Chemo- and regio-selective functionalization of Morita–Baylis–Hillman bromides with anthranilic acid

Yusuf Zulykama, Ulagamani Uma, Palanisamy Chitra Devi, and Paramasivan T. Perumal

Abstract: Nucleophilic substitution products of Morita–Baylis–Hillman adducts and their derivatives are valuable synthons. In an attempt to ameliorate the functionality of these functionalized motifs, we report the regio- and chemo-selective functionalization of Morita–Baylis–Hillman bromides with anthranilic acid.

Key words: Morita–Baylis–Hillman reaction, Morita–Baylis–Hillman bromides, nucleophilic substitution, anthranilic acid.

Résumé : Les produits de substitution nucléophile des adduits de Morita–Baylis–Hillman et de leurs dérivés sont des synthons très utiles. Afin d'améliorer la fonctionnalité de ces motifs fonctionnalisés, on a réalisé la fonctionnalisation régio- et chimio-sélective des bromures de Morita–Baylis–Hillman avec l'acide anthranilique.

Mots-clés : réaction de Morita–Baylis–Hillman, bromures de Morita–Baylis–Hillman, substitution nucléophile, acide anthranilique.

[Traduit par la Rédaction]

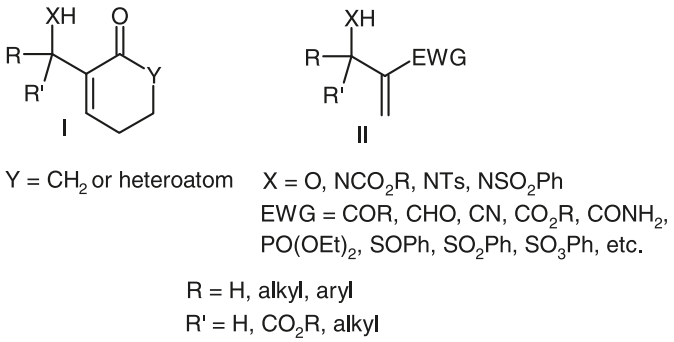
Introduction

The Morita–Baylis–Hillman reaction[1–4] (MBH), a powerful C–C bond forming reaction, has earned overwhelming popularity in recent years. The MBH adduct comprise of a contiguous assembly of three different functionalities and a chiral center. The versatility of the functionality of MBH adducts have made them valuable synthetic intermediates. Efforts of various research groups contributing to the widening of the substrate scope[1] of the MBH reaction have further diversified the functionality of MBH adducts (Fig. 1).

Functionalization of MBH adducts and their derivatives is an active area of research, as it provides valuable synthetic intermediates, which have been successfully translated into various useful synthetic targets, including substituted alkenes,[5] carbocycles,[6] heterocycles,[7] and several biologically relevant molecules.[1e,1g] The repertoire of nucleophiles added to MBH adducts includes carbon,[8] hydrogen,[9] heteroatomic nucleophiles,[10] aromatics,[11] and heteroaromatics.[12] In addition to newer nucleophiles[13] being added to MBH acetates/bromides, the synthetic potential of previously reported nucleophilic substitution products is illustrated by newer applications.[14]

Nucleophilic substitution of MBH adducts and their derivatives with monofunctional aromatics and their further elaboration to several synthetic targets have been extensively studied.[15] Basavaiah et al.[16] synthesized chromones from phenol[16b–16d] substitution products and successfully applied the same strategy to the synthesis of antifungal agents.

Fig. 1. The Morita–Baylis–Hillman adduct.



Aniline substitution products have been elaborated to synthesize indenoquinolinones,[17a] polysubstituted quinolines,[17b] quinolones, quinolinols, indanones and indenoindenones,[17c] and β-lactam.[17d,17e] The fascinating post modifications of nucleophilic substitution products of monofunctional aromatics made the nucleophilic substitution of bifunctional aromatics intriguing. However, literature scanning reveals only a few reports of nucleophilic substitution of MBH derivatives with bifunctional aromatics.[18] Kim et al.[18a] added *o*-phenylenediamine on Baylis–Hillman acetates and subsequently converted to benzodiazepinones and benzoimidazoles. Basavaiah and Satyanarayana[18b] reported one-pot transformation of the Baylis–Hillman acetates to fused pyrimidones via a reaction with 2-aminopyridine in aqueous media. The synthetic utility of dinaphthol substitution products were illustrated in the synthesis of bis-chromones.[18c] In this context, we were prompted to explore this avenue of MBH chemistry, and herein, we wish to report the results of our

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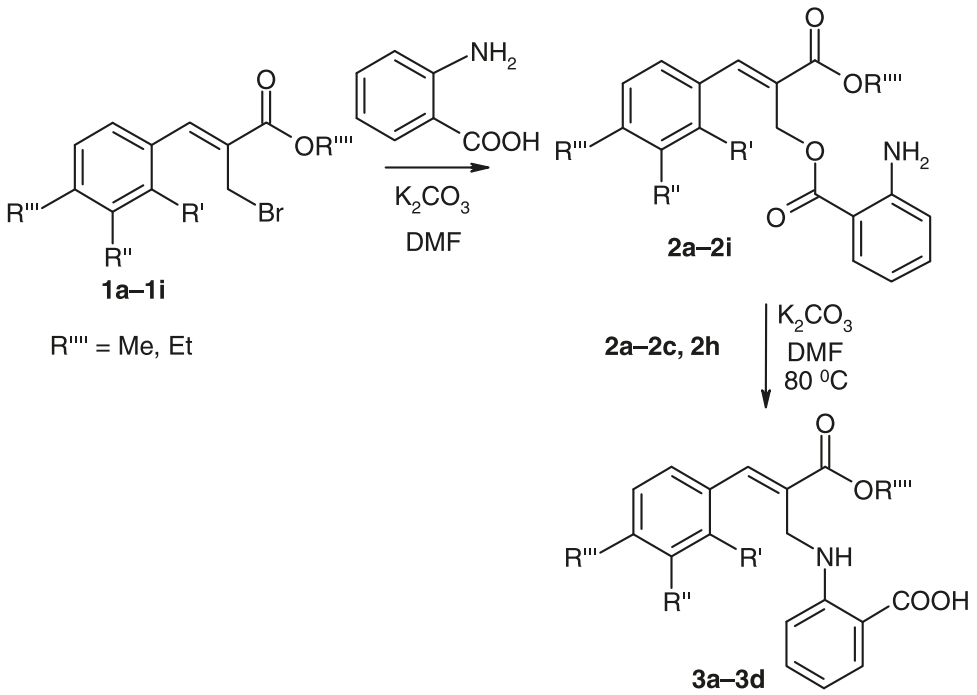
Scheme 1.



investigation of the chemo- and regio-selectivity of nucleophilic substitution of MBH bromides with anthranilic acid.

