# The Baylis—Hillman Chemistry in Aqueous Media: Elucidation of Mechanism for Synthesis of Ether Side-Product Leads to an Efficient Approach to C—O Bond Formation

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# The Baylis–Hillman chemistry in aqueous media: elucidation of mechanism for synthesis of ether side-product leads to an efficient approach to C–O bond formation☆

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**Abstract**—The formation of an ether from the Baylis–Hillman (BH) adduct during the BH reaction of 5-isoxazolecarboxaldehydes is a common phenomenon if the reaction is allowed to proceed for longer periods. The amount of formation of such ethers depends on the acrylates used and is most significant for *tert*-butyl acrylates. A study of the plausible mechanism for the formation of these side-products led to reactions of acetates of BH adducts with phenol in aqueous media to yield the corresponding 3-phenoxy alk-2-enoates in good yields. The successful translation of solution phase methodology to solid phase for application towards combinatorial chemistry is discussed. 

The Baylis–Hillman (BH) reaction[1–4] continues to draw enormous attention from various research groups as it leads to multifunctional derivatives, which have been successfully translated into a wide spectrum of synthetically important molecules.[5–12] This carbon–carbon bond forming reaction in general involves the reaction between an aldehyde and an electron deficient alkene in the presence of a tertiary amine or Lewis acid. Recently, work towards variation of typical BH reactions has also been reported.[13–16] However as the typical BH reaction is marked by an exceptionally slow rate of reaction and limited choice of substrates, most of the recent publications have focused on these aspects thereby generating new knowledge.[17–24] The reaction rates could be increased by the use of either physical methods such as increased pressure,[25] microwave[26] or ultrasound[27] or by using mixture of Lewis acid with a wide variety of additives.[28–32] Despite various means discovered to accelerate this reaction, research groups are still probing new conditions and recently Rayner et al.[33] have shown that through the use of supercritical carbon dioxide in conjunction with high pressure under neat conditions, the reaction is accelerated appreciably. In this communication they also reported the unprecedented formation of ethers between the BH adducts as a side product. Simultaneously, Basavaiah et al.[34] also reported the tandem C–C and C–O bond formation during the BH reaction of aldehydes and acrylonitrile left for more than 8 days. Our interest in the BH reaction relates to identification of 5-isoxazolecarboxaldehyde as a very fast reacting substrate, which easily helps us in studying the various aspects of this reaction.[35–37] In our continued efforts to study the synthetic and mechanistic details of BH reaction of 5-isoxazolecarboxaldehydes, we have observed that if the reactions of this substrate with acrylates in the presence of DABCO are left for longer periods (ca. 2–10 h), another significant product starts appearing in the reaction mixture. Earlier since we were working up our reactions within 20–30 min, we did not observe the formation of any other product (as mentioned in our earlier publication[36]). The formation of ethers from 5-isoxazolecarboxaldehydes under conventional conditions is therefore in contrast to reports of Rayner et al. or Basavaiah et al. where these products were obtained only under extreme conditions or on continuing the reaction for a long duration, respectively. During studies on the mechanistic details towards the formation of ethers, we discovered that phenol reacts with acetates of BH adducts under aqueous conditions leading to the corresponding 3-phenoxy alk-2-enoates in good yields. With a view of expanding the scope of this methodology to combinatorial synthesis we have also successfully carried out these reactions on solid phase. The details of our studies are presented herein.

All the BH reactions of 5-isoxazolecarboxaldehydes (**1**) were realized as reported earlier.[11] However instead of working them up on completion, these reactions were allowed to continue further for 2–10 h. In all these reactions

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*Keywords*: Baylis–Hillman reaction; 5-isoxazolecarboxaldehyde; phenol; 3-phenoxy alk-2-enoates; solid phase.

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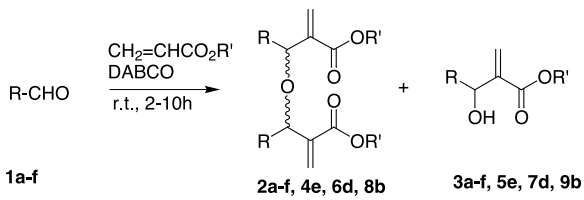



**Scheme 1.** For R and R′ refer to Table 1.

we observed the formation of a non-polar compound (**2a**–**f**, **4e**, **6d**, **8b**) in addition to the usual adduct (**3a**–**f**, **5e**, **7d**, **9b**) which could be easily isolated through column chromatography (Scheme 1). The detailed spectroscopic analysis coupled with HMQC and HMBC studies of these products led to the conclusion that they are dimeric structures having an ether linkage. It was interesting to note that the formation and yields of the ethers depended on the type of acrylate employed. In the case of *tert*-butyl acrylate, such ethers were obtained in appreciable amounts (4–13%); but in the case of *n*-butyl, ethyl or methyl acrylate the yields were restricted to 1–2% only. The HPLC analysis of these ethers gave single peak at $\lambda_{max}$=220 nm having retention time between 16–18 min (depending on the acrylate used) in an isocratic system on an RP-18 column (3.9×300 mm) using acetonitrile/water (70:30, v/v) at a flow rate of 0.7 mL/min for 35 min. However, from the $^1$H NMR spectra we observed that except for ethers **2a** and **2b**, which were obtained almost as single diastereoisomer, rest of the compounds existed as approximately 1:1 mixture of *meso* and *dl* diastereoisomers. This observation was confirmed through repeated experiments. Though at this point of time it is difficult to explain this finding, but this could be due to the steric bulk on the phenyl group of the isoxazole moiety. In contrast to the report of Rayner et al., we observed the formation of such ethers even when DMSO or DMF were used as solvent.

The plausible mechanism for the formation of the ethers is shown in Figure 1. To explain the formation of ethers, we presume that the reaction may be proceeding through $S_N2'$ mechanism via the intermediate **III**. This intermediate (**III**) may act as Michael acceptor while the hydroxyl group of the BH adduct act as nucleophile to furnish the ether. In principle such intermediate could also be obtained from the acetate of the BH adduct in the presence of DABCO which could then undergo nucleophilic addition to yield the ether. This hypothesis led us to carry out the reaction of an acetate of the BH adduct with its corresponding adduct in the presence of DABCO in aqueous THF. However, we could not obtain the ether through this route. It could also be envisaged that if such an ether results through dehydration of the two BH adducts, then the reaction could proceed in the presence of various dehydrating agents such as molecular sieves, phosphorus pentoxide, boron trifluoride etherate or phosphorus tribromide, but in our hands none of these reagents were successful. In addition to these attempts, leaving the BH adducts in DABCO for the period in which the ether was formed also did not yield any positive results. Further reaction of acetates with 4-nitrobenzyl alcohol or 4-methoxy benzyl alcohol in the presence of DABCO in aqueous media were also unsuccessful. Thus, unlike the earlier reports[34,35] we failed to obtain ethers from BH adducts. In light of these observations we presume that the plausible mechanism for the formation of the ether could be as shown in Figure 2. The second step (first step being the formation of a complex between the alkene and DABCO) in the usual mechanism of the BH reaction furnishes the intermediate **IV** that could be the actual nucleophilic species, which attacks the intermediate **III** leading to the

