geometry of the compounds **28** & **29** obtained at B3LYP/6-31G* level.

3. Conclusions

The observed regio- and stereo-selectivities in the reactions of the *C*-(3-indolyl)-*N*-phenylnitrone to obtained **21**–**26** and **28**–**30** are rationalized in terms of frontier orbital controlled 1,3-dipolar cycloadditions involving HOMO-dipole–LUMO-dipolarophile interaction, corroborated by DFT calculations, and the configuration (*Z*/*E*) of the nitrone as well as approach (*endo*-/*exo*-) of addends in the transition states. The formation of the di-indole acrylic acid ethyl ester derivatives (**28**, **29**) and the 3-(1*H*-indol-3-yl)-acrylic acid ethyl ester derivative (**30**) by reactions of the *C*-(3-indolyl)-*N*-phenylnitrone with allenic esters (**27a**–**c**) result from tandem reorganization of the initially formed cycloadducts (domino processes)[20] and because of the potential biological activities of these compounds, this methodology will be useful in indole related science. The constrained mimetics of the indole-3-propanoic acids (**21**–**26** & **28**–**30**) are expected to be more valuable than their flexible counterpart (**15**).[13] The dipole moments based on the energy-minimized conformations of these compounds are in the desired range for easy membrane transport. The reactions carried out under monomode microwave irradiation were very clean, attended with high yields and required shortened reaction times.

4. Experimental section

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 internal standard and coupling constants (J) are reported in Hz. IR spectra were recorded with Shimadzu DR-2001 FT-IR spectrophotometer on KBr pellets. Mass spectra, ESI-method were recorded on Bruker Daltonics Esquire 300 mass spectrometers. The CEM-Discover Focused Monomode Microwave reactor (2450 MHz, 300 W) was used for microwave irradiation. CHN analysis was performed on thermoelectron CHN analyser EA1112 at Department of Chemistry, Guru Nanak Dev University, Amritsar. All melting points are uncorrected and measured in open glass-capillaries on a Veego MP-D digital melting point apparatus.

3-Formylindole was procured from Sigma–Aldrich, and Phenylhydroxylamine was prepared by reducing nitrobenzene with Zn/NH_4Cl.[12b] Allenic esters were prepared by method of Lang and Hansen.[12b]

The X-ray data for compound **29** and compound **30** were collected at 298 K on a Siemens P4 Single crystal X-ray diffractometer. The θ–2θ scan mode was used to measure the intensities, up to a maximum of 2θ=60° (compound **29**), and 55° (compound **30**), with graphite monochromatised Mo Kα radiations (λ=0.71073 Å). To monitor the stability of the crystal 3 standard reflections were measured after every 97 reflections. The data were corrected for Lorentz and polarization effects and a psi-scan absorption correction was also applied in case of compound **30**.

4.2. General procedure for synthesis of *C*-(3-indolyl)-*N*-phenylnitrone (19)

3-Formylindole (2.8 mmol), was dissolved in dry ethanol (30 ml) and to the clear solution, *N*-Phenylhyroxylamine hydrochloride (2.8 mmol) was added, and the contents were allowed to

stand at room temperature for overnight. Then, solvent was evaporated under vacuum to obtain the viscous yellow oil, which was crystallized in chloroform–ether (1:2) to obtain nitrone as light yellow powder (yield 90%). The nitrone was dried under vacuum and stored under refrigeration.

4.2.1. *C-(3-Indolyl)-N-phenylnitrone (**19**)*

Yellow powder (ether–chloroform, 2:1), mp 92–94 °C. Yield (90%). IR (KBr): 1631, 1612, 1575, 1519, 1444, 1242, 1124 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 11.61 (br s, 1H, *NH*), 9.27 (s, 1H, C3b–*H*), 8.42 (s, 1H, C2–*H*), 7.89 (unresolved dd, 1H, *J*∼6.8 Hz, C4–*H*), 7.72 (d, 1H, *J*=6.9 Hz, C7–*H*), 7.55–7.43 (m, 3H, arom.–Hs & C6–*H*), 7.25–7.14 (m, 4H, arom.–Hs & C5-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.9 (q), 136.4 (C7a), 128.5 (C3a), 127.6 (C3b), 125.1 (C2), 124.3 (2CH), 122.6 (2CH), 121.7 (C6), 120.4 (C4), 119.6 (C5), 115.1 (CH), 112.3 (C7), 107.8 (C3) ppm. Mass (ESI): 236.8 (M^+), 259.8 ($M+Na)^+$. Anal. Calcd for $C_{15}H_{12}N_2O$ requires C 76.25, H 5.12, N 11.86, and found C 76.29, H 5.09, N 11.84.

