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ORIGINAL ARTICLE

# Synthesis, characterization and coordination chemistry of substituted β-amino dicarbonyls

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β-Amino dicarbonyls;
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**Abstract** An efficient and facile method for the synthesis of novel structurally diverse β-amino dicarbonyl compounds is described by exploring the aza-Michael addition reaction in an aqueous medium as a key step. Thereby, 2-(aryl-disubstituted-amino-1-yl-methyl)-malonic acid diethyl esters were achieved in a good to excellent yields. These products were easily isolated with enough purity just by using simple recrystallization. The crystals of the compounds (**17**) and (**24**) have been obtained and studied by X-ray crystallographic analyses.

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## 1. Introduction

The HIV-1 Integrase (HI) is a valid target for chemotherapeutic intervention due to its involvement in the viral replication process (Goldgur et al., 1999; Walker et al., 2007; Gopi et al., 2009). The chemical inhibition of HI could be reached via intermolecular coordination between HI/chemical inhibitor/metals ($Mg^{2+}$ and $Mn^{2+}$, co-factors of the HI), leading to the formation of bimetallic complexes (Lebon et al., 2002; Dayam et al., 2007; Dayam and Neamati, 2004; Sechi et al., 2009; Zenga et al., 2008). In fact, the most successful strategy to inhibit the HI is to explore the structural core of β-diketo acid type, as briefly illustrated in Fig. 1 (Sorrell et al., 1991; Bacchi et al., 2008; Sechi et al., 2006; Orvig and Abrams, 1999). In view of this, it is highly desirable to obtain the improved protocols for the synthesis of β-diketo acid (Amslinger, 2010).

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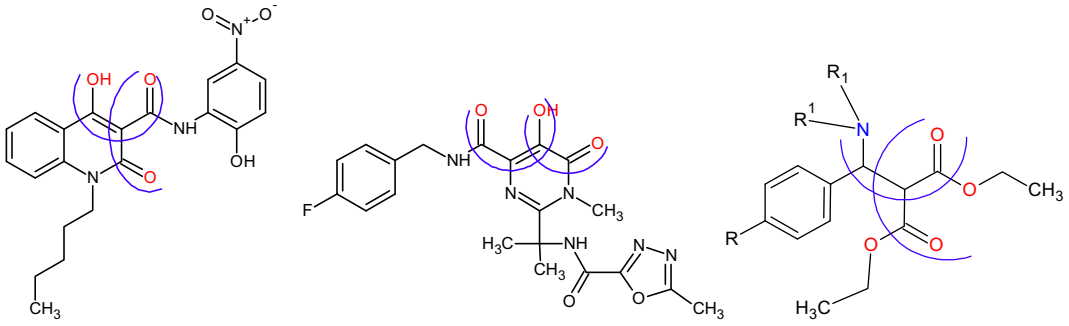



**Figure 1** Some of the HIV inhibitors under clinical trials or those (**I** and **Elviltegavir**) were recently approved by US FDA.

For the preparation of such polydentate ligands, the aza-Michael addition seems to be a key-step (Hayashi et al., 1996). Among the large number of unconventional methodologies, this kind of reaction has widely been employed to generate structurally diverse β-amino dicarbonyl compounds (Zhu et al., 2009; Kumar et al., 2008). Most of these unconventional methodologies have used Lewis acids, which although leading to satisfactory yields but it still requires the alternatives (Basu et al., 2004; Wabnitz and Spencer, 2002). Moreover, the use of an aqueous medium (Ranu and Banerjee, 2007; Ranu and Mandal, 2007; Ranu et al., 2005) has been a successful source in achieving expected results in better yield with greener touch eliminating the use of hazardous solvents. Usually, these types of substrates are less reactive or conversely more resistant to undergo the Michael addition which results in low conversion of the desired adducts. From the synthetic point of view, this is a considerable limitation on the Michael reaction process and poses a significant challenge.

To this end, we decided to investigate the feasibility of applying the aza-Michael reactions to the more challenging substituted alkene derivatives. Our idea is to explore the application of this key-step to the synthesis of a set of polydentate O,O,N-ligands (Scheme 1), in order to highlight the versatility of the procedure as well as to generate some insights regarding the 3D crystalline structure of two compounds (**17**) and (**24**).

## 2. Chemistry

Our synthetic strategy is very clear. In the first step, 2-arylidene-malonic acid ethyl esters (**1**)–(**13**) were prepared by the condensation of substituted arylaldehydes with diethyl-malonate in ethanol under reflux condition, using piperazine and glacial acetic acid as a catalyst. This procedure furnished the intermediates, 2-arylidene-malonic acid ethyl esters (**1**)–(**13**), quickly and in excellent yields (Scheme 1).

To further explore the scope and limitations of the aza-Michael reaction, compound (**1**) was chosen as the model precursor because of its thermo stability and also due to the less reactivity of pyrazole towards traditional aza-Michael addition. It was found that the stirring of compound (**1**) and pyrazole together in water at room temperature for 12 h led to the formation of 71% of (**15**) (Scheme 2). During the investigation of experimental conditions, it was possible to observe that the acid catalyst (AcOH, 0.1 mol%) accelerates the reaction but it is not essential (Meskini et al., 2010a,b,c).

Having well established and developed reaction conditions, it was identified that precursors (**1**)–(**13**) reacted quickly; with various secondary amines under catalyst-free conditions to provide the desired adducts (**14**)–(**35**) in good to excellent yields. These products were characterized using spectroscopic ($^1$H and $^{13}$C NMR, IR and MS) and micro-analytical data.

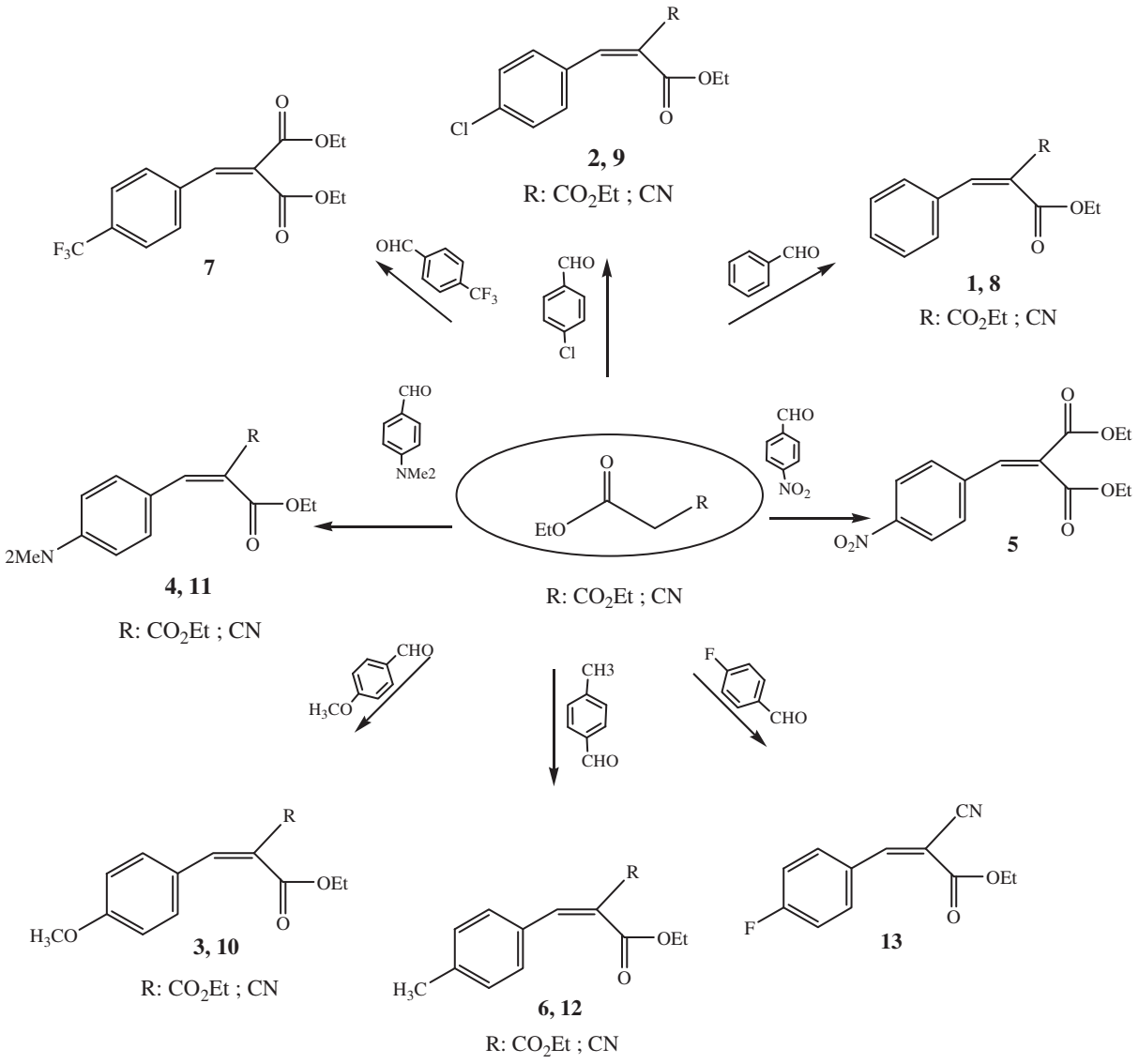
The compounds (**14**)–(**35**) are insoluble in water. The compound (**16**) has been recrystallized from ethanol to obtain the single suitable crystal and studied by X-ray diffraction study (Meskini et al., 2010a,b,c). Since, NaOH is a strong base therefore it is likely that the compounds are saponified into carboxylate units upon dissolution to form substituted β-amino dicarboxylates of sodium. However, we were unable to obtain the hypothetical bimetallic species by conventional means. The attempts to crystallise the substituted β-amino dicarboxylate derivative of (**16**) resulted in crystallisation of a polymeric complex; the poly[[bis{l3-2-[(3,5-dimethyl-1H-pyrazol-1-yl)(phenyl)methyl]propanedioato}tetrasodium](I) 7.5-hydrate] (**16′**) (Scheme 3). The compound (**16′**) has been used then in our laboratory as a starting material in organometallic chemistry and surprisingly its coordination mode has not been reported previously in literature. Since it is such an important precursor its structure will be briefly described here (Fig. 2).

The coordination of $Cu(NO_3)_2{\cdot}2H_2O$ to β-amino dicarboxylate ligands (**14**)–(**35**) in basic medium led us to obtain bimetallic complexes (Scheme 4 and Fig. 3).

## 3. Results and discussion

In order to get more insight into the theoretically possible points of metallic coordination, we have aimed to replace the phenyl by 4-chloro-phenyl, 4-methyl-phenyl or trifluoromethyl-phenyl fragments (Scheme 2).

Analyzing the X-ray crystallography data (Figs. 4 and 5), it has revealed that the crystal is subject of a weak torsion around the C1–C2 bond, of dihedral angle [N(1), C(1), C(2), H(2)] equal to 68.04(2)°. The nitrogen atom N(1) is trivalent with N(1)–C(1), N(1)–C(15) and N(1)–C(22) bonds of 1.484(1), 1.473(2) and 1.471(2) Å, respectively; they do not remain trans, indicating a cis 1,2-addition. Confirmation of the *cis*-addition is also indicated by the ORTEP of compound (**24**) in which it is easy to see the dihedral angle [N(1), C(1), C(2), H(2)] in the same range. This observed geometric form was confirmed by studying the crystallographic features for the compounds (**17**) and (**24**).




**Scheme 1** Synthetic protocol for the generation of aminodicarbonyl precursors (**1**)–(**13**).

The solid state structures for (**17**) and (**24**) (Figs. 4 and 5) were in full agreement with the proposed one than in solution (see Table 1).