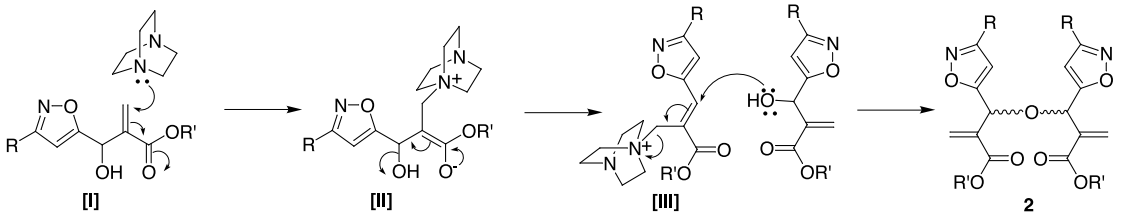



**Figure 1.**

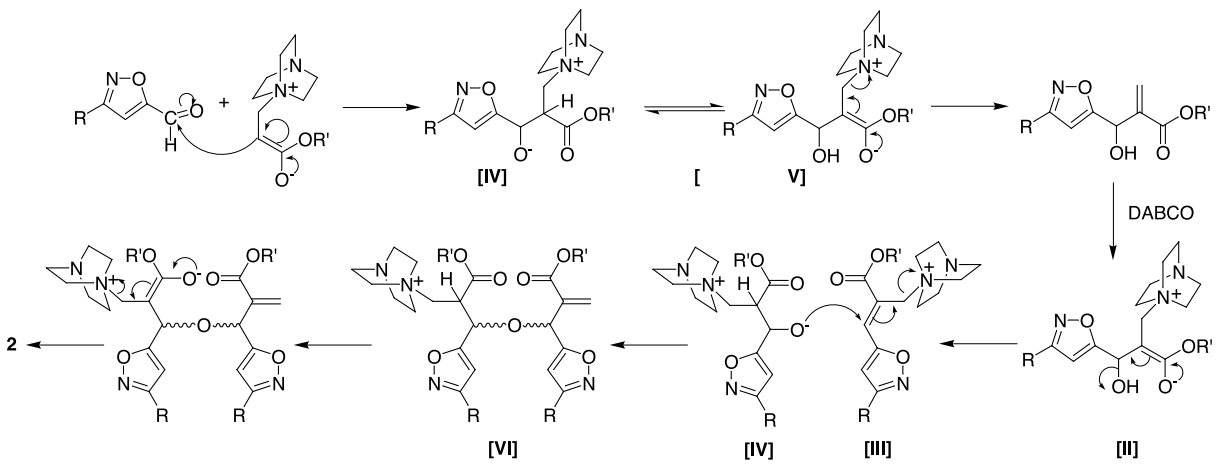
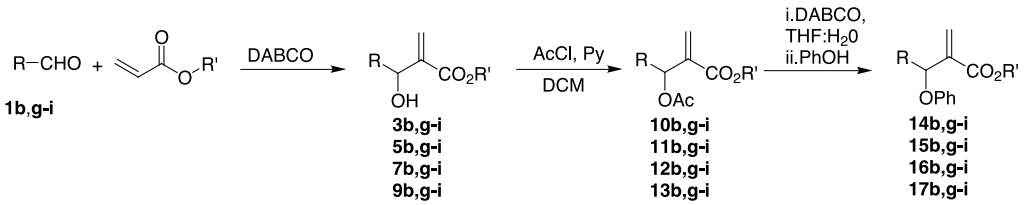



**Figure 2.**

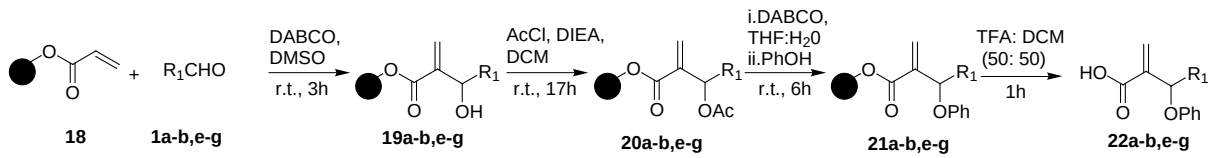



**Scheme 2.**

**Table 1**. Yields and physical state of reported compounds

| Compd. no. | R | R′ | Yield (%) | Mp (°C) |
|---|---|---|---|---|
| **2a** | 3-Phenylisoxazol-5-yl | *t*-Bu | 7 (9:1)[a] | 173–175 (white) |
| **2b** | 3-(4-Methylphenyl)isoxazol-5-yl | *t*-Bu | 13[b] | 145–146 (white) |
| **2c** | 3-(2-Benzyloxyphenyl)isoxazol-5-yl | *t*-Bu | 6 (1:1)[a] | 102–104 (white) |
| **2d** | 3-(4-Chlorophenyl)isoxazol-5-yl | *t*-Bu | 4 (1:1)[a] | Low melting sticky solid (pale yellow) |
| **2e** | 3-(2-Chlorophenyl)isoxazol-5-yl | *t*-Bu | 5 (1:1)[a] | 107–109 (pale yellow) |
| **2f** | 3-(2,4-Dichlorophenyl)isoxazol-5-yl | *t*-Bu | 5 (1:1)[a] | 107–109 (pale yellow) |
| **3a** | 3-Phenylisoxazol-5-yl | *t*-Bu | 64 | 78–80 (white) |
| **3b** | 3-(4-Methylphenyl)isoxazol-5-yl | *t*-Bu | 64 | 155–156 (white) |
| **3c** | 3-(2-Benzyloxyphenyl)isoxazol-5-yl | *t*-Bu | 72 | 79–80 (white) |
| **3d** | 3-(4-Chlorophenyl)isoxazol-5-yl | *t*-Bu | 64 | 75–76 (pale yellow) |
| **3e** | 3-(2-Chlorophenyl)isoxazol-5-yl | *t*-Bu | 68 | Oil (pale yellow) |
| **3f** | 3-(2, 4-Dichlorophenyl)isoxazol-5-yl | *t*-Bu | 61 | Oil (yellow) |
| **4e** | 3-(2-Chlorophenyl)isoxazol-5-yl | *n*-Bu | 1.5 (1:1)[a] | Oil (pale yellow) |
| **5e** | 3-(2-Chlorophenyl)isoxazol-5-yl | *n*-Bu | 71 | Oil (pale yellow) |
| **6d** | 3-(4-Chlorophenyl)isoxazol-5-yl | Et | 1 (1:1)[a] | 128–129 (white) |
| **7d** | 3-(4-Chlorophenyl)isoxazol-5-yl | Et | 72 | 89–90 (white) |
| **8b** | 3-(4-Methylphenyl)isoxazol-5-yl | Me | 1 (1:1)[a] | 128–130 (white) |
| **9b** | 3-(4-Methylphenyl)isoxazol-5-yl | Me | 82 | 95–96 (white) |
| **10b** | 3-(4-Methylphenyl)isoxazol-5-yl | *t*-Bu | 79 | 75–76 (white) |
| **10g** | 3-Nitrophenyl | *t*-Bu | 71 | Oil (yellow) |
| **10h** | 4-Nitrophenyl | *t*-Bu | 82 | Oil (pale yellow) |
| **10i** | 4-Trifluoromethylphenyl | *t*-Bu | 76 | Oil (pale yellow) |
| **11b** | 3-(4-Methylphenyl)isoxazol-5-yl | *n*-Bu | 78 | Oil (pale yellow) |
| **11g** | 3-Nitrophenyl | *n*-Bu | 71 | Oil (pale yellow) |
| **11h** | 4-Nitrophenyl | *n*-Bu | 74 | Oil (pale yellow) |
| **11i** | 4-Trifluoromethylphenyl | *n*-Bu | 88 | Oil (colourless) |
| **12b** | 3-(4-Methylphenyl)isoxazol-5-yl | Et | 69 | Oil (colourless) |
| **12g** | 3-Nitrophenyl | Et | 68 | Oil (pale yellow) |
| **12h** | 4-Nitrophenyl | Et | 69 | Oil (pale yellow) |
| **12i** | 4-Trifluoromethylphenyl | Et | 74 | Oil (pale yellow) |
| **12b** | 3-(4-Methylphenyl)isoxazol-5-yl | Me | 83 | Oil (pale yellow) |
| **12g** | 3-Nitrophenyl | Me | 73 | Oil (pale yellow) |
| **12h** | 4-Nitrophenyl | Me | ND | – |
| **12i** | 4-Trifluoromethylphenyl | Me | 71 | Oil (pale yellow) |
| **14b** | 3-(4-Methylphenyl)isoxazol-5-yl | *t*-Bu | 86 | Oil (colourless) |
| **14g** | 3-Nitrophenyl | *t*-Bu | 81 | Oil (pale yellow) |
| **14h** | 4-Nitrophenyl | *t*-Bu | 88 | Oil (pale yellow) |
| **14i** | 4-Trifluoromethylphenyl | *t*-Bu | 89 | Oil (colourless) |
| **15b** | 3-(4-Methylphenyl)isoxazol-5-yl | *n*-Bu | 83 | Oil (pale yellow) |
| **15g** | 3-Nitrophenyl | *n*-Bu | 93 | Oil (pale yellow) |
| **15h** | 4-Nitrophenyl | *n*-Bu | 83 | 72–74 (pale yellow) |
| **15i** | 4-Trifluoromethylphenyl | *n*-Bu | 85 | Oil (colourless) |
| **16b** | 3-(4-Methylphenyl)isoxazol-5-yl | Et | 86 | Oil (pale yellow) |
| **16g** | 3-Nitrophenyl | Et | 86 | Oil (pale yellow) |
| **16h** | 4-Nitrophenyl | Et | 91 | 100–101 (pale yellow) |
| **16i** | 4-Trifluoromethylphenyl | Et | 82 | 62–63 (colourless) |
| **17b** | 3-(4-Methylphenyl)isoxazol-5-yl | Me | 87 | Oil (pale yellow) |
| **17g** | 3-Nitrophenyl | Me | 89 | Oil (pale yellow) |
| **17h** | 4-Nitrophenyl | Me | ND | – |
| **17i** | 4-Trifluoromethylphenyl | Me | 90 | Low melting solid |
| **22a** | 3-Phenylisoxazol-5-yl | – | 25 (62)[c] | Oil (colourless) |
| **22b** | 3-(4-Methylphenyl)isoxazol-5-yl | – | 31 (71)[c] | 120–122 |
| **22e** | 3-(2-Chlorophenyl)isoxazol-5-yl | – | 23 (56)[c] | Oil (colourless) |
| **22f** | 3-(2, 4-Dichlorophenyl)isoxazol-5-yl | – | 27 (66)[c] | Oil (colourless) |
| **22g** | 3-Nitrophenyl | – | 25 (62)[c] | 126–127 (pale yellow) |

