Highly Substituted Isoxazoles: The Baylis-Hillman reaction of substituted 4-isoxazolecarbaldehydes and attempted cyclization to isoxazole-annulated derivatives[1]

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Abstract: In an attempt to understand the effect of position of the formyl group on the efficiency of Baylis-Hillman reaction within isoxazolecarboxaldehydes, the reactions of substituted 4-isoxazolecarboxaldehydes to obtain highly substituted isoxazoles are described. Attempts to obtain isoxazole-annealed derivatives from these Baylis-Hillman adducts involving S_NR'-S_NAr substitution strategy are also described.

Key words: Baylis-Hillman reaction, 4-isoxazolecarboxaldehyde, DABCO, DMAP.

The Baylis-Hillman reaction,[2] which has witnessed an extraordinary exploitation in the recent past, is now considered to be a standard synthetic methodology in the arsenal of organic and medicinal chemists. Various reasons ascribed to such phenomenal expansion in the scope of this C-C bond forming reaction include atom-economy, easy reaction conditions (even water as solvent),[3] multifunctional products that can be diversified further for accessing heterocycles,[4] intermediates that serve as synthons for natural products,[5] adaption of chemistry on the solid phase for combinatorial synthesis and others.[6] To add upon, this reaction gains significant importance from medicinal point of view if it is carried out with privileged scaffolds.[7] The slow reaction rate that was considered to be one of the major drawback of this reaction, has been almost overcome using either physical or chemical means.[2] However not much attention has been paid towards understanding plausible mechanism behind unusually fast Baylis-Hillman reaction experienced by some electrophiles.

Isoxazole is a privileged structure that is documented to be associated with wide range of biological activities.[8] In our objective to generate isoxazole-based chemical libraries in parallel utilizing solution and solid phase chemistry, we initiated our studies with 5-isoxazolecarboxaldehydes. We discovered that 5-isoxazolecarboxaldehyde is one of the fastest reacting substrate for the Baylis-Hillman reaction.[9] This has been synthetically and medicinally attractive proposition for us since it helps in obtaining various intermediates in an expedited fashion and isoxazole-derivatives from the Baylis-Hillman-mediated chemistry have led to molecules with potent bioresponse.[10] We have observed that results of this substrate, with respect to Baylis-Hillman reaction, can be generalized and extended to other aldehydes.[11] During our efforts to find reasons behind unusual fast reactivity of 5-isoxazolecarboxaldehydes we have proposed, it is quite likely that the proton abstraction in the intermediate step is aided by the heteroatom present in the molecule thereby facilitating the elimination of base (Fig. 1).[12] This hypothesis was outcome of the earlier observation made by Hofmann and Rabe where they have proposed the formation of an zwitterionic intermediate that allows elimination of H_α and base aided by basic heteroatom of aldehyde.[13] To provide a chemical basis to our hypothetical assumption, we envisioned that substituted 4-isoxazolecarboxaldehydes would be a slow reacting substrate as compared to its isomer since here there will be no heteroatom to assist the elimination of base. To substantiate this we carried out the synthesis of substituted 4-isoxazolecarboxaldehyde and subjected them to Baylis-Hillman reaction. As expected, in contrast to 5-isoxazolecarboxaldehydes, substituted 4-isoxazolecarboxaldehydes are sluggish electrophiles for the Baylis-Hillman reaction. In addition it was envisaged that BH adducts of 3-(2-chlorophenyl)-5-methyl-4-isoxazolecarboxaldehyde could be cyclized to obtain isoxazole-annealed derivatives employing S_NR'-S_NAr substitution strategy.[14] Our initial attempts toward this objective along with the details of conventional BH reaction with substituted 4-isoxazolecarboxaldehydes are presented herein.

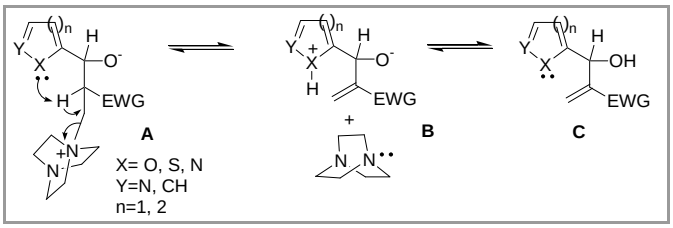
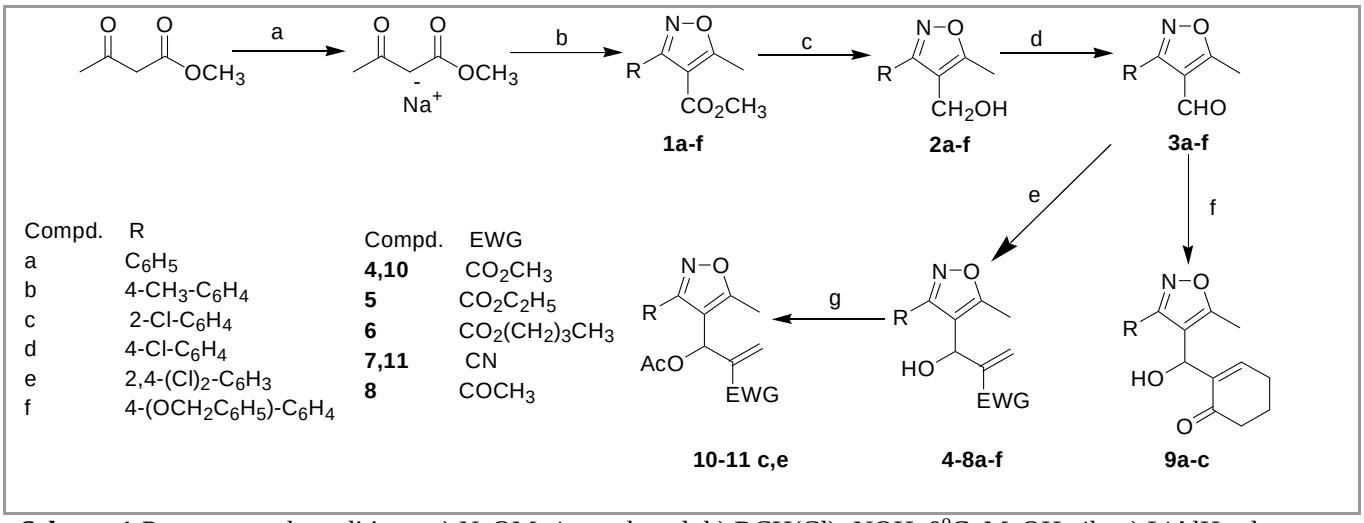


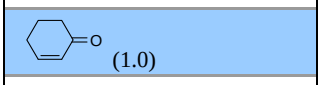
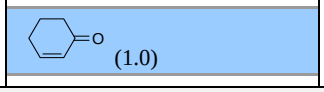
Figure 1 Proton abstraction is aided by the lone pair of the hetero atom leading to immediate release of the base.

The substituted 4-isoxazolecarboxaldehydes were prepared as reported in the literature.[15] In the first instance methyl acetoacetate was treated with sodium methoxide to generate the intermediate that was then treated in situ with benzohydroximinoyl chloride to generate 3-substituted phenyl-5-methyl-4-isoxazole-methylcarboxylate (**1a-f**). This ester upon careful reduction with lithium aluminum hydride furnished the methyl alcohols (**2a-f**) quantitatively. Further these alcohols upon oxidation with pyridinium chlorochromate furnished the substituted 4-isoxazolecarboxaldehydes (**3a-f**) in excellent yields. These aldehydes were then subjected to Baylis-Hillman reaction under neat conditions. Interestingly



Scheme 1 *Reagents and conditions*: a) NaOMe in methanol; b) RCH(Cl)=NOH, 0°C, MeOH, 4h; c) $LiAlH_4$, dry diethyl ether, 40 °C 1h; d) PCC, DCM, r.t., 30 min; e) DABCO, alkene, r.t., 2d; e) DMAP, cyclohexenone, r.t., 7d; f) AcCl, pyridine, r.t., 30 min.