## 4. Experimental protocols

### *4.1. Materials and methods*

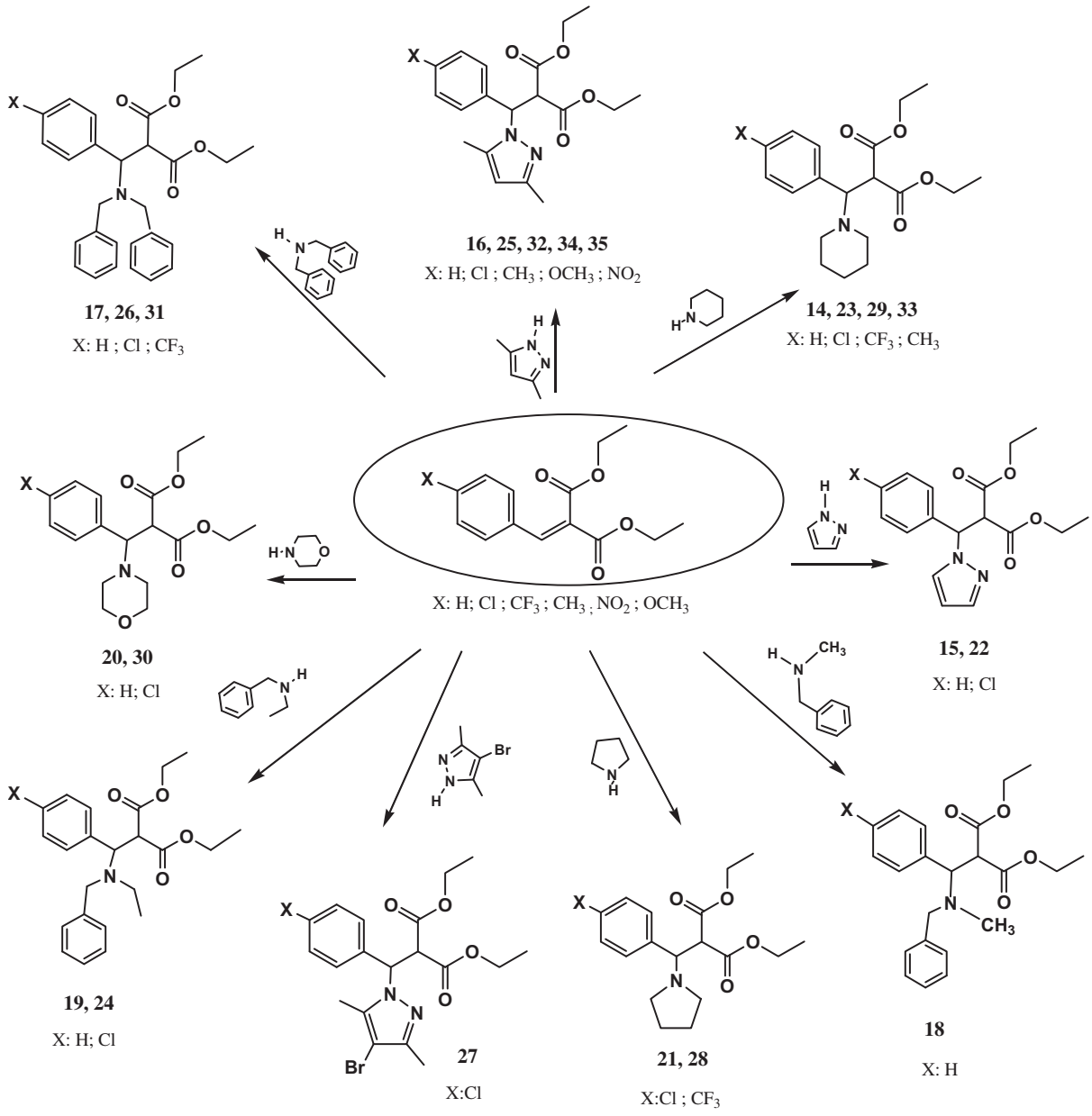
Infrared spectra were recorded on a PYE Unicam SP3-300 spectrometer as KBr pellets. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on Bruker spectrometer (250 and 400 MHz) using TMS as internal standard. Chemical shifts are reported downfield from the standard in ppm. The FAB mass spectra were obtained on a NERMANG R10-LOC instrument. For the chemical ionisation ($DCI/NH_3/CH_3$), the compounds were dissolved in DMSO or MeOH and dispersed in a matrix solution, currently the 3-nitrobenzyl (MNBA) or glycerol (GLY). Elemental analyses were performed (Morocco). All common laboratory chemicals were purchased from commercial sources and used without further purification.

### *4.2. General procedure for the synthesis of intermediates (**1**)–(**13**)*

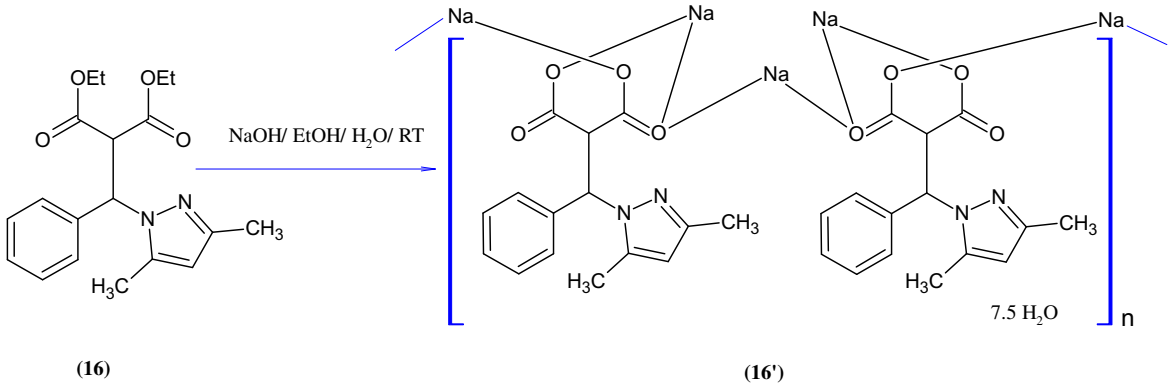
To a solution of ethyl malonate (15 g, 93 mmol) in 40 mL of ethanol, were added the respective aldehyde (100 mmol), followed by the addition of 1.5 mL of piperidine and 1 mL of glacial acetic acid. The reaction mixture was then stirred at reflux temperature of ethanol for 12 h, until thin-layer chromatography indicated the complete consumption of the starting material. After removing the solvent under vacuum, the crude product was washed with a saturated solution of sodium bisulfite (20 mL). The product was extracted by diethyl ether ($2 \times 20$ mL), dried with sodium sulphate and evaporated to give the respective pure yellow oils for (**1**–**3**, **6**, **7**) and microcrystals or white powder for (**4**, **5**, **8**–**13**).

#### *4.2.1. 2-Benzylidene-malonic acid diethyl ester (**1**)*

Yield: 71%; $R_f = 0.7$ (ether/hexane: 1/1); IR (KBr, $\nu$ $cm^{-1}$): 2875–2982 (CH), 1722 (C═O), 1629–1497 (C═C), 1294–1254 (C–O); $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.72 (s,




**Scheme 2** Synthetic protocol for the generation of aminodicarbonyl compounds (**14**)–(**35**).




**Scheme 3** Polymerization of (**16**) to produce poly[[bis{l3-2-[(3,5-dimethyl-1H-pyrazol-1-yl)(phenyl)methyl]propanedioato}tetrasodium](I) 7.5-hydrate] (**16′**).

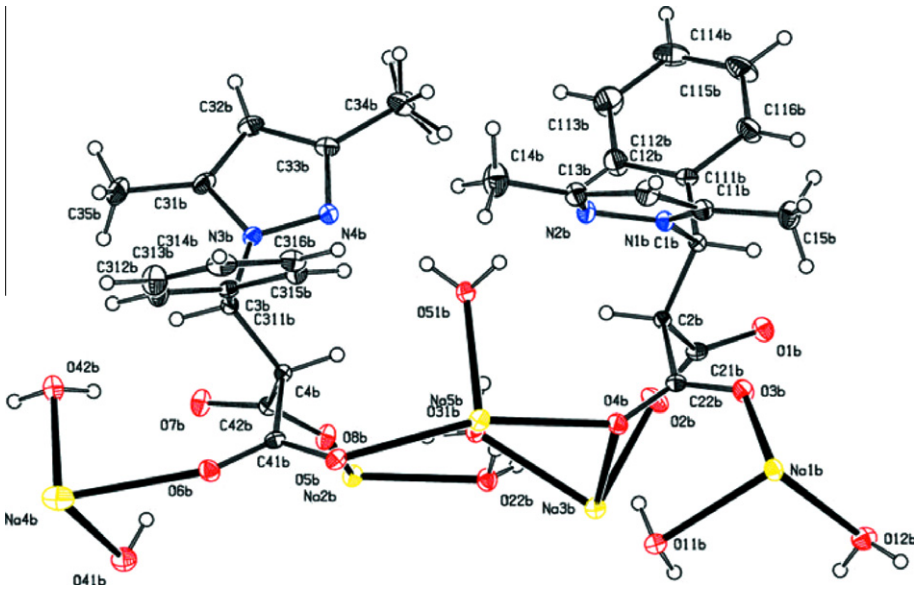
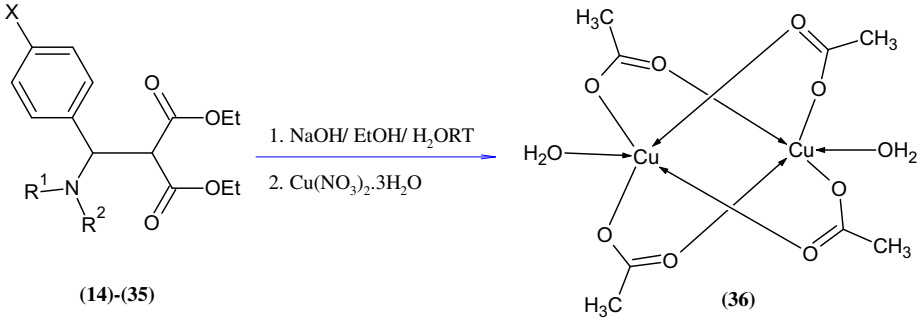