[a] Ratio of *meso* and C-2 symmetrical diastereoisomers through $^1$H NMR.
[b] Exist as single diastereoisomer.
[c] Yields of pure product after column chromatography. Figure in parentheses is the respective purity based on analytical HPLC of the crude product.




**Scheme 3.**

ether. It is quite likely that as the formation of the nucleophilic species **IV** is not possible during the reaction between acetate with its corresponding BH adduct under conventional reaction conditions, we failed in our attempts to obtain ether from the BH adduct. However, it can be added here that under extreme conditions,[33] the hydroxyl group of BH adduct might act as nucleophile as shown in Figure 1.

Nevertheless, we reasoned that if the hydroxyl group of the BH adducts or substituted benzyl alcohols are not strong enough a nucleophile to undergo addition to the intermediate **III**, some stronger and stable nucleophile such as phenoxide ion might yield such ethers. Therefore, we carried out the reactions of acetates with phenol in the presence of DABCO in THF/water and as envisioned, the reactions were complete within a few minutes. A careful survey of the literature indicated that the addition of phenols has earlier been reported directly on BH adduct[38] or on acetates[39] and bromo-derivatives[40] of BH adducts. The direct addition under Mitsunobu conditions leads to addition of phenols on the double bond.[38] On the other hand, the addition of phenols to bromo-derivatives of BH adducts gave similar products[40] as ours in the presence of $Et_3N$, while acetates in the presence of $Pd^0$ and/or KF/alumina gave similar product or a mixture of products depending upon conditions.[39] Thus we have for the first time discovered an efficient approach towards the synthesis of 3-phenoxy prop-2-enoates from acetates of BH adducts in aqueous media. To show the general applicability of this reaction we have carried out the reaction with wide variety of substrates (Scheme 2, Table 1).

With an objective to expand the scope and utility of this reaction towards combinatorial chemistry we have also successfully translated this methodology to solid phase (Scheme 3). The acrylate resin obtained by reaction of Wang resin with acryloyl chloride,[41] was subjected to BH reaction with various 3-substituted phenyl-5-isoxazole-carboxaldehydes in parallel format to obtain the BH adducts (**19a**,**b**,**e**–**g**). This was followed by conversion of the hydroxyl group to the corresponding acetate derivatives (**20a**,**b**,**e**–**g**). The formation of acetate was confirmed by on-bead FTIR. Further reaction of acetates (**20a**,**b**,**e**–**g**) with phenol in THF/water and final cleavage of resins furnished the products (**22a**,**b**,**e**–**g**).

Thus in conclusion, the elucidation of mechanism of the formation of the ether, which is not an unusual phenomenon in the case of 5-isoxazolecarboxaldehydes, has led to an easy access to 3-phenoxy prop-2-enoates from acetates of BH adducts. The solution phase methodology has also been successfully translated to the solid phase for the use in combinatorial chemistry. This will provide an additional diversity option at position 3 in propionic acid derivatives (BH adducts) for the generation of chemical libraries.

## 1. Experimental

### 1.1. General

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. $^1$H NMR spectra were recorded either on a Bruker Avance DRX-300 or Bruker DPX-200 FT spectrometers, using TMS as an internal standard (chemical shifts in $\delta$ values, $J$ in Hz). The FABMS were recorded on JEOL/ SX-102 spectrometers and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer. The $^1$H NMR of compounds **2a**–**f**, **4e**, **6d**, **8b** is being reported as diastereoisomeric mixture. The reaction of 4-nitro benzaldehyde with methyl acrylate was not carried out; therefore, there is no corresponding spectroscopic detail for compound **17h**. For spectroscopic data of BH adducts of 5-isoxazolecarboxaldehydes see Ref. 36. However, the data for the unreported BH adducts (**3d**, **3f**, **7d**) is being provided here.