Table 1 Effect of alkene, base and solvent on Baylis-Hillman reaction of substituted 4-isoxazolecarboxaldehyde[a, b]

Entry	Alkene (amount in equivalents)	Base (amount in equivalents)	Solvent	Reaction Time (days)	Yield (%)
1	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	Neat	2	42
2	CH_2=$CHCO_2Me$ (2.0)	DABCO (0.5)	Neat	2	59
3	CH_2=CHCN (1.0)	DABCO (0.5)	Neat	2	56
4	CH_2=CHCN (2.0)	DABCO (0.5)	Neat	2	89
5	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	MeOH	7	07
6	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	MeOH: H_2O (1:1)	7	05
7	CH_2=$CHCO_2Me$ (1.5)	aq. Me_3N 30% (2.5)	MeOH	5	23
8	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	Dioxane: H_2O (1:1)	7	No reaction
9	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	Dichloromethane	7	No reaction
10	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	THF	7	No reaction
11	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	DMSO	1	10
12	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	DMF	1	20
13	 (1.0)	DABCO (0.5)	Neat	7	No reaction
14[c]	 (1.0)	DMAP (1.0)	Dioxane: water (3:2)	7	21

[a]All reactions were carried out with 2.5 mmol of **3b**. [b] For comparison with substituted 5-isoxazolecarboxaldehyde see ref. 9. [c] Reactions of substituted 5-isoxazolecarboxaldehydes with cyclohexenone in the presence of DMAP (0.2 equivalent) in dioxane: water are completed within 1h to give products in 90-95% yields (unpublished).

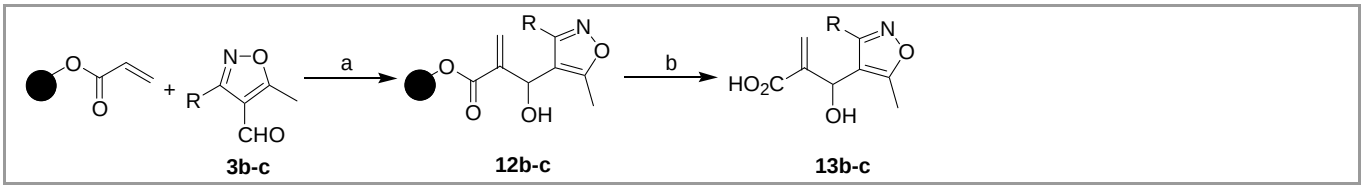
even after 24h of reaction time reactions did not go to completion. Here it would be relevant to state that compared to aldehydes **4d** and **4f**, the reactions were fast for all other aldehydes. However, upon work up and column chromatography we recovered 5-10% of the unreacted aldehydes along with the desired products in moderate yields only. Similar to our earlier experience with Baylis-Hillman reactions of substituted 5-isoxazolecarboxaldehyde, we observed that in substituted 4-isoxazolecarboxaldehydes too, as the reaction progressed the reaction mixture became unusually thick thereby preventing the stirring of magnetic bar. However in contrast to the Baylis-Hillman reaction of 5-isoxazolecarboxaldehyde, the formation of thick slurry here was not indicative of completion of reaction. Assuming this as the possible reason for substrate not being consumed completely, we decided to add solvents and evaluate their effect on the progress of reaction. For our studies, we also included some recently reported observations of fast and efficient Baylis-Hillman reaction in homogenous medium.[3a] Thus as a model we conducted reaction of compound **3b** with methyl acrylate under various solvent conditions. The results are shown in Table 1. In contrast to earlier report,[16] it was surprising that the neat conditions work best in our hands compared to any solvent. In our earlier work[9] we have observed that DMF and DMSO too serve

as good solvents for the reaction and they also address the solvent condition to be applied for solid phase reactions.[12] But in this study we found that DMSO led to formation of an unidentified highly polar product in major quantity.

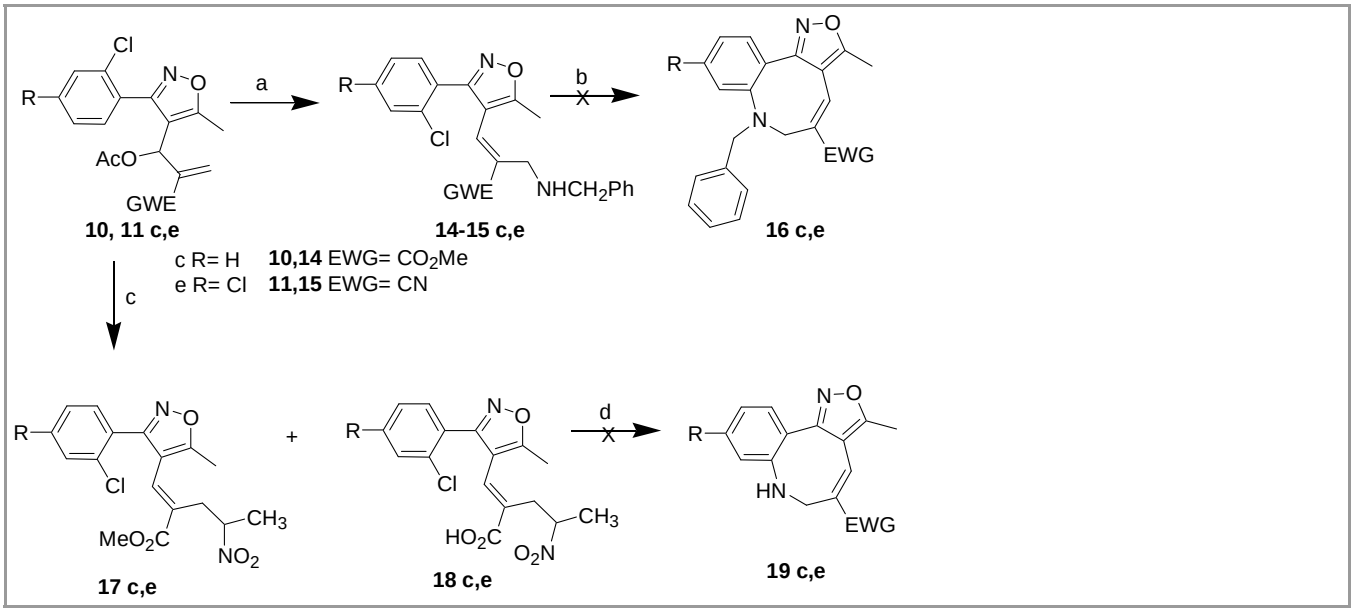
In an attempt to find optimal conditions to obtain maximum yields we increased the amount of the base and the activated alkene too. It was observed that if the base is taken as 0.5 equivalent and the activated alkene is 2 equivalent, the reaction was more efficient and the yields were better. Of the different activated alkenes employed, acrylonitrile gave the best results since no starting material was recovered and yields of 79-89 % were achieved. This was in precedence with the earlier observation made by Basavaiah et al.[17] Notably in these aldehydes though the reactions were allowed to run for more than 74h, in no case we observed the formation of ether side-product as in 5-isomer.[18]

During this study, we also carried out base-mediated Baylis-Hillman reaction with cyclohexenone and acrylamide. The aldehydes (**3a-c**) were treated with cyclohexenone in the presence of DMAP in dioxane: water. Here too as compared to 5-isoxazolecarboxaldehydes, the reactions did not go to completion and products (**9a-c**) were isolated in low yields only. On the other the initial attempts of Baylis-Hillman reaction of these aldehydes with acrylamide in the presence of DABCO were unsuccessful. For solid-phase Baylis-Hillman reactions using substituted 4-isoxazolecarboxaldehyde as electrophile, the acrylic acid was immobilized onto the 2-chloro-trityl chloride resin using standard technique. The acrylate resin was then subjected to Baylis-Hillman reaction with **3 b-c** in DMF. The reaction was continued for 48h followed by a repeat cycle. The resin was washed, dried and finally cleaved to obtain the Baylis-Hillman adduct **13 a-c** in low yields. Hence here too as compared to the 5-isomer[14] reactions were slow and yields were also average only.

Thus as envisioned, the substituted 4-isoxazolecarboxaldehydes are less reactive electrophiles for Baylis-Hillman reaction as compared to their 5-position isomer. It was suggested by the earlier workers[13] that the basicity of the heteroatom affecting the migration of protons could be the reason for fast Baylis-Hillman reaction. However we have observed that 5- isoxazolecarboxaldehyde reacts even faster than the 3-pyridinecarbox-



Scheme 2: *Reagents and Conditions* a) DABCO, DMF, r.t., 48h X 2.; b) TFA: DCM (5: 95, v/v), 20 min.



Scheme 3: *Reagents and Conditions*: a) $PhCH_2NH_2$, Et_3N, THF, 70 °C, 1h. b) continued for 48h. c) $EtNO_2$, K_2CO_3, 60-70 °C, 30 min, **18c, e** were observed only if the reaction was continued for 24h.

aldehyde (exemplified by Hoffman and Rabe as the fastest reacting electrophile) during the Baylis-Hillman reaction that could be possibly explained on the basis of Fig. 1. The proximity of the heteroatom to

the methyl bond bearing the base is more in 5-isoxazole than in 4-isoxazole derivatives that facilitate the elimination of the base. This fact was also confirmed through the Drieding's model of the intermediate.