**Figure 2** ORTEPs drawing of compounds (**16′**) (Meskini et al., 2010a,b,c).




**Scheme 4** Synthetic protocol for the generation of bimetallic compound (**36**).

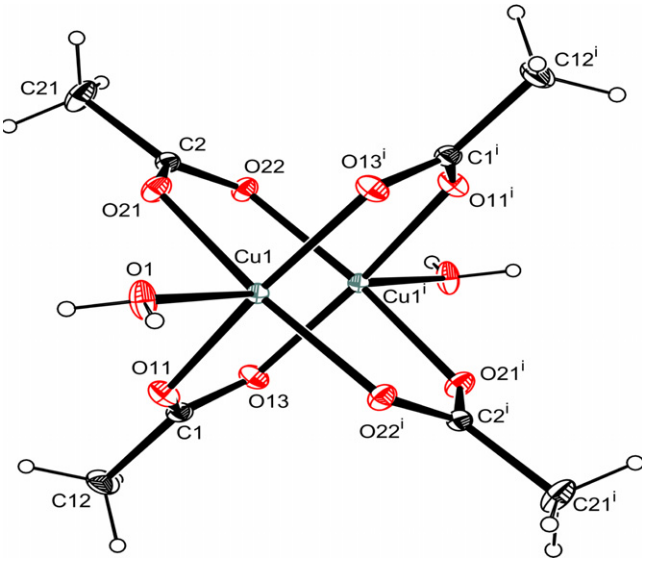



**Figure 3** Ortep of the complex $Cu_2(CH_3COO^-)_4(H_2O)_2$ (**36**).

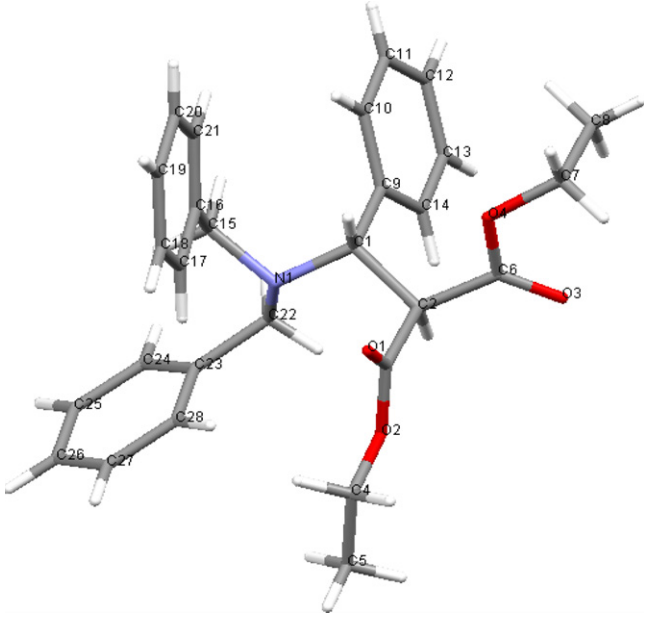



**Figure 4** ORTEP drawing of compound (**17**).

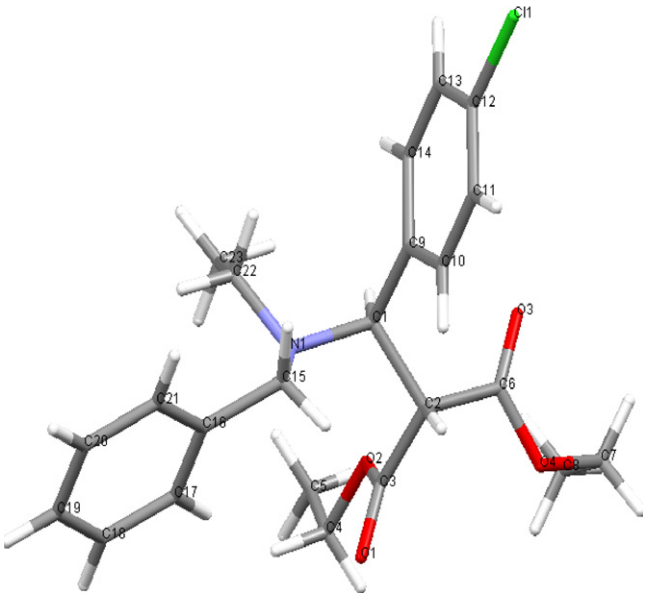



**Figure 5** ORTEP drawing of compound (**24**).

**Table 1** Crystallographic data for compounds (**17**) and (**24**).

| | Compound **17** | Compound **24** |
|---|---|---|
| Formula | $C_{28}H_{31}N_1O_4$ | $C_{23}H_{28}Cl_1N_1O_4$ |
| *M* | 445.54 | 417.91 |
| *Crystal system* | | |
| Space group | *P*-1 | *P*-1 |
| *a* (Å) | 7.9880 (3) | 8.4744 (3) |
| *b* (Å) | 10.9559 (4) | 11.1119 (4) |
| *c* (Å) | 14.8493 (7) | 13.2992 (4) |
| $\alpha$ (°) | 77.269 (4) | 70.866 (3) |
| $\beta$ (°) | 85.682 (4) | 77.862 (3) |
| $\gamma$ (°) | 68.709 (4) | 71.331 (3) |
| *Z* | 2 | 2 |
| $\lambda$(Mo-Ka) (Å) | 0.71069 | 0.71073 |
| $\mu$ ($mm^{-1}$) | 0.083 | 0.199 |
| *T* (K) | 110 | 110 |
| $h, k, l_{max}$ | 10, 13, 18 | 10, 14, 16 |
| $\theta_{max}$ | 27.000 | 27.000 |
| $R_1[I > 2p(I)]$, all data | 0.0376 (3467) | 0.0314 (3751) |
| $wR_2[I > 2p(I)]$, all data | 0.0900 (5108) | 0.0889 (4836) |
| CCDC number | 734201 | 734199 |

1H, C═C*H*–Ph), 7.45–7.32 (m, 5H, Ph), 4.32 (q, 2H, 2OC$H_2$–$CH_3$, $^3J$ = 7.2 Hz), 4.28 (q, 2H, 2OC$H_2$–$CH_3$, $^3J$ = 7.2 Hz), 1.31 (t, 3H, 2OCH$_2$C$H_3$, $^3J$ = 7.1 Hz), 1.25 (t, 3H, 2OCH$_2$C$H_3$, $^3J$ = 7.1 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.6–166.2 (2*C*═O), 142.0 (PhCH), 132.8 ($C_{quat}$, Ph), 130.5 ($2C_{tert,meta}$), 129.4 ($C_{tert,para}$), 128.7 ($2C_{tert,ortho}$), 126.1 ($C_{quat}$, ═C), 61.6–61.6 (2C, 2O*C*H$_2$CH$_3$), 14.1–13.8 (2C, 2OCH$_2$*C*H$_3$); SM (IE): Calc. for $C_{14}H_{16}O_4$: 248; $[M+H]^+$ (*m*/*z*) = 249 (100%).

*4.2.2. 2-(4-Chlorobenzylidene)-malonic acid diethyl ester (**2**)*
Yield: 77%; $R_f$ = 0.73 (ether/hexane: 1/1); IR (KBr, $\nu$ $cm^{-1}$): 2906–2982 (CH), 1724 (C═O), 1591–1631 (C═C), 1254–1308 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.7 (s, 1H, C═C*H*–Ph), 7.45–7.30 (m, 4H, Ph), 4.31–4.4 (2q, 4H, 2OC$H_2$CH$_3$, $^3J$ = 7.12 Hz), 1.31–1.25 (2t, 6H, 2OCH$_2$C$H_3$, $^3J$ = 7.11 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.3–163.8 (2*C*═O), 140.0 (ClPh–*C*H═C), 132.9 ($C_{quat}$, C–Cl–Ph), 130.3 ($2C_{meta}$), 130.4 ($C_{quat}$, para/Cl), 129.0 ($2C_{ortho}$), 125.4 (C═*C*–$(CO_2Et)_2$), 61.4 and 61.7 (2O*C*H$_2$CH$_3$), 13.7 and 13.8 (2OCH$_2$*C*H$_3$); SM (IE): Calc. for $C_{14}H_{15}ClO_4$: 282.07; $[M+H]^+$ (*m*/*z*) = 283 (100%).

*4.2.3. 2-(4-Methoxybenzylidene)-malonic acid diethyl ester (**3**)*
Yield: 66%; $R_f$ = 0.71 (ether/hexane: 1/1); IR (KBr, $\nu$ $cm^{-1}$): 2840–2982 (CH), 1725 (C═O), 1512–1574 (C═C), 1253–1305 (C–O), 1170, 1118, 892.416; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.7 (s, 1H, C═C*H*–Ph), 6.90–7.40 (m, 4*H*, arom), 4.20–4.30 (2q, 4H, 2OC$H_2$–$CH_3$, $^3J$ = 7.15 Hz), 1.30–1.40 (2t, 6H, 2OCH$_2$C$H_3$, $^3J$ = 7.14 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 165–161.57 (2*C*═O), 141.79 (–*C*H═), 182 (–$C_{quat}$, *C*–$OCH_3$–Ph), 131.59 ($2C_{meta}$, arom), 127 ($C_{quat}$, para/$OCH_3$), 130.87 ($2C_{ortho}$, arom), 125.41 (═*C*–$(CO_2Et)_2$), 61.63–61.45 (2*C*H$_2$–CH$_3$), 13.97–14.06 (2O*C*H$_3$CH$_2$), 3.23 (s, 3H, OC$H_3$–Ph).

*4.2.4. 2-(4-Dimethylaminobenzylidene)-malonic acid diethyl ester (**4**)*
Yield: 83%; $R_f$ = 0.24 (ether/hexane: 1/1); mp: 120 °C; IR (KBr, $\nu$ $cm^{-1}$): 2905–2987 (CH), 1721 (C═O), 1582–1527 (C═C), 1298–1318 (C–O), 1226, 1113, 727, 419; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.62 (s, 1H, C═C*H*–Ph), 6.61 (d, 2*H*, arom), 7.34 (d, 2*H*, arom), 4.20–4.30 (2q, 4H, 2OC$H_2$CH$_3$, $^3J$ = 7.18 Hz), 1.29–1.30 (2t, 6H, 2OCH$_2$C$H_3$, $^3J$ = 7.17 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 165.05–167.93 (2*C*═O), 142.63 (–*C*H═C), 151 ($C_{quat}$, *C*–$N(CH_3)_2$–Ph), 111.54 ($2C_{meta}$, arom), 120.15 ($C_{quat}$, para/$N(CH_3)_2$), 131.88 ($2C_{ortho}$, arom), 119.97 (C═*C*–$(CO_2Et)_2$), 61.35–61.03 (2O*C*H$_2$CH$_3$), 14.27–14.54 (2O*C*H$_3$CH$_2$).

*4.2.5. 2-(4-Nitrobenzylidene)-malonic acid diethyl ester (**5**)*
Yield: 45%; $R_f$ = 0.22 (ether/hexane: 1/1); mp: 168 °C; IR (KBr, $\nu$ $cm^{-1}$): 2852–2988 (CH), 1713 (C═O), 1492–1518 (C═C), 1250–1299 (C–O), 1199, 1063, 748, 412; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.7 (s, 1H, C═C*H*–Ph), 8.3 (d, 2*H*, arom), 7.8 (d, 2*H*, arom), 4.3–4.40 (2q, 4H, 2OC$H_2$CH$_3$), 1.2–1.30 (2t, 6H, 2OCH$_2$C$H_3$); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.26–165.2 (2*C*═O), 138.78 (Ph–*C*H═C), 205 (–$C_{quat}$, *C*–$NO_2$–Ph), 123 ($2C_{meta}$, arom), 120.15 ($C_{quat}$, para/$N(CH_3)_2$), 130.26 ($2C_{ortho}$, arom), 130 (═*C*–$(CO_2Et)_2$), 61.62 (C, 2O*C*H$_2$CH$_3$), 13.25–14.45 (C, 2O*C*H$_3$CH$_2$).

*4.2.6. 2-(4-Methylbenzylidene)-malonic acid diethyl ester (**6**)*
Yield: 76%; $R_f$ = 0.67 (ether/hexane: 1/1); IR (KBr, $\nu$ $cm^{-1}$): 2906–2982 (CH), 1723 (C═O), 1590–1632 (C═C), 1254–1308 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.7 (s, 1H, C═C*H*–Ph), 7.17–7.20 (d, 2H, Ph, $^3J$ = 8.1 Hz), 7.35–7.37 (d, 2H, Ph, $^3J$ = 8.1 Hz), 4.27–4.39 (2q, 4H, 2OC$H_2$CH$_3$, $^3J$ = 7.12 Hz), 1.29–1.36 (2t, 6H, 2OCH$_2$C$H_3$, $^3J$ = 7.19 Hz), 2.25 (s, 3H, C$H_3$–Ph); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.95–163.8 (2C═O), 142.15 ($CH_3$–Ph–*C*H═), 141.16 ($C_{quat}$, $CCH_3$Ph), 129.55 ($2C_{meta}$), 130.1 ($C_{quat}$, para/$CH_3$), 129.58 ($2C_{ortho}$), 125.19 (C═*C*–$(CO_2Et)_2$), 61.6–61.5 (2O*C*H$_2$CH$_3$), 21.4 (*C*H$_3$Ph); 14.1–13.9 (2OCH$_2$*C*H$_3$); SM (IE): Calc. for $[M]^+$ $C_{15}H_{18}O_4$: 262.04. $[M+H]^+$ (*m*/*z*) = 263 (100%).

*4.2.7. 2-(4-Triflоromethyl-benzylidene)-malonic acid diethyl ester (**7**)*

Yield: 77%; $R_f$ = 0.81 (ether/hexane: 1/1); IR (KBr, $\nu$ $cm^{-1}$): 2905–2987 (CH), 1728 (C═O), 1593–1631 (C═C), 1252–1312 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.57 (s, 1H, C═C*H*Ph), 7.53–7.50 (d, $2H_{ortho}$, Ph, $^3J$ = 9 Hz), 7.47–7.44 (d, $2H_{meta}$, Ph, $^3J$ = 9 Hz), 4.27–4.31 (2q, 4H, $2OCH_2CH_3$, $^3J$ = 7.19 Hz), 1.28–1.31 (2t, 6H, $2OCH_2CH_3$, $^3J$ = 7.19 Hz); $^{13}$C NMR (3000 MHz, $CDCl_3$) $\delta$ ppm: 165.88–163.52 (2C═O), 140.05 ($CF_3PhCH$═), 136.46 ($C_{quat}$, $CF_3Ph$), 129.07 ($2C_{meta}$), 131.01 ($C_{quat}$, para/$CF_3$), 129.82 ($2C_{ortho}$), 125.92 (C═$C(CO_2Et)_2$), 61.81–61.57 ($2OCH_2CH_3$), 77.52 ($CF_3Ph$), 13.51–13.61 ($2OCH_3CH_2$); SM (IE): Calc. for $[M]^+$ $C_{15}H_{15}O_4F_3$: 316.02. $[M+H]^+$ ($m/z$) = 317 (100%).

*4.2.8. Ethyl 2-cyano-3-phenylacrylate (E) (**8**)*

Yield: 80%; $R_f$ = 0.64 (ether/hexane: 1/1); mp: 91 °C; IR (KBr, $\nu$ $cm^{-1}$): 2900–3068 (CH), 1721.76 (C═O), 1605–1443 (C═C), 1252–1292 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 8.22 (s, 1H, C═C*H*–Ph), 7.47–7.79 (m, 5H, Ph), 4.33–4.4 (2q, $2OCH_2CH_3$, $^3J$ = 7.2 Hz), 1.35–1.40 (2t, $2OCH_2CH_3$, $^3J$ = 7.1 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 162.39 (*C*═O), 154.93 (Ph–*C*H═C), 115.44 (*C*═N), 131.48 ($C_{quat}$, Ph), 133.27 ($2C_{tert,meta}$), 131.03 ($C_{tert,para}$), 129.26 ($2C_{tert,ortho}$), 103.06 ($C_{quat}$, ═$C(CO_2Et)$), 62.68 (C, $OCH_2CH_3$), 14.14 (C, $OCH_2CH_3$).