### 1.2. General procedure for BH reaction

To a mixture of DABCO (0.056 g, 0.5 mmol) and appropriate alkene (10 mmol) that had been stirred at rt for 20 min was added appropriate aldehyde from **1a**–**f** (10 mmol) under stirring and the reaction was allowed to proceed for a period for 2 h in case of *tert*-butyl acrylate while 8–10 h in other cases. Thereafter 5% aq. HCl soln. was added to the reaction mixture to neutralize the base and extracted with ethyl acetate (2×100 mL).The organic layers were combined, washed with brine (100 mL), dried ($Na_2SO_4$) and evaporated under vacuum to yield an oily residue. The residue was purified by column chromatography over silica gel (230–400 mesh) using hexanes/ethyl acetate as eluent. Elution with 90:10, v/v mixture furnished the ethers (**2a**–**f**, **4e**, **6d**, **8b**) while further elution with 70:30 v/v mixture gave the BH adducts (**3a**–**f**, **5e**, **7d**, **9b**). The ethers were recrystallized from methanol.

**1.2.1. 2-[[2-*tert*-Butoxycarbonyl-1-(3-phenyl-isoxazol-5-yl)-allyloxy]-(3-phenyl-isoxazol-5-yl)-methyl]-acrylic acid *tert*-butyl ester (2a).** [Found C, 69.65; H, 6.18; N, 5.18. $C_{34}H_{36}N_2O_7$ requires C, 69.84; H, 6.20; N, 4.79%]; $\nu_{max}$ (KBr) 1701 ($CO_2$Bu-*t*) cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.41 (s, 18H, 2×$(CH_3)_3$), 1.44 (s, 18H, 2×$(CH_3)_3$), 5.63 (s, 2H, 2×OCH), 5.66 (s, 2H, 2×1H of $CH_2$), 6.10 (s, 2H, 2×1H

of $CH_2$), 6.23 (s, 2H, 2×1H of $CH_2$), 6.52 (s, 2H, 2×1H of $CH_2$), 6.54 (s, 4H, 4×CH), 7.41–7.42 (m, 6H, Ar-H), 7.43–7.46 (m, 6H, Ar-H), 7.69–7.74 (m, 4H, Ar-H), 7.78–7.81 (m, 4H, Ar-H); $\delta_C$ NMR (75.4 MHz) 27.9 ($CH_3$), 70.1 (CH), 82.0 (C), 101.2 (CH), 126.8 (CH), 127.3 ($CH_2$), 130.1 (CH), 138.1 (C), 162.3 (C), 163.8 (C), 170.4 (C); Mass (FABMS+) *m/z* % 585 ($M^+$+1).

**1.2.2. 2-[[2-*tert*-Butoxycarbonyl-1-(3-(4-methyl-phenyl)-isoxazol-5-yl)-allyloxy]-(3-(4-methyl-phenyl)-isoxazol-5-yl)-methyl]-acrylic acid *tert*-butyl ester (2b).** Obtained as single diastereoisomer; [Found C, 68.65; H, 6.48; N, 4.17. $C_{36}H_{40}N_2O_7.H_2O$ requires C, 68.55; H, 6.71; N, 4.44%]; $\nu_{max}$ (KBr) 1701 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.40 (s, 18H, 2×$(CH_3)_3$), 2.39 (s, 6H, 2×$CH_3$), 5.61 (s, 2H, 2×OCH), 6.22 (s, 2H, 2×1H of $CH_2$), 6.50 (s, 4H, 2×1H of $CH_2$ and 2×CH), 7.24 (d, 4H, *J*=8.0 Hz, Ar-H), 7.67 (d, 4H, *J*=8.0 Hz, Ar-H); Mass (FABMS+) *m/z* % 613 ($M^+$+1).

**1.2.3. 2-([3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-{1-[3-(4-benzyloxy-phenyl)-isoxazol-5-yl]-2-*tert*-butoxycarbonyl-allyloxy}-methyl)-acrylic acid *tert*-butyl ester (2c).** [Found C, 72.65; H, 6.18; N, 3.62. $C_{48}H_{48}N_2O_9$ requires C, 72.34; H, 6.07; N, 3.52%]; $\nu_{max}$ (KBr) 1705 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.32 (s, 18H, 2×$(CH_3)_3$), 1.35 (s, 18H, 2×$(CH_3)_3$), 5.01–5.04 (m, 8H, 4×$OCH_2$), 5.52 (s, 2H, 2×OCH), 5.56 (s, 2H, 2×OCH), 6.03 (s, 2H, 2×1H of $CH_2$), 6.14 (s, 2H, 2×1H of $CH_2$), 6.35–6.421 (m, 8H, 4×1H of $CH_2$ and 4×CH), 6.88–7.01 (m, 8H, Ar-H), 7.34 (brs, 20H, Ar-H), 7.55–7.71 (m, 8H, Ar-H); Mass (FABMS+) *m/z* % 797 ($M^+$+1).

**1.2.4. 2-{{2-*tert*-Butoxycarbonyl-1-[3-(4-chloro-phenyl)-isoxazol-5-yl]-allyloxy}-[3-(4-chloro-phenyl)-isoxazol-5-yl]-methyl}-acrylic acid *tert*-butyl ester (2d).** [Found C, 62.65; H, 5.18; N, 4.62. $C_{34}H_{34}Cl_2N_2O_7$ requires C, 62.48; H, 5.24; N, 4.29%]; $\nu_{max}$ (Neat) 1706 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.41 (m, 18H, 2×$(CH_3)_3$), 1.43 (m, 18H, 2×$(CH_3)_3$), 5.62 (s, 2H, 2×OCH), 5. 65 (s, 2H, 2×OCH), 6.11 (s, 2H, 2×1H of $CH_2$), 6.21 (s, 2H, 2×1H of $CH_2$), 6.44–6.51 (m, 8H, 4×1H of $CH_2$ and 4×CH), 7.33–7.45 (m, 8H, Ar-H), 7.60–7.74 (m, 8H, Ar-H); Mass (ESMS+) *m/z* % 676.53 ($M^+$+Na).

**1.2.5. 2-{{2-*tert*-Butoxycarbonyl-1-[3-(2-chloro-phenyl)-isoxazol-5-yl]-allyloxy}-[3-(2-chloro-phenyl)-isoxazol-5-yl]-methyl}-acrylic acid *tert*-butyl ester (2e).** [Found C, 62.41; H, 5.08; N, 4.33. $C_{34}H_{34}Cl_2N_2O_7$ requires C, 62.48; H, 5.24; N, 4.29%]; $\nu_{max}$ (KBr) 1698 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$), 1.42 (s, 18H, 2×$(CH_3)_3$), 1.44 (s, 18H, 2×$(CH_3)_3$), 5.58 (s, 2H, 2×OCH), 5. 62 (s, 2H, 2×OCH), 6.03 (s, 2H, 2×1H of $CH_2$), 6.18 (s, 2H, 2×1H of $CH_2$), 6.43 (s, 2H, 2×1H of $CH_2$), 6.45 (s, 2H, 2×1H of $CH_2$), 6.60 (m, 4H, 4×CH), 7.33–7.45 (m, 12H, Ar-H), 7.60–7.64 (m, 4H, Ar-H); Mass (FABMS+) *m/z* % 653 ($M^+$+1).