To explore the synthetic utility of the Baylis-Hillman products described herein we decided to work upon an earlier reported[14] synthetic strategy. It was envisioned that if acetates (**10-11**) of the Baylis-Hillman adducts of the 2-halophenyl substituted aldehyde are treated with amine under forced conditions, the Michael adduct could undergo cyclization *in situ* through S_NAr substitution to yield isoxazole annealed derivatives (**16**).

Toward this objective in the first instance compounds **4 c, e** and **7 c, e** were converted to the corresponding acetates (**10-11 c, e**). These acetates were then refluxed with benzylamine in the presence of triethylamine. However, in all cases we obtained the allyl amines (**14 c, e**) while no cyclized derivative (**16**) was obtained. The amines were formed within an hour of reaction time and the product remained unchanged even after 48h of refluxing. The tlc (hexane: ethyl acetate, 70: 30, v/v) on basic alumina indicated the presence of two spots very close to each other, which upon separation and spectroscopic analysis were identified as *E* (less polar) and *Z* (more polar) isomer. The ^{1}H NMR spectrum of the mixture indicated these isomers to be present in almost equal quantity. The stereochemistry to the amines was assigned on the basis of nOe studies across the double bond of the polar isomer because the =CH proton could be easily irradiated in this spectrum. Irradiation of =CH proton at δ = 6.50 ppm showed an increase of the allylic CH_2 protons at δ = 3.70 ppm by 3.07 % while irradiation of $=CH_2$ led to increase for =CH proton by 5.74 % indicating the *Z* stereochemistry of amines. In the *E* isomer the =CH was merged with the aromatic proton that made difficult to irradiate it. We also carried out the similar synthetic sequence with compounds **7c** and **7e** to obtain the allylic amines **15 c, e**. These amines were notably less polar as compared to **14** and could even be monitored on silica gel plates using same solvent system. These amines were obtained with high degree of stereoselectivity. During nOe studies of these amines, the stereochemistry across double bond was assigned as *Z* since irradiation of =CH proton at δ = 6.72 ppm led to enhancement of allylic CH_2 at δ = 3.48 ppm (5.02 %) while irradiation of CH_2 proton led to increase in the signal of =CH proton by 6.73 %. Thus irrespective of the stereochemistry, the amines failed to cyclize to furnish the desired products.

In another strategy, the compounds **10 c, e** were treated with nitroalkane. Here too though the S_NR' reaction of the nitronate ion was successful to afford **17 c, e**, but the intramolecular S_NAr and subsequent elimination of nitrous acid to furnish the desired compound (**19**) did not take place. The stereochemistry of these products was assigned as *E* based on the literature.[19] However, heating the reaction mixture for prolonged period led to decrease in the yield of the prod ucts as there was appreciable formation of polar impurities that were not isolated. But a mass spectrum of the mixture did indicate the presence of molecular ion peak corresponding to acrylic acid derivative (**18c, e**) that may have obviously resulted due to hydrolysis of the ester in the presence of base.

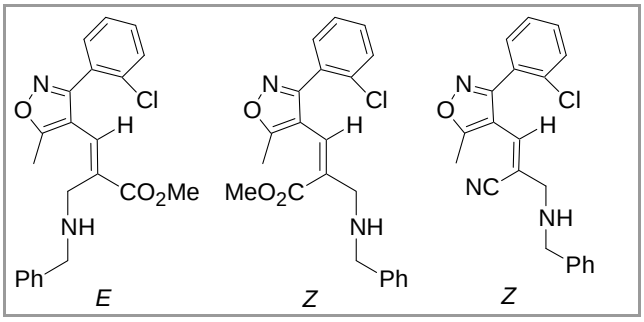


Figure 2. Stereochemistry of allylamines.

In conclusion we have described the Baylis-Hillman reaction of substituted 4-isoxazolecarboxaldehyde in solution and solid phase and have shown the influence of position of the formyl group within a heterocycle on the rate of reaction. We speculate that Baylis-Hillman adducts of 4-isoxazolecarboxaldehyde described herein will be of high synthetic importance for obtaining isoxazole-annealed carbocycles and heterocycles and isoxazole-based biodynamic agents. In addition it will be interesting to study the Baylis-Hillman reaction of substituted 3-isoxazolecarboxaldehyde, which we presume will be faster as compared to the 4-isomer and will also give an insight into the basicity of the heteroatom affecting the rate of Baylis-Hillman reaction within a heterocycle. Work toward these perspectives is underway and will form part of our future communications.

Experimental Section

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using Perkin Elmer's Spectrum RX I FTIR spectrophotometer while ^{1}H NMR spectra were recorded on Bruker DPX-200 FT spectrometers, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The FABMS spectra were recorded on JEOL/ SX-102 spectrometer and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. Elemental analyses were performed either on Carlo Erba 1108 or Elementar's Vario EL *III* microanalyzer. All yields of Baylis-Hillman adducts are based on exclusion of 5-10% aldehyde that was recovered unreacted in all reactions except for that with acrylonitrile.

Baylis-Hillman reaction-General Procedure: To a mixture of DABCO (0.3 g, 2.67 mmol) and appropri-

ate alkene (10.6 mmol) that has been stirred at r.t. for 20 min. was added appropriate aldehyde from **3a-f** (5.3 mmol) under stirring and the reaction was allowed to proceed for a period 72 h. Thereafter 5% aq. HCl soln. (50 mL) was added to the reaction mixture to neutralize the base and extracted with ethyl acetate (2x100 mL). The organic layers were combined, washed with brine (100 mL), dried over anhyd. Na_2SO_4 and evaporated under vacuum to yield an oily residue. The residue was purified by column chromatography over silica gel (60-120 mesh) using hexane: ethyl acetate as eluent. A mixture of hexane: ethyl acetate (85:15, v/v) yielded the starting material while further elution with 60:40 mixture furnished the desired products.

2-[Hydroxy-(5-methyl-3-phenyl-isoxazol-4-yl)-methyl]-acrylic acid methyl ester (4a)

59% as colourless oil; IR (neat, cm^{-1}) 1719 (CO_2Me), 3407 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.49 (s, 3H, CH_3), 2,96, 2.97 (d, 1H, *J*= 3.8 Hz, OH), 3.74 (s, 3H, CO_2CH_3), 5.62 (t, 1H, J_1= 1.4 Hz, J_2= 2.0 Hz, CH), 5.733, 5.736 (d, 1H, J_1= 0.6 Hz, 1H of $=CH_2$), 6.32 (s, 1H, 1H of $=CH_2$), 7.42-7.45 (m, 3H, Ar-H), 7.56-7.61 (m, 2H, Ar-H); Mass (FABMS+) *m/z* 274 (M^+ + 1). Anal. calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.89; H, 5.50; N, 5.22 %.

2-[Hydroxy-(5-methyl-3-p-tolyl-isoxazol-4-yl)-methyl]-acrylic acid methyl ester (4b)

59 % as pale yellow oil; IR (neat, cm^{-1}) 1710 (CO_2Me), 3397 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.98, 2.99 (d, 1H, *J*= 3.6 Hz, OH), 3.74 (s, 3H, CO_2CH_3), 5.61 (brs, 1H, CH), 5.73 (s, 1H, 1H of $=CH_2$), 6.32 (s, 1H, 1H of $=CH_2$), 7.21, 7.25 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.45, 7.49 (d, 2H, *J*= 8.0 Hz, Ar-H); Mass (FABMS+) *m/z* 288 (M^+ + 1). Anal. calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.66; H, 5.98; N, 4.70 %.

2-{[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid methyl ester (4c)

59% as colourless oil; IR (neat, cm^{-1}) 1718 (CO_2Me), 3402 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.52 (s, 3H, CH_3), 2.82 (brs, 1H, OH), 3.66 (s, 3H, CO_2CH_3), 5.37 (s, 1H, CH), 5.69 (s, 1H, 1H of $=CH_2$), 6.20 (s, 1H, 1H of $=CH_2$), 7.35-7.48 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 308 (M^+ + 1). Anal. calcd. for $C_{15}H_{14}ClNO_4$: C, 58.55; H, 4.59; N, 4.55. Found: C, 58.60; H, 4.69; N, 4.50%.

