



# Formation and reductive ring opening reactions of indolyl-isoxazolidines: access to novel natural product analogs and precursors

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## ABSTRACT

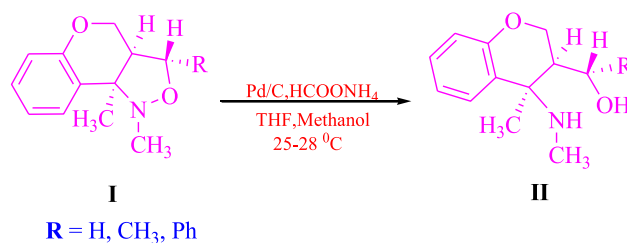
Regio- and stereoselective 1,3-dipolar cycloadditions of C-(3-indolyl)-N-phenylnitron (2) with variedly substituted dipolarophiles were carried out to obtain syn- C4 and C5 substituted indolyl-isoxazolidines **6a–c** and **7a–f**, respectively. Reduction of obtained isoxazolidines, by employing various reducing agents, causes cleavage of the N–O bond, which is accompanied by concomitant cleavage of C–N bond leading to the formation of a library of novel indole based natural product analogs and precursors.

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## 1. Introduction

1,3-Dipolar cycloaddition is a versatile tool in the hands of synthetic organic chemists to generate various biologically important target molecules and their precursors.<sup>1</sup> Notably, substituted isoxazolidines have been synthesized via 1,3-dipolar cycloadditions of nitrones with alkenes and are important precursors to  $\beta$ -amino acids,<sup>2</sup>  $\beta$ -lactams,<sup>3</sup> 1,3-amino alcohols,<sup>4a</sup> and pyrrolidinones<sup>4b</sup> obtained through reductive N–O bond cleavage. Earlier, we have reported the formation of conformationally constrained  $\beta^{2,3}$ -amino alcohols by reductive cleavage of the N–O bond of tricyclic isoxazolidines with ammonium formate in the presence of palladium on charcoal (Pd/C) or zinc-acetic acid (Scheme 1).<sup>5a</sup>

There are available various literature reports, where oxazolidinones have been subjected to reductive ring opening to get natural products, precursors for natural products and peptidomimetics.<sup>5b–h</sup>



Scheme 1.

On the other hand, the indole moiety is a prominent and privileged structural motif found in numerous natural products, metabolites, neurotransmitters and various synthetic compounds with interesting biological activities (Fig. 1). A large number of indole alkaloids are reported to possess cytotoxic, analgesic, anxiolytic, anti-inflammatory, and immunomodulating activities.<sup>6a</sup>

Inspired by reported significance of indole based scaffolds<sup>6a</sup> and in continuation of our previous work,<sup>5a,6b</sup> we have examined 1,3-dipolar cycloaddition reactions of C-(3-indolyl)-N-phenylnitron with various dipolarophiles to obtain variously substituted indolyl-isoxazolidines; reductive cleavage of N–O bond of the obtained

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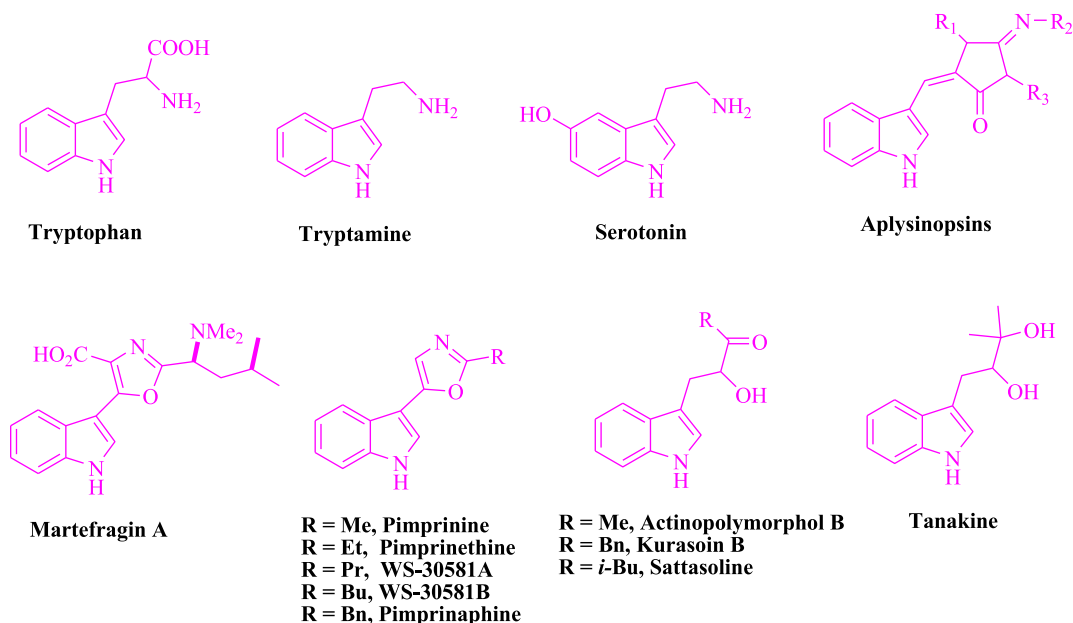


Fig. 1. Structures of some naturally occurring indoles.

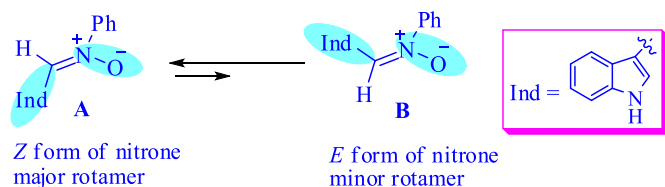


Fig. 2. E and Z conformations of nitrone (2).

isoxazolidines was anticipated to furnish valuable precursors for the preparation of pharmaceuticals, natural products and peptidomimetic scaffolds.

## 2. Results and discussion

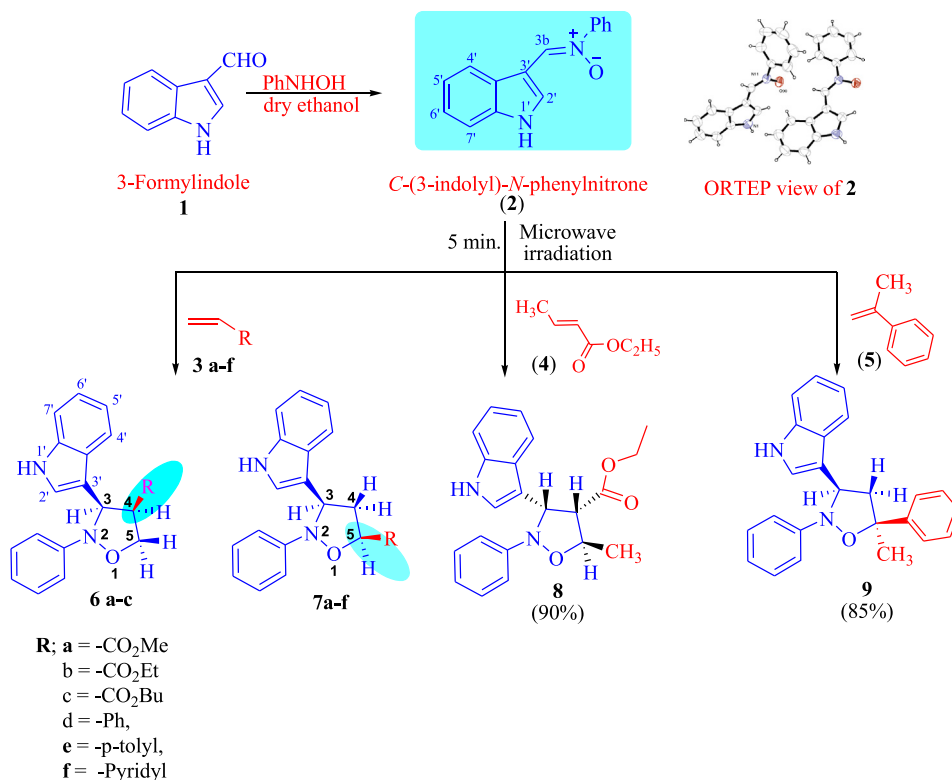
### 2.1. (a) Regio- and stereoselective 1,3-dipolar cycloadditions of C-(3-indolyl)-N-phenylnitron (2) with variously substituted dipolarophiles (3–5)

Initially, the reactions of C-(3-indolyl)-N-phenylnitron (2) with various monosubstituted and disubstituted dipolarophiles (**3a–f**, **4** and **5**) were carried out by irradiating equimolar amount of the addends in a focused monomode microwave reactor.<sup>6</sup> After completion of the reactions (monitored by TLC) the residues obtained were resolved by column chromatography over silica gel to obtain the cycloadducts **6–9**, which were characterized spectroscopically (<sup>1</sup>H NMR, <sup>13</sup>C NMR and HRMS). The results are summarized in Scheme 2 and Table 1.

The assigned regiochemistry of addition in **6a–c** is based on <sup>1</sup>H NMR chemical shift of methylene-Hs (C5–Hs) located at δ 4.55–4.41 and this downfield shifted position in <sup>1</sup>H NMR is indicative of the attachment of methylene carbon to oxygen in **6a–c**. These conclusions are corroborated by the observed proton connectivities (couplings) and <sup>13</sup>C NMR chemical shift assignments, which clearly indicated that C4–H is vicinal to both C3–H and C5–Hs. The *syn/anti*-stereochemistry in **6a–c** involving indole group at C3 and the ester functionality at C4 of isoxazolidine ring is based on <sup>1</sup>H NMR couplings involving C3–H and C4–H, and follows from the premise that the *cis*-vicinal <sup>1</sup>H coupling

constants are always higher than *trans* in case of isoxazolidines and related heterocycles.<sup>7</sup> Thus, for instance, in the case of **6b**, C3–H appeared as a doublet at δ 5.44 (*J* = 8.6 Hz); the high value of *J*<sub>3,4</sub> alluded to *cis* arrangement. However, in the case of **7a–f**, <sup>1</sup>H NMR clearly indicated that the methylene hydrogens (C4–Hs) are coupled with both C3–H and C5–H, and is corroborated by <sup>13</sup>C chemical shifts of various carbons of isoxazolidine moiety. For instance, the <sup>13</sup>C NMR resonance of methylene carbon (C4) in **7a–f** appeared in the range δ 37–45, clearly indicating that it is not attached to oxygen. The assigned stereochemistry in cycloadducts (**7a–f**) is also based on NMR spectral evidence. The *syn* relationship between indole moiety at C3 and various substituents at C5 in **7a–f** are based on <sup>1</sup>H NMR couplings involving C3–, C4– and C5–Hs and followed from the consistent observation<sup>6,7b–d,8</sup> that the *cis* vicinal <sup>1</sup>H coupling are always higher (5–9 Hz) than the *trans* (0–6 Hz) in case of isoxazolidines. For instance, in compound **7f** the values of coupling constants *J*<sub>3,4a</sub> = 8.2 Hz, *J*<sub>3,4b</sub> = 5.4 Hz, *J*<sub>5,4a</sub> = 7.5 and *J*<sub>5,4b</sub> = 4.2 Hz, indicated that both C3–H and C5–H shows higher coupling and hence *cis* relationship with C4–Ha, thereby, establishing a *cis* relationship between C3–H and C5–H.