*4.2.9. Ethyl 2-cyano-3-(4-chlorophenyl) acrylate (E) (**9**)*

Yield: 86%; $R_f$ = 0.72 (ether/hexane: 1/1); mp: 125 °C; IR (KBr, $\nu$ $cm^{-1}$): 2893–3024 (CH); 1724.24 (C═O), 1598–1467 (C═C), 1248–1311 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 8.21 (s, 1H, C═CH–Ph), 7.16–8.05 (m, 4H, Ph), 4.33–4.40 (q, 2H, $OCH_2CH_3$, $^3J$ = 7.20 Hz), 1.35 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.20 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 162.38 (*C*═O), 153.49 (Cl–Ph–*C*H═C), 115.45 (*C*═N), 127.87 ($C_{quat}$, C–Cl–Ph), 133.54 ($2C_{meta}$), 133.66 ($C_{quat}$, para/Cl), 116.85 ($2C_{ortho}$), 102.54 (C═*C*–$(CO_2Et)$), 62.79 ($OCH_2CH_3$), 14.15 ($OCH_2CH_3$).

*4.2.10. Ethyl 2-cyano-3-(4-methoxyphenyl) acrylate (E) (**10**)*

Yield: 83%; $R_f$ = 0.63 (ether/hexane: 1/1); mp: 114 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 8.18 (s, 1H, C═C*H*–Ph), 7.33–8.03 (m, 4H, Ph), 4.2–4.46 (q, 2H, $OCH_2CH_3$, $^3J$ = 7.20 Hz), 2.35 (s, 3H, $CH_3$–OPh), 1.35–1.41 (2t, 6H, $2CH_2$–$CH_3$, $^3J$ = 7.20 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 163.33 (C═O), 154.25 ($CH_3O$–Ph–*C*H═C), 115.45 (C═N), 127.87 ($C_{quat}$, –$CH_3$–O*C*Ph), 132.43 ($2C_{meta}$), 131.86 ($C_{quat}$, para/$OCH_3$), 119.41 ($2C_{ortho}$), 101.83 (C═*C*–$(CO_2Et)$), 61.42 ($OCH_2CH_3$), 14.03 ($OCH_{2-}CH3$).

*4.2.11. Ethyl 2-cyano-3-(4-dimethylaminophenyl)acrylate (E) (**11**)*

Yield: 94%; $R_f$ = 0.75 (ether/hexane: 1/1); mp: 93 °C; IR (KBr, $\nu$ $cm^{-1}$): 2832–2936 (CH), 1702 (C═O), 1565–1610 (C═C), 1271–1296 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 8.08 (s, 1H, C═C*H*–Ph), 6.69–7.96 (m, 4H, Ph), 4.31–4.38 (q, 2H, $OCH_2CH_3$, $^3J$ = 7.20 Hz), 3.11 (s, 6H, $N(CH_3)_2$), 1.36–1.41 (2t, 3H, $OCH_2CH_3$, $^3J$ = 7.20 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 164.26 (C═O), 154.50 ($NMe_2$–Ph–CH═), 117.53 (C═N), 154.11 ($C_{quat}$, $NMe_2$–Ph), 111.50 ($2C_{meta}$), 119.42 ($C_{quat}$, para/$NMe_2$), 134.02 ($2C_{ortho}$), 94.16 (C═C–$(CO_2Et)$), 61.85 ($OCH_2$–$CH_3$), 39.98 ($CH_3$–NPh) 14.28 ($OCH_2CH_3$); SM(IE): $C_{14}H_{16}O_2N_2$: $[M]^+$ ($m/z$) = 244 (100%).

*4.2.12. Ethyl 2-cyano-3-(4-methylphenyl)acrylate (E) (**12**)*

Yield: 88%; $R_f$ = 0.61 (ether/hexane: 1/1); mp: 112 °C; $^1$H NMR (300 MHz, CDCl3) $\delta$ ppm: 8.23 (s, 1H, C═C*H*–Ph), 2.45 (s, 3H, $CH_3$–Ph), 7.28–7.93 (m, 4H, Ph), 4.35–4.43 (q, 2H, $2OCH_2CH_3$, $^3J$ = 7.20 Hz), 1.38–1.43 (2t, 6H, $2OCH_2CH_3$, $^3J$ = 7.20 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 162.78 (C═O), 154.99 ($pCH_3$–Ph–*C*H═), 115.78 (C═N), 128.90 ($C_{quat}$, C–$pCH_3$–Ph), 130.04 ($2C_{meta}$), 131.26 ($C_{quat}$, para/$CH_3$), 130.04 ($2C_{ortho}$), 101.61 (C═C–$(CO_2Et)$), 62.59 ($OCH_2$–$CH_3$), 14.18 ($OCH_2CH_3$), 21.87 ($CH_3$–Ph); SM (IE): $C_{13}H_{13}O_2N$: $[M]^+$ $^{(m/z)}$ = 215 (100%). $[M-OEt]^+$ ($m/z$) = 170.

*4.2.13. Ethyl 2-cyano-3-(4-flurophenyl)acrylate (E) (**13**)*

Yield: 64%; $R_f$ = 0.73 (ether/hexane: 1/1); mp: 123 °C; IR (KBr, $\nu$ $cm^{-1}$): 2900–3068 (CH), 1721 (C═O), 1572–1605 (C═C), 1252–1299 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 8.25 (s, 1H, C═C*H*–Ph), 7.46–7.96 (m, 4H, Ph), 4.36–4.43 (q, 2H, $OCH_2CH_3$, $^3J$ = 7.20 Hz), 1.39–1.43 (2t, 6H, $2OCH_2CH_3$, $^3J$ = 6.90 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 162.22 (*C*═O), 153.36 (p-F–Ph–*C*H═C), 115.25 (*C*═N), 139.58 ($C_{quat}$, –F–CPh), 129.68 ($2C_{meta}$), 129.90 ($C_{quat}$, para/F), 132.19 ($2C_{ortho}$), 103.5 (C═*C*–$(CO_2Et)$), 62.86 ($OCH_2CH_3$), 14.14 ($OCH_2CH_3$).

*4.3. General procedure for the synthesis of compounds (**14**)–(**35**)*

To a solution of the substituted 2-arylidenemalonic acid diethyl esters (**1**)–(**13**) (5 mmol) in water (25 mL) was added (6 mmol) of the respective secondary amines (morpholine; 3,5-dimethyl-1H-pyrazole; 4-bromo-3,5-dimethyl-pyrazole; piperidine; pyrolydene; pyrazole; ethylbenzylamine; dibenzylamine and methylbenzylamine) in the presence or absence of acetic acid (0.1 mol%) and the stirring was continued at room temperature until the complete consumption of the starting material as indicated by TLC. After removing solvent, the crude products were dissolved in diethyl ether (2 × 20 mL) and washed with water until the pH became neutral. The organic solvent was dried over sodium sulphate and then evaporated to give the respective yellow oils which then purified by recrystallisation in (hexane/ether: 2/1) mixture. We have obtained pure compounds as white crystals (**14**)–(**35**).

*4.3.1. 2-[(Phenyl)-piperidin-1-yl-methyl]-malonic acid diethyl ester (**14**)*

White crystals; Yield: 80%; $R_f$ = 0.72 (ether/hexane: 1/1); mp: 68 °C; IR (KBr, $\nu$ $cm^{-1}$): 2848–2974 (C–H, Ph), 2754–2800 (C–H, aliph), 1702–1740 (C═O), 1514–1450 (C═C), 1313–1257 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 1.00 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.1 Hz), 1.26 (m, 2H, –$C^{3'}H_2$–, pr), 1.35 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.1 Hz), 1.50 (m, 4H, $2C^{2'}H_2$, pr), 2.20 (s large, 2H, $C^{1'}H_2$, pr), 2.59 (s large, 2H, $C^{1'}H_2$, pr), 4.02 (dq, $2H_{AB}$, O–$CH_2$–$CH_3$, $^2J_{A-B}$ = 10.7 Hz, $^3J$ = 6.9 Hz), 4.23 (d, 1H, $C^2H$–$(CO_2Et)_2$, $^3J$ = 12.1 Hz), 4.33 (dq, 2H, $OCH_2CH_3$, $J_{A-B}$ = 0.2 Hz, $^3J$ = 7.1 Hz), 4.43 (d, 1H, Ph–$C^3H$, $^3J$ = 12 Hz), 7.15–7.34 (m, 5H, Ph); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 167.22–168.04 (2C═O), 133.93 ($C_{quat}$, Ph), 128.69 ($2C_{tert,ortho}$, Ph), 127.80 ($C_{tert,para}$, Ph),

127.53 ($2C_{tert,meta}$, Ph), 69.15 ($C_{tert}$, $PhC^2H$), 61.30–61.15 (2C, $2OCH_2CH_3$), 54.96 ($C_{tert}$, $C^2H(CO_2Et)_2$), 50.55 (2C, $2C^{1'}H_2$, pr), 26.50 (2C, $2C^{2'}H_2$, pr), 24.40 (C, $C^{3'}H_2$, pr), 14.30–13.75 (2C, $2OCH_2CH_3$); SM (IE): $[M]^+$ $C_{19}H_{27}NO_4$: 333.19; $[M+H]^+$ ($m/z$) = 334 (35%); 174 (100%); Element. analysis: Calc. $C_{19}H_{27}NO_4$: %C = 68.46 ; %H = 8.40; %N = 4.20. Found: %C = 67.89; %H = 7.89; %N = 4.22.

*4.3.2. 2-(Phenyl-pyrazol-1-yl-methyl)-malonic acid diethyl (**15**)*

White crystals; Yield: 76%; $R_f$ = 0.45 (ether/hexane: 1/1); mp: 89 °C; IR (KBr, $\nu$ $cm^{-1}$): 2896–2985 (CH), 1748 (C=O), 1514–1595 (C=C), 1292–1308 (C–O), 1175, 1139, 1013, 866, 753, 440; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.30–7.46 (m, 4H, aromat, $^3J$ = 8.35 Hz), 6.20 (t, 1H, $C^{4'}$Pz, $^3J$ = 2 Hz), 7.5 (d, 2H, $C^{3'}$H and $C^{5'}$HPz, $^3J$ = 14.4 Hz), 5.85 (d, 1H, $PhC^3H$, $^3J$ = 11.36 Hz), 4.80 (d, 1H, $C^2H(CO_2Et)_2$, $^3J$ = 11.11 Hz), 3.95 (dq, $2H_{AB}$, $OCH_2CH_3$, $J_{AB}$ = 14.30 Hz, $^3J$ = 7.11 Hz), 4.12 (dq, $2H_{AB}$, $OCH_2CH_3$, $J_{AB}$ = 14.30 Hz, $^3J$ = 7.11 Hz), 1.15 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.13 Hz), 1.01 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.13 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.37 (C=O), 166.61 (C=O), 137.15 ($C_{quat}$, Ph), 128.62 ($C_{tert}$, $2C_{meta}$/arm, Ph), 129.76 ($C_{tert}$, $2C_{ortho}$/arm, Ph), 139.56 ($C_{tert}$, $C^{5'}$–Pz), 128.67 ($C_{tert}$, $C^{3''}$–Pz), 105.71 ($C_{tert}$, $C^4$H, Pz), 61.87–61.76 ($C_{sec}$, $2CH_2$, ester), 64.22 ($C_{tert}$, $C^3$HPh), 57.33 ($C_{tert}$, $C^2H(CO_2Et)_2$), 13.87 (C, $OCH_2CH_3$), 13.69 (C, $OCH_2CH_3$); SM (IE): $[M]^+$ $C_{17}H_{20}O_4$: 316, 35; $[M+H]^{+\cdot}$ ($m/z$) = 317, $[M-CH(CO_2Et)_2]^+$ ($m/z$) = 157 (100%); Element. analysis: Calc. $C_{17}H_{20}O_4$: %C = 64.54; %H = 6.37; %N = 8.8. Found: %C = 67.37; %H = 6.34; %N = 8.56.