2-{[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid methyl ester (4d)

54% as colourless oil; IR (neat, cm^{-1}) 1718 (CO_2Me), 3402 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.48 (s, 3H, CH_3), 2.97, 2.99 (d, 1H, *J*= 3.6 Hz, OH), 3.74 (s, 3H, CO_2CH_3), 5.60 (brs, 1H, CH), 5.73 (s, 1H, 1H of $=CH_2$), 6.31 (s, 1H, 1H of $=CH_2$), 7.44, 7.48 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.56, 7.60 (d, 2H, *J*= 8.0 Hz, Ar-H); Mass (FABMS+) *m/z* 308 (M^+ + 1). Anal. calcd. for $C_{15}H_{14}ClNO_4$: C, 58.55; H, 4.59; N, 4.55. Found: C, 58.36; H, 4.28; N, 4.89 %.

2-{[3-(2,4-Dichloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid methyl ester (4e)

51% as colourless oil; IR (neat, cm^{-1}) 1718 (CO_2Me), 3402 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.51 (s, 3H, CH_3), 2.76, 2.78 (d, 1H, *J*= 4.0 Hz, OH), 3.68 (s, 3H, CO_2CH_3), 5.35, 5.37 (d, 1H, *J*= 4.0 Hz, CH), 5.71 (s, 1H, 1H of $=CH_2$), 6.22 (s, 1H, 1H of $=CH_2$), 7.31 (s, 2H, Ar-H), 7.49 (s, 1H, Ar-H); Mass (FABMS+) *m/z* 342 (M^+ + 1). Anal. calcd. for $C_{15}H_{13}Cl_2NO_4$: C, 52.65; H, 3.83; N, 4.09;. Found: C, 52.67; H, 3.95; N, 3.90 %.

2-{[3-(4-Benzyloxy-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid methyl ester (4f)

47% as colourless oil; IR (neat, cm^{-1}) 1718 (CO_2Me), 3399 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.46 (s, 3H, CH_3), 2.98 (brs, 1H, OH), 3.74 (s, 3H, CO_2CH_3), 5.10 (s, 2H, OCH_2), 5.62 (s, 1H, CH), 5.73 (s, 1H, 1H of $=CH_2$), 6.32 (s, 1H, 1H of $=CH_2$), 7.00, 7.04 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.28-7.35 (m, 5H, Ar-H), 7.52, 7.56 (d, 2H, *J*= 8.0 Hz, Ar-H),; Mass (FABMS+) *m/z* 380 (M^+ + 1). Anal. calcd. for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.64; H, 5.75; N, 3.79 %.

2-[Hydroxy-(5-methyl-3-phenyl-isoxazol-4-yl)-methyl]-acrylic acid ethyl ester (5a)

57% as colourless oil; IR (neat, cm^{-1}) 1707 (CO_2Et), 3431 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, 3H, *J*= 7.2 Hz, CH_3), 2.49 (s, 3H, CH_3), 3.02, 3.04 (d, 1H, *J*= 3.6 Hz, OH), 4.20 (q, 2H, *J*= 7.0 Hz, CO_2CH_2), 5.62 (t, 1H, J_1= 1.4 Hz, J_2= 1.8 Hz, CH), 5.71 (s, 1H, 1H of $=CH_2$), 6.32 (s, 1H, 1H of $=CH_2$), 7.41-7.45 (m, 3H, Ar-H), 7.56-7.61 (m, 2H, Ar-H); Mass (FABMS+) *m/z* 288 (M^+ + 1). Anal. calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.11; H, 6.01; N 4.77 %.

2-[Hydroxy-(5-methyl-3-p-tolyl-isoxazol-4-yl)-methyl]-acrylic acid ethyl ester (5b)

55 % as colorless oil; IR (neat, cm^{-1}) 1710 (CO_2Et), 3397 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, 3H, *J*= 7.2 Hz, CH_3), 2.39 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.98, 2.99 (d, 1H, *J*= 3.6 Hz, OH), 4.20 (q, 2H, *J*= 7.0 Hz, CO_2CH_2), 5.61 (brs, 1H, CH), 5.72 (s, 1H, 1H of $=CH_2$), 6.32 (s, 1H, 1H of $=CH_2$), 7.21, 7.25 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.45, 7.49 (d, 2H, *J*= 8.0 Hz, Ar-H); Mass (FABMS+) *m/z* 302 (M^+ + 1). Anal. calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.81; H, 6.66; N, 4.70 %.

2-{[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid ethyl ester (5c)

50% as colourless oil; IR (neat, cm^{-1}) 1711 (CO_2Et), 3401 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, 3H, *J*= 7.2 Hz, CH_3), 2.52 (s, 3H, CH_3), 2.77 (brs, 1H, OH), 4.14 (q, 2H, *J*= 7.0 Hz, CO_2CH_2), 5.37 (s, 1H, CH), 5.64 (s, 1H, 1H of $=CH_2$), 6.17 (s, 1H, 1H of $=CH_2$), 7.35-7.44 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 322 (M^+ + 1). Anal. calcd. for $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; N, 4.35. Found: C, 60.04; H, 5.02; N, 4.57 %.

2-{[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid ethyl ester (5d)

50% as colourless oil; IR (neat, cm^{-1}) 1711 (CO_2Et), 3402 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, 3H, *J*= 7.2 Hz, CH_3), 2.50 (s, 3H, CH_3), 3.04, 3.06 (d, 1H, *J*= 3.6 Hz, OH), 4.20 (q, 2H, *J*= 7.2 Hz, CO_2CH_2), 5.59 (brs, 1H, CH), 5.70 (s, 1H, 1H of $=CH_2$), 6.26 (s, 1H, 1H of $=CH_2$), 7.42, 7.44 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.52, 7.56 (d, 2H, *J*= 8.0Hz, Ar-H); Mass (FABMS+) *m/z* 322 (M^+ + 1). Anal. calcd. for $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; N, 4.35. Found: C, 59.36; H, 4.92; N, 4.42 %.

2-{[3-(2,4-Dichloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid ethyl ester (5e)

52% as colourless oil; IR (neat, cm^{-1}) 1709 (CO_2Et), 3402 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, 3H, *J*= 7.2 Hz, CH_3), 2.52 (s, 3H, CH_3), 2.87, 2.89 (d, 1H, *J*= 4.0 Hz, OH), 4.14 (q, 2H, *J*= 7.0 Hz, CO_2CH_2), 5.35, 5.37 (s, 1H, *J*= 4.0 Hz, CH), 5.65 (s, 1H, 1H of $=CH_2$), 6.19 (s, 1H, 1H of $=CH_2$), 7.31 (s, 2H, Ar-H), 7.48 (s, 1H, Ar-H); Mass (FABMS+) *m/z* 356 (M^+ + 1). Anal. calcd. for $C_{16}H_{15}Cl_2NO_4$: C, 53.95; H, 4.24; N, 3.93. Found: C, 54.19; H, 4.37; N, 4.01 %.

2-{[3-(4-Benzyloxy-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid ethyl ester (5f)

45% as colourless oil; IR (neat, cm^{-1}) 1718 (CO_2Et), 3399 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, 3H, *J*= 7.2 Hz, CH_3), 2.50 (s, 3H, CH_3), 3.04, 3.06 (d, 1H, *J*= 3.6 Hz, OH), 4.20 (q, 2H, *J*= 7.2 Hz, CO_2CH_2), 5.59 (brs, 1H, CH), 5.70 (s, 1H, 1H of $=CH_2$), 6.26 (s, 1H, 1H of $=CH_2$), 7.42, 7.44 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.52, 7.56 (d, 2H, *J*= 8.0 Hz, Ar-H); Mass (FABMS+) *m/z* 394 (M^+ + 1). Anal. calcd. for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.28; H, 6.19; N, 3.84 %.

2-[Hydroxy-(5-methyl-3-phenyl-isoxazol-4-yl)-methyl]-acrylic acid butyl ester (6a)

56% as colourless oil; IR (neat, cm^{-1}) 1709 (CO_2Bu-n), 3430 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, 3H, *J*= 7.2 Hz, CH_3), 1.25-1.38 (m, 2H, CH_2), 1.53-1.63 (m, 2H, CH_2), 2.48 (s, 3H, CH_3), 3.02, 3.04 (d, 1H, *J*= 3.8 Hz, OH), 4.14 (t, 2H, *J*= 6.6 Hz, CO_2CH_2), 5.61 (t, 1H, J_1= 1.4 Hz, J_2= 2.2 Hz, CH), 5.71 (s, 1H, 1H of $=CH_2$), 6.31 (s, 1H, 1H of $=CH_2$), 7.41-7.44 (m, 3H, Ar-H), 7.57-7.62 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 12.60 (CH_3), 14.04 (CH_3), 19.44 (CH_2), 30.87 (CH_2), 64.30 (CH), 65.38 (CH_2), 109.97 (CH), 113.51 (CH), 126.16 (CH_2), 128.96 (2 X CH), 129.11 (2 X CH), 129.39 (CH), 129.93 (CH), 140.78 (C), 162.93 (C), 166.59 (C), 168.90 (C); Mass (FABMS+) *m/z* 316 (M^+ + 1). Anal. calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.58; H, 7.04; N, 4.51 %.