The formation of cycloadducts **6a–c** as minor regioisomer of addition can be rationalized in terms of the frontier molecular orbital controlled cycloaddition involving HOMO (dipole)-LUMO (dipolarophiles) interaction.<sup>6,9</sup> To rationalize the effect of 3-indolyl moiety on the molecular orbitals of 1,3-dipole, the DFT (Density functional theory) calculations were performed using GGA-DFT package DMol-3<sup>6d,e</sup> on C-(3-indolyl)-N-phenylnitron (2), α, N-diphenyl nitron (2A) and C-(chrom-4-one-3-yl)-N-phenylnitron (2B) in Z conformation, whose cycloaddition reactions have been reported by us earlier (Table 2).<sup>6b,c,10</sup> The calculations revealed that nitron 2 has high lying HOMO as compared to other nitrones 2A and 2B. Therefore, formation of 4-substituted regioisomer is obtained even with less electron deficient dipolarophiles. Normally, 4-substituted isoxazolidines are obtained in reactions involving highly electron deficient dipolarophiles such as nitro-olefins,<sup>9</sup> wherein HOMO (dipole)-LUMO (dipolarophiles) interaction intervenes, however, in the case of relatively electron rich dipoles having a high lying HOMO result in obtaining of 4-regioisomers even with less electron deficient dipolarophile such as acrylates.



**Scheme 2.** Synthesis of variously substituted Indolyl-Isoxazolidines (6–9).

**Table 1**  
Reaction time and yields (%) of products 6–9

Serial no.	Dipolarophile	Reaction time (min)	Yield (%) <sup>a</sup> of various products 6:7, 8 and 9	
1	3; R=–O <sub>2</sub> Me	5	6a (40%)	7a (45%)
2	R=–CO <sub>2</sub> Et	5	6b (45%)	7b (50%)
3	R=–CO <sub>2</sub> Bu	5	6c (40%)	7c (55%)
4	R=–Ph	5	6d (–)	7d (90%)
5	R=–p-Tolyl	5	6e (–)	7e (88%)
6	R=–Pyridyl	5	6f (–)	7f (80%)
7	4	5	8 (88%)	
8	5	5	9 (90%)	

<sup>a</sup> Based on isolated pure products along with, in some cases, <sup>1</sup>H NMR spectral analysis of mixture fractions from column chromatography.

Formation of mixture of regioisomers in addition of nitrones with dipolarophiles such as acrylates, nitro-olefins and acrylonitrile has precedents,<sup>9</sup> whereas, the regioselective addition leading to major products 7a–f, is a consequence of LUMO (dipole)-HOMO (dipolarophiles) interactions anticipated for 1,3-cycloadditions involving nitrones.<sup>9,10</sup>

The observed *syn*-selective cycloaddition of the C-(3-indolyl)-N-phenylnitrone (2) to acrylates (3a–c) leading to 6a–c, the minor cycloadducts, can be rationalized in terms *exo*-mode of addition of nitrone in Z-form<sup>13a</sup> (approach 1, Fig. 3). Alternatively, the stable Z-forms (A) of nitrones are reported to exist in equilibrium with a small amount of the *E*-isomer (B) of the nitrone under reaction conditions (Fig. 2); involvement of nitrone in its more reactive, i.e., less stable *E*-form in cycloaddition leading to major reaction products is preceded.<sup>9d</sup> Therefore, addition of nitrone (2) in *E*-form through an *endo*-transition state, known to be favored for a variety of reason,<sup>6,9d</sup> can also explain the obtained *syn* stereochemistry in the case of 6a–c (approach II, Fig. 3).

Similarly, corresponding *syn* cycloadducts 7a–f (C5-substituted regio-isomer), can originate from an *exo*-mode of addition of the substituent on the dipolarophiles with the nitrone in its Z-form (approach III) or/and *endo*-mode of addition of dipolarophiles with nitrone reacting in *E* form (approach IV) as shown in Fig. 4.<sup>10</sup>

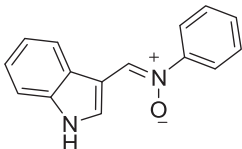
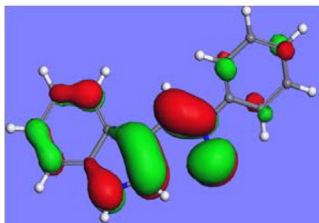
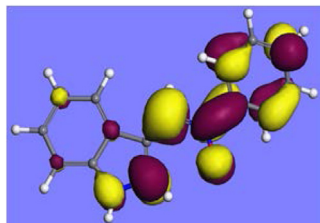
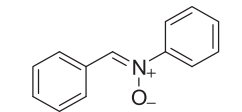
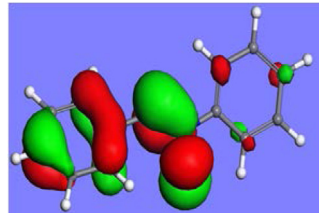
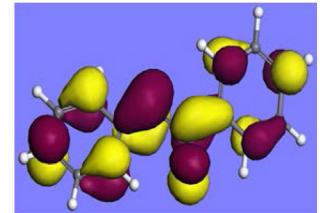
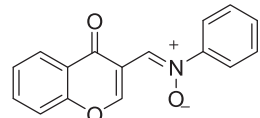
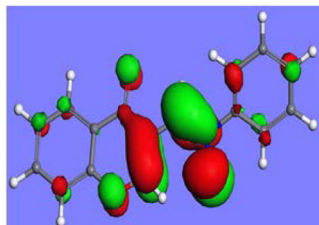
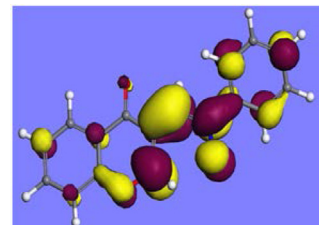
Further, the investigations were extended to disubstituted dipolarophiles such as ethyl crotonate (4) and  $\alpha$ -methyl styrene (5). The reaction of nitrone (2) with ethyl crotonate (4) afforded a single product, which has been characterized as cycloadduct 8 by comparison of the spectroscopic data with the data reported for cycloadducts derived from addition of some nitrones to crotonates.<sup>11</sup> The structures of cycloadducts 8 and 9 were established spectroscopically (<sup>1</sup>H NMR, <sup>13</sup>C NMR and HRMS); finally, confirmed by X-ray crystallography (Fig. 5).<sup>13b,c</sup>

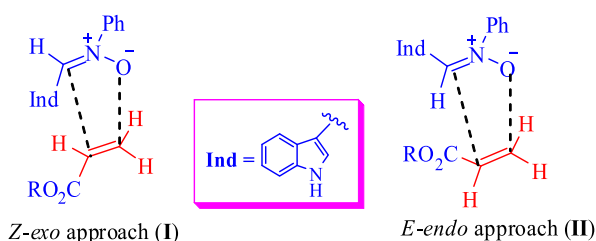
Though, the regiochemistry of addition to 4 and 5 was anticipated in the light of literature reports,<sup>9</sup> however, in the case of cycloadduct 8, the obtained *stereo*-selectivity can be rationalized in terms of addition of nitrone in its Z-form with ester moiety of 4 being *exo*-oriented and methyl moiety is *endo*-oriented or nitrone in its *E*-form approaches with ester moiety being *endo*-oriented and methyl is *exo*-oriented. Similarly, cycloadduct 9 can originate from an *exo*-orientation of the phenyl substituent on the dipolarophile 5 with the nitrone in its Z-form or nitrone in its *E*-form approaches with phenyl moiety being *endo*-oriented.

## 2.2. (b) Cleavage of N–O bond of obtained isoxazolidines (6–9)

Earlier, we have reported the formation of conformationally constrained  $\beta^{2,3}$ -amino alcohols, which are valuable precursors for pharmaceuticals and peptidomimetic scaffolds, via reductive cleavage of the N–O bond of tricyclic isoxazolidines.<sup>5a</sup> Therefore, the cleavage of N–O bond of obtained indolyl-isoxazolidines was investigated under reductive conditions as employed earlier.<sup>5a</sup>

**Table 2**  
HOMO and LUMO energies and HOMO-LUMO gap energies for nitrones **2**, **2A** and **2B** by DFT calculations

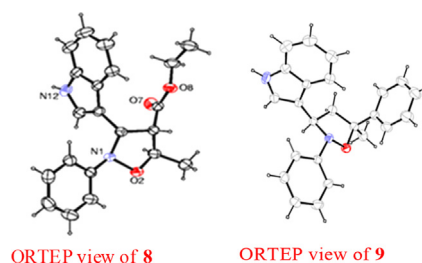
Nitrones	Molecular orbital of HOMO-LUMO of nitrones	HOMO-LUMO gap energies	
 C-(3-indolyl)-N-phenylnitron ( <b>2</b> )	 HOMO (-4.276 eV)	 LUMO (-2.448 eV)	1.828
 $\alpha$ ,N-diphenyl nitron ( <b>2A</b> )	 HOMO (-4.688 eV)	 LUMO (-3.117 eV)	1.571
 C-(chrom-4-one-3-yl)-N-phenylnitron ( <b>2B</b> )	 HOMO (-5.079 eV)	 LUMO (-3.454 eV)	1.625



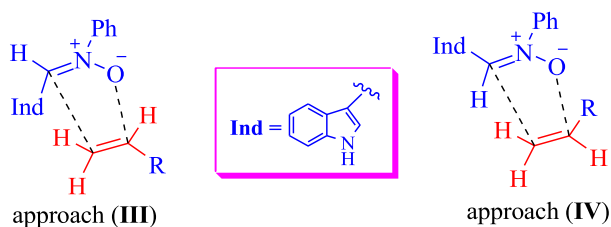
**Fig. 3.** 1,3-dipolar cycloadditions of nitron (**2**) to substituted acrylates (**3a–c**).