**1.2.6. 2-{{2-*tert*-Butoxycarbonyl-1-[3-(2,4-dichloro-phenyl)-isoxazol-5-yl]-allyloxy}-[3-(2,4-dichloro-phenyl)-isoxazol-5-yl]-methyl}-acrylic acid *tert*-butyl ester (2f).** [Found C, 56.89; H, 4.25; N, 3.62. $C_{34}H_{32}Cl_4N_2O_7$ requires C, 56.52; H, 4.46; N, 3.87%]; $\nu_{max}$ (KBr) 1698 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.42 (s, 18H, 2×$(CH_3)_3$), 1.44 (s, 18H, 2×$(CH_3)_3$), 5.65 (s, 2H, 2×OCH), 5. 68 (s, 2H, 2×OCH), 6.10 (s, 2H, 2×1H of $CH_2$), 6.23 (s, 2H, 2×1H of $CH_2$), 6.49 (s, 2H, 2×1H of $CH_2$), 6.52 (s, 2H, 2×1H of $CH_2$), 6.64 (s, 2H, 2×CH), 6.66 (s, 2H, 2×CH), 7.27–7.70 (m, 12H, Ar-H); Mass (ESMS+) *m/z* % 745.93 ($M^+$+Na).

**1.2.7. 2-{[3-(4-Chloro-phenyl)-isoxazol-5-yl]-hydroxy-methyl}-acrylic acid *tert*-butyl ester (3d).** [Found C, 60.57; H, 5.20; N, 4.01. $C_{17}H_{18}ClNO_4$ requires C, 60.81; H, 5.40; N, 4.17%]; $\nu_{max}$ (KBr) 1707 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.47 (s, 9H, 2×$(CH_3)_3$), 5.62 (s, 1H, OCH), 6.01 (s, 1H, 1H of $CH_2$), 6.44 (s, 1H, 1H of $CH_2$), 6.58 (s, 1H, CH), 7.42 (d, 2H, *J*=8.0 Hz, Ar-H), 7.73 (d, 2H, *J*=8.0 Hz, Ar-H); Mass (FABMS+) *m/z* % 336 ($M^+$+1).

**1.2.8. 2-{[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-hydroxy-methyl}-acrylic acid *tert*-butyl ester (3f).** [Found C, 54.87; H, 4.92; N, 3.81. $C_{17}H_{17}Cl_2NO_4$ requires C, 55.15; H, 4.63; N, 3.78%]; $\nu_{max}$ (neat) 1713 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.45 (s, 9H, 2×$(CH_3)_3$), 3.63 (d, 1H, *J*=8.0 Hz, OH), 5.69 (d, 1H, *J*=8.0 Hz, OCH), 6.02 (s, 1H, 1H of $CH_2$), 6.46 (s, 1H, 1H of $CH_2$), 6.72 (s, 1H, CH), 7.33 (dd, 1H, $J_1$=2.0 Hz, $J_2$=8.0 Hz, Ar-H), 7.51 (d, 1H, *J*=2.0 Hz, Ar-H), 7.68 (d, 2H, *J*=8.0 Hz, Ar-H); Mass (FABMS+) *m/z* % 371 ($M^+$+1).

**1.2.9. 2-{{2-Butoxycarbonyl-1-[3-(2-chloro-phenyl)-isoxazol-5-yl]-allyloxy}-[3-(2-chloro-phenyl)-isoxazol-5-yl]-methyl}-acrylic acid butyl ester (4e).** [Found C, 62.65; H, 5.18; N, 4.56. $C_{34}H_{34}Cl_2N_2O_7$ requires C, 62.48; H, 5.24; N, 4.29%]; $\nu_{max}$ (neat) 1719 ($CO_2$Bu-*n*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 0.86–0.93 (m, 12H, 4×$CH_3$), 1.25–1.37 (m, 8H, 4×$CH_2$), 1.57–1.64 (m, 8H, 4×$CH_2$), 4.12–4.19 (m, 8H, 4×$CH_2$), 5.71 (s, 2H, 2×OCH), 5.75 (s, 2H, 2×OCH), 6.19 (s, 2H, 2×1H of $CH_2$), 6.35 (s, 2H, 2×1H of $CH_2$), 6.60 (s, 2H, 2×1H of $CH_2$), 6.63 (s, 2H, 2×1H of $CH_2$), 6.71 (s, 4H, 4×CH), 7.30–7.47 (m, 12H, 4×3Ar-H), 7.70–7.79 (m, 4H, 4×1 Ar-H); Mass (ESMS+) *m/z* % 676.93 ($M^+$+Na).

**1.2.10. 2-([3-(4-Chloro-phenyl)-isoxazol-5-yl]-{1-[3-(4-chloro-phenyl)-isoxazol-5-yl]-2-ethoxycarbonyl-allyl-oxy}-methyl)-acrylic acid ethyl ester (6d).** [Found C, 60.65; H, 4.18; N, 5.02. $C_{30}H_{26}Cl_2N_2O_7$ requires C, 60.31; H, 4.39; N, 4.69%]; $\nu_{max}$ (KBr) 1709 ($CO_2$Et) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.21–1.33 (m, 12H, 4×$CH_3$), 4.13–4.24 (m, 8H, 4×$CH_2$), 5.54 (s, 2H, 2×OCH), 5.67 (s, 2H, 2×OCH), 6.32 (s, 2H, 2×1H of $CH_2$), 6.53 (s, 2H, 2×1H of $CH_2$), 6.61 (s, 2H, 2×1H of $CH_2$), 6.73 (s, 2H, 2×1H of $CH_2$), 7.26 (s, 2H, 2×CH), 7.30 (s, 2H, 2×CH), 7.40–7.48 (m, 8H, Ar-H), 7.70–7.79 (m, 8H, 2×4Ar-H); Mass (FABMS+) *m/z* % 597 ($M^+$+1).

**1.2.11. 2-{[3-(4-Chloro-phenyl)-isoxazol-5-yl]-hydroxy-methyl}-acrylic acid ethyl ester (7d).** [Found C, 58.87; H, 4.20; N, 4.69. $C_{15}H_{14}ClNO_4$ requires C, 58.55; H, 4.59; N, 4.55%]; $\nu_{max}$ (KBr) 1714 ($CO_2$Et) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.27 (t, 3H, *J*=7.2 Hz, $CH_3$), 4.11 (q, 2H, *J*=7.2 Hz, $CH_3$), 5.87 (s, 1H, OCH), 6.17 (s, 1H, 1H of $CH_2$), 6.46 (s, 1H, 1H of $CH_2$), 6.59 (s, 1H, CH), 7.33 (d, 2H, *J*=8 0 Hz, Ar-H), 7.65 (d, 2H, *J*=8.0 Hz, Ar-H); Mass (FABMS+) *m/z* % 308 ($M^+$+1).

**1.2.12. 2-[[2-Methoxycarbonyl-1-(3-(4-methyl-phenyl)-isoxazol-5-yl)-allyloxy]-(3-(4-methyl-phenyl)-isoxazol-5-yl)-methyl]-acrylic acid methyl ester (8b).** [Found C,

68.36; H, 5.17; N, 5.55. $C_{30}H_{28}N_2O_7$ requires C, 68.17; H, 5.34; N, 5.30%]; $\nu_{max}$ (KBr) 1719 ($CO_2Me$) $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 2.40 (s, 12H, 4×$CH_3$), 3.76 (s, 6H, 2×$CO_2CH_3$), 3.86 (s, 6H, 2×$CO_2CH_3$), 5.66 (s, 2H, 2×OCH), 5.69 (s, 2H, 2×OCH), 6.10 (s, 2H, 2×1H of $CH_2$), 6.13 (s, 2H, 2×1H of $CH_2$), 6.54 (s, 2H, 2×1H of $CH_2$), 6.61 (s, 2H, 2×1H of $CH_2$), 6.73 (s, 2H, 2×1H of $CH_2$), 7.00 (s, 2H, 2×CH), 7.15 (s, 2H, 2×CH), 7.22–7.35 (m, 8H, Ar-H), 7.67–7.77 (m, 8H, Ar-H); Mass (ESMS+) *m/z* % 551.67 ($M^+$+Na).