2-[Hydroxy-(5-methyl-3-p-tolyl-isoxazol-4-yl)-methyl]-acrylic acid butyl ester (6b)

56% as colourless oil; IR (neat, cm^{-1}) 1711 (CO_2Bu-n), 3409 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, 3H, *J*= 7.2 Hz, CH_3), 1.28-1.39 (m, 2H, CH_2), 1.53-1.64 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.01, 3.03 (d, 1H, *J*= 3.6 Hz, OH), 4.14 (t, 2H, *J*= 6.6 Hz, CO_2CH_2), 5.61 (brs, 1H, CH), 5.72 (s, 1H, 1H of $=CH_2$), 6.32 (s, 1H, 1H of $=CH_2$), 7.21, 7.25 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.49, 7.53 (d, 2H, *J*= 8.0 Hz, Ar-H); Mass (FABMS+) *m/z* 330 (M^+ + 1). Anal. calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.66; H, 7.39; N, 4.26 %.

2-{[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid butyl ester (6c)

55% as colourless oil; IR (neat, cm^{-1}) 1710 (CO_2Bu-n), 3403 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, 3H, *J*= 7.2 Hz, CH_3), 1.27-1.42 (m, 2H, CH_2), 1.51-1.65 (m, 2H, CH_2), 2.54 (s, 3H, CH_3), 2.91 (brs, 1H, OH), 4.08 (q, 2H, *J*= 7.0 Hz, CO_2CH_2), 5.37 (s, 1H, CH), 5.63 (s, 1H, 1H of $=CH_2$), 6.16 (s, 1H, 1H of $=CH_2$), 7.31-7.48 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 350 (M^+ + 1). Anal. calcd. for $C_{18}H_{20}ClNO_4$: C, 61.80; H, 5.76; N, 4.00. Found: C, 62.02; H, 5.89; N, 4.01 %.

2-{[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid butyl ester (6d)

49% as colourless oil; IR (neat, cm^{-1}) 1711 (CO_2Bu-n), 3401 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, 3H, *J*= 7.2 Hz, CH_3), 1.27-1.42 (m, 2H, CH_2), 1.51-1.65 (m, 2H, CH_2), 2.54 (s, 3H, CH_3), 2.91 (brs, 1H, OH), 4.08 (q, 2H, *J*= 7.0 Hz, CO_2CH_2), 5.37 (s, 1H, CH), 5.63 (s, 1H, 1H of $=CH_2$), 6.16 (s, 1H, 1H of $=CH_2$), 7.31-7.48 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 350 (M^+ + 1). Anal. calcd. for $C_{18}H_{20}ClNO_4.H_2O$: C, 58.78; H, 6.03; N, 3.81. Found: C, 58.81; H, 6.29; N, 4.12 %.

2-{[3-(2,4-Dichloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid butyl ester (6e)

56% as colourless oil; IR (neat, cm^{-1}) 1711 (CO_2Bu-n), 3401 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, 3H, *J*= 7.2 Hz, CH_3), 1.28-1.39 (m, 2H, CH_2), 1.52-1.63 (m, 2H, CH_2), 2.51 (s, 3H, CH_3), 2.85, 2.87 (d, 1H, *J*= 4.4 Hz, OH), 4.08 (q, 2H, *J*= 7.0 Hz, CO_2CH_2), 5.55, 5.37 (d, 1H, *J*= 4.0 Hz, CH), 5.65 (s, 1H, 1H of $=CH_2$), 6.18 (s, 1H, 1H of $=CH_2$), 7.31 (s, 2H, Ar-H), 7.48 (s, 1H, Ar-H); Mass (FABMS+) *m/z* 384 (M^+ + 1). Anal. calcd. for $C_{18}H_{19}Cl_2NO_4$: C, 56.26; H, 4.98; N, 3.65. Found: C, 55.95; H, 4.73; N, 3.30 %.

2-{[3-(4-Benzyloxy-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid butyl ester (6f)

46% as colourless oil; IR (neat, cm^{-1}) 1718 (CO_2Bu-n), 3399 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, 3H, *J*= 7.2 Hz, CH_3), 1.27-1.42 (m, 2H, CH_2), 1.51-1.65 (m, 2H, CH_2), 2.54 (s, 3H, CH_3), 2.91 (brs, 1H, OH), 4.08 (q, 2H, *J*= 7.0 Hz, CO_2CH_2), 5.37 (s, 1H, CH), 5.63 (s, 1H, 1H of $=CH_2$), 6.16 (s, 1H, 1H of $=CH_2$), 7.31-7.48 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 422 (M^+ + 1). Anal. calcd. for $C_{25}H_{27}NO_5$: C,

71.24; H, 6.46; N, 3.32. Found: C, 71.21; H, 6.83; N, 3.56 %.

2-[Hydroxy-(5-methyl-3-phenyl-isoxazol-4-yl)-methyl]-acrylonitrile (7a)

90% as white solid, m.p. 86-88 ^{o}C; IR (KBr, cm^{-1}) 2234 (CN), 3402 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.53 (m, 4H, s of CH_3 merged with d of OH), 5.33 (t, 1H, J_1= 2.0 Hz, J_2= 2.4 Hz, CH), 6.02, 6.03 (2s almost merged, 2H, =CH_2), 7.44-7.49 (m, 3H, Ar-H), 7.54-7.59 (m, 2H, Ar-H); Mass (FABMS+) *m/z* 241 (M^+ + 1). Anal. calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.14; H, 5.22; N, 11.59 %.

2-[Hydroxy-(5-methyl-3-p-tolyl-isoxazol-4-yl)-methyl]-acrylonitrile (7b)

89% as white solid, m.p. 116-118 ^{o}C; IR (KBr, cm^{-1}) 2223 (CN), 3404 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H, CH_3), 2.45 (s, 2H, CH_3), 3.39, 3.41 (d, 1H, *J*= 4.0 Hz, OH), 5.27, 5.28 (d, 1H, *J*= 3.6 Hz, CH), 6.00 (s, 2H, =CH_2), 7.20, 7.24 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.39, 7.43 (d, 2H, *J*= 8.0 Hz, Ar-H); Mass (FABMS+) *m/z* 255 (M^+ + 1). Anal. calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.05; H, 5.68; N, 11.18 %.

2-{[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylonitrile (7c)

79% as pale yellow oil; IR (neat, cm^{-1}) 2231 (CN), 3397 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.55 (s, 3H, CH_3), 2.72 (brs, 1H, OH), 5.11 (s, 1H, CH), 5.88 (s, 1H, 1H of =CH_2), 5.89 (s, 1H, 1H of =CH_2), 7.36-7.47 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 275 (M^+ + 1). Anal. calcd. for $C_{15}H_{14}ClN_2O_2$: C, 62.18; H, 4.87; N, 9.67. Found: C, 62.34; H, 5.10; N, 10.05 %.

2-{[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylonitrile (7d)

79% as pale yellow solid, m.p. 75-77 ^{o}C; IR (KBr, cm^{-1}) 2230 (CN), 3425 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.53 (s, 3H, CH_3), 2.59, 2.61 (d, 1H, J= 3.6 Hz, OH), 5.32 (s, 1H, CH), 6.05 (2s almost merged, 2H, 2H of =CH_2), 7.41, 7.45 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.54, 7.58 (d, 2H, *J*= 8.0 Hz, Ar-H); Mass (FABMS+) *m/z* 275 (M^+ + 1). Anal. calcd. for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.03; N, 10.19. Found: C, 60.89; H, 4.29; N, 9.85 %.

2-{[3-(2,4-Dichloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylonitrile (7e)

79% as white solid, m.p. 127-129 ^{o}C; IR (KBr, cm^{-1}) 2230 (CN), 3397 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.44, 2.46 (d, 1H, *J*= 4.0 Hz, OH), 2.56 (s, 3H, CH_3), 5.11 (t, 1H, J_1 = J_2= 2.0 Hz, CH), 5.94 (t, 2H, J_1 1.8 Hz, J_2= 2.2 Hz, =CH_2), 7.36 (s, 2H, Ar-H), 7.51 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 50.32 Hz) δ 12.52 (CH_3), 65.56 (CH), 113.75 (C), 116.87(C), 124.24(C), 126.66 (C), 127.91 (CH), 130.06 (CH_2), 130.23 (CH), 133.29 (CH), 134.69 (C), 137.27 (C), 159.89 (C), 169.58 (C); Mass (FABMS+) *m/z* 309 (M^+ + 1). Anal. calcd. for $C_{14}H_{10}Cl_2N_2O_2$: C, 54.39; H, 3.26; N, 9.06. Found: C, 54.77; H, 3.26; N, 8.84 %.