Initially, compound **7b** was subjected to reduction with  $\text{HCOONH}_4$  (5 equiv) and 5% Pd/C (5 equiv) in a mixture of solvents (THF:Methanol) at room temperature. The obtained product was characterized spectroscopically ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS) as *ethyl-2-*

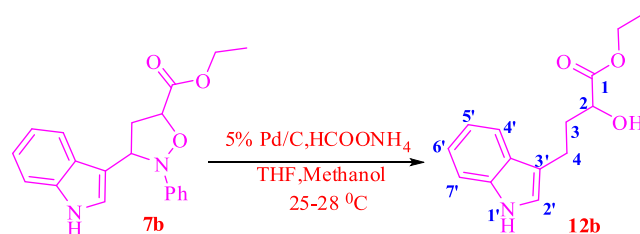
*hydroxy-4-(1H-indol-3-yl) butanoate (12b)*, derived from cleavage of N–O bond along with reductive loss of aniline moiety, in 61% yield. Some unconsumed starting material was also recovered after



**Fig. 5.** ORTEP diagram of compounds **8** and **9**.



**Fig. 4.** 1,3-dipolar cycloadditions of nitron (**2**) to monosubstituted dipolarophiles (**3d–f**).



**Scheme 3.** Reductive cleavage of N–O bond of comp. (**7b**).

6 h (Scheme 3) and no amino alcohol was detected.  $^1\text{H}$  NMR of compound **12b** showed a doublet at  $\delta$  2.90 ppm (1H), exchangeable with  $\text{D}_2\text{O}$ , which was ascribed to OH group. The presence of ester moiety in **12b** is confirmed by quartet (2H) and triplet (3H) at  $\delta$  4.18 and  $\delta$  1.26, respectively with mutual coupling constant of  $J=7.0$  Hz. The presence of two methylene ( $2\times\text{CH}_2$ ) groups were further corroborated by  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral evidences. The assigned structure is also supported by proton-carbon connectivities via HSQC spectrum. The peak corresponding to the mass of **12b** with  $m/z$  270.1099 (calcd  $m/z$  270.1101  $[\text{M}+\text{Na}]$ ) was observed in the high resolution mass spectrum (HRMS), which confirmed the assigned structure.

In order to obtain the desired amino-alcohol product via cleavage of N–O bond of **7b**, a variety of other reductive conditions were evaluated (Table 3). However, reaction of **7b** under various reductive conditions results in the formation of **12b** only, in varied yields and no desired amino-alcohol product was formed.

**Table 3**  
Optimization of reductive ring opening of isoxazolidine **7b**: Screening of reducing agents

Entry	Reducing agent	Solvent	Yield (%)	Time (h)
1	Zn (5 equiv)	AcOH	35	11
2	Zn (10 equiv)	AcOH	40	10
3	Zn (5 equiv)	AcOH:H <sub>2</sub> O	36	12
4	Zn (10 equiv)	AcOH:H <sub>2</sub> O	42	12
5	Zn–HCOONH <sub>4</sub> (5 equiv)	THF:MeOH	52	8
6	Zn–HCOONH <sub>4</sub> (10 equiv)	THF:MeOH	58	8
7	5% Pd/C–HCOONH <sub>4</sub> (5 equiv)	THF:MeOH	61	6
8	5% Pd/C–HCOONH <sub>4</sub> (10 equiv)	THF:MeOH	65	4
9	10% Pd/C–HCOONH <sub>4</sub> (5 equiv)	THF:MeOH	68	2
10	10% Pd/C–HCOONH <sub>4</sub> (10 equiv)	THF:MeOH	85	0.5

It was observed that the use of an excess (10 equiv) of ammonium formate and 10% Pd/C in THF–MeOH solvent, efficiently cleaved the N–O and C–N bonds of compound **7b** at RT to furnish compound **12b** in good yield and in less time than Zn/acetic acid and Zn/HCOONH<sub>4</sub> (entry 10, Table 3); the reaction is also very neat and clean.

Further, to investigate the substrate influence on reductive cleavage of N–O bond of isoxazolidines and to examine whether the obtained reductive loss of aniline moiety is a general behavior of 3-(1H-Indol-3-yl)-isoxazolidine derivatives (**6–9**); these were subjected to the optimized reductive conditions (entry 10, Table 3). As observed, when compounds **6a–c** (bearing ester moiety at C4) were subjected to reduction, these afforded compounds **10a–c** in good yields along with indolyl acrylates (**11a–c**) as minor products (Scheme 4), whereas, reductive N–O bond cleavage of isoxazolidines **7a–f** (C5-substituted regioisomer) and cycloadduct **9** led to the formation of compounds **12a–f** and **13** (Scheme 5); the formation of compounds **10–13** revealed that the concomitant reductive cleavage of C–N bond leads to loss of aniline moiety is general behavior of the indolyl-isoxazolidines, under optimized reductive conditions.

All the products were isolated and purified by column chromatography (silica gel 60–120 mesh, eluted with ethyl acetate: Hexane (4:6)) and the assigned structures of adducts (**10a–c**, **11a–c**, **12a–f** and **13**) are based on rigorous spectroscopic analysis

( $^1\text{H}$ ,  $^{13}\text{C}$  NMR including COSY, HSQC and HRMS). The  $^1\text{H}$  NMR spectra of compound **10b** clearly indicated the presence of quartet (2H) and triplet (3H) at  $\delta$  4.18 and  $\delta$  1.24 ppm with coupling constant of  $J=7.0$  Hz attributed to ester moiety. The broad singlet observed at  $\delta$  2.65 ppm (1H, exchangeable with  $\text{D}_2\text{O}$ ) was assigned to the OH-proton. Another doublet of two protons was observed at  $\delta$  3.82 ppm, ascribable to the methylene group vicinal to OH and ester group, and this downfield shift confirms that this methylene group is attached to heteroatom. Other  $^1\text{H}$  and  $^{13}\text{C}$  NMR assignments were in agreement with the assigned structure. The peak corresponding to the mass of **10b** with  $m/z$  248.1272 (calcd  $m/z$  248.1281  $[\text{M}+\text{H}]^+$ ) was observed in the high resolution mass spectrum (HRMS), which also confirmed the molecular formula ( $\text{C}_{14}\text{H}_{17}\text{NO}_3$ ) for assigned structure.

On the other hand, in the case of compounds **11a–c**, the presence of *trans*-substituted olefinic moiety, besides ester function, was revealed by appearance of two mutually coupled  $^1\text{H}$  resonance doublets at  $\delta$  7.92–7.85 and  $\delta$  6.59–6.43 (coupling constant value of  $J=15.9$ – $16.0$  Hz); a characteristic feature of  $\alpha,\beta$ -unsaturated ester function. The peaks at  $m/z$  224.0675, 216.1011 and 266.1140 in the HRMS of compounds **11a**, **11b**, and **11c**, respectively, confirmed the assigned structures (calcd  $m/z$  224.0681  $[\text{M}+\text{Na}]^+$ , 216.1019  $[\text{M}+\text{H}]^+$ , 266.1151  $[\text{M}+\text{Na}]^+$ , respectively); as the obtained indolyl-acrylates (**11a–c**) are known compounds and these were further confirmed by comparison of melting points with literature data.