*4.3.3. 2-[(Phenyl)-(3,5-dimethyl-pyrazol-1-yl)-methyl]-malonic acid diethyl ester (**16**)*

White crystals; Yield: 76%; $R_f$ = 0.69 (ether/hexane: 1/1); mp: 88 °C; IR (KBr, $\nu$ $cm^{-1}$): 2868–2974 (C–H), 1747–1719 (C=O), 1586–1554 (C=C), 1460–1419 (C=N), 1269–1264 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.45–7.25 (m, 5H, Ph), 5.78 (d, 1H, Ph–$C^3$H, $^3J$ = 11.2 Hz), 5.74 (s, 1H, $H^{4'}$, Pz), 4.9 (d, 1H, $PhC^3HC^2H$, $^3J$ = 11.4 Hz), 4.16–3.99 (2q, 2H, $OCH_2CH_3$, $^3J$ = 7.3 Hz), 3.97 (q, 2H, $OCH_2CH_3$, $^3J$ = 7.1 Hz), 2.25 (s, 1H, $C^{3'}H_3$, Pz), 2.21 (s, 1H, $C^{5'}H_3$, Pz), 1.17 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.1 Hz), 0.98 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.1 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.90–166.85 (2C=O), 147.3 ($C_{quat}$, $C^{5'}$, Pz), 139.30 ($C_{quat}$, Ph), 137.30 ($C_{quat}$, $C^{3'}$, pyrazol), 128.50/128.3/127.93 (5C, Ph), 105 ($C_{tert}$, $C^{2'}$H, Pz), 61.57 (2C, $2OCH_2CH_3$), 60.35 ($C_{tert}$, $PhC^3HC^2H$), 57.52 ($C_{tert}$, Ph–$C^3HC^2H$), 13.87 (C, $C^{5'}H_3$, Pz), 13.67 (C, $C^{3'}H_3$, Pz), 13.64–10.06 (2C, $2OCH_2CH_3$); SM (IE): Calc. $[M]^+$ $C_{19}H_{24}N_2O_4$: 344.17. Found $[M+H]^+$ ($m/z$) = 345.28 (11%), 83 (100%); Element. analysis: Calc. $C_{19}H_{24}N_2O_4$: %C = 66.27; %H = 6.97; %N = 8.13. Found: %C = 65.71; %H = 5.80; %N = 8.78.

*4.3.4. 2-[(Phenyl)-3,5-dimethyl-pyrazol-1-yl -methyl]-malonic sodium (**16'**)*

White powder; Yield: 95%; $R_f$ = 0 (ether/hexane: 1/1); mp > 260 °C; IR (KBr, $\nu$ $cm^{-1}$): 2900 (CH); 1583 (C=O), 1497 (C=C), 1455 (C=N), 1326–1250 (C–O); $^1$H NMR (300 MHz, $D_2O$) $\delta$ ppm: 7.15–7.32 (m, 5H, Ph), 5.68 (d, 1H, Ph–$C^3$H, $^3J$ = 11.2 Hz), 5.72 (s, 1H, $H^{2'}$, Pz), 4.23 (d, 1H, $PhC^3HC^2H$, $^3J$ = 11.4 Hz), 1.99 (s, 1H, $C^{1'}H$, Pz), 2.25 (s, 1H, $C^{3'}H$, Pz); $^{13}$C NMR (300 MHz, $D_2O$) $\delta$ ppm: 175.57 (C=O), 175.29 (C=O), 148.51 ($C_{quat}$, $C^{1'}$, Pz), 141.10 ($C_{quat}$, Ph), 138.86 ($C_{quat}$, $C^{3'}$, Pz), 128.65 ($C_{meta}$, 2H, Ph), 127.92 ($C_{ortho}$, 2H, Ph), 127.43 ($C_{para}$, 1H, Ph), 104.72 ($C_{tert}$, $C^{2'}$H, Pz), 62.95 ($C_{tert}$, $PhC^3HC^2H$), 61.33 ($C_{tert}$, Ph–$C^3HC^2H$), 12.21 (C, $C^{1'}$H3, Pz), 10.67 (C, $C^{3'}H_3$, Pz).

*4.3.5. 2-[(Phenyl)-3,5-dimethyl-pyrazol-1-yl-methyl]-malonic acid (**16''**)*

White powder; Yield: 83%; mp: 154 °C; $R_f$ = 0.22 (ether/hexane: 1/1); IR (KBr, $\nu$ $cm^{-1}$): 2918–3068 (CH), 1705 (C=O), 1555–1500 (C=C), 1459–1484 (C=N), 3406 (OH), 1343–1273 (C–O), 1146, 104, 951; $^1$H NMR (300 MHz, acetone) $\delta$ ppm: 7.27–7.44 (m, 5H, Ph), 5.89 (d, 1H, Ph–$C^3$H, $^3J$ = 11.2 Hz), 5.83 (s, 1H, $H^{2'}$, Pz), 4.78 (d, 1H, $PhC^3HC^2H$, $^3J$ = 11.4 Hz), 4.19 (s, O*H*, $CO_2H$), 2.15 (s, 1H, $C^{1'}H$, Pz), 2.26 (s, 1H, $C^{3'}H$, Pz); $^{13}$C NMR (300 MHz, acetone) $\delta$ ppm: 167.07 (C=O), 167.43 (C=O), 146.73 ($C_{quat}$, $C^{1'}$, pyrazol), 140.73 ($C_{quat}$, Ph), 139.96 ($C_{quat}$, $C^{3'}$, Pz), 127.58–130.35 ($C_{tert}$, 5*C*H, Ph), 105.15 ($C_{tert}$, $C^{2'}$H, pyrazol), 59.75 ($C_{tert}$, $PhC^3HC^2H$), 57.75 ($C_{tert}$, Ph–$C^3HC^2H$), 12.72 (C, $C^{1'}H_3$, Pz), 10.08 (C, $C^{3'}H_3$, Pz).

*4.3.6. 2-[(Phenyl)-dibenzyl amino-1-yl-methyl]-malonic acid diethyl ester (**17**)*

White crystals; Yield: 76%; $R_f$ = 0.53 (ether/hexane: 1/1); mp: 119 °C; IR (KBr, $\nu$ $cm^{-1}$): 2883–2930 (C–H), 1747 (C=O), 1584–1600 (C=C), 1323–1252 (C–O), 1157, 1110, 1037; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.23–7.45 (m, 15H, arom), 4.59 (d, 1H, $PhC^3H$, $^3J$ = 12.0 Hz), 4.44 (d, 1H, $C^2H(CO_2Et)_2$, $^3J$ = 12.0 Hz), 3 (d, 2H, $CH_2Ph$, $^3J$ = 13.5 Hz), 3.98 (d, 2H, $CH_2Ph$, $^3J$ = 13.5 Hz), 3.94 (dq, $2H_{AB}$, $^2J_{AB}$ = 14.29 Hz, $^3J$ = 7.13 Hz), 4.22 (dq, $2H_{AB}$, $J_{AB}$ = 14.29 Hz, $^3J$ = 7.13 Hz), 1.28 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.11 Hz), 0.95 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.11 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 167.51–166.86 (2C=O), 139.05 ($C_{quat}$, C, Ph), 133.79 ($2C_{quat}$, 2Ph), 129.27–127.0 ($C_{tert}$, Ph), 61.79 ($C_{tert}$, $C^3$H–Ph), 61.60 (C, $OCH_2CH_3$, ester), 61.13 (C, $OCH_2CH_3$, ester), 55.39 ($C_{tert}$, $C^2H(CO_2Et)_2$), 53.94 ($2C_{sec}$, $2CH_2N$), 13.92–13.65 (2C, $2OCH_2CH_3$); SM (IE): Calc. $[M]^+$ $C_{28}H_{31}NO_4$: 445.55. Found $[M+H]^+$ ($m/z$) = 446; $[M-CH(CO_2Et)_2]^{+\cdot}$ ($m/z$) = 286 (100%); Element. analysis: Calc. $C_{28}H_{31}NO_4$: %C = 75.48; %H = 7.01; %N = 3.14. Found: %C = 75.46; %H = 7.02; %N = 3.12.

*4.3.7. 2-[(Phenyl)-benzyl methyl-1-yl-methyl]-malonic acid diethyl ester (**18**)*

White crystals; Yield: 78%; $R_f$ = 0.45 (ether/hexane: 1/1); mp: 107 °C; IR (KBr, $\nu$ $cm^{-1}$): 2860–2984 (C–H), 1745 (C=O), 1216–1301 (C–O), 1584–1601 (C=C), 1138, 1021; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 1.01 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.2 Hz), 1.33 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.2 Hz), 3.25 (d, 1H, $CH_2Ph$, $^3J$ = 13.5 Hz), 3.5 (d, 1H, $CH_2Ph$, $^3J$ = 13.2 Hz), 4.32 (d, H, $C^2H(CO_2Et)_2$, $^3J$ = 12.20 Hz), 4.65 (d, H, Ph–$C^3H$, $^3J$ = 12.15 Hz), 4.01 (dq, $2H_{AB}$, $OCH_2CH_3$, $^2J_{AB}$ = 14.34 Hz, $^3J$ = 7.06 Hz), 4.35 (dq, $2H_{AB}$, $OCH_2CH_3$, $^2J_{AB}$ = 14.34 Hz, $^3J$ = 7.06 Hz), 2.05 (s, 3H, $CH_3N$), 7.2–74 (m, 10H, Ph); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 167.93 (C=O), 167.97 (C=O), 133.4 ($C_{quat}$, *C*–(Ph)), 132.6 ($C_{quat}$, $CPhCH_2$), 126.91–128.03 ($C_{tert}$, 10CH arom), 67.47 ($C_{tert}$, $C^3$HPh); 61.24–61.3 (2C, $2CH_2CH_3$, ester), 55.39 ($C_{tert}$, $C^2$H–($CO_2Et$)), 58.70 ($C_{sec}$, $C^{1'}H_2N$), 36.94 ($C_{tert}$, $CH_3N$), 14.15–13.73 (2C, $2OCH_2CH_3$); SM (IE): Calc. $[M]^+$ $C_{28}H_{30}NO_4Cl$: 369.45. Found $[M+H]^{+\cdot}$ ($m/z$) = 370;

$[M-CH(CO_2Et)_2]^+$ ($m/z$) = 159 (100%); Element. analysis: Calc. $C_{28}H_{30}NO_4Cl$: %C = 71.52; %H = 7.37; %N = 3.79. Found: %C = 71.48; %H = 7.35; %N = 3.81.

*4.3.8. 2-[(Benzyl-ethyl-amine)-phenyl)-methyl]-malonic acid diethyl ester (**19**)*

White crystals; Yield: 82%; $R_f$ = 0.51 (ether/hexane: 1/1); mp: 92 °C; IR (KBr, $\nu$ cm$^{-1}$): 2872–2935 (CH), 1731 (C═O), 1490–1594 (C═C), 1290–1303 (C–O), 1179, 1012; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.18–7.38 (m, 10H, 2Ph), 4.65 (d, 1H, PhC$^3$*H*, $^3J$ = 12.1 Hz), 4.42 (d, 1H, C$^2$*H*$(CO_2Et)_2$, $^3J$ = 12.0 Hz), 3.98 (d, 1H, C*H*$_2$Ph, $^3J$ = 13.80 Hz), 2.95 (d, 1H, NC*H*$_2$CH$_3$, $^3J$ = 13.80 Hz), 2.1 (dq, 1H$_{AB}$, NC*H*$_2$CH$_3$, $J_{AB}$ = 12.94 Hz, $^3J$ = 7.2 Hz), 2.55 (dq, 1H$_{AB}$, NC*H*$_2$Ph, $^2J_{AB}$ = 12.94 Hz, $^3J$ = 7.2 Hz), 4.0 (dq, 2H$_{AB}$, OC*H*$_2$CH$_3$, $J_{AB}$ = 14.1 Hz, $^3J$ = 7.0 Hz), 4.3 (dq, 2H$_{AB}$, OC*H*$_2$CH$_3$, $^2J_{AB}$ = 14.1 Hz, $^3J$ = 7.0 Hz), 1.04 (t, 3H, NCH$_2$C*H*$_3$, $^3J$ = 7.2 Hz), 1.1 (t, 3H, OCH$_2$C*H*$_3$, $^3J$ = 7.2 Hz), 1.45 (t, 3H, OCH$_2$C*H*$_3$, $^3J$ = 7.2 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.91–167.47 (2C═O), 139.42 (C$_{quat}$, *C*–, Ph), 133.06 (C$_{quat}$, CH$_2$Ph), 126.91–130.19 (C$_{tert}$, 2Ph), 61.32–61.60 (C$_{sec}$, 2O*C*H$_2$CH$_3$), 61.83 (C$_{tert}$, *C*$^3$HPh), 55.50 (C$_{tert}$, *C*$^2$H$(CO_2Et)_2$), 43.41 (C$_{sec}$, N*C*H$_2$CH$_3$), 55.32 (C$_{sec}$, N*C*H$_2$Ph), 13.40 (C$_{tert}$, NCH$_2$*C*H$_3$), 13.77 (C$_{tert}$, OCH$_2$*C*H$_3$), 14.06 (C$_{tert}$, OCH$_2$*C*H$_3$); SM (IE): Calc. $[M]^+$ $C_{23}H_{29}NO_4$: 383.16. Found $[M+H]^+$ ($m/z$) = 384; $[M-CH(CO_2Et)_2]^{+\cdot}$ ($m/z$) = 224 (100%); Element. analysis: Calc. $C_{23}H_{29}NO_4$: %C = 72.04; %H = 7.63; %N = 3.65. Found: %C = 72.0; %H = 7.63; %N = 3.64.