### 1.3. General procedure for acetylation

As reported in Ref. 36.

### 1.4. General procedure for 3-phenoxy prop-2-enoates

To the solution of appropriate compound from **10**–**13b**,**g**–**i** (0.001 mol) in a mixture of THF/$H_2O$ (4 mL, 50:50 v/v) was added DABCO (112 mg, 0.001 mol) under stirring at rt. After 15 min. phenol (0.087 mL, 0.001 mol) was added and the reaction was continued for 0.5–1.5 h. Thereafter, the mixture was extracted with ethyl acetate (2×20 mL). The organic layers were combined, dried ($Na_2SO_4$) and evaporated to obtain an oily residue. To prepare an analytical sample the residue was passed through a small band of silica gel (60–120 mesh) using hexanes/ethyl acetate (95:5, v/v). The pure 3-phenoxy prop-2-enoates were obtained as solids or colourless oils.

**1.4.1. 2-[Phenoxy-(3-(4-methyl phenyl)-isoxazol-5-yl)-methyl]-acrylic acid *tert*-butyl ester (14b).** [Found: C, 73.59; H, 6.12; N, 3.77. $C_{24}H_{25}NO_4$ requires C, 73.63; H, 6.43; N, 3.57%]; $\nu_{max}$ (neat) 1705 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.45 (s, 9H, $C(CH_3)_3$), 2.38 (s, 3H, $CH_3$), 6.05 (s, 1H, OCH), 6.28 (s, 1H, 1H of $CH_2$), 6.47 (s, 1H, 1H of $CH_2$), 6.81 (s, 1H, CH), 6.97–7.02 (m, 3H, Ar-H), 7.22–7.31 (m, 4H, Ar-H), 7.24 (d, 2H, *J*=8.0 Hz, Ar-H), 7.67 (d, 2H, *J*=8.0 Hz, Ar-H); Mass (FABMS+) *m/z* % 392 ($M^+$+1).

**1.4.2. 2-[(3-Nitro-phenyl)-phenoxy-methyl]-acrylic acid *tert*-butyl ester (14g).** [Found: C, 67.51; H, 5.68; N, 4.15. $C_{20}H_{21}NO_5$ requires C, 67.59; H, 5.95; N, 3.94%]; $\nu_{max}$ (neat) 1708 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.44 (s, 9H, $C(CH_3)_3$), 5.95 (s, 1H, OCH), 6.17 (s, 1H, 1H of $CH_2$), 6.36 (s, 1H, 1H of $CH_2$), 6.84–6.95 (m, 3H, Ar-H), 7.23–7.25 (m, 2H, Ar-H), 7.51 (t, 1H, *J*=7.9 Hz, Ar-H), 7.81 (d, 1H, *J*=7.7 Hz, Ar-H), 8.15 (d, 1H, *J*=7.2 Hz, Ar-H), 8.33 (s, 1H, Ar-H); Mass (FABMS+) *m/z* % 356 ($M^+$+1).

**1.4.3. 2-[(4-Nitro-phenyl)-phenoxy-methyl]-acrylic acid *tert*-butyl ester (14h).** [Found: C, 67.41; H, 5.73; N, 4.10. $C_{20}H_{21}NO_5$ requires C, 67.59; H, 5.95; N, 3.94%]; $\nu_{max}$ (neat) 1713 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.43 (s, 9H, $C(CH_3)_3$), 5.91 (s, 1H, OCH), 6.17 (s, 1H, 1H of $CH_2$), 6.34 (s, 1H, 1H of $CH_2$), 6.87–6.91 (m, 3H, Ar-H), 7.21–7.25 (m, 2H, Ar-H), 7.63 (d, 2H, *J*=8.5 Hz, Ar-H), 8.20 (d, 2H, *J*=8.5 Hz, Ar-H); Mass (FABMS+) *m/z* % 356 ($M^+$+1).

**1.4.4. 2-[Phenoxy-(4-trifluoromethyl-phenyl)-methyl]-acrylic acid *tert*-butyl ester (14i).** [Found: C, 66.55; H, 5.82. $C_{21}H_{21}F_3O_5$ requires C, 66.66; H, 5.59%]; $\nu_{max}$ (neat) 1712 ($CO_2$Bu-*t*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.43 (s, 9H, $C(CH_3)_3$), 5.85 (s, 1H, OCH), 6.14 (s, 1H, 1H of $CH_2$), 6.32 (s, 1H, 1H of $CH_2$), 6.87–6.91 (m, 3H, Ar-H), 7.20–7.25 (t, 2H, Ar-H), 7.58 (s, 4H, Ar-H); Mass (ESMS+) *m/z* % 401 ($M^+$+Na).

**1.4.5. 2-[Phenoxy-(3-(4-methyl phenyl)-isoxazol-5-yl)-methyl]-acrylic acid butyl ester (15b).** [Found: C, 73.85; H, 6.48; N, 3.61. $C_{24}H_{25}NO_4$ requires C, 73.63; H, 6.43; N, 3.57 %]; $\nu_{max}$ (neat) 1706 ($CO_2$Bu-*n*) $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.90 (t, 3H, *J*=6.0 Hz, $CH_3$), 1.26–1.38 (m, 2H, $CH_2$), 1.56–1.68 (m, 2H, $CH_2$), 2.39 (s, 3H, $CH_3$), 4.21 (q, 2H, *J*=6.0 Hz, $CH_2$), 6.16 (s, 1H, OCH), 6.34 (s, 1H, 1H of $CH_2$), 6.57 (s, 1H, 1H of $CH_2$), 6.59 (s, 1H, CH), 6.82–6.96 (m, 3H, Ar-H), 7.22–7.32 (m, 5H, Ar-H), 7.67 (d, 2H, *J*=8.0 Hz, Ar-H); Mass (FABMS+) *m/z* % 392 ($M^+$+1).

**1.4.6. 2-[(3-Nitro-phenyl)-phenoxy-methyl]-acrylic acid butyl ester (15g).** [Found: C, 67.84; H, 6.02; N, 4.13. $C_{20}H_{21}NO_5$ requires C, 67.59; H, 5.95; N, 3.94%]; $\nu_{max}$ (neat) 1716 ($CO_2$Bu-*n*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 0.90 (t, 3H, *J*=7.2 Hz, $CH_3$), 1.23–1.38 (m, 2H, $CH_2$), 1.54–1.68 (m, 2H, $CH_2$), 4.16 (t, 2H, *J*=6.6 Hz, $CH_2$), 6.08 (s, 1H, OCH), 6.22 (s, 1H, 1H of $CH_2$), 6.46 (s, 1H, 1H of $CH_2$), 6.89–6.99 (m, 3H, Ar-H), 7.21–7.29 (m, 2H, Ar-H), 7.51 (t, 1H, *J*=8.0 Hz, Ar-H), 7.81 (d, 1H, *J*=7.7 Hz, Ar-H), 8.15 (d, 2H, *J*=8.0 Hz, Ar-H), 8.34 (s, 1H, Ar-H); Mass (ESMS+) *m/z* % 551.67 ($M^+$+Na).