2-{[3-(4-Benzyloxy-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylonitrile (7f)

79% as white solid, m.p. 66-68 ^{o}C; IR (KBr, cm^{-1}) 2231 (CN), 3396 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.46 (s, 3H, CH_3), 3.02, 3.04 (d, 1H, *J*= 3.6 Hz, OH), 5.09 (s, 2H, OCH_2), 5.28 (s, 1H, CH), 6.02 (s, 2H, =CH_2), 6.99-7.04 (d, 2H, *J*= 8.6 Hz, Ar-H), 7.33-7.52 (m, 7H, Ar-H); Mass (FABMS+) *m/z* 346 (M^+ + 1). Anal. calcd. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.66; H, 5.42; N, 8.21%.

3-[Hydroxy-(5-methyl-3-phenyl-isoxazol-4-yl)-methyl]-but-3-en-2-one (8a)

48% as pale yellow oil; IR (neat, cm^{-1}) 1685 (COMe), 3433 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.49 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.10 (brs, 1H, OH), 5.67 (s, 1H, CH), 5.87 (s, 1H, 1H of =CH_2), 6.15 (s, 1H, 1H of =CH_2), 7.40-7.49 (m, 3H, Ar-H), 7.54-7.64 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 12.58 (CH_3), 26.77 (CH_3), 64.15 (CH), 127.22 (CH_2), 128.91 (2 X CH), 129.21 (2 X CH), 129.51(CH), 129.92 (CH), 148.16 (C), 162.66 (C), 168.90 (C), 200.53 (C); Mass (FABMS+) *m/z* 258 (M^+ + 1). Anal. calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.36; H, 5.47; N, 5.28 %.

3-[Hydroxy-(5-methyl-3-p-tolyl-isoxazol-4-yl)-methyl]-but-3-en-2-one (8b)

48% as pale yellow oil; IR (neat, cm^{-1}) 1674 (COMe), 3421 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.34 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.11, 3.33 (d, 1H, *J*= 3.2 Hz, OH), 5.66 (s, 1H, CH), 5.86 (s, 1H, 1H of =CH_2), 6.15 (s, 1H, 1H of =CH_2), 6.03 (s, 2H, =CH_2), 7.19, 7.23 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.43, 7.47 (d, 2H, *J*= 8.0 Hz, Ar-H); Mass (FABMS+) *m/z* 272 (M^+ + 1). Anal. calcd. for $C_{16}H_{17}NO_3$. 1/2H_2O: C, 68.32; H, 6.40; N, 4.98. Found: C, 68.78; H, 6.60; N, 5.00 %.

3-{[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-but-3-en-2-one (8c)

56% as pale yellow oil; IR (neat, cm^{-1}) 1680 (COMe), 3434 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.22 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.56, 2.57 (d, 1H, *J*= 3.2 Hz, OH), 5.41 (s, 1H, CH), 5.84 (s, 1H, 1H of =CH_2), 6.02 (s, 1H, 1H of =CH_2), 7.33-7.46 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 292 (M^+ + 1). Anal. calcd. for $C_{15}H_{14}ClNO_3$: C, 61.76; H, 4.84; N, 4.80. Found: C, 61.80; H, 5.01; N, 4.97 %.

3-{[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-but-3-en-2-one (8d)

46% as pale yellow oil; IR (neat, cm^{-1}) 1676 (COMe), 3424 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.31 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.54, 2.55 (d, 1H, *J*= 3.2 Hz, OH), 5.41 (s, 1H, CH), 5.83 (s, 1H, 1H of =CH_2), 6.03 (s, 1H, 1H of =CH_2), 7.36-7.63 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 292 (M^+ + 1). Anal. calcd. for $C_{15}H_{14}ClNO_3$: C, 61.76; H, 4.84; N, 4.80. Found: C, 61.91; H, 5.15; N, 4.69 %.

3-{[3-(2,4-Dichloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-but-3-en-2-one (8e)

48% as pale yellow oil; IR (neat, cm^{-1}) 1629 (COMe), 3434 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.25 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.74, 2.76 (d, 1H, *J*= 4.0 Hz, OH), 5.39, 5.41 (d, 1H, *J*= 3.6 Hz, CH), 5.88 (s, 1H, 1H of $=CH_2$), 6.06 (s, 1H, 1H of $=CH_2$), 7.33 (s, 2H, Ar-H), 7.47 (s, 1H, Ar-H); Mass (FABMS+) *m/z* 326 (M^+ + 1). Anal. calcd. for $C_{15}H_{13}Cl_2NO_3$: C, 55.23; H, 4.02; N, 4.29. Found: C, 54.88; H, 4.37; N, 4.18 %.

3-{[3-(4-Benzyloxy-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-but-3-en-2-one (8f)

42% as pale yellow oil; IR (neat, cm^{-1}) 1679 (COMe), 3434 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.31 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.50 (s, 1H, OH), 5.08 (s, 1H, OCH_2), 5.65 (s, 1H, CH), 5.87 (s, 1H, 1H of $=CH_2$), 6.13 (s, 1H, 1H of $=CH_2$), 6.97, 7.01 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.29-7.61 (m, 7H, Ar-H); Mass (FABMS+) *m/z* 363 (M^+ + 1). Anal. calcd. for $C_{22}H_{21}NO_4.H_2O$: C, 69.27; H, 6.07; N, 3.67. Found: C, 69.38; H, 5.68; N, 3.72 %.

Baylis-Hillman reaction of cyclohexenone- General Procedure: A mixture of appropriate compound from **1a-d** (4 mmol), DMAP (50 mol%) and cyclohexenone (4 mmol) in 5 mL of dioxane: water (3: 2, v/v) mixture was stirred at r.t. for 7 days. Thereafter the reaction mixture was extracted with ethyl acetate (2 X 30 mL). The usual work up of the organic layer furnished a residue that was column chromatographed over silica gel. Elution with mixture of hexane: ethyl acetate (85: 15, v/v) as eluent yielded the starting aldehyde while further elution with 40: 60, v/v furnished the desired products.

2-[Hydroxy-(5-methyl-3-phenyl-isoxazol-4-yl)-methyl]-cyclohex-2-enone (9a)

23% as yellow solid, m. p. 79-81 ^oC; IR (KBr, cm^{-1}) 1668 (CO), 3330 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ ^1H NMR ($CDCl_3$) δ 1.87-1.92 (m, 2H, CH_2), 2.24-2.26 (m, 2H, CH_2), 2.37-2.42 (m, 2H, CH_2), 2.51 (s, 3H, CH_3), 3.38, 3.39 (d, 1H, *J*= 3.4 Hz, OH), 5.30 (s, 1H, CH), 6.64 (t, 1H, *J*= 4.0 Hz, =CH), 7.41-7.46 (m, 3H, Ar-H), 7.52-7.55 (m, 2H, Ar-H); Mass (FABMS+) *m/z* 284 (M^+ + 1). Anal. calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.29; H, 5.85; N, 4.77 %.

2-[Hydroxy-(5-methyl-3-p-tolyl-isoxazol-4-yl)-methyl]-cyclohex-2-enone (9b)

25% as light brown solid, m. p. 79-81 ^oC; IR (KBr, cm^{-1}) 1670 (CO), 3336 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ ^1H NMR ($CDCl_3$) δ 1.91-1.98 (m, 2H, CH_2), 2.26-2.28 (m, 2H, CH_2), 2.38-2.46 (m, 5H, s of CH_3 merged with m of CH_2), 2.49 (s, 3H, CH_3), 3.46 (brs, 1H, OH), 5.64 (s, 1H, CH), 6.66 (t, 1H, *J*= 4.0 Hz, =CH), 7.18, 7.22 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.40, 7.44 (d, 2H, *J*= 8.0 Hz, Ar-H); Mass (FABMS+) *m/z* 298 (M^+ + 1). Anal. calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.98; H, 6.08; N, 5.00 %.