*4.3.9. 2-[(4-Chlorophenyl)-morpholin-4-yl-methyl]-malonic acid diethyl ester (**20**)*

White crystals; Yield: 96%; $R_f$ = 0.55 (ether/hexane: 1/1); mp: 68–69 °C; IR (KBr, $\nu$ cm$^{-1}$): 2935–2985 (C–H, 4-Cl–Ph), 2826–2887 (C–H), 1747 (C═O), 1712 (C═O), 1590–1489 (C═C), 1306–1258 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.35 (d, 2H, ortho, $^3J$ = 8.30 Hz), 7.12 (d, 2H, meta, $^3J$ = 8.30 Hz), 4.25–4.39 (m, 3H, OC*H*$_2$CH$_3$ + PhC$^3$*H*), 4.20 (d, 1H, C$^2$*H* $(CO_2Et)_2$, $^3J$ = 10.3 Hz), 3.90–4.07 (m, 2H, OC*H*$_2$CH$_3$), 3.93 (s, 4H, C$^{2'}$*H*$_2$OC$^{2'}$*H*$_2$), 2.53 (s, 2H, C$^{1'}$*H*$_2$), 2.30 (s, 2H, C$^{1'}$*H*$_2$), 1.06 (t, 3H, OCH$_2$C*H*$_3$, $^3J$ = 7.1 Hz), 1.06 (t, 3H, OCH$_2$C*H*$_3$, $^3J$ = 7.1 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 167.6 (2C═O), 134.8 (C$_{quat}$, p-CCl, Ph), 131.8 (C$_{quat}$, Ph, para/Cl), 130 (C$_{tert}$, 2C-ortho, Ph), 128.4 (C$_{tert}$, 2C-meta, Ph), 68.0 (C$_{tert}$, *C*$^3$H–Ph), 67.1 (2C, 2*C*$^{2'}$H$_2$O, mor), 61.6 (C, O*C*H$_2$CH$_3$), 61.5 (C, O*C*H$_2$CH$_3$), 54.6 (C$_{tert}$, *C*$^2$H$(CO_2Et)_2$), 49.5 (2C, 2C$^{1'}$H$_2$N, mor), 14.3 (C, OCH$_2$*C*H$_3$), 13.8 (C, OCH$_2$*C*H$_3$); SM (IE): Calc. $[M]^+$ $C_{18}H_{24}ClNO_5$: 369.13. Found $[M+H]^+$ ($m/z$) = 370 (15%); $[M-CH(CO_2Et)_2]^+$ ($m/z$) = 210 (100%); Element. analysis: Calc. $C_{18}H_{24}NO_5Cl$: %C = 58.53; %H = 6.50; %N = 3.79. Found: %C = 58.60; %H = 6.71; %N = 4.03.

*4.3.10. 2-[(4-Chlorophenyl)-pyrrolidin-1-yl-methyl]-malonic acid diethyl ester (**21**)*

White crystals; Yield: 73%; $R_f$ = 0.68 (ether/hexane: 1/1); mp: 79 °C; IR (KBr, $\nu$ cm$^{-1}$): 2969 (C–H, Ph), 2674–2806 (C–H), 1747–1720 (C═O), 1592–1464 (C═C), 1329–1256 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.29–7.29 (m, 2H,Ph), 7.14–7.18 (m, 2H, Ph), 4.5 (d, 1H, PhC$^3$*H*, $^3J$ = 11.40 Hz), 4.09 (d, 1H, C$^2$*H*$(CO_2Et)_2$, $^3J$ = 11.40 Hz), 4.25 (q, 2H, OC*H*$_2$CH$_3$, $^3J$ = 7.1 Hz), 3.95 (m, 2H, OC*H*$_2$CH$_3$), 2.49 (m, 2H, N–C$^{1'}$*H*$_2$, pyr), 2.35 (m, 2H, NC$^{1'}$*H*$_2$, pyr), 1.59 (m, 4H, 2C$^{1'}$H$_2$C$^{2'}$*H*$_2$, pyr), 1.30 (t, 3H, OCH$_2$C*H*$_3$, $^3J$ = 7.1 Hz), 1.03 (t, 3H, OCH$_2$C*H*$_3$, $^3J$ = 7.1 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.97–167.88 (2C═O), 133.35 (C$_{quat}$, *C*Cl, Ph), 133.22 (C$_{quat}$, Ph, para/Cl), 130.35 (C$_{tert}$, 2C$_{ortho}$, Ph), 128.05 (C$_{tert}$, 2C$_{meta}$, Ph), 64.05 (C$_{tert}$, *C*$^3$HPh), 61.40 (C, O*C*H$_2$CH$_3$), 61.30 (C, O*C*H$_2$CH$_3$), 56.50 (C$_{tert}$, *C*$^2$H$(CO_2Et)_2$), 48.41–46.88 (2C, 2*C*$^{1'}$H$_2$N, pyr), 22.84 (2C, 2C$^{1'}$H$_2$*C*$^{2'}$H$_2$), pyr), 13.91–14.12 (2C, 2OCH$_2$*C*H$_3$); SM (IE): Calc. $[M]^+$ $C_{18}H_{24}ClNO_4$: 353.14. Found $[M+H]^{+\cdot}$ ($m/z$) = 354 (18%); $[M-CH(CO_2Et)_2]^+$ ($m/z$) = 194 (100%); $[M-pyrol]^+$ ($m/z$) = 283; Element. analysis: Calc. $C_{18}H_{24}ClNO_4$: %C = 62.12; %H = 7.08; %N = 3.18. Found: %C = 62.10; %H = 7.28; %N = 4.04.

*4.3.11. 2-(4-Chlorophenyl)-pyrazol-1-yl-methyl]-malonic acid diethyl ester (**22**)*

White crystals; Yield: 71%; $R_f$ = 0.65 (ether/hexane; 1/1); mp: 89 °C; IR (KBr, $\nu$ cm$^{-1}$): 2896–2985 (CH), 1748 (C═O), 1514–1595 (C═C), 1292–1308 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.28–7.44 (m, 4H, Ph, $^3J$ = 8.68 Hz), 6.20 (t, 1H, Pz, $^3J$ = 2.08 Hz), 7.5 (d, 2H, C$^{3'}$H, C$^5$H, Pz, $^3J$ = 14.27 Hz), 5.85 (d, 1H, PhC$^3$*H*, $^3J$ = 11.33 Hz), 4.80 (d, 1H, C$^2$*H*$(CO_2Et)_2$, $^3J$ = 11.33 Hz), 4.10 (dq, 2H$_{AB}$, OC*H*$_2$CH$_3$, $J_{AB}$ = 14.32 Hz, $^3J$ = 7.11 Hz), 4.01 (dq, 2H$_{AB}$, OC*H*$_2$CH$_3$, $J_{AB}$ = 14.32 Hz, $^3J$ = 7.11 Hz), 2.25 (s, 3H, C*H*$_3$, Pz), 2.20 (s, 3H, C*H*$_3$, Pz), 1.13 (t, 3H, OCH$_2$C*H*$_3$, $^3J$ = 7.11 Hz), 1.04 (t, 3H, OCH$_2$C*H*$_3$, $^3J$ = 7.11 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.36 (C═O), 166.26 (C═O), 147.65 (C$_{quat}$, Pz), 139.3 (C$_{quat}$, Pz), 135.7 (C$_{quat}$, *C*Cl, Ph), 134.62 (C$_{quat}$, Ph, para/Cl), 129.83 (C$_{tert}$, 2C$_{meta}$/bras, Ph), 128.7 (C$_{tert}$, 2C$_{ortho}$/bras, Ph), 129.27 (C$_{tert}$, *C*$^{3'}$, Pz), 105.45 (C$_{tert}$, *C*$^{4'}$H, Pz), 61.75–61.70 (C$_{sec}$, 2O*C*H$_2$CH), 59.55 (C$_{tert}$, *C*$^3$HPh), 57.45 (C$_{tert}$, *C*$^2$H$(CO_2Et)_2$), 13.87 (C, OCH$_2$*C*H$_3$), 13.75 (C, OCH$_2$*C*H$_3$), 13.66 (C, *C*H$_3$, Pz), 10.95 (*C*H$_3$, Pz); SM (IE): Calc. $[M]^+$ $C_{17}H_{19}N_2O_4Cl$: 350.5. Found $[M+H]^+$ ($m/z$) = 351 (15%); $[M-CH(CO_2Et)_2]^+$ ($m/z$) = 191 (100%); $[M-Pz]^+$ ($m/z$) = 283 (21%); Element. analysis: Calc. $C_{18}H_{24}ClNO_4$: %C = 64.55; %H = 6.32; %N = 8.86. Found: %C = 64.46; %H = 6.62; %N = 9.06.

*4.3.12. 2-[(4-Chlorophenyl)-piperidin-1-yl-methyl]-malonic acid diethyl ester (**23**)*

White crystals; Yield: 67%; $R_f$ = 0.65 (ether/hexane: 1/1); mp: 65 °C; IR (KBr, $\nu$ cm$^{-1}$): 1755–1737 (C═O), 2973–2848 (C–H), 1493–1452 (C═C), 1312–1257 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 1.05 (t, 3H, OCH$_2$C*H*$_3$, $^3J$ = 7.10 Hz), 1.26 (m, 2H, C$^{3'}$*H*$_2$, $^3J$ = 5.9 Hz), 1.35 (t, 3H, OCH$_2$C*H*$_3$, $^3J$ = 7.10 Hz), 1.48 (m, 4H, 2C$^{2'}$*H*$_2$), 2.16 (m, 2H, NC$^{1'}$*H*$_2$), 2.46 (m, 2H, NC$^{1'}$*H*$_2$), 4.16 (d, H, C$^2$*H*$(CO_2Et)_2$, $^3J$ = 12.10 Hz), 4.35 (d, H, PhC$^3$*H*, $^3J$ = 12.20 Hz), 4.02 (dq, 2H$_{AB}$, OC*H*$_2$CH$_3$, $J_{AB}$ = 11.3 Hz), 4.30 (dq, 2H$_{AB}$, OC*H*$_2$CH$_3$, $J_{AB}$ = 10.7 Hz), 7.1 (d, 2H, arom-ortho, $^3J$ = 10.7 Hz), 7.32 (d, 2H, arom-meta, $^3J$ = 10.9 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 167.71 (C═O), 167.03 (C═O), 133.4 (C$_{quat}$, Cl*C*Ph), 132.6 (C$_{quat}$, para/Cl), 129.9 (C$_{tert}$, 2C$_{meta}$, Ph), 128.04 (C$_{tert}$, 2C$_{ortho}$, Ph), 69.5 (C$_{tert}$, *C*$^3$HPh), 61.4–61.3 (2C, 2O*C*H$_2$CH$_3$), 54.95 (C$_{tert}$, *C*$^2$H$(CO_2Et)$), 50.51 (2C, 2*C*$^{1'}$H$_2$N), 26.4 (2C, 2*C*$^{2'}$H$_2$CH$_2$N), 24.40 (C, N$(CH_2)_2$*C*$^{3'}$H$_2$), 14.3–13.8 (2C, 2OCH$_2$*C*H$_3$); SM (IE): Calc. $[M]^+$ $C_{19}H_{26}ClNO_4$: 367.16. Found $[M+H]^{+\cdot}$ ($m/z$) = 368 (16%); $[M-CH(CO_2Et)_2]^{+\cdot}$ ($m/z$) = 256

(100%); $[M-PhCl]^{+\cdot}$ ($m/z$) = 249; Element. analysis: Calc. $C_{19}H_{26}ClNO_4$: %C = 62.12; %H = 7.08; %N = 3.18. Found: %C = 62.10; %H = 7.28; %N = 3.14.