4.3. General procedure for the reaction of *C*-(3-indolyl)-*N*-phenylnitrone (19) with various dipolarophiles (20a–f) under monomode microwave irradiation

In the 150 ml round bottom flask, added the *C*-(3-indolyl)-*N*-phenylnitrone (**19**, 1.28 mmol) and dipolarophiles (**20a–f**, 1.0 equiv). Then, the flask containing the contents, fitted with a condenser was placed in the cavity of the microwave reactor. After closing the cavity of the reactor with the cavity lid, the contents were irradiated (150 W, 100 °C) for 5 min (1 min hold time and 4 min running time) till all the nitrone was consumed (TLC). In case of dipolarophiles (**20c** & **20f**), they were first dissolved in dry benzene (1 ml) to get suspension, which was then allowed to react with nitrone (**19**). After completion of the reaction, the residues were loaded onto silica gel column (60–120 mesh, column packed in hexane); elution of column using hexane–chloroform (gradient) afforded **21**–**26**. The reported yields based on isolated pure products and relative proportions determined in the mixtures by ^1H NMR spectroscopy.

4.3.1. *syn-3-(1H-Indol-3-yl)-2-phenyl-isoxazolidine-4-carboxylic acid methyl ester (**21a**)*

Brownish viscous oil. Yield (327 mg, 80%). IR ($CHCl_3$): 3382, 2980, 1731, 1599, 1521, 1426, 1216 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.34 (br s, 1H, *NH*), 7.78 (d, 1H, *J*=6.6 Hz, C4′–*H*), 7.69 (d, 1H, *J*=7.5 Hz, C7′–*H*), 7.26 (s, 1H, C2′–*H*), 7.16–7.04 (m, 6H, arom.–Hs & C6′, C5′–*Hs*), 6.97 (t, 1H, *J*=7.2 Hz, arom.–*H*), 5.46 (d, 1H, *J*=8.1 Hz, C3–*H*), 4.57 (unresolved dd, 1H, *J*∼7.9, C5–*Ha*), 4.41 (dd, 1H, *J*=10.8 Hz & 6.5 Hz, C5-*Hb*), 3.79 (unresolved ddd, 1H, *J*∼8.2 Hz & 5.9 Hz, C4-*H*), 3.09 (s, 3H, O*CH*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1 (C=O), 150.3 (q), 135.7 (C7a′), 128.9 (C3a′), 125.9 (C2′), 123.9 (2CH), 122.5 (2CH), 121.9 (C6′), 119.5 (C4′), 118.5 (C5′), 115.3 (CH), 112.1 (C7′), 111.3 (C3′), 67.2 (C5), 64.6 (C3), 51.8 (C4), 51.4 (OCH_3) ppm. Mass (ESI): 345.0 ($M+Na)^+$. Anal. Calcd for $C_{19}H_{18}N_2O_3$ requires C 70.79, H 5.63, N 8.69, and found C 70.81, H 5.65, N 8.67.