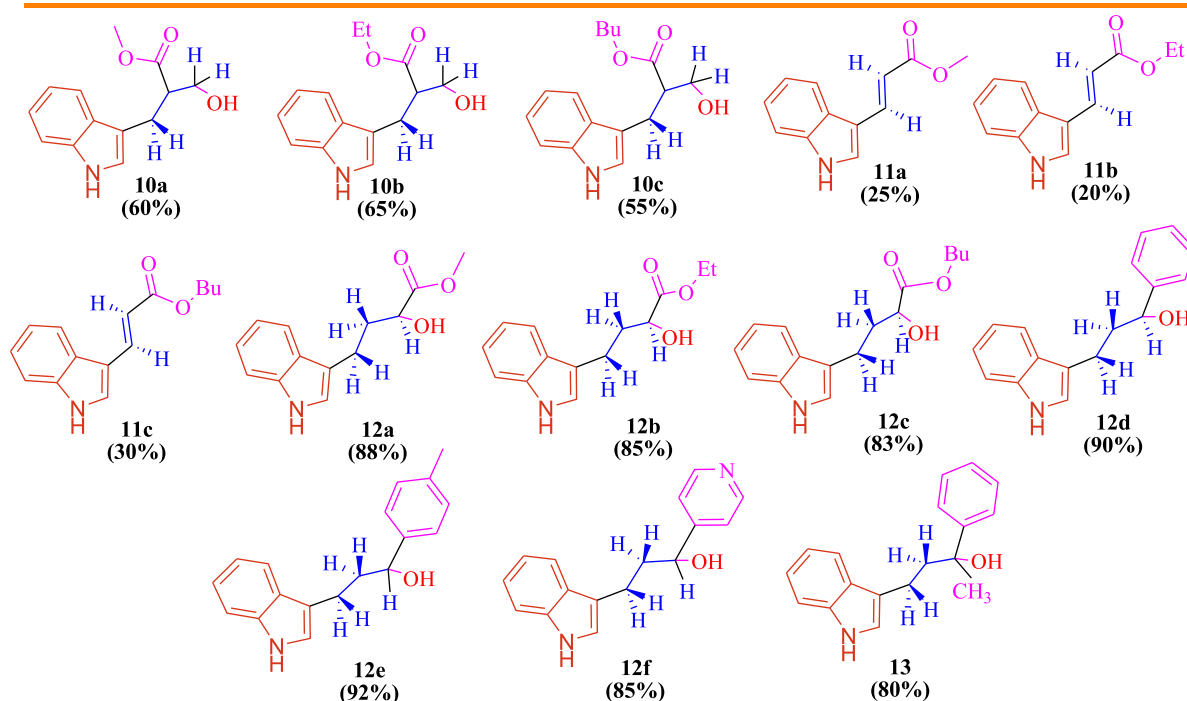
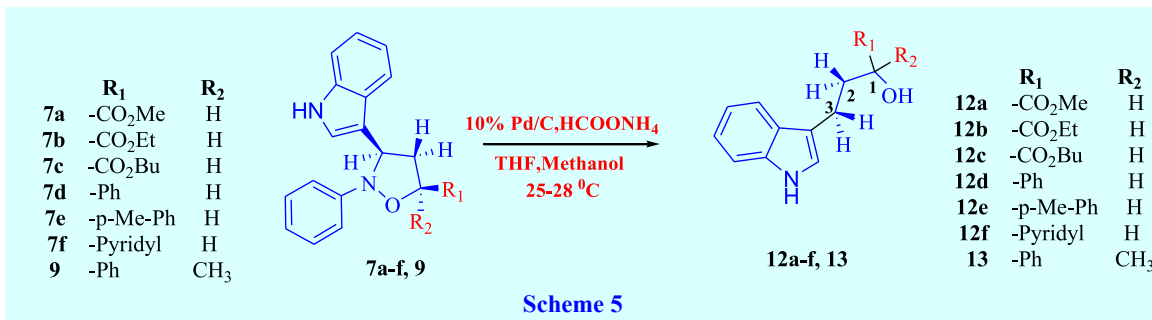
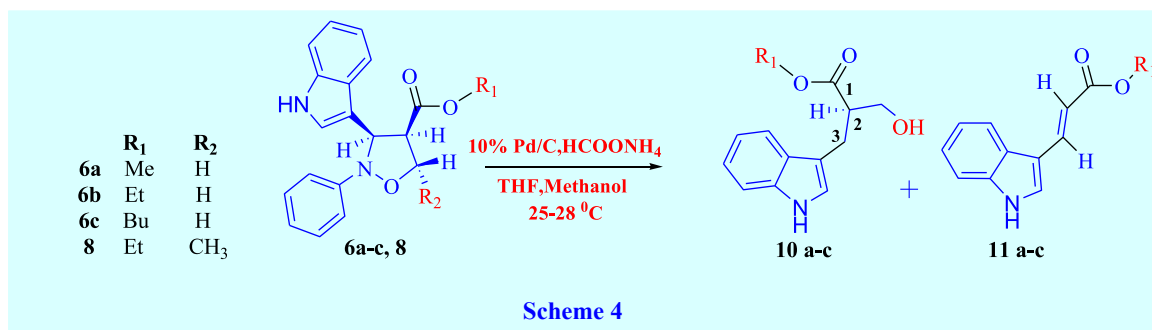
Mechanistically, the major transformation of cycloadducts **6a–c** and **7a–f**, leading to the formation of **10a–c** and **12a–f**, respectively, involves the reductive cleavage of N–O bond and concomitant cleavage of C–N bond of isoxazolidine moiety leading to loss of aniline moiety (Schemes 6 and 7). The reductive cleavage of allylic and benzylic C–N bond under drastic conditions has precedents,<sup>12</sup> however, in present study, complete loss of aniline moiety occurs under much milder conditions and no amino alcohol is formed as reported earlier<sup>5a</sup>.

The formation of minor products **11a–c**, results from the reductive cleavage of N–O bond followed by sequence of retro Aldol reaction and loss of aniline moiety (Scheme 6). Apparently, compounds **10a–c** and **11a–c** have been derived from common intermediate **[C]** and compounds **12a–f** and **13** are derived from an analogous intermediate **[D]** as shown in Schemes 6 and 7, however, it is not clear whether retro-aldol triggers eliminative loss of aniline moiety or cleavage of C–N bond triggers retro-aldol reaction. Apparently, the differing behavior of isoxazolidines (**6–9**) on reductive cleavage, leading to loss of aniline moiety as compared to formation of amino alcohols reported by us earlier,<sup>5a</sup> is a consequence of contiguous position of aniline moiety to electron rich C3 of indole nucleus.

To establish the general behavior of such C3 indolyl-isoxazolidines, isoxazolidine (**16a**) was synthesized by addition of nitron (**15**) to 4-methylstyrene (**3e**, Scheme 8). The compound **16** was isolated chromatographically and characterized spectroscopically ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS). Isoxazolidine **16a** was subjected to reductive cleavage under optimized conditions, which led to the formation of compound **17** (Scheme 8); isolated chromatographically and characterized spectroscopically ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS). This clearly indicates the general applicability of the developed procedure to synthesize substituted indole derivatives (**10–13** and **17**).

To further establish that the loss of aniline moiety is a specific feature of indol-3-yl substituted isoxazolidines, pyridyl-isoxazolidine derivative (**20a**) was synthesized by addition of nitron<sup>7a</sup> (**19**) to 4-methylstyrene (**3e**, Scheme 9). The compound **20** was isolated chromatographically and characterized spectroscopically ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS). However, when compound **20a** was subjected to reductive cleavage under optimized conditions, it led to the formation of amino alcohol derivative (**21**,





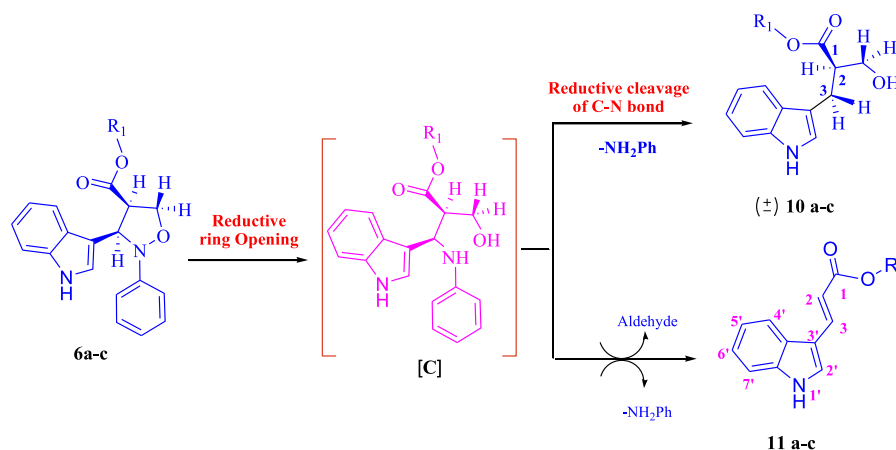
**Schemes 4 and 5.** Reductive ring opening of Indolyl-isoxazolidines **6–9**; **Reaction conditions:** 1.5 mmol of substrate (**6–9**), 10 equiv of 10% Pd/C, 10 equiv of HCOONH<sub>4</sub>, THF/MeOH (1:3), RT.

**Scheme 9**), which was isolated chromatographically and characterized spectroscopically (<sup>1</sup>H NMR, <sup>13</sup>C NMR and HRMS). These experiments firmly confirmed our earlier observation that the loss of aniline moiety during reductive cleavage is a consequence of its contiguous position to the electron rich C3-position of indole nucleus.

### 3. Conclusions

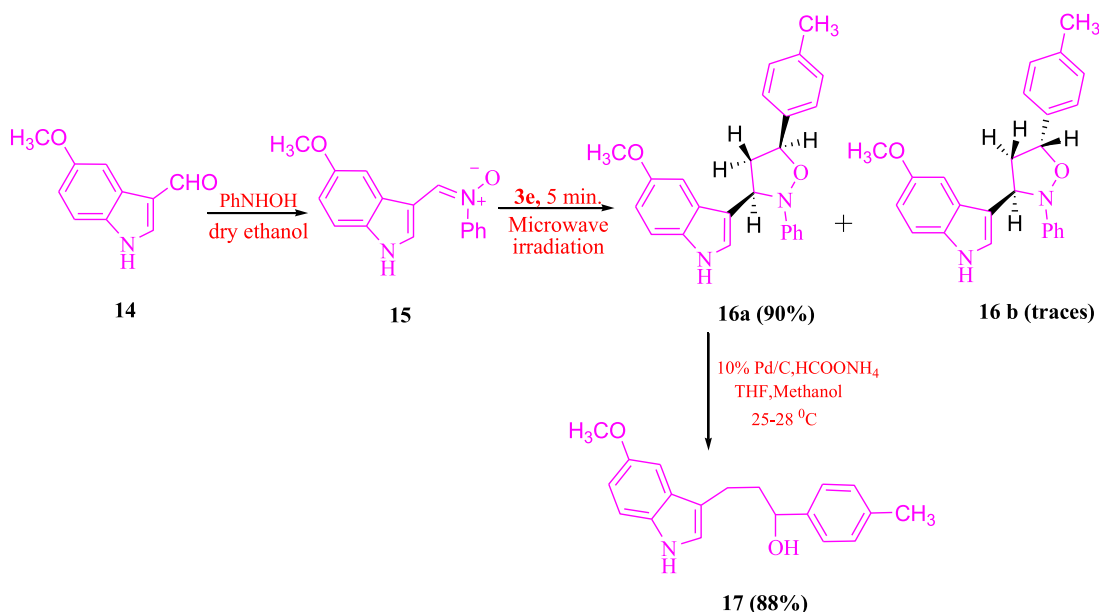
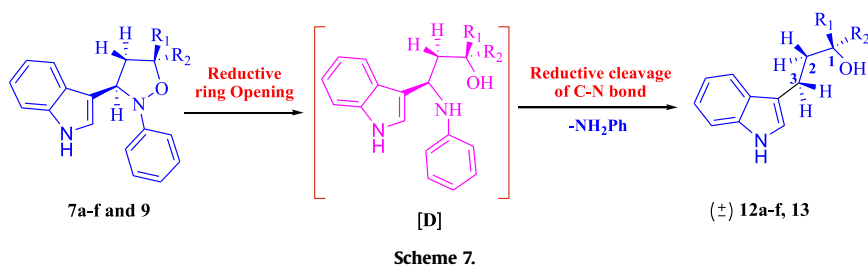
Regio- and stereoselective 1,3-dipolar cycloadditions of nitron (2) with variously substituted dipolarophiles (3–5) lead