Results and discussion

Recently, we have reported the functionalization of MBH bromides with symmetric and asymmetric bifunctional aromatics,[19] and in continuation of our interest in this avenue of MBH chemistry, we intended to study the functionalization of MBH bromides with anthranilic acid. Accordingly, a solution of MBH bromide (**1a**) in DMF was treated with anthranilic acid in the presence of potassium carbonate to furnish **2a** in 61% isolated yield (Scheme 1).

The presence of two stretching absorptions in the IR spectrum of **2a** (3266 and 3468 cm^{-1}) indicated that the N-terminal of the anthranilic acid moiety is free. Moreover, the downfield appearance of the allylic protons (δ 5.15 ppm) confirmed the formation of O-linked products. The reaction was then extended to other MBH bromides (**1b**–**1i**), and the results are assembled in Table 1.

The stereochemistry of the products **2a**–**2i** was settled on the basis of difference nuclear Overhauser effect (NOE) experiments on **2f**. Irradiation of the methylene protons at δ 5.0 ppm led to the enhancement of the aromatic signal at δ 7.33 by 5.25%. However, there was comparatively less enhancement in the olefinic signal (0.69%) implying they are spatially far, and thus confirming *E* stereochemistry (Fig. 2). Further irradiation of the ester methyl proton resulted in the enhancement of the olefinic peak, confirming their spatial proximity.

To study the regio- and chemo-selective outcome of the reaction, we further treated MBH bromide with anthranilic acid in the presence of K_2CO_3 in DMF at 80 °C. TLC monitoring revealed the formation of a new minor product in addition to O-linked product. Prolonging the heating did not improve the yield of the minor product. The new product was characterized by IR, NMR, and Mass studies. The IR spectrum of the product exhibited only one stretching absorption, suggesting secondary amine functionality. The allylic protons were observed at δ 4.26 ppm (as compared with the O-linked allylic protons at δ 4.92–5.15 ppm), confirming the formation of N-linked product **3a**. Small coupling was observed in the allylic proton signal due to the NH proton further confirming the formation of N-linked products. However, the carboxyl proton was not detected in the ^1H NMR spectrum, and the presence of the carboxyl group in the product was confirmed through IR and ^{13}C spectral analysis.

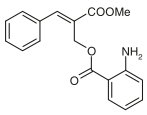
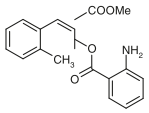
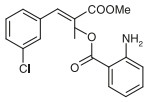
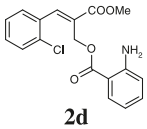
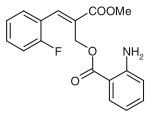
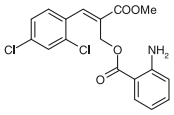
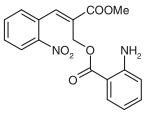
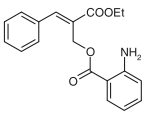
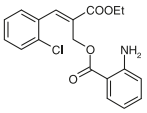
Interestingly, on heating O-linked anthranilic acid, substitution products **2a** in DMF with K_2CO_3 at 80 °C, N-linked S_N2 products **3a** was obtained in comparatively good yields (Scheme 1).[20] The generality of the reaction was demonstrated by the successful conversion of O-linked products **2b**, **2c**, and **2h** to **3b**, **3c**, and **3d**, respectively (Table 2).

With the O-linked anthranilic acid products in our hands, we intended to further derivatize these substitution products by treatment with trifluoroacetic anhydride (Scheme 2). Consequently, **2a** was stirred in trifluoroacetic anhydride at ice temperature under nitrogen atmosphere, and we observed solidification of the reaction mixture immediately. TLC profile of the reaction mixture showed two new spots. The major product was assigned the structure **4a** and the minor product was found to be **5a**.[20]

The formation of **5a** can be explained as the result of the reaction of **4a** with **2a**. In the ^1H NMR spectrum of **5a**, the signal for the BH moiety was observed in duplicate, indicating that the bisfunctionalisation[21] of anthranilic moiety with the MBH bromides at both the N- and O-terminal had occurred.

The diastereotropic methylenic protons were observed as four doublets at δ 4.46, 5.02, 5.11, and 5.36 ppm. Further

Table 1. S_N2 substitution of Morita–Baylis–Hillman bromides with anthranilic acid.

Entry	O-linked S_N2 substitution product	Yield (%)[a]
1	 **2a**	61
2	 **2b**	81
3	 **2c**	68
4	 **2d**	63
5	 **2e**	83
6	 **2f**	75
7	 **2g**	59
8	 **2h**	60
9	 **2i**	70

[a] Isolated yield.

Fig. 2. Difference NOE studies of **2f**.

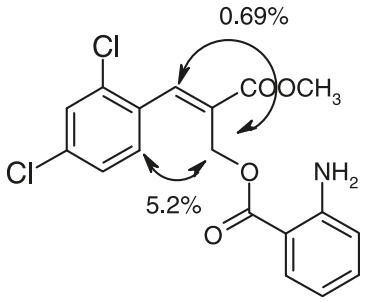
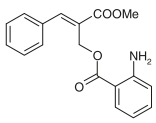
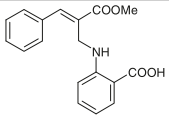
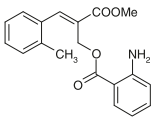
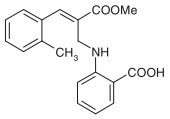
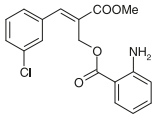
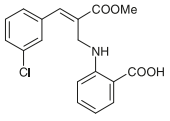
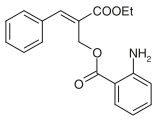
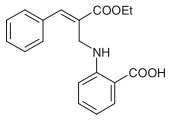


Table 2. Syntheses of S_N2 N-linked anthranilic acid substitution products.