**1.4.7. 2-[(4-Nitro-phenyl)-phenoxy-methyl]-acrylic acid butyl ester (15h).** [Found: C, 67.60; H, 5.89; N, 3.92. $C_{20}H_{21}NO_5$ requires C, 67.59; H, 5.95; N, 3.94%]; $\nu_{max}$ (KBr) 1700 ($CO_2$Bu-*n*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 0.90 (t, 3H, *J*=7.2 Hz, $CH_3$), 1.24–1.38 (m, 2H, $-CH_2$), 1.55–1.65 (m, 2H, $CH_2$), 4.16 (t, 2H, *J*=6.0 Hz, $CH_2$), 6.04 (s, 1H, OCH), 6.22 (s, 1H, 1H of $CH_2$), 6.44 (s, 1H, 1H of $CH_2$), 6.87–6.99 (m, 3H, Ar-H), 7.25–7.29 (m, 2H, Ar-H), 7.65 (d, 2H, *J*=8.7 Hz, Ar-H), 8.20 (d, 2H, *J*=8.7 Hz, Ar-H); Mass (ESMS+) *m/z* % 551.67 ($M^+$+Na).

**1.4.8. 2-[Phenoxy-(4-trifluoromethyl-phenyl)-methyl]-acrylic acid butyl ester (15i).** [Found: C, 66.87; H, 5.49. $C_{21}H_{21}F_3O_3$ requires C, 66.66; H, 5.59%]; $\nu_{max}$ (neat) 1715 ($CO_2$Bu-*n*) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 0.89 (t, 3H, *J*=7.2 Hz, $CH_3$), 1.25–1.36 (m, 2H, $CH_2$), 1.55–1.63 (m, 2H, $CH_2$), 4.16 (t, 2H, *J*=6.6 Hz, $CH_2$), 5.98 (s, 1H, OCH), 6.18 (s, 1H, 1H of $CH_2$), 6.41 (s, 1H, 1H of $CH_2$), 6.88–6.98 (m, 3H, Ar-H), 7.24–7.28 (m, 2H, Ar-H), 7.59 (s, 4H, Ar-H); Mass (ESMS+) *m/z* % 401.00 ($M^+$+Na).

**1.4.9. 2-[Phenoxy-(3-(4-methyl phenyl)-isoxazol-5-yl)-methyl]-acrylic acid ethyl ester (16b).** [Found: C, 73.02; H, 6.09; N, 3.66. $C_{22}H_{21}NO_4$ requires C, 72.70; H, 5.82; N, 3.85%]; $\nu_{max}$ (neat) 1714 ($CO_2$Et) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.28 (t, 3H, *J*=7.2 Hz, $CH_3$), 2.38 (s, 3H, $CH_3$), 4.13 (q, 2H, *J*=7.2 Hz, $CH_2$), 6.07 (s, 1H, OCH), 6.19 (s, 1H, 1H of $CH_2$), 6.47 (s, 1H, 1H of $CH_2$), 6.59 (s, 1H, CH), 6.82–6.84 (m, 3H, Ar-H), 6.90–6.97 (m, 2H, Ar-H), 7.24 (d, 2H, *J*=8 0 Hz, Ar-H), 7.67 (d, 2H, *J*=8.0 Hz, Ar-H); Mass (FABMS+) *m/z* % 364 ($M^+$+1).

**1.4.10. 2-[(3-Nitro-phenyl)-phenoxy-methyl]-acrylic acid ethyl ester (16g).** [Found: C, 66.14; H, 5.39; N, 3.92.

$C_{18}H_{17}NO_5$ requires C, 66.04; H, 5.23; N, 4.27%]; $\nu_{max}$ (neat) 1714 ($CO_2Et$) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.27 (t, 3H, $J$=8.0 Hz, $CH_3$), 4.22 (q, 2H, $J$=8.0 Hz, $CH_2$), 6.10 (s, 1H, OCH), 6.22 (s, 1H, 1H of $CH_2$), 6.46 (s, 1H, 1H of $CH_2$), 6.80–6.99 (m, 3H, Ar-H), 7.15–7.29 (m, 2H, Ar-H), 7.51 (t, 1H, $J$=7.9 Hz, Ar-H), 7.81 (d, 1H, $J$=8.0 Hz, Ar-H), 8.15 (d, 2H, $J$=8.0 Hz, Ar-H), 8.34 (s, 1H, Ar-H); Mass (FABMS+) $m/z$ % 328 ($M^+$+1).

**1.4.11. 2-[(4-Nitro-phenyl)-phenoxy-methyl]-acrylic acid ethyl ester (16h).** [Found: C, 66.31; H, 5.28; N, 4.54. $C_{18}H_{17}NO_5$ requires C, 66.04; H, 5.23; N, 4.27%]; $\nu_{max}$ (KBr) 1699 ($CO_2Et$) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.26 (t, 3H, $J$=7.1 Hz, $CH_3$), 4.29 (q, 2H, $J$=7.1 Hz, $CH_2$), 6.06 (s, 1H, OCH), 6.22 (s, 1H, 1H of $CH_2$), 6.44 (s, 1H, 1H of $CH_2$), 6.88–6.99 (m, 3H, Ar-H), 7.21–7.29 (m, 2H, Ar-H), 7.65 (d, 2H, $J$=8.7 Hz, Ar-H), 8.20 (d, 2H, $J$=8.7 Hz, Ar-H); Mass (FABMS+) $m/z$ % 328 ($M^+$+1).

**1.4.12. 2-[Phenoxy-(4-trifluoromethyl-phenyl)-methyl]-acrylic acid ethyl ester (16i).** [Found: C, 65.37; H, 5.06. $C_{19}H_{17}F_3O_3$ requires C, 65.14; H, 4.89%]; $\nu_{max}$ (neat) 1705 ($CO_2Et$) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.26 (t, 3H, $J$=7.2 Hz, $CH_3$), 4.21 (q, 2H, $J$=7.1 Hz, $CH_2$), 6.00 (s, 1H, OCH), 6.19 (s, 1H, 1H of $CH_2$), 6.42 (s, 1H, 1H of $CH_2$), 6.88–6.99 (m, 3H, Ar-H), 7.20–7.25 (m, 2H, Ar-H), 7.59 (s, 4H, Ar-H)); Mass (FABMS+) $m/z$ % 351 ($M^+$+1).

**1.4.13. 2-[Phenoxy-(3-(4-methyl phenyl)-isoxazol-5-yl)-methyl]-acrylic acid methyl ester (17b).** [Found: C, 71.96; H, 5.61; N, 3.92. $C_{21}H_{19}NO_4$ requires C, 72.19; H, 5.48; N, 4.01%]; $\nu_{max}$ (neat) 1720 ($CO_2Me$) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 2.38 (s, 3H, $CH_3$), 3.78 (s, 3H, $CO_2CH_3$), 6.06 (s, 1H, OCH), 6.12 (s, 1H, 1H of $CH_2$), 6.34 (s, 1H, 1H of $CH_2$), 6.56 (s, 1H, CH), 6.80–7.32 (m, 7H, Ar-H), 7.67 (d, 2H, $J$=8.0 Hz, Ar-H); Mass (FABMS+) $m/z$ % 350 ($M^+$+1).