2-{[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-cyclohex-2-enone (9c)

17% as pale yellow oil; IR (neat, cm^{-1}) 1664 (CO), 3398 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ ^1H NMR ($CDCl_3$) δ 1.79-1.88 (m, 2H, CH_2), 2.15-2.21 (m, 2H, CH_2), 2.23-2.30 (m, 2H, CH_2), 2.56 (s, 3H, CH_3), 3.08, 3.10 (d, 1H, *J*= 3.8 Hz, OH), 5.36, 5.38 (d, 1H, *J*= 3.8 Hz, CH), 6.58 (t, 1H, *J*= 4.0 Hz, =CH), 7.32-7.46 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 317 (M^+ + 1). Anal. calcd. for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.08; N, 4.41. Found: C, 64.45; H, 5.08; N, 4.56 %.

Baylis Hillman reaction on solid support-General Procedure: The 2-chlorotrityl chloride resin (200 mg, 1.4 mmol/g, Novabiochem) after swelling with dry dichloromethane (DCM) was treated with acrylic acid (4 folds) and triethylamine (6 folds) in DCM as reported earlier.[6d] The resins were divided into two PP syringes fitted with frits. To each reaction vessel (RV), DABCO (3 folds) in 200 μL DMF was added and left for 15min. Thereafter solution of different aldehydes (**3-b**, **c**) (5 folds.) in 300 μL of DMF was added to respective RV and the reaction was shaken at 600 rpm. After 48h the reaction sequence was repeated for another 48h. Thereafter the resins were washed using DMF (X3), MeOH (X3) DCM (X2) and ether (X2). Finally the resins were cleaved with 5% TFA in DCM for 20 min. The filtrate was evaporated and lyophilized using tert-butanol: water (4:1).

2-[Hydroxy-(5-methyl-3-p-tolyl-isoxazol-4-yl)-methyl]-acrylic acid (13b)

34% purity based on analytical HPLC of crude product (R_t= 13.78 min at λ_{max} of 220nm in a gradient run of 0-100% acetonitrile in water in 20 min on a RP-18e column (150 X 5mm) having particle size of 5μm); 21% as white solid m.p. 165-166 ^oC; IR (KBr, cm^{-1}) 1697 (CO), 3446 (OH); ^1H NMR ($CDCl_3$+ a drop of $DMSOd_6$, 200 MHz) δ 2.38 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.76 (s, 1H, OH), 5.54 (s, 1H, CH), 5.88 (s, 1H, 1H of $=CH_2$), 6.28 (s, 1H, 1H of $=CH_2$), 7.20, 7.24 (d, 2H, *J*= 8.0 Hz, Ar-H), 7.58, 7.62 (d, 2H, *J*= 8.0 Hz, Ar-H); Mass (FABMS+) *m/z* 274 (M^+ + 1). Anal. calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.18; H, 5.59; N, 4.81 %.

2-{[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-hydroxy-methyl}-acrylic acid (13c)

29% purity based on analytical HPLC of crude product (R_t= 12.93 min at λ_{max} of 220nm in a gradient run of 0-100% acetonitrile in water in 20 min on a RP-18e column (150 X 5mm) having particle size of 5μm); 19% as pale yellow solid, m.p. 148-149 ^oC; IR (KBr, cm^{-1}) 1702 (CO_2H), 3395 (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.50 (s, 3H, CH_3), 3.73 (s, 1H, OH), 5.35 (s, 1H, CH), 5.82 (s, 1H, 1H of $=CH_2$), 6.32 (s, 1H, 1H of $=CH_2$), 7.31-7.48 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 293 (M^+ + 1). Anal. Calcd. for $C_{16}H_{14}ClNO_5$:C, 57.25; H, 4.12; N, 4.77. Found: 57.11; H, 4.39; N, 4.51 %.

Acetylation-General Procedure: To a stirred solution of appropriate compound from **4, 7c, e** (3.25 mmol) in dry dichloromethane (5 mL) was added pyridine (0.48 mL, 6.0 mmol) followed by a dropwise addition of solution of acetyl chloride (0.46 mL, 6.5 mmol) in dry dichloromethane (3 mL) at 0 ^{o}C. After the addition was complete, the reaction was continued at r.t. for 1h. The reaction mixture was extracted with dichloromethane (2 X 30 mL) and water (50mL). The organic layers were combined, washed with brine, dried over anhyd. Na_2SO_4 and evaporated to obtain an oily residue. The residue was purified on a small band of silica gel (60-120 mesh) using hexane: ethyl acetate (85: 15, v/v) as eluent to obtain pure acetates.

2-{Acetoxy-[3-(2-chloro-phenyl)-5-methyl-isoxazol-4-yl]-methyl}-acrylic acid methyl ester (10c)

85% as white solid, m.p. 93-95 ^{o}C; IR (KBr, cm^{-1}) 1708 (CO_2Me), 1745 (OCOMe); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.06 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 5.36 (s, 1H, =CH_2), 6.12 (s, 1H, =CH_2), 6.45 (s, 1H, CH), 7.22-7.47 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 12.08 (CH_3), 21.11 (CH_3), 52.43 (CH_3), 64.89 (CH), 111.89 (C), 125.98 (CH_2), 126.63 (CH), 128.87 (CH), 129.89 (CH), 131.21 (CH), 132.17 (CH), 134.56 (C), 136.69 (C), 160.88 (C), 165.27 (C), 169.46 (C); Mass (FABMS+) *m/z* 350 (M^+ + 1). Anal. calcd. for $C_{17}H_{16}ClNO_5$: C, 58.38; H, 4.61; N, 4.00. Found: C, 58.49; H, 4.43; N, 4.05 %.

2-{Acetoxy-[3-(2,4-dichloro-phenyl)-5-methyl-isoxazol-4-yl]-methyl}-acrylic acid methyl ester (10e)

82% as white solid, m.p. 76-78 ^{o}C; IR (KBr, cm^{-1}) 1704 (CO_2Me), 1738 (OCOMe); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.06 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 5.44 (s, 1H, =CH_2), 6.16 (s, 1H, =CH_2), 6.43 (s, 1H, CH), 7.24-7.35 (m, 2H, Ar-H), 7.48-7.49 (m, 1H, Ar-H); Mass (FABMS+) *m/z* 384 (M^+ + 1). Anal. calcd. for $C_{17}H_{15}Cl_2NO_5$: C, 53.14; H, 3.94; N, 3.65. Found: C, 52.88; H, 3.91; N, 3.70 %.

Acetic acid 1-[3-(2-chloro-phenyl)-5-methyl-isoxazol-4-yl]-2-cyano-allyl ester (11c)

88% as white solid, m.p. 49-51 ^{o}C; IR (neat, cm^{-1}) 1750 (OCOMe), 2231 (CN); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.09 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 5.68, 5.69 (d, 1H, *J*= 1.4 Hz, =CH_2), 5.91, 5.92 (d, 1H, *J*= 1.4 Hz, =CH_2), 6.13 (s, 1H, CH), 7.35-7.47 (m, 4H, Ar-H); Mass (FABMS+) *m/z* 317 (M^+ + 1). Anal. calcd. for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; N, 8.84. Found: C, 60.93; H, 4.14; N, 8.92 %.

Acetic acid 2-cyano-1-[3-(2,4-dichloro-phenyl)-5-methyl-isoxazol-4-yl]-allyl ester (11e)

86% as white solid, m.p. 80-82 ^{o}C; IR (neat, cm^{-1}) 1744 (OCOMe), 2232 (CN); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.11 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 5.76 (s, 1H, =CH_2), 5.97 (s, 1H, =CH_2), 6.12 (s, 1H, CH), 7.31-7.39 (s, 2H, Ar-H), 7.50-7.53 (m, 7H, Ar-H); Mass (FABMS+) *m/z* 351 (M^+ + 1). Anal. calcd. for $C_{16}H_{12}Cl_2N_2O_3$: C, 54.72; H, 3.44; N, 7.98. Found: C, 54.54; H, 3.38; N, 7.60 %.

Reaction with benzylamine-General Procedure: To the appropriate acetate from **4, 7 c, e** (0.7 mmol) in THF was added triethyl amine (0.2 mL, 1.4 mmol) followed by benzylamine (0.234 mL, 2.1 mmol) and the mixture was refluxed under stirring in an oil bath. The reaction on completion was extracted with ethyl acetate (2 X 30 mL) and water (40 mL). The organic layers were pooled together, dried over anhyd. Na_2SO_4 and evaporated to obtain an oily residue. The amines **14 c, e** were purified through chromatography on basic alumina using hexane: ethyl acetate (75: 25, v/v) as eluent. On the other hand amines **15 d, e** were purified on silica gel (230-400 mesh) using hexane: ethyl acetate (70: 30, v/v) as eluent.