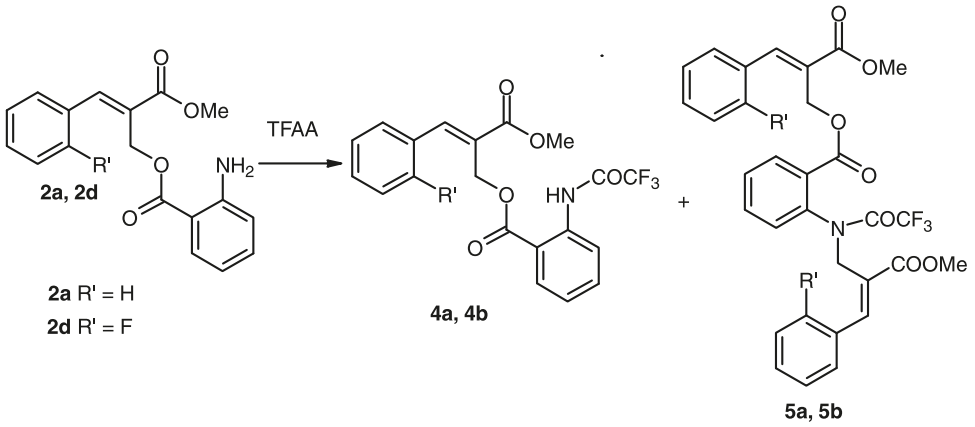
Entry	*O*-linked S_N2 product	*N*-linked S_N2 product	Yield(%)[a]
1	 **2a**	 **3a**	57
2	 **2b**	 **3b**	55
3	 **2c**	 **3c**	59
4	 **2h**	 **3d**	54

[a] Isolated yield.

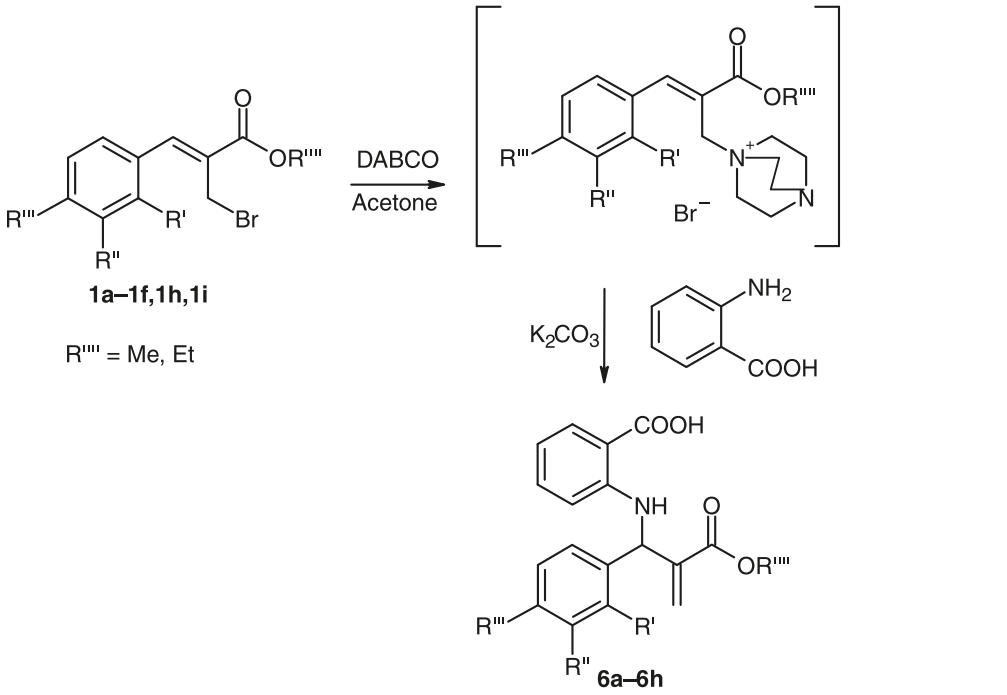
mass spectral analysis [604 (M^+ + Na)] confirmed the formation of the product. Next, it was our interest to obtain S_N2' anthranilic acid substitution products adopting DABCO-salt strategy.[22] In accordance, the MBH bromide (**1a**) was stirred with an equivalent of DABCO in acetone for 30 min at ambient temperature. After the salt formation as indicated by the TLC, anthranilic acid and potassium carbonate were added and stirring continued for an hour to afford **6a** (Scheme 3).

In the ^{1}H NMR of **6a**, two singlets were obtained for the olefinic protons and were observed at δ 5.63 and 6.39 ppm, confirming the formation of S_N2' products. The signal due to the benzylic proton at δ 5.87 ppm was split into a doublet by the NH proton (J = 6.1 Hz), and also the signal for the NH proton was observed as a doublet at δ 8.11 ppm (J = 6.1 Hz), confirming that the S_N2' product was N-linked. For **6a**–**6h**, the carboxyl proton was not detected in ^{1}H NMR spectra. However, the presence of the carboxyl group in the product was confirmed through IR and ^{13}C spectral analyses. Table 3 reveals the results of S_N2' substitution of MBH bro-

Scheme 2.



Scheme 3.



mides with anthranilic acid. Salt formation of anthranilic acid with DABCO explains the formation of N-linked S_N2' product and not the O-linked S_N2' product.

Conclusion

In conclusion, we have demonstrated a simple and practical methodology for the chemo- and regio-selective functionalization of MBH bromides with anthranilic acid. Extension of the same methodology to other bifunctional nucleophiles and their chemical transformation to synthetically important scaffolds are underway.