**1.4.14. 2-[(3-Nitro-phenyl)-phenoxy-methyl]-acrylic acid methyl ester (17g).** [Found: C, 65.33; H, 5.12; N, 4.44. $C_{17}H_{15}NO_5$ requires C, 65.16; H, 4.85; N, 4.47%]; $\nu_{max}$ (neat) 1720 ($CO_2Me$) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 3.76 (s, 3H, $CO_2CH_3$), 6.12 (s, 1H, OCH), 6.22 (s, 1H, 1 H of $CH_2$), 6.46 (s, 1H, 1H of $CH_2$), 6.89–6.99 (m, 3H, Ar-H), 7.21–7.29 (m, 2H, Ar-H), 7.52 (t, 1H, $J$=7.9 Hz, Ar-H), 7.81 (d, 1H, $J$=8.0 Hz, Ar-H), 8.15 (d, 1H, $J$=8.0 Hz, CH), 8.34 (s, 1H, Ar-H); Mass (FABMS+) $m/z$ % 314 ($M^+$+1).

**1.4.15. 2-[Phenoxy-(4-trifluoromethyl-phenyl)-methyl]-acrylic acid methyl ester (17i).** [Found: C, 64.39; H, 4.67. $C_{18}H_{15}F_3O_3$ requires C, 64.28; H, 4.50%]; $\nu_{max}$ (neat) 1705 ($CO_2Et$) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 3.76 (s, 3H, $CO_2CH_3$), 6.03 (s, 1H, OCH), 6.19 (s, 1H, 1H of $CH_2$), 6.42 (s, 1H, 1H of $CH_2$), 6.88–6.98 (m, 3H, Ar-H), 7.20–7.28 (m, 2H, Ar-H), 7.59 (s, 4H, Ar-H); Mass (FABMS+) $m/z$ % 337 ($M^+$+1).

### 1.5. General procedure for solid phase reactions

The Wang (500 mg, 1.13 mmol/g, Novabiochem) acrylate resin was prepared as described in literature.[41] The resins were divided into five PP syringes fitted with frits. To each reaction vessel (RV), DABCO (3 equiv.) in 200 μL was added and left for 15 min. Thereafter solution of different aldehydes (**1a**–**b**,**e**–**g**) (5 equiv.) in 300 μL of DMSO was added to respective RV and the reaction was shaken at 600 rpm. After 3 h (24 h for **1g**) the resins were washed using DMF (×3), MeOH (×3) and DCM (×2). To these RVs was then added DCM (1 mL) followed by DIEA (10 equiv.) and acetyl chloride (8 equiv.). The reaction mixture was stirred for 17 h at rt and then washed with DCM (×2), THF/$H_2O$ (1:1) (×2), THF (×2), MeOH (×2) and DCM (×2). Further to this resin was added THF/$H_2O$ mixture (1 mL, 9.5:0.5, v/v) and DABCO (three folds). After shaking this mixture for 15 min, phenol (10 equiv.) was added. The RVs were shaken at 600 rpm for 6 h and washed with DMF (×2), MeOH (×2), DCM (×3) and ether (×2). The resin was finally cleaved with 50% TFA in DCM for 1 h, filtrate evaporated and lyophilised using *tert*-butanol/$H_2O$ (4:1). These products were purified through column chromatography on silica gel using chloroform: methanol (98:2, v/v) to obtain the final compounds (**22a**–**b**,**e**–**g**) in 23–31% yields.

**1.5.1. 2-[Phenoxy-(3-phenyl-isoxazol-5-yl)-methyl]-acrylic acid (22a).** [Found C, 70.81; H, 4.65; N, 4.52. $C_{19}H_{15}NO_4$ requires C, 71.02; H, 4.71; N, 4.36%]; $\nu_{max}$ (neat) 1682 ($CO_2H$) $cm^{-1}$; $\delta_H$ (200 MHz, $DMSOd_6$) 5.99 (s, 1H, OCH), 6.21 (s, 1H, 1H of $CH_2$), 6.36 (s, 1H, 1H of $CH_2$), 6.61 (s, 1H, CH), 7.21–7.24 (m, 5H, Ar-H), 7.42–7.44 (m, 3H, Ar-H), 7.78–7.79 (m, 2H, Ar-H); Mass (FABMS+) $m/z$ % 322 ($M^+$+1).

**1.5.2. 2-[Phenoxy-(3-(4-methyl phenyl)-isoxazol-5-yl)-methyl]-acrylic acid (22b).** [Found C, 71.73; H, 4.99; N, 4.19. $C_{20}H_{17}NO_4$ requires C, 71.63; H, 5.11; N, 4.18%]; $\nu_{max}$ (KBr) 1697 ($CO_2H$) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 2.38 (s, 3H, $CH_3$), 6.31 (s, 1H, OCH), 6.33 (s, 1H, 1H of $CH_2$), 6.58 (s, 1H, 1H of $CH_2$), 6.69 (s, 1H, CH), 6.96–7.04 (m, 3H, Ar-H), 7.22–7.33 (m, 4H, Ar-H), 7.67 (d, 2H, $J$=8.0 Hz, Ar-H); Mass (FABMS+) $m/z$ % 336 ($M^+$+1).

**1.5.3. 2-{[3-(2-Chloro-phenyl)-isoxazol-5-yl]-phenoxy-methyl}-acrylic acid (22e).** [Found C, 63.97; H, 4.01; N, 3.98. $C_{19}H_{14}ClNO_4$ requires C, 64.14; H, 3.97; N, 3.94%]; $\nu_{max}$ (neat) 1684 ($CO_2H$) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 6.19 (s, 1H, OCH), 6.24 (s, 1H, 1H of $CH_2$), 6.34 (s, 1H, 1H of $CH_2$), 6.68 (s, 1H, CH), 6.96–7.04 (m, 3H, Ar-H), 7.22–7.33 (m, 4H, Ar-H), 7.63–7.78 (m, 2H, Ar-H); Mass (FABMS+) $m/z$ % 356 ($M^+$+1).

**1.5.4. 2-{[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-phenoxy-methyl}-acrylic acid (22f).** [Found C, 58.40; H, 3.59; N, 3.73. $C_{19}H_{13}Cl_2NO_4$ requires C, 58.48; H, 3.36; N, 3.59 %]; $\nu_{max}$ (neat) 1699 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 6.22 (s, 1H, OCH), 6.37 (s, 1H, 1H of $CH_2$), 6.59 (s, 1H, 1H of $CH_2$), 6.75 (s, 1H, CH), 6.84 (dd, 1H, $J_1$=2.0 Hz, $J_2$=8.0 Hz, Ar-H), 6.96–7.05 (m, 3H, Ar-H), 7.23–7.35 (m, 2H, Ar-H), 7.38 (d, 1H, $J$=2.0 Hz, Ar-H), 7.68 (d, 2H, $J$=8.0 Hz, Ar-H); Mass (FABMS+) $m/z$ % 390 ($M^+$+1).

**1.5.5. 2-[(3-Nitro-phenyl)-phenoxy-methyl]-acrylic acid (22g).** [Found C, 63.96; H, 4.67; N, 4.44. $C_{16}H_{13}NO_5$ requires C, 64.21; H, 4.38; N, 4.68 %]; $\nu_{max}$ (KBr)1700 ($CO_2H$) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 6.20 (s, 1H, OCH), 6.24 (s, 1H, 1H of $CH_2$), 6.61 (s, 1H, 1H of $CH_2$), 6.81–7.00 (m, 3H, Ar-H), 7.20–7.30 (m, 2H, Ar-H), 7.53 (t, 1H, $J$=

7.9 Hz, Ar-H), 7.81 (d, 1H, $J$=7.7 Hz, Ar-H), 8.16 (d, 2H, $J$=8.0 Hz, Ar-H), 8.34 (s, 1H, Ar-H); Mass (FABMS+) $m/z$ % 300 ($M^+$+1).

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