2-(Benzylamino-methyl)-3-[3-(2-chloro-phenyl)-5-methyl-isoxazol-4-yl]-acrylic acid methyl ester (14c)

81% as mixture of *E* (colourless oil) and *Z* (colourless oil); IR (neat, cm^{-1}) 1718 (CO_2Me), 3350 (NH); ^{1}H NMR ($CDCl_3$, 200 MHz) **(*E*)** δ 2.45 (s, 3H, CH_3), 3.18 (s, 1H, NH), 3.56 (s, 5H, CH_2 merged with CO_2Me), 3.76 (s, 2H, CH_2), 7.15-7.48 (s, 10H, =CH merged with Ar-H). **(*Z*)** δ 2.38 (s, 3H, CH_3), 3.18 (s, 1H, NH), 3.43 (s, 2H, CH_2), 3.56 (s, 3H, CO_2Me), 3.70 (s, 2H, CH_2), 6.49 (s, 1H, =CH), 7.15-7.48 (s, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) (as mixture) δ 12.38 (CH_3), 12.49 (CH_3), 46.32 (CH_2), 52.22 (2 X CH_2), 52.47 (2 X CH_3), 53.74 (CH_2), 112.14 (C), 112.87 (C), 125.99 (CH), 127.21 (2 X CH), 127.47 (2 X CH), 128.45 (2 X CH), 128.54 (2 X CH), 128.76 (2 X CH), 128.99 (CH), 129.30 (CH), 130.41 (CH), 130.56, (CH), 131.27 (CH), 131.48 (CH), 131.90 (CH), 132.21 (CH), 133.73 (2 X C), 135.52 (2 X C), 140.09 (2 X C), 161.07 (2 X C), 167.11 (2 X C), 167.68 (2 X C); Mass (FABMS+) *m/z* 397 (M^+ + 1). Anal. calcd. for $C_{22}H_{21}ClN_2O_3$: C, 66.58; H, 5.33; N, 7.06. Found: C, 66.77; H, 5.39; N, 6.95 %.

2-(Benzylamino-methyl)-3-[3-(2,4-dichloro-phenyl) -5-methyl-isoxazol-4-yl]-acrylic acid methyl ester (14e)

75% as mixture of *E* (colourless oil) and *Z* (colourless oil); IR (neat, cm^{-1}) 1714 (CO_2Me), 3350 (NH); ^{1}H NMR ($CDCl_3$, 200 MHz) **(*E*)** δ 2.45 (s, 3H, CH_3), 3.16 (s, 2H, CH_2), 3.45 (s, 3H, CO_2CH_3), 3.77 (s, 2H, CH_2), 7.15-7.39 (m, 8H, 7 X Ar-H and =CH_2), 7.48 (s, 1H, Ar-H). **(*Z*)** δ 2.37 (s, 3H, CH_3), 3.49 (s, 2H, CH_2), 3.56 (s, 3H, CO_2CH_3), 3.71 (s, 2H, CH_2), 6.48 (s, 1H, =CH_2), 7.15-7.39 (m, 7H, 7 X Ar-H), 7.48 (s, 1H, Ar-H); Mass (FABMS+) *m/z* 430 (M^+ + 1). Anal. calcd. for $C_{22}H_{20}Cl_2N_2O_3$: C, 61.26; H, 4.67; N, 6.49. Found: C, 61.22; H, 4.51; N, 6.60 %.

2-(Benzylamino-methyl)-3-[3-(2-chloro-phenyl)-5-methyl-isoxazol-4-yl]-acrylonitrile (*Z*) (15c)

69% as colourless oil; IR (neat, cm^{-1}) 2218 (CN), 3399 (NH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.60 (s, 3H, CH_3), 3.47 (s, 2H, CH_2), 3.74 (s, 2H, CH_2), 6.72

(s, 1H, =CH), 7.19-7.52 (m, 5H, Ar-H and NH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 14.11 (CH_3), 51.65 (CH_2), 52.23 (CH_2), 112.08 (C), 117.18 (C), 117.61 (C), 127.60 (CH), 127.80 (CH), 128.23 (C), 128.63 (2 X CH), 128.98 (2 X CH), 130.44 (CH), 131.84 (CH), 132.25 (CH), 133.81 (CH), 139.18 (2 X C), 161.01 (C), 168.54 (C); Mass (FABMS+) *m/z* 364 (M^+ + 1). Anal. Calcd. for $C_{21}H_{18}ClN_3O$: C, 69.32; H, 4.99; N, 11.55. Found: C, 69.52; H, 5.12; N, 11.66 %.

2-(Benzylamino-methyl)-3-[3-(2,4-dichloro-phenyl) -5-methyl-isoxazol-4-yl]-acrylonitrile (*Z*) (15e)

79% as off white solid, m.p.85-86 °C; IR (neat, cm^{-1}) 2218 (CN), 3399 (NH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.59 (s, 3H, CH_3), 3.48 (s, 2H, CH_2), 3.75 (s, 2H, CH_2), 6.72 (s, 1H, =CH), 7.20-7.31 (m, 5H, Ar-H), 7.38 (s, 2H, Ar-H), 7.50 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 14.05 (CH_3), 51.89 (CH_2), 52.56 (CH_2), 112.03 (C), 117.60 (C), 117.98 (C), 126.89 (C), 127.78 (CH), 128.06 (CH), 128.48 (2 X CH), 128.97 (2 X CH), 130.40 (CH), 132.91 (CH), 133.05 (CH), 134.57 (C), 137.39 (C), 139.52 (C), 160.19 (C), 168.77 (C); Mass (FABMS+) *m/z* 398 (M^+ + 1). Anal. Calcd. for $C_{21}H_{17}Cl_2N_3O$: C, 63.33; H, 4.30; N, 10.55. Found: C, 62.93; H, 4.65; N, 10.25 %.

Reaction with Nitroethane-General Procedure: To the prestirred mixture of K_2CO_3 (414 mg, 3.0 mmol) and nitroethane (0.14 mL, 2.0 mmol) in DMF was added a solution of appropriate compound from **4 c, e** (1.0 mmol) in DMF and reaction mixture was stirred at 60 °C for 1h. Thereafter the reaction mixture was neutralized with aqueous HCl (20%). Usual work of the reaction mixture led to an oily residue that was purified through column chromatography using hexane: ethyl acetate (85:15, v/v) as eluent to obtain the nitroalkenes.

3-[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-2-(2-nitro-propyl)-acrylic acid methyl ester (*E*) (17c)

79% as pale yellow oil; IR (neat, cm^{-1}) 1718 (CO_2Me), 1656, 1550 (NO_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31, 1.34 (d, 3H, J= 6.6 Hz, CH_3), 2.24-2.35 (m, 1H, 1H of CH_2), 2.43 (s, 3H, CH_3), 2.60-2.71 (m, 1H, 1H of CH_2), 3.78 (s, 3H, CO_2Me), 4.65-4.78 (m, 1H, CH), 7.35-7.50 (m, 5H, 4 X Ar-H merged with =CH); Mass (ESMS+) *m/z* 365.60 (M^+ + 1), 387.27 (M^+ + Na). Anal. Calcd. for $C_{17}H_{17}ClN_2O_5$; C, 55.97; H, 4.70; N, 7.68. Found C, 56.08; H, 4.99; N, 7.63 %.

3-[3-(2,4-Dichloro-phenyl)-5-methyl-isoxazol-4-yl]-2-(2-nitro-propyl)-acrylic acid methyl ester (*E*) (17e)

77% as white solid, m.p. 115-116 °C; IR (KBr, cm^{-1}) 1713 (CO_2Me), 1643, 1546 (NO_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35, 1.38 (d, 3H, J= 6.6 Hz, CH_3), 2.31-2.40 (m, 1H, 1H of CH_2), 2.43 (s, 3H, CH_3), 2.60-2.70 (m, 1H, 1H of CH_2), 3.79 (s, 3H, CO_2Me), 4.76-4.80 (m, 1H, CH), 7.32-7.42 (m, 3H, 2 X Ar-H merged with =CH), 7.49 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 12.54 (CH_3), 19.52 (CH_3), 34.16 (CH_2), 52.82 (CH_3), 81.91 (CH), 111.47 (C), 127.24 (C), 128.00 (CH), 130.50 (CH), 131.35 (C), 131.45 (CH), 132.78 (CH), 130.44 (CH), 134.41 (C), 137.11 (C), 159.80 (C), 166.64 (C), 168.02 (C); Mass (FABMS+) *m/z* 399 (M^+ + 1). Anal. calcd. for $C_{17}H_{16}Cl_2N_2O_5$: C , 51.14; H, 4.04; N, 7.02. Found: C, 50.83; H, 4.10; N, 6.83 %.

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