*4.3.13. 2-[(4-Chlorophenyl)-benzylethylamino-methyl]-malonic acid diethyl ester (**24**)*

White crystal; Yield: 84%; $R_f$ = 0.56 (ether/hexane: 1/1); mp: 70–72 °C; IR (KBr, $\nu$ cm$^{-1}$): 2808–2985 (CH), 1732 (C=O), 1594–1595 (C=C), 1248–1291 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.24–7.37 (m, 4H, PhCl, $^3J$ = 8.43 Hz), 7.23–7.1 (m, 5H, Ph, $^3J$ = 4.42 Hz), 4.62 (d, 1H, ClPhC$^3H$, $^3J$ = 12.30 Hz), 4.24 (d, 1H, C$^2H$(CO$_2$Et)$_2$, $^3J$ = 12.30 Hz), 2.9 (d, 1H, C$H$–Ph, $^3J$ = 13.80 Hz), 3.9 (d, 1H, C$H$–Ph, $^3J$ = 13.80 Hz), 2.1 (m, 1H, C$H$CH$_3$, $^3J$ = 12.90 Hz), 2.55 (m, 1H, C$H$CH$_3$, $^3J$ = 12.90 Hz), 4.01 (dq, 2H$_{A-B}$, OC$H_2$CH$_3$, $J_{AB}$ = 14.10 Hz, $^3J$ = 7.07 Hz), 4.30 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $J_{AB}$ = 14.10 Hz, $^3J$ = 7.07 Hz), 1.15 (t, 3H, NCH$_2$–C$H_3$), 1.30 (t, 3H, OCH$_2$–C$H_3$, $^3J$ = 7.07 Hz), 1.01 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.07 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.93 (C=O), 167.84 (C–O), 139.41 (C$_{quat}$, CCl, Ph), 133.54 (C$_{quat}$, Ph, para/Cl), 130.81 (C$_{tert}$, 2$C_{meta}$, Ph–Cl), 128.15 (C$_{tert}$, 2$C_{ortho}$, Ph–Cl), 128.28 (C$_{tert}$, 2$C_{meta}$, Ph), 128.15 (C$_{tert}$, 2$C_{ortho}$, Ph), 126.91 (C$_{tert}$, 2$C_{para}$, Ph), 61.75–61.70 (C$_{sec}$, 2O$C$H$_2$CH$_3$), 61.75 (C$_{tert}$, $C^3$HPhCl), 55.47 (C$_{tert}$, $C^2$H(CO$_2$Et)$_2$), 14.07 (C$_{tert}$, 2OCH$_2$$C$H$_3$), 13.79 (C$_{tert}$, OCH$_2$$C$H$_3$), 13.41 (C$_{tert}$, NCH$_2$$C$H$_3$), 54.21 (C$_{sec}$, N$C$H$_2$CH$_3$); SM (IE): Calc. $[M]^+$ $C_{23}H_{28}ClNO_4$: 417.5; $[M+H]^+$ ($m/z$) = 418 (12%). Found $[M-CH(CO_2Et)_2]^+$ ($m/z$) = 258 (100%); $[M-N(CH_2Ph,C_2H_5)]^+$ ($m/z$) = 283; Element. analysis: Calc. $C_{23}H_{28}ClNO_4$: %C = 66.18; %H = 6.71; %N = 3.35. Found: %C = 65.53; %H = 6.66; %N = 3.55.

*4.3.14. 2-[(4-Chlorophenyl)-3,5-dimethyl-pyrazol-1-yl-methyl]-malonic acid diethyl ester (**25**)*

White crystals; Yield: 83%; $R_f$ = 0.67 (ether/hexane: 1/1); mp: 83 °C; IR (KBr, $\nu$ cm$^{-1}$): 2981–2935 (CH), 1764 (C=O), 1594–1554 (C=C), 1490–1463 (C=N), 1300–1257 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.25–7.44 (m, 4H, Ph, $^3J$ = 8.25 Hz), 5.74 (s, 1H, Pz), 5.70 (d, 1H, PhC$^3H$, $^3J$ = 11.3 Hz), 4.84 (d, 1H, C$^2H$(CO$_2$Et)$_2$, $^3J$ = 11.3 Hz), 4.12 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $J_{AB}$ = 14.3 Hz, $^3J$ = 7.2 Hz), 4.0 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $J_{AB}$ = 14.3 Hz, $^3J$ = 7.2 Hz), 2.25 (s, 3H, C$H_3$, Pz), 2.20 (s, 3H, C$H_3$, Pz), 5.75 (s, 1H, $C^{4'}$, Pz), 1.16 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.1 Hz), 1.04 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.1 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.60 (C=O), 166.75 (C=O), 147.65 (C$_{quat}$, Pz), 139.3 (C$_{quat}$, Pz), 138.9 (C$_{quat}$, CCl, Ph), 134.25 (C$_{quat}$, Ph, para/Cl), 129.4 (C$_{tert}$, 2$C_{meta}$, Ph), 128.7 (C$_{tert}$, 2C$_{ortho}$, Ph), 105.45 (C$_{tert}$, CH, Pz), 61.75–61.70 (C$_{sec}$, 2O$C$H$_2$CH$_3$), 59.55 (C$_{tert}$, $C^3$HPh), 57.45 (C$_{tert}$, $C^2$H(CO$_2$Et)$_2$), 13.87 (C$_{tert}$, OCH$_2$$C$H$_3$), 13.75 (C$_{tert}$, OCH$_2$$C$H$_3$), 13.66 (C$_{tert}$, C$H_3$, Pz), 10.95 (C$_{tert}$, C$H_3$, Pz); MS (IE): Calc. $[M]^+$ $C_{19}H_{23}ClN_2O_4$: 378.13. Found $[M+H]^+$ ($m/z$) = 379 (17%); $[M-CH(CO_2Et)_2]^+$ ($m/z$) = 219 (100%); $[M-Pz)]^+$ ($m/z$) = 283; Element. analysis: Calc. $C_{19}H_{23}ClN_2O_4$: %C = 60.31; %H = 6.08; %N = 7.40. Found: %C = 60.43; %H = 6.05; %N = 7.69.

*4.3.15. 2-[(4-Chlorophenyl)-dibenzyl amino-1-yl-methyl]-malonic acid diethyl ester (**26**)*

White crystals; Yield: 67%; $R_f$ = 0.42 (ether/hexane: 1/1); mp: 112 °C; IR (KBr, $\nu$ cm$^{-1}$): 2811–2980 (CH); 1722 (CO), 1591 (C=C), 1257–1301 (C–O), 1181, 1092, 822, 747, 416; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.24–7.44 (m, 4H, arom, Ph–Cl, $^3J$ = 6.60 Hz), 7.23–7.31 (m, 10H, arom, Ph, $^3J$ = 4.15 Hz), 4.56 (d, 1H, ClPhC$^3H$, $^3J$ = 12.12 Hz), 4.33 (d, 1H, C$^2H$(CO$_2$Et)$_2$, $^3J$ = 12.12 Hz), 3.0 (d, 1H, 2C$H$Ph, $^3J$ = 13.50 Hz), 3.9 (d, 1H, 2C$H$Ph, $^3J$ = 13 Hz), 3.98 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $^2J_{AB}$ = 14.10 Hz, $^3J$ = 7.10 Hz), 4.20–4.40 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $^2J_{AB}$ = 14.11 Hz, $^3J$ = 7.10 Hz), 1.30 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.10 Hz), 1.01 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.10 Hz), 1.25 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.10 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.74–167.26 (2C=O), 138.71 (C$_{quat}$, CCl, Ph), 133.68 (C$_{quat}$, p-Cl–Ph), 130.47 (C$_{tert}$, 2$C_{meta}$, p-Cl–Ph), 128.91 (C$_{tert}$, 2$C_{ortho}$, p-Cl–Ph), 128.29 (C$_{quat}$, 2$C$, 2Ph), 128.34 (C$_{tert}$, 4$C_{meta}$, 2Ph), 128.29 (C$_{tert}$, 4$C_{ortho}$, 2Ph), 127.15 (C$_{tert}$, 2$C_{para}$, 2Ph), 61.73 (C$_{sec}$, 2OC$H_2$CH$_3$), 61.04 (C$_{tert}$, $C^3$HPhCl), 55.26 (C$_{tert}$, $C^2$H(CO$_2$Et)$_2$), 13.75 (C$_{tert}$, OCH$_2$$C$H$_3$), 13.92 (C$_{tert}$, OCH$_2$$C$H$_3$), 61.31 (C$_{sec}$, 2$C$H$_2$Ph); SM (IE): Calc. $[M]^+$ $C_{28}H_{30}NO_4Cl$: 479.99. Found $[M+H]^{+\cdot}$ ($m/z$) = 481; $[M-CH(CO_2Et)_2]^{+\cdot}$ ($m/z$) = 320 (100%); Element. analysis: Calc. $C_{28}H_{30}NO_4Cl$: %C = 70.06; %H = 6.30; %N = 2.92. Found: %C = 69.98; %H = 6.27; %N = 2.91.

*4.3.17. 2-[(4-Chlorophenyl)-4-bromo,3,5-dimethyl-pyrazol-1-yl-methyl]-malonique acid diethyl (**27**)*

White crystals; Yield: 86%; $R_f$ = 0.53 (ether/hexane: 1/1); mp: 95 °C; IR (KBr, $\nu$ cm$^{-1}$): 2984–2939 (CH), 1758 (C=O), 1595–1543 (C=C), 1490–1463 (C=N), 1300–1265 (C–O); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.26–7.39 (m, 4H, Ph, $^3J$ = 6.30 Hz), 5.78 (d, 1H, PhC$^3H$, $^3J$ = 11.3 Hz), 4.83 (d, 1H, C$^2H$(CO$_2$Et)$_2$, $^3J$ = 11.3 Hz), 4.20 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $J_{AB}$ = 13.54 Hz, $^3J$ = 7.2 Hz), 4.0 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $J_{AB}$ = 13.54 Hz, $^3J$ = 7.2 Hz), 2.24 (s, 3H, CH$_3$, Pz), 2.18 (s, 3H, CH$_3$, Pz), 1.13 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz), 1.02 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.08 (C=O), 167.01 (C=O), 146.29 (C$_{quat}$, Pz), 137.5 (C$_{quat}$, Pz), 136.58 (C$_{quat}$, CCl, Ph), 134.35 (C$_{quat}$, Ph, para/Cl), 127.88 (C$_{tert}$, 2$C_{meta}$, Ph), 128.31 (C$_{tert}$, 2C$_{ortho}$, Ph), 94.83 (C$_{quat}$, C$^4$Br, Pz), 61.47–61.70 (C$_{sec}$, 2O$C$H$_2$CH$_3$), 59.88 (C$_{tert}$, C$^3$HPh), 56.99 (C$_{tert}$, $C^2$H(CO$_2$Et)$_2$), 13.86 (OCH$_2$$C$H$_3$), 14.08 (OCH$_2$$C$H$_3$), 12.41(CH$_3$, Pz), 11.26 (CH$_3$, Pz); MS (IE): Calc. $[M]^+$ $C_{19}H_{22}ClN_2O_4Br$: 456. Found $[M+H]^+$ ($m/z$) = 457; $[M-CH(CO_2Et)_2]^+$ ($m/z$) = 297 (100%); $[M-pyrazol)]^+$ ($m/z$) = 361.

*4.3.18. 2-[(4-Trifloromethyl-phenyl)-pyrrolidin-1-yl-methyl]-malonic acid diethyl ester (**28**)*

White crystals; Yield: 73%; $R_f$ = 0.62 (ether/hexane: 1/1); mp: 73 °C; IR (KBr, $\nu$ cm$^{-1}$): 2875–2940 (C–H), 1745 (C=O), 1585–1618 (C=C), 1269–1264 (C–O), 1153, 1112, 1066; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.33 (d, 2H$_{ortho}$, $^3J$ = 8.03 Hz), 7.60 (d, 2H$_{meta}$, $^3J$ = 8.03 Hz), 4.6 (d, 1H, Ph–C$^3$H, $^3J$ = 11.25 Hz), 4.13 (d, 1H, PhC$^3$HC$^2H$, $^3J$ = 11.25 Hz), 4.3 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $^2J_{AB}$ = 10.08 Hz, $^3J$ = 7.3 Hz), 4.0 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $^2J_{AB}$ = 10.08 Hz, $^3J$ = 7.3 Hz), 2.35 (s, 2H, C$^{1'}H_2$–pyr), 2.47 (s, 2H, C$^{1'}H_2$–pyr), 1.6 (m, 4H, C$^{2'}H$, pyr), 1.3 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz); 1.6 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.89–167.75 (2C=O), 138.95 (C$_{quat}$, CF$_3$Ph), 129.0 (C$_{quat}$, p-CF$_3$Ph), 128.11 (C$_{tert}$, C$_{meta}$, Ph), 125.90 (C$_{tert}$, C$_{ortho}$, Ph), 64.27 (C$_{tert}$, C$^{3'}$H, Ph), 55.83 [C$_{tert}$, C$^{2'}$H, CH$^{3'}$=C$H^{2'}$(CO$_2$Et)$_2$], 61.93–61.45 (2C,

2O$CH_2CH_3$), 48.50–47.06 (2$C_{sec}$, 2$C^{2'}$H, pyr), 22.84 (2$C_{sec}$, 2$C^{1'}$H, pyr), 13.66–14.03 (2$C_{tert}$, 2O$CH_2CH_3$); SM (IE): Calc. $[M]^+$ $C_{19}H_{24}NO_4F_3$: 387.39. Found $[M+H]^+$ ($m/z$) = 388; $[M-CH(CO_2Et)_2]^{+\cdot}$ ($m/z$) = 228 (100%); Element. analysis: Calc. $C_{19}H_{24}NO_4F$: %C = 58.91; %H = 6.24; %N = 3.62. Found: %C = 60.01; %H = 6.25; %N = 3.61.