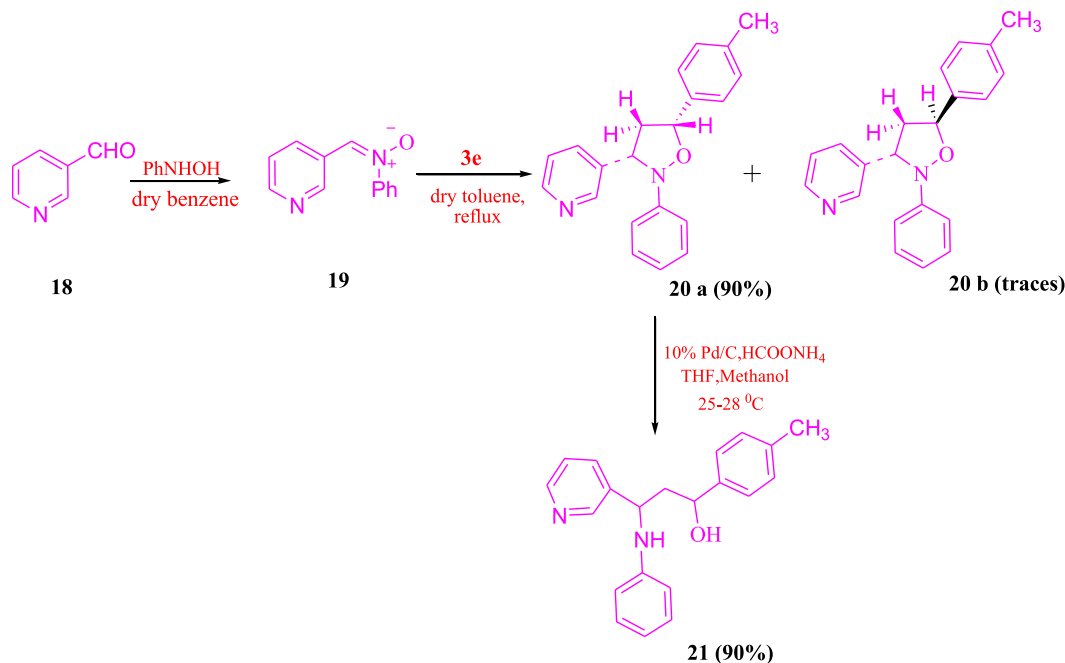
to syn- C4 and C5 substituted indolyl-isoxazolidines **6a–c** and **7a–f**, respectively. The obtained isoxazolidines were subjected to reduction under variety of conditions, however, with ammonium formate and 10% Pd/C at RT, results in the formation of a novel compounds (**10a–c**, **12a–f** and **13**) along with indolyl-acrylates (**11a–c**) via reductive ring opening of isoxazolidine moiety and concomitant cleavage of C–N bond leading to loss of aniline moiety; the observed facile concomitant cleavage of C–N bond under milder conditions is a new characteristic feature not observed in related isoxazolidines.<sup>4b,5,6</sup> That the loss of aniline moiety is



a consequences of its contiguous position to electron rich C3 atom of indole nucleus has been established by carrying out further experiments with methoxy-indolyl-isoxazolidine (**16a**) and pyridyl-isoxazolidine (**20a**). Moreover, due to the structural resemblance of  $\alpha$ -hydroxy ketones **12a–c** with the naturally

occurring and pharmacologically active  $\alpha$ -hydroxy ketones kurasoins and sattazolin, the obtained chemistry has lots of potential; therefore, these findings should be of considerable interest for the construction of novel bio-active molecules, natural product precursors and peptidomimetic scaffolds.





## 4. Experimental section

### 4.1. Materials and equipments

Starting materials and reagents were purchased from commercial suppliers and used after further purification (crystallization/distillation).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance 500 MHz NMR spectrometer using  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$  as a solvent. Chemical shifts are given in ppm with TMS as an internal reference.  $J$  values are given in Hertz. Mass spectra were recorded on a Bruker micrOTOF Q II Mass spectrometer (LC MS/MS). The CEM-Discover Focused Monomode Microwave reactor (2450 MHz, 300 W) was used for microwave irradiation. Reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel GF-254. Column chromatography was performed with 60–120 mesh silica. All melting points are uncorrected and measured in open glass-capillaries using Veego Precision Digital Melting Point Apparatus.

### 4.2. Synthesis

**4.2.1. General procedure for synthesis of C-(3-indolyl)-N-phenyl-nitron (2).** 3-Formylindole (2.8 mmol) was dissolved in dry ethanol (30 ml) and to the clear solution *N*-phenylhydrazone 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 nitrones (**2**) as light yellow powder (yield 90%). The nitrone was dried under vacuum and stored under refrigeration.

**4.2.2. General procedure for the reaction of C-(3-indolyl)-N-phenyl-nitron (2) with various dipolarophiles (3a–f, 4 and 5) under monomode microwave irradiation.** C-(3-indolyl)-N-phenyl-nitron (**2**, 1.28 mmol) and dipolarophiles (**3a–f**, **4** and **5**; 1.0 equiv) were added in the 150 ml round bottom flask, fitted with a condenser,

which 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 nitrones (**2**) was consumed (monitored by TLC). 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 **6–9**. The reported yields were based on isolated pure products and relative proportions determined in the mixtures by  $^1\text{H}$  NMR spectroscopy.

**4.2.2.1. 3-(1*H*-Indol-3-yl)-2-phenyl-isoxazolidine-4-carboxylic acid ethyl ester (6b).**  $R_f$  0.54 ( $\text{CHCl}_3$ /hexane 8:2); Brownish viscous oil, Yield (225 mg, 45%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.22 (br s, 1H, NH), 7.73 (d, 1H,  $J=6.9$  Hz, C4'–H), 7.67 (d, 1H,  $J=7.2$  Hz, C7'–H), 7.27 (s, 1H, C2'–H), 7.12–7.01 (m, 6H, arom.-Hs & C6', C5'–Hs), 6.89 (t, 1H,  $J=6.8$  Hz, arom.-H), 5.44 (d, 1H,  $J=8.6$  Hz, C3–H), 4.57 (dd, 1H,  $J=11.2$  Hz & 7.6 Hz, C5–Ha), 4.41 (dd, 1H,  $J=11.2$  Hz & 5.6 Hz, C5–Hb), 3.92 (q, 2H,  $J=7$  Hz,  $\text{OCH}_2$ ), 3.79 (unresolved ddd, 1H,  $J=8.6$  Hz & 7.6 Hz, C4–H), 1.27 (t, 3H,  $\text{CH}_3$ ) ppm.

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  171.1, 152.3, 134.6, 129.8, 123.8, 122.9, 121.9, 119.5, 118.5, 116.4, 115.3, 112.1, 111.3, 68.2, 65.6, 61.8, 56.4, 15.2.

**HRMS** (ESI,  $m/z$ ): calcd for  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$   $[\text{M}+\text{Na}]^+$ , 359.1366, found 359.1358.

**4.2.2.2. 3-(1*H*-Indol-3-yl)-2-phenyl-isoxazolidine-4-carboxylic acid butyl ester (6c).**  $R_f$  0.56 ( $\text{CHCl}_3$ /hexane 8:2); Brownish viscous oil, Yield (200 mg, 40%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.24 (br s, 1H, NH), 7.76 (d, 1H,  $J=6.8$  Hz, C4'–H), 7.69 (d, 1H,  $J=7.4$  Hz, C7'–H), 7.28 (s, 1H, C2'–H), 7.21–7.12 (m, 6H, arom.-Hs & C6', C5'–Hs), 6.86 (t, 1H,  $J=7$  Hz, arom.-H), 5.43 (d, 1H,  $J=8$  Hz, C3–H), 4.52 (dd, 1H,  $J=11.8$  Hz & 8.9 Hz, C5–Ha), 4.43 (dd, 1H,  $J=11.8$  Hz & 5.4 Hz, C5–Hb), 4.19 (m, 2H,  $\text{OCH}_2$ ), 3.77 (unresolved ddd, 1H,  $J=8.9$  Hz & 8 Hz, C4–H), 1.56 (m, 2H,  $\text{CH}_2$ ), 1.33 (m, 2H,  $\text{CH}_2$ ), 1.10 (t, 3H,  $\text{CH}_3$ ).



**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  172.4, 150.7, 135.7, 128.9, 125.7, 123.2, 122.5, 121.9, 119.4, 118.7, 115.2, 111.1, 110.3, 69.2, 66.6, 65.8, 54.4, 33.2, 21.2, 14.3.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>, 365.1859, found 365.1862.

4.2.2.3. 3-(1*H*-Indol-3-yl)-2-phenyl-isoxazolidine-5-carboxylic acid methyl ester (**7a**).  $R_f$  0.55 (CHCl<sub>3</sub>/hexane 8:2); Brownish viscous oil, Yield (225 mg, 45%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.26 (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,  $J=6.2$  Hz, arom.-H), 5.21 (dd, 1H,  $J=7.5$ , 3 Hz, C5-H), 4.65 (dist dd, 1H,  $J=8.0$  Hz, C3-H), 3.11 (s, 3H, OCH<sub>3</sub>), 2.95 (dt, 1H,  $J_{gem}=12.8$  &  $J=8$  Hz, C4-Ha), 2.67 (ddd, 1H,  $J_{gem}=12.8$  Hz &  $J=7.5$ , 3 Hz, C4-Hb).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  170.1, 150.3, 135.7, 128.9, 125.9, 123.9, 122.5, 121.9, 119.5, 118.5, 115.3, 112.1, 111.3, 67.2, 64.6, 51.8, 40.2.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> [M+Na]<sup>+</sup>, 345.1209, found 345.1201.