4.3.2. *anti-3-(1H-Indol-3-yl)-2-phenyl-isoxazolidine-4-carboxylic acid methyl ester (**21b**)*

Brownish viscous oil. Yield (53 mg, 13%). IR ($CHCl_3$): 3411, 3012, 2952, 1731, 1598, 1521, 1489, 1428, 1215 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.13 (br s, 1H, *NH*), 7.82 (d, 1H, *J*=7.8 Hz, C4′–*H*), 7.72 (d, 1H, *J*=7.8 Hz, C7′–*H*), 7.27 (d, 1H, *J*=2.5 Hz, C2′–*H*), 7.26–7.13 (m, 4H arom.–Hs & C6′, C5′–*Hs*), 7.05 (dd, 2H, *J*=7.8 Hz & 2.9 Hz, arom.–Hs), 6.93 (t, 1H, *J*=7.2 Hz, arom.–*H*), 5.28 (d, 1H, *J*=5.4 Hz, C3–*H*), 4.44–4.41 (m, 2H, C5–*Hs*), 3.71 (unresolved ddd, 1H, *J*∼7.9 Hz & 5.4 Hz, C4–*H*), 3.67 (s, 3H, O*CH*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0 (C=O), 150.4 (q), 136.7 (C7a′), 129.6 (C3a′), 126.2 (C2′), 123.5 (2CH), 122.3 (2CH), 119.9 (C6′), 119.4 (C4′), 116.7 (C5′), 115.2 (CH), 112.4 (C7′) 111.3 (C3′), 68.7 (C5), 66.7 (C3), 56.3 (C4), 52.3 (OCH_3) ppm. Mass (ESI): 345.0 ($M+Na)^+$. Anal. Calcd for $C_{19}H_{18}N_2O_3$ requires C 70.79, H 5.63, N 8.69, and found C 70.76, H 5.60, N 8.72.

4.3.3. *anti-3-(1H-Indol-3-yl)-2-phenyl-isoxazolidine-4-carbonitrile (**22**)*

Light brown viscous oil. Yield (334 mg, 91%). IR ($CHCl_3$): 3411, 2238, 1596, 1488, 1456, 1419, 1217, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.16 (br s, 1H, *NH*), 7.80 (d, 1H, *J*=7.8 Hz, C4′–*H*), 7.72 (d, 1H, *J*=7.8 Hz, C7′–*H*), 7.27–7.03 (m, 5H, arom.–Hs & C6′–*H*, C2′–*H*), 7.02–6.96 (m, 3H, arom.–*Hs* & C5′–*Hs*), 5.01 (d, 1H, *J*=5.7 Hz, C3–*H*), 4.48 (dd, 1H, *J*=10.4 Hz & 8.1 Hz, C5-Ha), 4.35 (dd, 1H, *J*=10.4 Hz & 5.7 Hz), 3.68 (unresolved ddd, 1H, *J*∼8.0 Hz & 5.7 Hz, C4-*H*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.5 (q), 135.6 (C7a′), 128.9 (C3a′), 125.3 (C2′), 122.7 (2CH), 122.3 (2CH), 120.9 (C6′), 119.7 (C4′), 118.9 (C5′), 117.8 (CN), 115.4 (CH), 112.7 (C7′), 71.5 (C3), 66.4 (C5), 44.7 (C4). Mass (ESI): 289.1 (M^+), 312.1 ($M+Na)^+$. Anal. Calcd for $C_{18}H_{15}N_3O$ requires C 74.72, H 5.23, N 14.52, and found C 74.76, H 5.20, N 14.55.

4.3.4. *anti-3-(1H-Indol-3-yl)-2-phenyl-isoxazolidine-4-carboxylic acid amide (**23**)*

Colourless solid (hexane–chloroform, 2:1), mp 152–154 °C. Yield (358 mg, 92%). IR (KBr): 3432, 3047, 1685, 1581, 1496, 1474, 1214, 1150 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.12 (br s, 1H, *NH*), 7.82 (d, 1H, *J*=7.2 Hz, C4′–*H*), 7.74 (d, 1H, *J*=7.8 Hz, C7′–*H*), 7.27–7.11 (m, 4H arom.–Hs & C6′, C5′–*Hs*, C2′–*H*), 7.08 (dd, 2H, *J*=7.8 Hz & 2.9 Hz, arom.–Hs), 6.93 (t, 1H, *J*=7.2 Hz, arom.–*H*), 6.60 and 5.54 (br s, 1H each, –*NH*$_2$) 5.42 (d, 1H, *J*=5.6 Hz, C3–*H*), 4.53 (unresolved dd, 1H, *J*∼8.1 Hz, C5–*Ha*), 4.38 (dd, 1H, *J*=11.2 Hz & 5.9 Hz, C5–*Hb*), 3.78 (unresolved ddd, 1H, *J*∼8.3 Hz & 5.4 Hz, C4–*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.8 (–$CONH_2$), 151.4 (q), 136.6 (C7a′), 128.6 (C3a′), 125.9 (C2′), 124.5 (2CH), 122.3 (2CH), 120.7 (C6′), 119.4 (C4′), 116.7 (C5′), 115.2 (CH), 112.4 (C7′) 111.3 (C3′), 68.7 (C5), 66.7 (C3), 56.3 (C4). Mass (ESI): 307.0 (M^+), 330.1 ($M+Na)^+$. Anal. Calcd for $C_{18}H_{17}N_3O_2$ requires C 70.34, H 5.58, N 13.67, and found C 70.38, H 5.56, N 13.64.