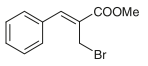
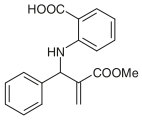
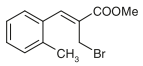
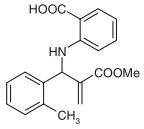
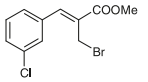
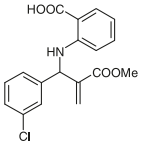
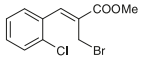
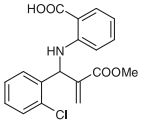
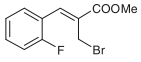
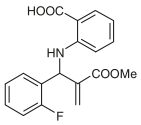
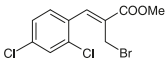
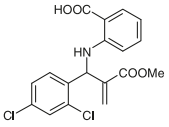
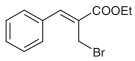
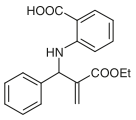
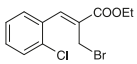
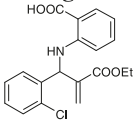
Experimental section

Melting points were determined in open capillary tubes and are uncorrected. IR measurements were carried out using KBr pellets in PerkinElmer Spectrometer RXI FTIR. Nuclear magnetic resonance spectra were recorded on a Bruker spectrometer or a JEOL spectrometer. ^{1}H NMR spectra were recorded at 300 MHz or 500 MHz in $CDCl_3$ or DMSO-d_6 combination with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz or 125 MHz spectrometer in $CDCl_3$ or DMSO-d_6 combination with the same internal standard. The chemical shifts are given in δ in ppm scale. Mass spectra were recorded on a varian VG 70–70H mass spectrometer or on a Thermo Finnigan LCQ Advantage MAX 6000 ESI spectrometer. TLC was performed on silica gel alumina plates. Column chromatography was carried out using 100–200 mesh silica gel.

General procedure for the syntheses of 2a–2i

To a stirred solution of Baylis–Hillman bromide (0.3 g, 1.18 mmol) in DMF (5 mL) was added anthranilic acid (0.16 g, 1.18 mmol) and K_2CO_3 (0.19 g, 1.18 mmol). The reaction mixture was stirred at room temperature. After the disappearance of the starting compound (TLC), reaction mixture was poured into water and extracted with ethyl ace-

Table 3. S_N2' substitution of BH bromides with anthranilic acid.

Entry	BH bromide	N-linked S_N2' substitution product	Yield (%)[a]
1	 **1a**	 **6a**	60
2	 **1b**	 **6b**	55
3	 **1c**	 **6c**	59
4	 **1d**	 **6d**	65
5	 **1e**	 **6e**	67
6	 **1f**	 **6f**	63
7	 **1h**	 **6g**	61
8	 **1i**	 **6h**	65

[a] Isolated yield.

tate (3 × 30 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Column purification (15% ethyl acetate in hexane) furnished the products.

Methyl 2-(2-aminophenylcarbonyloxymethyl)-3-phenyl prop-2-enoate (2a)

Yellow solid; mp 68 °C. IR (KBr) ν: 1617, 1692, 2952, 3366, 3468 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.83 (s, 3H), 5.15 (s, 2H), 5.79 (br s, 2H), 6.60 (d, *J* = 9.15 Hz, 1H), 6.63 (t, *J* = 9.15 Hz, 1H), 7.38–7.44 (m, 6H), 7.82 (t, *J* = 8.05 Hz, 1H), 8.04 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.49, 59.34, 110.58, 111.66, 116.34, 116.79, 126.82, 128.91, 129.67, 129.75, 131.47, 134.34, 145.92, 150.75, 167.6, 167.88. MS *m*/*z*: 311 (M^+). Anal. calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.20; H, 5.49; N, 4.52.

Methyl 2-(2-aminophenylcarbonyloxymethyl)-3-(2-methylphenyl) prop-2-enoate (2b)

Brown solid; mp 60 °C. IR (KBr) ν: 1616, 1692, 2944, 3373, 3483 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 3.84 (s, 3H), 5.03 (s, 2H), 5.73 (br s, 2H), 6.61 (d, *J* = 7.65 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 7.18–7.28 (m, 5H), 7.81 (d, *J* = 7.65 Hz, 1H), 8.13 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.12, 52.45, 59.46, 110.71, 116.36, 116.73, 126.05, 127.63, 128.86, 129.49, 130.33, 131.46, 133.68, 134.28, 137.21, 145.04, 150.62, 167.37, 167.75. MS *m*/*z*: 325 (M^+). Anal. calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.90; N, 4.30. Found: C, 70.25; H, 5.92; N, 4.29.

Methyl 2-(2-aminophenylcarbonyloxymethyl)-3-(3-chlorophenyl) prop-2-enoate (2c)

Pale yellow solid; mp 130 °C. IR (KBr) ν: 1050, 1630, 1684, 2928, 3372, 3480 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.83 (s, 3H), 5.11 (s, 2H), 5.75 (br s, 2H), 6.59 (t, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 6.85 Hz, 1H), 7.29–7.36 (m, 3H), 7.43 (s, 1H), 7.79 (d, *J* = 7.65 Hz, 1H), 7.95 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.60, 58.93, 110.39, 111.6, 115.3, 116.35, 116.78, 127.47, 128.33, 129.58, 129.63, 130.16, 131.37, 144.0, 150.77, 167.17, 167.66. MS *m*/*z*: 346 (M^+), 348 ($M^+ + 2$). Anal. calcd. for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; N, 4.05. Found: C,62.41; H, 4.65; N, 4.04.

Methyl 2-(2-aminophenylcarbonyloxymethyl)-3-(2-chlorophenyl) prop-2-enoate (2d)

Yellow solid; mp 84 °C. IR (KBr) ν: 1052, 1629, 1685, 2926, 3475, 3482 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 5.03 (s, 2H), 5.73 (br s, 2H), 6.60 (t, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 7.65 Hz, 2H), 7.29 (t, *J* = 7.65 Hz, 1H), 7.39 (d, *J* = 7.65 Hz, 1H), 7.41 (d, *J* = 7.65 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 8.13 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.58, 59.35, 110.50, 116.35, 116.75, 127.07, 128.82, 129.83, 129.98, 130.38, 130.68, 131.41, 133.05, 134.36, 142.51, 150.68, 166.94, 167.63. MS *m*/*z*: 345 (M^+), 347 ($M^+ + 2$). Anal. calcd. for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; N, 4.05. Found: C, 62.42; H, 4.64; N, 4.06.