4.2.2.4. 3-(1*H*-Indol-3-yl)-2-phenyl-isoxazolidine-5-carboxylic acid ethyl ester (**7b**).  $R_f$  0.57 (CHCl<sub>3</sub>/hexane 8:2); Brownish viscous oil, Yield (250 mg, 50%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.27 (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), 5.48 (dd, 1H,  $J=7.5$ , 3 Hz, C5-H), 4.65 (dist dd, 1H,  $J=8.0$  Hz, C3-H), 4.19 (q, 2H,  $J=7$  Hz, OCH<sub>2</sub>), 3.65 (dt, 1H,  $J_{gem}=12.8$  Hz &  $J=8$  Hz, C4-Ha), 3.45 (ddd, 1H,  $J_{gem}=12.8$  Hz &  $J=7.5$ , 3 Hz, C4-Hb), 1.23 (t, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  170.1, 151.7, 135.1, 130.1, 123.9, 123.2, 122.2, 119.7, 118.8, 115.9, 115.3, 112.3, 111.2, 69.2, 65.4, 61.6, 38.4, 14.9.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>, 337.1546, found 337.1539.

4.2.2.5. 3-(1*H*-Indol-3-yl)-2-phenyl-isoxazolidine-5-carboxylic acid butyl ester (**7c**).  $R_f$  0.54 (CHCl<sub>3</sub>/hexane 8:2); Brownish viscous oil, Yield (275 mg, 60%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.24 (br s, 1H, NH), 7.79 (d, 1H,  $J=6.5$  Hz, C4'-H), 7.72 (d, 1H,  $J=7$  Hz, C7'-H), 7.29 (s, 1H, C2'-H), 7.16–7.04 (m, 8H, arom.-Hs), 6.89 (t, 1H,  $J=7.2$  Hz, arom.-H), 5.26 (dd, 1H,  $J=8.0$ , 4.0 Hz, C5-H), 4.85 (dist dd, 1H,  $J=7.5$  Hz, C3-H), 4.23 (m, 2H, OCH<sub>2</sub>), 3.02 (dt, 1H,  $J_{gem}=13.8$  Hz &  $J=8.0$  Hz, C4-Ha), 2.59 (ddd, 1H,  $J_{gem}=13.8$  Hz &  $J=7.5$ , 4.0 Hz, C4-Hb), 1.52 (m, 2H, CH<sub>2</sub>), 1.34 (m, 2H, CH<sub>2</sub>), 0.82 (t, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  171.4, 151.3, 134.7, 129.2, 125.9, 122.8, 122.2, 121.5, 119.8, 117.9, 115.2, 112.1, 110.8, 68.9, 67.6, 65.8, 37.1, 34.2, 21.4, 14.8.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>, 365.1859, found 365.1836.

4.2.2.6. 3-(1*H*-indol-3-yl)-2,5-diphenyl-isoxazolidine (**7d**).  $R_f$  0.61 (CHCl<sub>3</sub>/hexane 8:2); Light brown solid, mp 123–125 °C; Yield (450 mg, 90%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.04 (br s, 1H, NH), 7.71 (d, 1H,  $J=8.2$  Hz, C4'-H), 7.41–6.86 (m, 14H, arom.-Hs), 5.23–5.18 (m, 2H, C3-H and C5-H), 3.21 (ddd, 1H,  $J_{gem}=11.4$  Hz &  $J=7.2$ , 3.5 Hz, C4-Ha), 2.64 (ddd, 1H,  $J_{gem}=11.4$  Hz &  $J=6.0$ , 4.5 Hz, C4-Hb).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  151.7, 138.5, 136.7, 134.4, 128.9, 128.2, 126.8, 125.3, 122.4, 121.9, 121.2, 118.7, 118.1, 116.9, 114.4, 110.8, 80.5, 65.8, 44.9.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O [M+H]<sup>+</sup>, 341.1648, found 341.1644.

4.2.2.7. 3-(1*H*-indol-3-yl)-2-phenyl-5-*p*-tolylisoxazolidine (**7e**).  $R_f$  0.58 (CHCl<sub>3</sub>/hexane 8:2); Colorless semisolid, Yield (440 mg, 88%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.14 (br s, 1H, NH), 7.80 (d, 1H,  $J=8$  Hz, C4'-H), 7.42–7.16 (m, 12H, arom.-Hs), 6.99 (t, 1H,  $J=7.5$  Hz, arom.-H), 5.24 (m, 2H, C3-H and C5-H), 3.23 (ddd, 1H,  $J_{gem}=12.8$  Hz &  $J=7.0$ , 4.5 Hz, C4-Ha), 2.68 (ddd, 1H,  $J_{gem}=12.8$  Hz &  $J=6.75$ , 2.5 Hz, C4-Hb), 2.38 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  152.9, 138.1, 136.9, 134.9, 129.2, 128.9, 127.0, 125.4, 122.3, 121.6, 121.3, 119.7, 119.3, 117.9, 114.2, 111.4, 80.5, 65.8, 46.5, 21.2.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O [M+Na]<sup>+</sup>, 377.1624, found 377.1618.

4.2.2.8. 3-(1*H*-indol-3-yl)-2-phenyl-5-(pyridin-4-yl)isoxazolidine (**7f**).  $R_f$  0.55 (CHCl<sub>3</sub>/hexane 8:2); Light yellow solid, mp 137–139 °C; yield (400 mg, 80%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.29 (br s, 1H, NH), 7.51–7.25 (m, 14H, arom.-Hs), 5.42 (dd, 1H,  $J=8.2$ , 5.4 Hz, C3-H), 5.02 (dd, 1H,  $J=7.5$ , 4.2 Hz, C5-H), 2.97 (ddd, 1H,  $J_{gem}=13.5$  Hz &  $J=8.2$ , 4.2 Hz, C4-Ha), 2.72 (ddd, 1H,  $J_{gem}=13.5$  Hz &  $J=7.5$ , 5.4 Hz, C4-Hb).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  151.7, 149.8, 149.0, 136.8, 128.9, 128.5, 125.3, 122.6, 122.4, 122.1, 121.2, 119.8, 116.7, 114.9, 111.4, 78.1, 65.2, 44.8.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O [M+H]<sup>+</sup>, 342.1600, found 342.1588.

4.2.2.9. 3-(1*H*-Indol-3-yl)-5-methyl-2-phenyl-isoxazolidine-4-carboxylic acid ethyl ester (**8**).  $R_f$  0.59 (CHCl<sub>3</sub>/hexane 8:2); Colorless solid, Yield (440 mg, 88%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.16 (br s, 1H, NH), 7.80 (d, 1H,  $J=7.8$  Hz, C4'-H), 7.72 (d, 1H,  $J=8$  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), 5.29 (d, 1H,  $J=10.0$  Hz, C3-H), 4.89 (dq, 1H,  $J=9.5$  Hz & 6.0 Hz, C5-H), 4.25 (q, 2H,  $J=7.5$  Hz, OCH<sub>2</sub>), 3.63 (dd, 1H,  $J=10.0$  Hz & 9.5 Hz, C4-H), 1.94 (d, 3H,  $J=6.0$  Hz, C5-CH<sub>3</sub>), 1.30 (t, 3H,  $J=7.5$  Hz, CH<sub>3</sub>) ppm.

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  170.7, 151.7, 136.7, 128.8, 125.9, 123.7, 122.8, 121.7, 120.5, 118.2, 114.4, 111.2, 109.7, 77.7, 68.1, 63.8, 59.3, 18.1, 14.1 ppm.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>, 351.1703, found 351.1700.

4.2.2.10. 3-(1*H*-indol-3-yl)-5-methyl-2,5-diphenyl-isoxazolidine (**9**).  $R_f$  0.58 (CHCl<sub>3</sub>/hexane 8:2); Colorless solid, mp 133–135 °C; Yield (450 mg, 90%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.17 (br s, 1H, NH), 7.62–6.84 (m, 15H, arom.-Hs), 4.83 (dist dd, 1H,  $J=8.0$  Hz, C3-H), 3.20 (dd, 1H,  $J_{gem}=12.5$  Hz &  $J=7.5$  Hz, C4-Ha), 2.86 (dd, 1H,  $J_{gem}=12.5$  Hz &  $J=5.4$  Hz, C4-Hb), 2.21 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  151.9, 137.7, 136.6, 134.8, 129.2, 128.9, 127.0, 124.7, 122.9, 121.6, 121.3, 119.7, 119.3, 117.9, 113.8, 112.4, 79.1, 65.82, 47.1, 22.1.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O [M+Na]<sup>+</sup>, 377.1624, found 377.1619.

4.2.2.11. 3-(5-Methoxy-1*H*-indol-3-yl)-2-phenyl-5-*p*-tolylisoxazolidine (**16a**).  $R_f$  0.58 (CHCl<sub>3</sub>/EtOAc 8:2); Cream white solid, Yield (450 mg, 90%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.00 (br s, 1H, NH), 7.40 (m, 2H, arom.-Hs), 7.31 (m, 4H, arom.-Hs), 7.23 (m, 6H, arom.-Hs), 6.98 (t, 1H,  $J=7.0$  Hz, arom.-H), 5.24 (dd, 1H,  $J=6.0$  Hz, 3.5 Hz, C5-H), 5.18 (dd, 1H,  $J=7.5$  Hz, 4.0 Hz, C3-H), 3.84 (s, 3H, OCH<sub>3</sub>), 3.23 (ddd, 1H,  $J_{gem}=13.1$  Hz &  $J=7.5$ , 3.5 Hz, C4-Ha), 2.67 (ddd, 1H,  $J_{gem}=13.1$  Hz &  $J=6.0$ , 4.0 Hz, C4-Hb), 2.37 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  152.8, 138.0, 135.2, 132.7, 129.2, 128.8, 128.4, 126.8, 125.7, 123.2, 122.4, 121.3, 117.5, 116.2, 114.3, 112.5, 80.3, 65.8, 55.8, 46.3, 21.1.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>25</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> [M+nNa]<sup>+</sup>, 407.1730, found 407.1736.