4.3.5. *anti-3-(1H-Indol-3-yl)-4-methyl-2-phenyl-isoxazolidine-4-carboxylic acid methyl ester (**24**)*

Yellow viscous oil. Yield (370 mg, 87%). IR ($CHCl_3$): 3409, 2950, 1733, 1596, 1488, 1456, 1201, 748 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.20 (br s, 1H, *NH*), 7.79 (d, 1H, *J*=7.8 Hz, C4′–*H*), 7.40 (d, 2H, *J*=8.1 Hz), 7.35–7.22 (m, 4H, arom.–Hs & C6′, C5′–*Hs*), 7.21 (d, 1H, *J*=2.3 Hz, C2′–*H*), 6.99 (dd, 2H, *J*=8.4 Hz & 3.2 Hz, arom.–*Hs*), 6.90 (t, 1H, *J*=7.2 Hz, arom.–*H*), 5.43 (s, 1H, C3–*H*), 4.61 (d, 1H, *J*=8.4 Hz, C5–*H*), 3.97 (d, 1H, *J*=8.4 Hz, C5–*H*), 3.73 (s, 3H, O*CH*$_3$), 1.56 (s, 3H, C4–*CH*$_3$) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5 (C=O), 150.4 (q), 135.5 (C7a′), 127.8 (C3a′), 124.9 (C2′), 123.7 (2CH), 122.1 (2CH), 120.9 (C6′), 119.5 (C4′), 118.5 (C5′), 115.3 (CH), 112.1 (C7′), 111.3 (C3′), 67.2 (C5), 64.6 (C3), 53.4 (C4), 51.9 (OCH_3), 18.2 (CH_3) ppm. Mass (ESI): 336.1 (M^+), 359.0 ($M+Na)^+$. Anal. Calcd for $C_{20}H_{20}N_2O_3$ requires C 71.41, H 5.99, N 8.33, and found C 71.46, H 6.01, N 8.30.

4.3.6. *anti-3-(1H-Indol-3-yl)-5-methyl-2-phenyl-isoxazolidine-4-carboxylic acid ethyl ester (**25**)*

Yellow viscous oil. Yield (365 mg, 88%). IR ($CHCl_3$): 3418, 2280, 1732, 1598, 1488, 1429, 1217, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.16 (br s, 1H, *NH*), 7.80 (d, 1H, *J*=7.8 Hz, C4′–*H*), 7.72 (d, 1H, *J*=7.8 Hz, C7′–*H*), 7.27–7.03 (m, 5H, arom. –Hs & C6′–*H*, C2′–*H*), 7.02–6.96 (m, 3H, arom. –*Hs* & C5′–*Hs*), 5.22 (d, 1H, *J*=5.9 Hz, C3–*H*), 4.38 (dq, 1H, *J*=8.9 Hz & 5.9 Hz, C5–*H*), 4.17 (q, 2H, *J*=7.2 Hz, O*CH*$_2$), 3.08 (dd, 1H, *J*=8.9 Hz & 6.7 Hz, C4–*H*), 1.51 (d, 3H, *J*=5.9 Hz, C5–*CH*$_3$), 1.22 (t, 3H, *J*=7.2 Hz, *CH*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1 (C=O), 150.3 (q), 135.7 (C7a′), 128.9 (C3a′), 125.9 (C2′), 123.9

(2CH), 122.5 (2CH), 121.9 (C6′), 119.5 (C4′), 118.5 (C5′), 115.3 (CH), 112.1 (C7′), 111.3 (C3′), 77.3 (C5), 71.0 (C3), 61.8 (–OCH_2), 55.4 (C4) ppm. Mass (ESI): 350.1 (M^+), 373.0 (M+Na)$^+$. Anal. Calcd for $C_{21}H_{22}N_2O_3$ requires C 71.98, H 6.33, N 7.99, and found C 72.01, H 6.36, N 7.94.