Methyl 2-(2-aminophenylcarbonyloxymethyl)-3-(2-fluorophenyl) prop-2-enoate (2e)

Yellow solid; mp 54 °C. IR (KBr) ν: 1239, 1616, 1717, 2951, 3373, 3480 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 5.11 (s, 2H), 5.79 (br s, 2H), 6.58 (t, *J* = 7.45 Hz, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 7.11 (t, *J* = 8 Hz, 1H), 7.21 (t, *J* = 8 Hz, 1H), 7.32 (q, *J* = 7.45 Hz, 1H), 7.41 (t, *J* = 8 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 8.08 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.55, 59.43, 110.37, 115.54, 115.97(d, *J* = 38.1 Hz), 116.78, 122.37 (d, *J* = 13.1 Hz), 124.51, 128.97, 130.44, 131.37, 131.62 (d, *J* = 8.35 Hz), 131.92, 134.37, 138.07,

150.81, 166.99, 167.72. MS *m/z*: 329 (M^+). Anal. calcd. for $C_{18}H_{16}FNO_4$: C, 65.65; H, 4.90; N, 4.25. Found: C, 65.72; H, 4.89; N, 4.26.

Methyl 2-(2-aminophenylcarbonyloxymethyl)-3-(2,4-dichlorophenyl) prop-2-enoate (2f)

Yellow solid; mp 144 °C. IR (KBr) ν: 1049, 1621, 1680, 2926, 3370, 3484 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 3.86 (s, 3H), 5.0 (s, 2H), 5.75 (br s, 2H), 6.60 (t, *J* = 6.9 Hz, 1H), 6.64 (d, *J* = 7.65 Hz, 1H), 7.24–7.27 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.44 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.68, 59.19, 110.29, 116.37, 116.79, 127.49, 129.36, 129.77, 131.10, 131.31, 131.59, 134.47, 135.13, 136.05, 141.20, 150.71, 166.73, 167.54. MS *m/z*: 382 (M^+), 384 (M^+ + 2), 386 (M^+ + 4). Anal. calcd. for $C_{18}H_{15}Cl_2NO_4$: C, 56.86; H, 3.98; N, 3.68. Found: C, 56.80; H, 3.97; N, 3.67.

Methyl 2-(2-aminophenylcarbonyloxymethyl)-3-(2-nitrophenyl) prop-2-enoate (2g)

Yellow oil. IR (neat) ν: 1351, 1524, 1620, 1721, 2955, 3374, 3482 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 4.92 (s, 2H), 5.72 (br s, 2H), 6.58 (t, *J* = 6.9 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 7.21 (t, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 7.65 Hz, 1H), 7.49 (t, *J* = 7.65 Hz, 1H), 7.60 (t, *J* = 7.65 Hz, 1H), 7.68 (d, *J* = 7.65 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.26 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.64, 59.06, 110.18, 116.26, 116.73, 125.19, 128.32, 130.01, 130.77, 131.03, 131.27, 134.0, 134.40, 142.40, 147.37, 150.71, 166.49, 167.42. MS *m/z*: 356 (M^+). Anal. calcd. for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.78; H, 4.52; N, 7.89.

Ethyl 2-(2-aminophenylcarbonyloxymethyl)-3-phenyl prop-2-enoate (2h)

Orange solid; mp 80 °C. IR (KBr) ν: 1625, 1689, 2949, 3357, 3466 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.30 (t, *J* = 6.9 Hz, 3H), 4.28 (q, *J* = 6.9 Hz, 2H), 5.15 (s, 2H), 5.73 (br s, 2H), 6.60 (t, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 6.9 Hz, 1H), 7.36 (q, *J* = 7.6 Hz, 4H), 7.44 (d, *J* = 6.9 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.35, 59.29, 61.32, 110.73, 116.63, 116.73, 127.26, 128.77, 128.85, 129.60, 131.48, 134.28, 134.45, 145.42, 150.65, 167.05, 167.86. MS *m/z*: 325 (M^+). Anal. calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.26; H, 5.91; N, 4.30.

Ethyl 2-(2-aminophenylcarbonyloxymethyl)-3-(2-chlorophenyl) prop-2-enoate (2i)

Brown oil. IR (neat) ν: 1620, 1690, 2952, 3365, 3472 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.31 (t, *J* = 7.65 Hz, 3H), 4.30 (q, *J* = 6.9 Hz, 2H), 5.05 (s, 2H), 5.83 (br s, 2H), 6.60 (t, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 7.65 Hz, 1H), 7.39 (t, *J* = 7.65 Hz, 2H), 7.78 (d, *J* = 7.65 Hz, 1H), 8.11 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.33, 59.35, 61.30, 110.50, 116.35, 116.75, 127.07, 128.82, 129.83, 129.98, 130.38, 130.68, 131.41, 133.05, 134.36, 142.51, 150.68, 166.94, 167.63. MS *m/z*: 360 (M^+), 362 (M^+ + 2). Anal. calcd. for $C_{19}H_{18}ClNO_4$: C, 63.42; H, 5.04; N, 3.89. Found: C, 63.50; H, 5.06; N, 3.90.

General procedure for the syntheses of 3a–3d

To a solution of **2a** (0.3 g, 0.96 mmol) in DMF (5 mL) was added K_2CO_3 (0.133 g, 0.96 mmol). The reaction mixture was heated at 80 °C. After the completion of the reaction as indicated by TLC, the reaction mixture was poured into water and extracted with ethyl acetate. The excess solvent was removed, and column purification (10% ethyl acetate in hexane) furnished the products.