4.2.2.12. 3-(2-Phenyl-5-*p*-tolylisoxazolidin-3-yl)pyridine (**20a**). R<sub>f</sub> 0.58 (CHCl<sub>3</sub>/EtOAc 8:2); Cream white solid, Yield (450 mg, 90%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.77 (br s, 1H, 2'-H), 8.59 (d, 1H,  $J$ =4.5 Hz, 6'-H), 7.97 (d, 1H,  $J$ =8.0 Hz, 4'-H), 7.37–7.28 (m, 6H, Ar-Hs), 7.21 (d, 2H,  $J$ =8.0 Hz, arom-Hs), 7.08 (d, 1H,  $J$ =8.5 Hz, arom-H), 7.00 (m, 1H, arom-H), 5.21 (dd, 1H,  $J$ =6.0 Hz, 4.0 Hz, C5-H), 5.01 (t, 1H,  $J$ =7.5 Hz, C3-H), 3.23 (ddd, 1H,  $J_{gem}$ =12.0 Hz &  $J$ =6.5, 5.0 Hz, C4-Ha), 2.46 (ddd, 1H,  $J_{gem}$ =12.0 Hz &  $J$ =7.0, 3.0 Hz, C4-Hb), 2.38 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  152.0, 148.8, 148.1, 138.6, 138.3, 134.3, 134.1, 129.3, 129.1, 126.8, 123.8, 121.7, 113.9, 80.5, 69.0, 48.1, 21.1.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O [M+nNa]<sup>+</sup>, 339.1467, found 339.1460.

4.2.3. General procedure for the reaction of (**6–9**) with Pd/C, HOOCNH<sub>4</sub> to synthesize (**10–13**). A solution of (**6–9**, **16a** and **20a** 1.5 mmol) in Ammonium formate (10 equiv), methanol (15 ml) and THF (5 ml) was stirred at room temperature (25–28 °C). Activated 10% palladium on charcoal (10 equiv) was added to the above solution and stirred the mixture for 30 min (monitored by TLC). The reaction mixture was filtered and the filtrate extracted with ether (30 ml). The aqueous phase was basified with aqueous sodium hydroxide (10%) and extracted with dichloromethane (3 × 50 ml). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure and vacuum. Purification by column chromatography (70% ethyl acetate in hexane) afforded (**10–13**, **17** and **21**).

4.2.3.1. Methyl-2-((1*H*-indol-3-yl)-methyl)-3-hydroxypropanoate (**10a**). R<sub>f</sub> 0.51 (CHCl<sub>3</sub>/EtOAc 7:3); Light brown semisolid, Yield (300 mg, 60%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.30 (br s, 1H, NH), 7.62 (d, 1H,  $J$ =7.5 Hz, C4'-H), 7.30 (d, 1H,  $J$ =7.5 Hz, C7'-H), 7.23 (t, 1H,  $J$ =7.5 Hz, C5'-H), 7.15 (t, 1H,  $J$ =7.5 Hz, C6'-H), 7.01 (s, 1H, C2'-H), 3.79 (d, 2H,  $J$ =5.4 Hz, CH<sub>2</sub>OH), 3.71 (s, 1H, OCH<sub>3</sub>), 3.20 (dd, 1H,  $J_{gem}$ =13.8 Hz &  $J$ =5.4 Hz, C3-Ha), 3.06 (dd, 1H,  $J_{gem}$ =13.8 Hz &  $J$ =7.5 Hz, C3-Hb), 3.02–2.97 (m, 1H, C2-H), 2.61 (bs, 1H, OH).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  174.8, 135.9, 127.5, 123.1, 122.2, 118.9, 118.2, 112.8, 110.7, 62.9, 61.1, 47.9, 23.8.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>13</sub>H<sub>15</sub>NO<sub>3</sub> [M+H]<sup>+</sup>, 234.1124, found 234.1118.

4.2.3.2. Ethyl-2-((1*H*-indol-3-yl)-methyl)-3-hydroxypropanoate (**10b**). R<sub>f</sub> 0.54 (CHCl<sub>3</sub>/EtOAc 7:3); Light brown semisolid, Yield (325 mg, 65%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.35 (br s, 1H, NH), 7.64 (d, 1H,  $J$ =7.5 Hz, C4'-H), 7.35 (d, 1H,  $J$ =7.5 Hz, C7'-H), 7.22 (t, 1H,  $J$ =7.5 Hz, C5'-H), 7.14 (t, 1H,  $J$ =7.5 Hz, C6'-H), 6.99 (s, 1H, C2'-H), 4.18 (q, 2H,  $J$ =7.0 Hz, OCH<sub>2</sub>), 3.82 (d, 2H,  $J$ =5.4 Hz, CH<sub>2</sub>OH), 3.20 (dd, 1H,  $J_{gem}$ =14.5 Hz &  $J$ =6.0 Hz, C3-Ha), 3.06 (dd, 1H,  $J_{gem}$ =14.5 Hz &  $J$ =8.0 Hz, C3-Hb), 3.02–2.97 (m, 1H, C2-H), 2.65 (bs, 1H, OH), 1.24 (t, 3H,  $J$ =7.0 Hz, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  175.3, 136.3, 127.3, 122.7, 121.9, 119.3, 118.6, 112.4, 111.3, 62.5, 60.8, 48.2, 24.0, 14.1.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub> [M+H]<sup>+</sup>, 248.1281, found 248.1272.

4.2.3.3. Butyl-2-((1*H*-indol-3-yl)-methyl)-3-hydroxypropanoate (**10c**). R<sub>f</sub> 0.53 (CHCl<sub>3</sub>/EtOAc 7:3); Light brown semisolid, Yield (275 mg, 55%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.35 (br s, 1H, NH), 7.64 (d, 1H,  $J$ =7.5 Hz, C4'-H), 7.35 (d, 1H,  $J$ =7.5 Hz, C7'-H), 7.22 (t, 1H,  $J$ =7.5 Hz, C5'-H), 7.14 (t, 1H,  $J$ =7.5 Hz, C6'-H), 6.99 (s, 1H, C2'-H), 4.31 (m, 2H, OCH<sub>2</sub>), 3.81 (d, 2H,  $J$ =5.0 Hz, CH<sub>2</sub>OH), 3.20 (dd, 1H,  $J_{gem}$ =13.5 Hz &  $J$ =5.4 Hz, C3-Ha), 3.10 (dd, 1H,  $J_{gem}$ =13.5 Hz &  $J$ =8.2 Hz, C3-Hb), 3.06–3.01 (m, 1H, C2-H), 2.60 (bs, 1H, OH), 1.43–1.35 (m, 4H, 2 × CH<sub>2</sub>), 0.99 (t, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  173.3, 134.3, 126.3, 123.7, 120.9, 119.4, 118.3, 112.2, 111.5, 82.1, 64.5, 62.8, 48.1, 36.8, 22.1, 14.8.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>3</sub> [M+H]<sup>+</sup>, 276.1594, found 276.1596.

4.2.3.4. Methyl-3-(1*H*-indol-3-yl)acrylate (**11a**). Off white solid, mp 91–93 °C; Yield (125 mg, 25%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.49 (br s, 1H, NH), 7.92 (d, 1H,  $J$ =15.9 Hz), 7.49–7.26 (m, 5H, arom.-Hs), 6.46 (d, 1H,  $J$ =15.9 Hz), 3.29 (s, 3H, OCH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  168.2, 138.1, 137.0, 128.7, 125.3, 123.3, 121.5, 120.5, 113.5, 111.7, 14.4.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>12</sub>H<sub>11</sub>NO<sub>2</sub> [M+Na]<sup>+</sup>, 224.0681, found 224.0675.

4.2.3.5. Ethyl-3-(1*H*-indol-3-yl)acrylate (**11b**). Off white solid, mp 97–99 °C; Yield (100 mg, 20%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.33 (br s, 1H, NH), 7.88 (d, 1H,  $J$ =15.9 Hz), 7.57–7.18 (m, 5H, arom.-Hs), 6.43 (d, 1H,  $J$ =15.9 Hz), 4.27 (q, 2H,  $J$ =7.2 Hz, OCH<sub>2</sub>), 1.35 (t, 3H,  $J$ =7.2 Hz, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  167.8, 137.7, 137.2, 130.6, 125.5, 123.4, 122.7, 120.8, 113.6, 111.4, 60.1, 14.1.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>13</sub>H<sub>13</sub>NO<sub>2</sub> [M+H]<sup>+</sup>, 216.1019, found 216.1011.

4.2.3.6. Butyl-3-(1*H*-indol-3-yl)acrylate (**11c**). Light brown viscous oil, Yield (150 mg, 30%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.37 (br s, 1H, NH), 7.85 (d, 1H,  $J$ =16.0 Hz), 7.52–7.28 (m, 5H, arom.-Hs), 6.59 (d, 1H,  $J$ =16.0 Hz), 4.31 (m, 2H, OCH<sub>2</sub>), 1.43–1.35 (m, 4H, 2 × CH<sub>2</sub>), 0.89 (t, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  168.3, 137.9, 137.1, 130.7, 125.3, 123.8, 122.5, 120.9, 112.6, 111.7, 67.3, 40.1, 20.3, 15.3.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>2</sub> [M+Na]<sup>+</sup>, 266.1151, found 266.1140.

4.2.3.7. Methyl-2-hydroxy-4-(1*H*-indol-3-yl)butanoate (**12a**). R<sub>f</sub> 0.48 (CHCl<sub>3</sub>/EtOAc 7:3); Light brown semisolid, Yield (440 mg, 88%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.02 (br s, 1H, NH), 7.64 (d, 1H,  $J$ =8.0 Hz, C4'-H), 7.38 (d, 1H,  $J$ =8.0 Hz, C7'-H), 7.21 (t, 1H,  $J$ =7.5 Hz, C5'-H), 7.14 (t, 1H,  $J$ =7.5 Hz, C6'-H), 7.03 (s, 1H, C2'-H), 4.29 (m, 1H, C2-H), 3.72 (s, 3H, OCH<sub>3</sub>), 3.04 (d, 1H,  $J$ =5 Hz, OH), 2.95 (m, 2H, CH<sub>2</sub>), 2.20 (m, 2H, CH<sub>2</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  175.8, 136.3, 127.4, 121.9, 121.6, 119.2, 118.8, 115.4, 111.1, 69.8, 52.4, 34.5, 29.7.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>13</sub>H<sub>15</sub>NO<sub>3</sub> [M+H]<sup>+</sup>, 234.1124, found 234.1114.