4.3.7. *anti*-3-(1H-Indol-3-yl)-2,5-diphenyl-tetrahydro-pyrrolo-[3,4-d]isoxazole-4,6-dione (**26a**)

Colourless solid (hexane–chloroform, 2:1), mp 183–185 °C. Yield (466 mg, 90%). IR (KBr): 3442, 3062, 1724, 1593, 1488, 1456, 1425, 1384, 1245, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.18 (br s, 1H, *NH*), 7.87 (d, 1H, *J*=7.2 Hz, C4′–*H*), 7.42 (d, 2H, *J*=7.2 Hz, C7′–*H*), 7.36–7.21 (m, 4H, arom.–Hs & C6′–*H*), 7.20 (d, 1H, *J*=2.1 Hz, C2′–*H*), 7.00–6.95 (m, 3H, arom. –*H*s & C5′–*H*s), 6.05 (s, 1H, C3–*H*), 5.12 (d, 1H, *J*=7.5 Hz, C5–*H*), 4.15 (d, 1H, *J*=7.5 Hz, C4–*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.4 (C=O), 172.2 (C=O), 150.4 (q), 148.1 (q) 136.7 (C7a′), 129.6 (C3a′), 126.2 (C2′), 125.2 (2CH), 123.5 (2CH), 122.3 (2CH), 121.6 (2CH), 120.3 (C6′), 119.4 (C4′), 116.7 (C5′), 115.2 (CH), 114.9 (CH), 112.4 (C7′), 111.3 (C3′), 76.9 (C5), 67.6 (C3), 56.6 (C4) ppm. Mass (ESI): 410.0 (M^++1), 432.0 (M+Na)$^+$. Anal. Calcd for $C_{25}H_{19}N_3O_3$ requires C 73.34, H 4.68, N 10.26, and found C 73.37, H 4.65, N 10.30.

4.3.8. *syn*-3-(1H-Indol-3-yl)-2,5-diphenyl-tetrahydro-pyrrolo-[3,4-d]isoxazole-4,6-dione (**26b**)

Light brown solid (hexane–chloroform, 2:1), mp 215–217 °C. Yield (25 mg, 5%). IR (KBr): 3424, 3064, 1718, 1593, 1488, 1456, 1425, 1384, 1245, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.16 (br s, 1H, *NH*), 7.73 (d, 1H, *J*=7.8 Hz, C4′–*H*), 7.47 (d, 2H, *J*=7.6 Hz, C7′–*H*), 7.32–7.19 (m, 5H, overlapping signals of arom. –*H*s & C6′–*H*, C2′–*H*), 7.09–6.98 (m, 3H, arom.–*H*s & C5′–*H*s), 5.95 (d, 1H, *J*=8.7 Hz, C3–*H*), 4.98 (d, 1H, *J*=9.9 Hz, C5–*H*), 4.13 (unresolved dd, 1H, *J*∼9.4 Hz, C4–*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.5 (C=O), 171.7 (C=O), 151.2 (q), 148.3 (q) 135.7 (C7a′), 128.7 (C3a′), 127.2 (C2′), 125.8 (2CH), 124.3 (2CH), 123.1 (2CH), 122.5 (2CH), 121.3 (C6′), 120.5 (C4′), 119.1 (C5′), 116.1 (CH), 115.7 (CH), 112.6 (C7′) 111.5 (C3′), 77.3 (C5), 68.5 (C3), 57.2 (C4) ppm. Mass (ESI): 409.1 (M^+), 432.0 (M+Na)$^+$. Anal. Calcd for $C_{25}H_{19}N_3O_3$ requires C 73.34, H 4.68, N 10.26, and found C 73.40, H 4.71, N 10.22.