Methyl 2-(2-carboxyphenylaminomethyl)-3-phenyl prop-2-enoate (3a)

Yellow solid; mp 110 °C. IR (KBr) ν: 1655, 1717, 2956, 3370 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 4.26 (br s, 2H), 6.44 (d, *J* = 8.4 Hz, 1H), 6.60 (t, *J* = 8.4 Hz, 1H), 7.27 (t, *J* = 8.4 Hz, 2H), 7.37–7.41 (m, 5H), 7.95 (s, 1H), 7.97 (t, *J* = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.70, 52.32, 109.50, 111.77, 115.16, 116.46, 116.83, 129.29, 130.24, 132.14, 134.71, 135.49, 143.24, 151.08, 167.93, 173.62. MS *m/z*: 311 (M^+). Anal. calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 6955; H, 5.48; N, 4.51.

Methyl 2-(2-carboxyphenylaminomethyl)-3-(2-methylphenyl)prop-2-enoate (3b)

Pale yellow solid; mp 125 °C. IR (KBr) ν: 1660, 1725, 2953, 3355 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.24 (s, 3H), 3.86 (s, 3H), 4.20 (br s, 2H), 6.22 ((d, *J* = 8.4 Hz, 1H), 6.55 (t, *J* = 7.65 Hz, 1H), 7.18–7.27 (m, 5H), 7.93 (d, *J* = 7.65 Hz, 1H), 7.93 (t, *J* = 6.1 Hz, 1H), 7.96 (s, 1H). MS *m/z*: 325 (M^+). Anal. calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.06; H, 5.88; N, 4.30.

Methyl 2-(2-carboxyphenylaminomethyl)-3-(3-chlorophenyl)prop-2-enoate (3c)

Pale yellow solid; mp 130 °C. IR (KBr) ν: 1037, 1657, 1719, 2950, 3360 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 4.25 (br s, 2H), 6.44 (d, *J* = 8.4 Hz, 1H), 6.60 (t, *J* = 7.65 Hz, 1H), 7.28 (t, *J* = 6.9 Hz, 1H), 7.37–7.41 (m, 5H), 7.94 (s, 1H), 7.95 (t, *J* = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.76, 52.40, 109.53, 111.83, 115.22, 128.25, 128.84, 129.01, 129.36, 129.47, 132.78, 134.45, 134.78, 135.56, 143.32, 151.14, 167.98, 173.70. MS *m/z*: 346 (M^+), 348 (M^+ + 2). Anal. calcd. for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; N, 4.05. Found: C,62.60; H, 4.68; N, 4.04.

Ethyl 2-(2-carboxyphenylaminomethyl)-3-phenyl prop-2-enoate (3d)

Brown oil. IR (neat) ν: 1655, 1720, 2985, 3360 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$) δ: 1.34 (t, *J* = 6.9 Hz, 3H), 4.26 (s, 2H), 4.29 (q, *J* = 6.9 Hz, 2H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.59 (t, *J* = 7.65 Hz, 1H), 7.26–7.30 (m, 2H), 7.37–7.41 (m, 5H), 7.93 (s, 1H), 7.95 (t, *J* = 6.1 Hz, 1H). MS *m/z*: 325 (M^+). Anal. calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.01; H, 5.87; N, 4.32.

General procedure for the syntheses of 4 and 5

2a (0.5 g, 1.6 mmol) was taken in a 50 mL RB flask, and 1 mL of TFAA was added under ice temperature in N_2 atmosphere. The reaction mixture solidified and was extracted with ethyl acetate. The excess solvent was removed and col-

umn purified (25% ethyl acetate in hexane) to obtain **4a** (63%) and **5a** (11%).

Methyl2-(2-trifluoroacetamidophenylcarbonyloxymethyl)-3-phenyl prop-2-enoate (4a)

White solid; mp 108 °C. IR (KBr) ν: 1616, 1635, 1685, 2955, 3332 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 5.24 (s, 2H), 7.21 (t, *J* = 7.65 Hz, 1H), 7.39–7.41 (m, 5H), 7.61 (t, *J* = 8.45 Hz, 1H), 8.06 (d, *J* = 8.45 Hz, 1H), 8.11 (s, 1H), 8.65 (d, *J* = 7.65 Hz, 1H), 12.24 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.57, 60.84, 114.63 (q, *J* = 287 Hz), 116.15, 116.93, 120.80, 124.85, 125.81, 128.99, 129.47, 129.97, 131.36, 134.07, 135.20, 139.10, 146.70, 154.92 (q, *J* = 36.9 Hz), 167.14, 167.96. MS *m/z*: 407 (M^+). Anal. calcd. for $C_{20}H_{16}F_3NO_5$: C, 58.97; H, 3.96; N, 3.44. Found: C, 58.85; H, 3.96; N, 3.45.

Methyl2-(2-trifluoroacetamidophenylcarbonyloxymethyl)-3-(2-fluoro-phenyl) prop-2-enoate (4b)

White solid; mp 120 °C. IR (KBr) ν: 1230, 1618, 1620, 1642, 1680, 2958 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 5.18 (s, 2H), 7.10 (t, *J* = 7.65 Hz, 1H), 7.14 (t, *J* = 7.65 Hz, 1H), 7.19 (t, *J* = 7.65 Hz, 1H), 7.32 (t, *J* = 7.65 Hz, 1H), 7.37 (t, *J* = 7.65 Hz, 1H), 7.60 (t, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 7.65 Hz, 1H), 8.09 (s, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 12.19 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.64, 60.91, 114.63 (q, *J* = 288.5 Hz), 116.02 (d, *J* = 22.7 Hz), 120.78, 122.12 (d, *J* = 11.9 Hz), 122.23, 124.50, 124.81, 128.09, 130.21, 131.30, 131.79 (d, *J* = 7.2 Hz), 131.85, 135.20, 139.03, 139.06, 154.93 (q, *J* = 39.3 Hz), 166.54, 167.80. MS *m/z*: 425 (M^+). Anal. calcd. for $C_{20}H_{15}F_4NO_5$: C, 56.48; H, 3.55; N, 3.29. Found: C, 56.39; H, 3.56; N, 3.30.