4.2.3.8. Ethyl-2-hydroxy-4-(1*H*-indol-3-yl)butanoate (**12b**). R<sub>f</sub> 0.46 (CHCl<sub>3</sub>/EtOAc 7:3); Light brown semisolid, Yield (425 mg, 85%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.00 (br s, 1H, NH), 7.65 (d, 1H,  $J=8.0$  Hz, C4'-H), 7.38 (d, 1H,  $J=8.0$  Hz, C7'-H), 7.22 (t, 1H,  $J=7.5$  Hz, C5'-H), 7.14 (t, 1H,  $J=7.5$  Hz, C6'-H), 7.03 (s, 1H, C2'-H), 4.26 (m, 1H, C2-H), 4.18 (q, 2H,  $J=7$  Hz, OCH<sub>2</sub>), 2.96 (m, 2H, CH<sub>2</sub>), 2.90 (d, 1H,  $J=5$  Hz, OH), 2.23 (m, 1H, CH<sub>2</sub>), 2.10 (m, 1H, CH<sub>2</sub>) 1.26 (t, 3H,  $J=7.0$  Hz, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  175.4, 136.3, 127.4, 121.9, 121.6, 119.2, 118.9, 115.2, 111.0, 69.8, 61.7, 34.6, 20.3, 14.1.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub> [M+Na]<sup>+</sup>, 270.1101, found 270.1099.

4.2.3.9. *Butyl-2-hydroxy-4-(1H-indol-3-yl)butanoate* (**12c**).  $R_f$  0.44 (CHCl<sub>3</sub>/EtOAc 7:3); Light brown semisolid, Yield (415 mg, 83%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.06 (br s, 1H, NH), 7.68 (d, 1H,  $J=8.0$  Hz, C4'-H), 7.42 (d, 1H,  $J=8.0$  Hz, C7'-H), 7.25 (t, 1H,  $J=7.5$  Hz, C5'-H), 7.11 (t, 1H,  $J=7.5$  Hz, C6'-H), 7.09 (s, 1H, C2'-H), 4.37 (m, 1H, C2-H), 4.21 (m, 2H, OCH<sub>2</sub>), 2.88 (m, 2H, CH<sub>2</sub>), 2.83 (d, 1H,  $J=4.5$  Hz, OH), 2.28 (m, 1H, CH<sub>2</sub>), 2.18 (m, 1H, CH<sub>2</sub>), 1.49–1.38 (m, 4H, 2 $\times$ CH<sub>2</sub>), 0.99 (t, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  174.7, 135.8, 126.8, 121.7, 121.7, 119.1, 118.6, 114.9, 110.7, 68.8, 62.7, 42.6, 34.6, 22.3, 20.4, 14.5.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>3</sub> [M+H]<sup>+</sup>, 276.1594, found 276.1580.

4.2.3.10. *3-(1H-indol-3-yl)-1-phenylpropan-1-ol* (**12d**).  $R_f$  0.51 (CHCl<sub>3</sub>/EtOAc 7:3); Light brown semisolid, Yield (450 mg, 90%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.00 (br s, 1H, NH), 7.63 (d, 1H,  $J=8$  Hz, C4'-H), 7.41–7.15 (m, 8H, arom.-Hs), 6.97 (s, 1H, C2'-H), 4.79 (t, 1H,  $J=6.5$  Hz, C1-H), 2.96–2.83 (m, 2H, C2-H), 2.30–2.18 (m, 3H, CH<sub>2</sub> & OH).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  144.7, 136.4, 128.5, 127.6, 127.5, 126.0, 121.9, 121.3, 119.2, 118.9, 115.9, 111.1, 74.2, 39.1, 21.5.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>17</sub>H<sub>17</sub>NO [M+Na]<sup>+</sup>, 274.1202, found 274.1191.

4.2.3.11. *3-(1H-indol-3-yl)-1-p-tolylpropan-1-ol* (**12e**).  $R_f$  0.54 (CHCl<sub>3</sub>/EtOAc 7:3); Off white semisolid, Yield (460 mg, 92%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.00 (br s, 1H, NH), 7.62 (d, 1H,  $J=8$  Hz, C4'-H), 7.37 (d, 1H,  $J=8.0$  Hz, C7'-H), 7.30–7.19 (m, 5H, arom.-Hs), 7.14 (t, 1H,  $J=7.5$  Hz, arom.-H), 6.99 (s, 1H, C2'-H), 4.76 (t, 1H,  $J=6.5$  Hz, C1-H), 2.94–2.81 (m, 2H, C2-H), 2.39 (s, 3H, CH<sub>3</sub>), 2.26 (dt, 1H,  $J_{gem}=13.7$  Hz &  $J=8.0$  Hz, C3-H), 2.16 (dt, 1H,  $J_{gem}=13.7$  Hz &  $J=6.0$  Hz, C3-Hb), 1.98 (bs, 1H, OH).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  141.7, 137.2, 136.3, 129.1, 127.5, 125.9, 121.9, 121.2, 119.1, 118.9, 116.0, 111.1, 74.0, 39.0, 21.5, 21.1.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>18</sub>H<sub>19</sub>NO<sub>3</sub> [M+H]<sup>+</sup>, 266.1539, found 266.1520.

4.2.3.12. *3-(1H-indol-3-yl)-1-(pyridin-4-yl)propan-1-ol* (**12f**).  $R_f$  0.52 (CHCl<sub>3</sub>/EtOAc 7:3); Light brown semisolid, Yield (425 mg, 85%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.02 (br s, 1H, NH), 7.61 (d, 1H,  $J=8$  Hz, C4'-H), 7.43–7.13 (m, 7H, arom.-Hs), 6.98 (s, 1H, C2'-H), 4.75 (t, 1H,  $J=7.0$  Hz, C1-H), 2.92–2.82 (m, 2H, C2-H), 2.32–2.19 (m, 3H, CH<sub>2</sub> & OH).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  156.1, 147.7, 147.3, 136.4, 128.5, 127.6, 126.0, 121.3, 118.9, 115.9, 111.1, 73.1, 40.1, 22.1.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O [M+Na]<sup>+</sup>, 275.1154, found 275.1137.

4.2.3.13. *4-(1H-indol-3-yl)-2-phenylbutan-2-ol* (**13**).  $R_f$  0.48 (CHCl<sub>3</sub>/EtOAc 7:3); Light brown semisolid, Yield (400 mg, 80%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.01 (br s, 1H, NH), 7.62 (d, 1H,  $J=8$  Hz, C4'-H), 7.43–7.17 (m, 8H, arom.-Hs), 6.99 (s, 1H, C2'-H), 4.77 (t, 1H,  $J=6.5$  Hz, C1-H), 2.97–2.85 (m, 2H, C2-H), 2.31–2.16 (m, 3H, CH<sub>2</sub> & OH).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  142.7, 136.4, 128.5, 127.6, 127.4, 126.2, 122.9, 121.7, 119.9, 118.7, 115.8, 111.2, 65.8, 38.2, 21.8, 14.7.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>18</sub>H<sub>19</sub>NO [M+H]<sup>+</sup>, 266.1539, found 266.1524.

4.2.3.14. *3-(5-Methoxy-1H-indol-3-yl)-1-p-tolylpropan-1-ol* (**17**).  $R_f$  0.33 (CHCl<sub>3</sub>/EtOAc 7:3); Yellow-brown semisolid, Yield (440 mg, 88%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.88 (br s, 1H, NH), 7.29 (m, 5H, arom.-Hs), 7.02 (s, 1H, C4'-H), 6.98 (s, 1H, C2'-H), 6.88 (m, 1H, arom.-H), 4.75 (t, 1H,  $J=6.5$  Hz, C1-H), 3.87 (s, 3H, OCH<sub>3</sub>), 2.88 (m, 2H, C2-H), 2.38 (s, 3H, CH<sub>3</sub>), 2.24 (dt, 1H,  $J_{gem}=13.5$  Hz &  $J=7.5$  Hz, C3-H), 2.14 (dt, 1H,  $J_{gem}=13.5$  Hz &  $J=6.5$  Hz, C3-Hb), 1.99 (bs, 1H, OH).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  153.8, 141.7, 137.2, 131.5, 129.1, 127.8, 125.9, 122.0, 115.7, 112.1, 111.7, 100.8, 74.0, 55.9, 38.9, 21.4, 21.1.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>19</sub>H<sub>21</sub>NO<sub>2</sub> [M+nNa]<sup>+</sup>, 318.1464, found 318.1458.

4.2.3.15. *3-(Phenylamino)-3-(pyridin-3-yl)-1-p-tolylpropan-1-ol* (**21**).  $R_f$  0.33 (CHCl<sub>3</sub>/EtOAc 7:3); Yellow-brown semisolid, Yield (450 mg, 90%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz):  $\delta$  8.58 (s, 1H, 2'-H), 8.37 (s, 1H, 6'-H), 7.73 (d, 1H,  $J=8.0$  Hz, 4'-H), 7.24–7.11 (m, 7H, arom.-Hs), 6.71 (t, 1H,  $J=7.5$  Hz, Ar-H), 6.51 (t, 2H,  $J=8.0$  Hz, Ar-Hs), 4.76 (dd, 1H,  $J=6.0$  & 3.0 Hz, C1-H), 4.61 (dd, 1H,  $J=5.5$  & 3.0 Hz, C3-H), 4.25 (br s, 2H, NH & OH), 2.36 (s, 3H, CH<sub>3</sub>), 2.32–2.27 (m, 1H, C2-Ha) 2.00–1.96 (m, 1H, C2-Hb).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz):  $\delta$  148.1, 147.9, 146.9, 141.6, 139.8, 137.4, 134.3, 129.2, 129.1, 125.6, 123.9, 117.9, 113.9, 72.6, 55.4, 47.3, 21.1.

**HRMS** (ESI,  $m/z$ ): calcd for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O [M+nNa]<sup>+</sup>, 341.1624, found 341.1617.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.tet.2015.12.032>.

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