4.4. General procedure for the reaction of *C*-(3-indolyl)-*N*-phenylnitrone (19) with allenic esters (27a–c) under monomode microwave irradiation

In the 150 ml round bottom flask, added the *C*-(3-indolyl)-*N*-phenylnitrone (**19**, 1.28 mmol) and allenic esters (**27a**–**c**, 1.0 equiv). Then, the flask containing the contents, fitted with the condenser was placed in the cavity of the microwave reactor. After closing the cavity of the reactor with the cavity lid, the contents were irradiated (150 W, 100 °C) for 3 min (1 min hold time and 2 min running time) till all the nitrone was consumed. After completion of the reaction monitored by TLC, the residues were loaded onto silica gel column (60–120 mesh, column packed in hexane); elution of column using hexane–chloroform (gradient) afforded 50–52. The reported yields based on isolated pure products and relative proportions determined in the mixtures by ^1H NMR spectroscopy.

4.4.1. 2-(3-Methyl-1H-indol-2-yl)-3-(1H-indol-3-yl)-acrylic acid ethyl ester (**28**)

Yellow viscous oil. Yield (385 mg, 84%). IR ($CHCl_3$): 3334, 3307, 2979, 1681, 1515, 1446, 1238, 748 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.35 (s, 1H, C8–*H*), 8.07 (br s, 1H, *NH*), 7.84 (br s, 1H, *NH*), 7.76 (dd, 2H, *J*=6.4 Hz & 2.1 Hz, arom.–Hs), 7.57 (d, 2H, *J*=7.5 Hz, arom.–Hs), 7.33–7.09 (m, 4H, arom. Hs), 6.36 (d, 1H, *J*=3.0 Hz, C2–H), 4.28 (q, 2H, *J*=13.9 Hz & 6.9 Hz, O*CH*$_2$), 2.09 (s, 3H, C3′–*CH*$_3$), 1.29 (t, 3H, *J*=6.9 Hz, *CH*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.9 (C=O), 136.1 (C8), 135.8 (C9), 135.3 (C7a′), 129.3 (C7a), 128.1 (C3a′), 127.7 (C3a), 126.9 (C2′), 123.1 (C4′), 122.0 (C3), 121.3 (C4), 119.6 (C5), 119.2 (C5′), 118.5 (C6′), 117.3 (C6), 111.7 (C3′), 111.3 (C7′), 111.1 (C7), 60.9 (O*CH*$_2$), 14.6 (*CH*$_3$), 9.4 (*CH*$_3$) ppm. Mass (ESI): 344.1 (M^+), 367.1 (M+Na)$^+$. Anal. Calcd for $C_{22}H_{20}N_2O_2$ requires C 76.72, H 5.85, N 8.13, and found C 76.75, H 5.89, N 8.09.

4.4.2. 2-(3-Ethyl-1H-indol-2-yl)-3-(1H-indol-3-yl)-acrylic acid ethyl ester (**29**)

Light yellow crystal (benzene–chloroform, 4:1), mp. 85–87 °C. Yield (428 mg, 90%). IR ($CHCl_3$): 3394, 3265, 2970, 1677, 1556, 1458, 1242, 729 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.39 (s, 1H, C8–*H*), 8.13 (br s, 1H, *NH*), 7.81 (unresolved dd, 2H, *J*∼7.3 Hz, arom.–Hs), 7.74 (br s, 1H, *NH*), 7.66 (d, 2H, *J*=7.5 Hz, arom.–Hs), 7.33–7.11 (m, 4H, arom.–Hs), 6.23 (d, 1H, *J*=3.0 Hz, C2–*H*), 4.28 (q, 2H, *J*=14.1 Hz & 7.2 Hz, O*CH*$_2$), 2.62 (q, 2H, *J*=15.0 Hz & 7.5 Hz, C3′–*CH*$_2$), 1.30 (t, 3H, *J*=7.2 Hz, CH$_3$), 1.15 (t, 3H, *J*=7.5 Hz, *CH*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.6 (C=O), 136.4 (C8), 136.1 (C9), 135.1 (C7a′), 129.1 (C7a), 128.2 (C3a′), 127.5 (C3a), 127.1 (C2), 126.1 (C2′), 123.0 (C4′), 121.7 (C3), 121.2 (C4), 119.4 (C5), 119.0 (C5′), 118.4 (C6′), 117.5 (C6), 116.2 (C3′), 111.5 (C7′), 111.3 (C7), 60.9 (OCH$_2$), 18.0 (C3′–*C*H$_2$), 14.8 (*C*H$_3$), 14.4 (*C*H$_3$) ppm. Mass (ESI): 358.0 (M^+), 381.1 (M+Na)$^+$. Anal. Calcd for $C_{23}H_{22}N_2O_2$ requires C 77.07, H 6.19, N 7.82, and found C 77.10, H 6.14, N 7.84.