2-(Methoxycarbonyl)-3-phenyl-2-propenyl-2-[2-(methoxy carbonyl)-3-phenylpropenyl]trifluoroacetamidobenzene carboxylate (5a)

Yellow oil. IR (neat) ν: 1617, 1620, 1637, 2945, 3340 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.61 (s, 3H), 3.80 (s, 3H), 4.46 (d, *J* = 14.5 Hz, 1H), 5.02 (d, *J* = 11.45 Hz, 1H), 5.11 (d, *J* = 11.45 Hz, 1H), 5.36 (d, *J* = 14.5 Hz, 1H), 6.96–6.98 (m, 3H), 7.22–7.23 (m, 3H), 7.32–7.34 (m, 5H), 7.38 (t, *J* = 7.65 Hz, 1H), 7.43 (t, *J* = 7.65 Hz, 1H), 7.76 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 44.78, 52.23, 52.42, 60.61 115.6 (q, *J* = 282 Hz), 115.30, 117.60, 125.87, 125.98, 128.71, 128.84, 129.0, 129.39, 129.50, 129.66, 129.77, 132.08, 132.12, 132.98, 133.88, 134.10, 136.93, 145.88, 146.25, 155.84 (q, *J* = 34.6 Hz), 167.14, 167.46. MS *m/z*: 604 (M^+ + Na). Anal. calcd. for $C_{31}H_{26}F_3NO_7$: C, 64.03; H, 4.51; N, 2.43. Found: C, 64.14; H, 4.53; N, 2.44.

2-(Methoxycarbonyl)-3-(2-fluorophenyl)-2-propenyl-2-[2-(methoxycarbonyl)-3-(2-fluorophenyl)propenyl] trifluoroacetamidobenzene carboxylate (5b)

Yellow oil. IR (neat) ν: 1225, 1619, 1640, 1689 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.68 (s, 3H), 3.85 (s, 3H), 4.34 (d, *J* = 13.75 Hz, 1H), 4.93 (d, *J* = 12.25 Hz, 1H), 5.03 (d, *J* = 11.45 Hz, 1H), 5.35 (d, *J* = 14.5 Hz, 1H), 6.86 (t, *J* = 7.65 Hz, 1H), 6.92 (t, *J* = 9.2 Hz, 1H), 6.98 (t, *J* = 7.65 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.07–7.11 (m, 2H), 7.23 (t, *J* = 8.4 Hz, 2H), 7.32–7.35 (m, 1H), 7.39 (t, *J* = 7.65 Hz, 1H), 7.48 (t, *J* = 7.65 Hz, 1H), 7.76 (s, 1H), 7.89 ((d, *J* = 6.9 Hz, 1H), 8.05 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.38, 52.53, 58.28, 60.65, 115.2 (q, *J* = 291.4 Hz), 115.66 (d, *J* = 21.4 Hz), 115.83 (d, *J* = 29.7 Hz), 121.86 (d, *J* = 13.1 Hz), 122.12 (d, *J* = 14.3 Hz), 128.1, 128.45, 129.62, 129.75, 130.30, 131.14, 131.20, 131.67, 131.74, 132.03, 132.13, 133.09, 135.12, 137.07, 138.66 (d, *J* = 15.5 Hz), 145.59, 156.02 (q, *J* = 35.7 Hz), 163.9, 166.60, 166.97. MS *m/z*: 617 (M^+). Anal. calcd. for $C_{31}H_{24}F_5NO_7$: C, 60.29; H, 3.92; N, 2.27. Found: C, 60.20; H, 3.93; N, 2.28.

General procedure for the syntheses of 6a–6h

To a stirred solution of Baylis–Hillman bromide (0.3 g, 1.18 mmol) in acetone (5 mL), DABCO (0.132 g, 1.18 mmol) was added. The reaction mixture was stirred for 30 min. The salt formation was confirmed by TLC. After the salt formation, anthranilic acid (0.16 g, 1.18 mmol) and K_2CO_3 (0.163 g, 1.18 mmol) were added. The reaction mixture was stirred at room temperature. After the formation of the product, as indicated by TLC, the reaction mixture was poured into water and extracted with ethyl acetate (3 × 30 mL). The organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. Column purification (20% ethyl acetate in hexane) furnished the products.

Methyl 3-(2-carboxylphenylamino)-2-methylene-3-phenyl propanoate (6a)

Yellow solid; mp 150 °C. IR (KBr) ν: 1664, 1716, 2951, 3365 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 5.63 (s, 1H), 5.87 (d, *J* = 6.1 Hz, 1H), 6.39 (s, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 6.63 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.34–7.37 (m, 3H), 7.39 (d, *J* = 6.9 Hz, 2H), 7.98 (d, *J* = 7.7 Hz, 1H), 8.11 (d, *J* = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.18, 57.61, 109.55, 112.68, 115.70, 126.24, 127.48, 127.96, 128.96, 132.72, 135.72, 140.06, 140.47, 150.19, 166.67, 173.89. MS *m/z*: 311 (M^+). Anal. calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.37; H, 5.51; N, 4.49.

Methyl 3-(2-carboxylphenylamino)-2-methylene-3-(2-methylphenyl) propanoate (6b)

White solid; mp 158 °C. IR (KBr) ν: 1667, 1724, 2955, 3354 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.28 (s, 3H), 3.62 (s, 3H), 5.66 (d, *J* = 6.9 Hz, 1H), 5.88 (s, 1H), 6.31 (s, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 6.58 (t, *J* = 7.65 Hz, 1H), 7.14–7.20 (m, 4H), 7.30 (t, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.65 Hz, 1H), 8.08 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 19.15, 52.59, 53.76, 111.28, 112.43, 115.90, 126.44, 126.82, 126.91, 128.31, 131.29, 132.28, 135.18, 136.65, 138.42, 140.06, 149.86, 166.53, 170.52. MS *m/z*: 325 (M^+). Anal. calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.06; H, 5.91; N, 4.32.