4.4.3. 3-(1H-Indol-3-yl)-acrylic acid ethyl ester (**30**)

Light yellow crystal (benzene–chloroform, 4:1), mp 89–91 °C. Yield (444 mg, 90%). IR ($CHCl_3$): 3354, 3168, 2965, 1729, 1578, 1465, 1248, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.52 (br s, 1H, *NH*), 7.92 (d, 1H, *J*=15.9 Hz, C8–*H*), 7.91 (d, 1H, *J*=2.1 Hz, C2–*H*), 7.48 (d, 1H, *J*=7.8 Hz, C4–*H*), 7.42 (dd, 1H, *J*=9.3 Hz & 3.6 Hz, arom.–*H*), 7.31–7.21 (m, 2H, arom.–*H*s), 6.46 (d, 1H, *J*=15.9 Hz, C9–*H*), 4.27 (q, 2H, *J*=14.1 Hz & 7.2 Hz, –O–*CH*$_2$–), 1.35 (t, 3H, *J*=7.2 Hz, –*CH*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.0 (C=O), 142.8 (C8), 136.0 (C7a), 128.1 (C3a), 124.3 (C2), 123.6 (C9), 122.3 (C5), 121.4 (C4), 120.7 (C6), 111.8 (C7), 59.6 (–O–*CH*$_2$), 13.7 (–CH$_3$) ppm. Mass (ESI): 238.1 (M+Na)$^+$. Anal. Calcd for $C_{13}H_{13}NO_2$ requires C 72.54, H 6.09, N 6.51, and found C 72.60, H 6.14, N 6.46.

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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.2009.05.093.

References and notes

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18. (a) Compound **29**: CCDC no. 634261; $C_{23}H_{22}N_2O_2$, formula weight=358.4, triclinic, *P*−1, *a*=8.988(3) Å, *b*=10.338(2) Å, *c*=11.918(3) Å, α=104.10(1)°, β=108.34(2)°, γ=102.75(1)°, *V*=964.8(5) Å^3, ρ_c=1.234 Mg m^{-3}, μ=0.079 mm^{-1}, *F*(000)=380, reflections collected=5860, full-matrix least-squares refinement techniques on F^2, parameters 247, *R*1=0.0530, *wR*2=0.1338, largest diff. peak and hole (0.229 and −0.259 e Å^{-3}); (b) Compound **30**: CCDC no. 643204; $C_{13}H_{13}N_1O_2$, formula weight=215.3, Monoclinic *P*21/*n*, *a*=9.061(1) Å, *b*=13.109(1) Å, *c*=9.888(1) Å, β=106.96°, *V*=1123.42(2) Å^3, ρ_c=1.273 Mg m^{-3}, μ=0.086 mm^{-1}, *F* (000)=456, reflections collected=2727, full-matrix least-squares refinement techniques on F^2, parameters=145, *R*1=0.0627, *wR*2=0.1381, largest diff. peak and hole (0.129 and −0.181 e A^{-3}); (c) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343; (d) Sheldrick, G. M. *SHELX97, A Program for Crystal Structure Analysis and Structure Refinement*; University of Göttingen: Göttingen, Germany, 1997; (e) Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837.
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