Methyl 3-(2-carboxylphenylamino)-2-methylene-3-(3-chlorophenyl) propanoate (6c)

Pale yellow solid; mp 162 °C. IR (KBr) ν: 1035, 1660, 1720, 2955, 3362 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.75 (s, 3H), 5.58 (d, *J* = 5.35 Hz, 1H), 5.87 (s, 1H), 6.42 (s, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 6.65 (t, *J* = 7.6 Hz, 1H), 7.28–7.29 (m, 3H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.37 (s, 1H),

7.99 (d, J = 6.9 Hz, 1H), 8.11 (d, J = 6.15 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.31, 57.17, 109.73, 112.54, 116.02, 125.62, 127.03, 127.68, 128.22, 130.25, 132.78, 134.75, 135.77, 139.97, 142.25, 149.97, 166.38, 173.74. MS *m*/*z*: 346 (M^+), 348 (M^+ + 2). Anal. calcd. for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; N, 4.05. Found: C, 62.46; H, 4.65; N, 4.04.

Methyl 3-(2-carboxylphenylamino)-2-methylene-3-(2-chlorophenyl) propanoate (6d)

Yellow solid; mp IR (KBr) ν: 1037, 1656, 1723, 2944, 3352 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.76 (s, 3H), 5.70 (s, 1H), 6.04 (d, J = 6.1 Hz, 1H), 6.44 (s, 1H), 6.56 (d, J = 8.4 Hz, 1H), 6.63 (t, J = 8.4 Hz, 1H), 7.23–7.25 (m, 2H), 7.32 (t, J = 6.9 Hz, 1H), 7.40–7.42 (m, 2H), 7.97 (d, J = 6.9 Hz,1H), 8.01 (d, J = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.37, 54.25, 109.67, 112.57, 115.96, 127.34, 128.03, 128.40, 129.24, 130.13, 132.66, 133.97, 135.85, 137.38, 139.50, 150.20, 166.45, 173.91. MS *m*/*z*: 346 (M^+), 348 (M^+ + 2). Anal. calcd. for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; N, 4.05. Found: C, 62.63; H, 4.67; N, 4.04.

Methyl 3-(2-carboxylphenylamino)-2-methylene-3-(2-fluorophenyl) propanoate (6e)

White solid; mp 130 °C. IR (KBr) ν: 1222, 1672, 1720, 3011, 3357 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.75 (s, 3H), 5.85 (s, 1H), 5.94 (d, J = 6.1 Hz, 1H), 6.42 (s, 1H), 6.63–6.65 (m, 2H), 7.06–7.10 (m, 1H), 7.11 (t, J = 7.65 Hz, 1H), 7.26–7.29 (m, 1H), 7.34 (q, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.20, 52.26, 109.64, 112.46, 115.82 (d, J = 38.15 Hz), 127.03 (d, J = 13.1 Hz), 127.13, 128.67, 129.66 (d, J = 8.35 Hz), 129.73, 132.72, 135.82, 139.39, 150.07, 159.65, 161.61, 166.36, 173.88. MS *m*/*z*: 329 (M^+). Anal. calcd. for $C_{18}H_{16}FNO_4$: C, 65.65; H, 4.90; N, 4.25. Found: C, 65.58; H, 4.88; N, 4.26.

Methyl 3-(2-carboxylphenylamino)-2-methylene-3-(2,4-dichlorophenyl) propanoate (6f)

Brown solid; mp 114 °C. IR (KBr) ν: 1043, 1656, 1722, 2948, 3355 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.76 (s, 3H), 5.71 (s, 1H), 5.95 (d, J = 5.35 Hz, 1H), 6.45 (s, 1H), 6.51 (d, J = 8.4 Hz, 1H), 6.65 (t, J = 7.65 Hz, 1H), 7.21 (t, J = 8.4 Hz, 1H), 7.34 (t, J = 8.4 Hz, 2H), 7.43 (s, 1H), 7.98 (d, J = 7.65 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.41, 54.02, 109.76, 112.45, 116.23, 127.64, 128.23, 129.35, 129.98, 132.74, 134.37, 134.69, 135.91, 136.14, 139.08, 149.96, 166.22, 173.75. MS *m*/*z*: 380 (M^+), 382 (M^+ + 2), 384 (M^+ + 4). Anal. calcd. for $C_{18}H_{15}Cl_2NO_4$: C, 56.86; H, 3.98; N, 3.68. Found: C, 56.92; H, 3.99; N, 3.69.

Ethyl 3-(2-carboxylphenylamino)-2-methylene-3-phenyl propanoate (6g)

White solid; mp 124 °C. IR (KBr) ν: 1650, 1719, 2982, 3359 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.08 (d, J = 7.65 Hz, 3H), 4.04 (m, 2H), 5.58 (d, J = 7.6 Hz, 1H), 5.81 (s, 1H), 6.24 (s, 1H), 6.57 (d, J = 7.6 Hz, 1H), 6.59 (d, J = 8.4 Hz,1H), 7.30–7.34 (m, 5H), 7.79 (d, J = 7.65 Hz, 2H), 8.44 (d, J = 7.65 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.34, 57.42, 61.14, 111.33, 112.69, 115.73, 126.47, 127.66, 128.13, 129.19, 132.25, 135.01, 140.76, 140.91, 149.81, 165.79, 170.54. MS *m*/*z*: 325 (M^+). Anal. calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.0; H, 5.91; N, 4.30.

Ethyl 3-(2-carboxylphenylamino)-2-methylene-3-(2-chlorophenyl) propanoate (6h)

Brown solid; mp 110 °C. IR (KBr) ν: 1038, 1656, 1715, 2984, 3356 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.21 (t, J = 6.9 Hz, 3H), 4.19 (m, 2H), 5.68 (s, 1H), 6.02 (d, J = 4.6 Hz, 1H), 6.43 (s, 1H), 6.57 (d, J = 8.4 Hz, 1H), 6.63 (t, J = 7.65 Hz, 1H), 7.23–7.25 (m, 2H), 7.32 (t, J = 7.65 Hz, 1H), 7.39–7.42 (m, 2H), 7.96 (d, J = 7.65 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.13, 54.34, 61.25, 109.59, 112.54, 115.90, 127.31, 127.63, 128.44, 129.19, 130.05, 132.64, 133.97, 135.83, 137.50, 139.74, 150.25, 165.95, 173.75. MS *m*/*z*: 360 (M^+), 362 (M^+ + 2). Anal. calcd. for $C_{19}H_{18}ClNO_4$: C, 63.42; H, 5.04; N, 3.89. Found: C, 63.50; H, 5.05; N, 3.88.

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