*4.3.19. 2-[(4-Trifloromethyl-phenyl)-piperidin-methyl]-malonic acid diethyl (**29**)*

White crystals; Yield: 67%; $R_f$ = 0.67 (ether/hexane: 1/1); mp: 92 °C; IR (KBr, $\nu$ $cm^{-1}$): 2875–2938 (CH), 1729 (C=O), 1491–1593 (C=C), 1291–1302 (C–O), 1180, 1011; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 1.03 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz), 1.35 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz), 1.26 (m, 2H, C$^{3'}$H$_2$, pip), 1.52 [m, 4H, 2(C$^{2'}$H$_2$), pip], 2.1 (s, 2H, C$^{1'}$H$_2$, pip), 2.51 (s, 2H, C$^{1'}$H$_2$, pip), 4.01 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $^2J_{AB}$ = 10.14 Hz, $^3J$ = 7.04 Hz), 4.22 (d, 1H, C$^2$H(CO$_2$Et)$_2$, $^3J$ = 12.11 Hz), 4.30 (dq, 2H, OC$H_2$CH$_3$, $^2J_{AB}$ = 10.14 Hz, $^3J$ = 7.02 Hz), 4.41 (d, 1H, PhC$^3$H, $^3J$ = 12.1 Hz), 7.27(d, 2H$_{ortho}$, $^3J$ = 8.1 Hz), 7.58 (d, 2H$_{meta}$, $^3J$ = 8.1 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.97–166 (2C=O), 129.50 ($C_{quat}$, arom), 138.17 ($C_{quat}$, C–$CF_3$); 129.05 (2$C_{tert}$, meta, Ph), 124.80 ($C_{tert}$, ortho, Ph), 54.74 [$C_{tert}$, PhC$^2$H(CO$_2$Et)$_2$], 68.63 ($C_{tert}$, PhC3$'$H), 61.45–61.35 (2C, 2O$CH_2CH_3$), 50.54 (2C, 2C$^{1'}$H$_2$, pip), 26.38 (2C, 2C$^{2'}$H$_2$, pip), 24.27 (C, C$^{3'}$H$_2$, pip), 14.25–13.72 (2C, 2OCH$_2$C$H_3$); SM (IE): Calc. $[M]^+$ $C_{20}H_{26}NO_4F_3$: 401.41. Found $[M+H]^{+\cdot}$ ($m/z$) = 402; $[M-CH(CO_2Et)_2]^+$ ($m/z$) = 242 (100%); Element. analysis: Calc. $C_{20}H_{26}NO_4F_3$: %C = 59.84; %H = 6.53; %N = 3.49. Found: %C = 59.82; %H = 6.51; %N = 3.47.

*4.3.20. 2-[(4-Trifloromethyl-phenyl)-morpholin-methyl]-malonic acid diethyl ester (**30**)*

White crystals; Yield: 96%; $R_f$ = 0.67 (ether/hexane: 1/1); mp: 103 °C; IR (KBr, $\nu$ $cm^{-1}$): 2870–2934 (CH), 1730 (C=O), 1491–1593 (C=C), 1291–1304 (C–O), 1181; 1014; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 1.33 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz), 1.01 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz), 3.54–3.66 (m, 4H, C$^{2'}$H$_2$, mor), 2.29 (s large, 2H, C$^{1'}$H$_2$, mor), 2.53 (s large, 2H, C$^{1'}$H$_2$, mor), 4.0 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $^2J_{AB}$ = 14.06 Hz, $^3J$ = 7.01 Hz), 4.33 (dq, 2H, OC$H_2$CH$_3$, $^2J_{AB}$ = 14.06 Hz, $^3J$ = 7.01 Hz), 4.25 (d, 1H, C$^2$H(CO$_2$Et)$_2$, $^3J$ = 12.13 Hz), 4.42 (d, 1H, PhC$^3$H, $^3J$ = 12.13 Hz), 7.64 (d, 2H$_{ortho}$, $^3J$ = 8.1 Hz), 7.28 (d, 2H$_{meta}$, $^3J$ = 8.1 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.62–167.42 (2C=O), 130.40 ($C_{quat}$, Ph), 137.51 ($C_{quat}$, CCF$_3$Ph), 125.08 (2$C_{tert}$, meta-arom), 129.96 ($C_{tert}$, ortho-arom), 54.49 ($C_{tert}$, PhC$^2$H(CO$_2$Et)$_2$), 68.11 ($C_{tert}$, PhC3$'$H), 61.62–61.54 (2C, 2O$CH_2CH_3$), 49.52 ($C_{sec}$, 2C$^{1'}$H$_2$, mor), 67.12 ($C_{sec}$, 2C$^{2'}$H$_2$, mor), 14.30–13.17 ($C_{tert}$, 2OCH$_2$C$H_3$); SM (IE): Calc. $[M]^+$ $C_{19}H_{24}NO_5F_3$: 403.39. Found $[M+H]^+$ ($m/z$) = 404; $[M-CH(CO_2Et)_2]^+$ ($m/z$) = 244 (100%); Element. analysis: Calc. $C_{19}H_{24}NO_5F_3$: %C = 56.57; %H = 6.00; %N = 3.47. Found: %C = 56.54; %H = 5.97; %N = 3.45.

*4.3.21. 2-[(4-Trifloromethyl-phenyl)-dibenzyl-methyl]-malonic acid diethyl ester (**31**)*

White crystals; Yield: 96%; $R_f$ = 0.67 (ether/hexane: 1/1); mp: 104 °C; IR (KBr, $\nu$ $cm^{-1}$): 2841–2902 (CH), 1731 (2C=O), 1585–1618 (C=C), 1257–1306 (C–O), 1164; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.25–7.72 (m, 4H, arom, Ph–$CF_3$, $^3J$ = 8.1 Hz), 7.35 (m, 10H, arom, Ph, $^3J$ = 6 Hz), 4.63 (d, 1H, $CF_3$PhC$^3H$, $^3J$ = 12 Hz), 4.4 (d, 1H, –C$^2H$(CO$_2$Et)$_2$, $^3J$ = 12 Hz), 3.0 (d, 1H, 2C$H$–Ph, $^3J$ = 13.50 Hz), 3.9 (d, 1H, 2C$H$Ph, $^3J$ = 13.62 Hz), 4.0 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $J_{AB}$ = 14.28 Hz, $^3J$ = 7.15 Hz), 4.20–4.40 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $J_{AB}$ = 14.28 Hz, $^3J$ = 7.15 Hz), 1.28 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.11 Hz), 1.0 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.11 Hz); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.66–167.14 (2C=O), 138.53 ($C_{quat}$, $C$–$CF_3$–Ph), 138.09 ($C_{quat}$, Ph, para/$CF_3$), 128.17–125.01 ($C_{tert}$, arom), 130.22–129.43 ($C_{quat}$, 2$C$/arom, 2Ph), 61.78–61.37 ($C_{sec}$, 2OC$H_2$CH$_3$), 61.28 ($C_{tert}$, $C^3$HPhCF$_3$), 55.11 ($C_{tert}$, $C^2$H(CO$_2$Et)$_2$), 53.15–53.94 ($C_{sec}$, 2$C$H$_2$–Ph), 13.67 ($C_{tert}$, OCH$_2$$C$H$_3$), 13.91 ($C_{tert}$, OCH$_2$$C$H$_3$); SM (IE): Calc. $[M]^+$ $C_{19}H_{24}N_1O_5F_3$: 513.54. Found $[M+H]^+$ ($m/z$) = 514; $[M-CH(CO_2Et)_2]^+$ ($m/z$) = 354 (100%); Element. analysis: Calc. $C_{19}H_{24}N_1O_5F_3$: %C = 67.82; %H = 5.89; %N = 2.73. Found: %C = 67.79; %H = 5.87; %N = 2.72.

*4.3.22. 2-[(3,5-Dimethyl-pyrazol-1-yl)-4-methylphenyl-methyl]-malonic acid diethyl (**32**)*

White crystals; Yield: 74%; $R_f$ = 0.45 (ether/hexane: 1/1); mp: 88 °C; IR (KBr, $\nu$ $cm^{-1}$): 2872–2926 (C–H), 1752 (C=O), 1514–1594 (C=C), 1263–1305 (C–O), 1148, 1027; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.08 (d, 2H$_{ortho}$, $^3J$ = 7.88 Hz), 7.32 (d, 2H$_{meta}$, $^3J$ = 8.80 Hz), 5.72 (s, 1H, C$^{4'}$, Pz), 5.75 (d, 1H, Ph–C$^3H$, $^3J$ = 11.31 Hz), 4.89 (d, 1H, C$^2H$–(CO$_2$Et)$_2$, $^3J$ = 11.31 Hz), 4.14 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $^2J_{AB}$ = 14.37 Hz, $^3J$ = 7.2 Hz), 3.97 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $^2J_{AB}$ = 14.37 Hz, $^3J$ = 7.2 Hz), 2.24 (s, 3H, C$H_3$, Pz), 2.19 (s, 3H, C$H_3$, Pz), 1.13 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz), 0.98 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz), 2.29 (s, 3H, C$H_3$Ph); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.94 (2$C$=O), 137.9 ($C_{quat}$, Pz), 144 ($C_{quat}$, Pz), 132 ($C_{quat}$, $C$CH$_3$, Ph), 130.05 ($C_{quat}$, para-CH$_3$–Ph), 129.0 ($C_{tert}$, 2$C_{meta}$, Ph), 127.77 ($C_{tert}$, 2$C_{ortho}$, Ph), 105.20 ($C_{tert}$, $C^{4'}$H, Pz), 61.55 ($C_{sec}$, 2O$CH_2$CH$_3$), 60.05 ($C_{tert}$, C$^3$H–Ph), 57.55 ($C_{tert}$, $C^2$H–(CO$_2$Et)$_2$), 13.8–13.70 (2$C_{sec}$, 2OCH$_2$$C$H$_3$), 21.09 ($C_{tert}$, CH$_3$–Ph), 10.97–12.20 ($C_{tert}$, 2$C$H$_3$, Pz); SM (IE): Calc. $[M]^+$ $C_{20}H_{26}N_2O_4$ = 358.43. Found $[M+H]^{+\cdot}$ ($m/z$) = 359; $[(M)-CH(CO_2Et)_2]^{+\cdot}$ ($m/z$) = 199 (100%); Element. analysis: Calc. $C_{20}H_{26}N_2O_4$: %C = 67.02; %H = 7.31; %N = 7.82. Found: %C = 66.97; %H = 7.32; %N = 7.82.

*4.3.23. 2-[(4-Methyl-phenyl)-piperidim-methyl]-malonic acid diethyl (**33**)*

White crystals; Yield: 67%; $R_f$ = 0.67 (ether/hexane: 1/1); mp: 91 °C; IR (KBr, $\nu$ $cm^{-1}$): 2873–2935 (CH), 1734 (C=O), 1493–1592 (C=C), 1289–1301 (C–O), 1180, 1013; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 1.32 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz), 1.29 (t, 3H, OCH$_2$C$H_3$, $^3J$ = 7.2 Hz), 1.26 (m, 2H, C$^{3'}$H$_2$, pip), 1.49 (m, 4H, 2C$^{2'}$$H_2$, pip), 2.18 (s, 2H, C$^{1'}$$H_2$, pip), 2.5 (s, 2H, C$^{1'}$H$_2$, pip), 4.1 (dq, 2H$_{AB}$, OC$H_2$CH$_3$, $^2J_{AB}$ = 9.74 Hz, $^3J$ = 7.08 Hz), 4.30 (dq, 2H, OC$H_2$CH$_3$, $^2J_{AB}$ = 9.74 Hz, $^3J$ = 7.08 Hz), 4.22 (d, 1H, C$^2H$(CO$_2$Et)$_2$, $^3J$ = 12.13 Hz), 4.35 (d, 1H, Ph–C$^3H$, $^3J$ = 12.13 Hz), 7.03 (d, 2H$_{ortho}$, $^3J$ = 8.82 Hz), 7.06 (d, 2H$_{meta}$, $^3J$ = 8.82 Hz), 2.25 (s, 3H, C$H_3$–Ph); $^{13}$C NMR (3000 MHz, $CDCl_3$) $\delta$ ppm: 167.20–168.08 (2C=O), 130.91 ($C_{quat}$, Ph), 137.05 ($C_{quat}$, CCH$_3$, Ph), 128.58 (2$C_{tert}$, meta, Ph), 58.50 ($C_{tert}$, ortho, Ph), 55.07 ($C_{tert}$, PhC$^2$H(CO$_2$Et)$_2$), 68.81 ($C_{tert}$, PhC3$'$H), 61.23–61.09 (2C, 2OCH$_2$CH$_3$), 50.53 (C, 2C$^{1'}$H$_2$, pip), 26.46 (2C,

$2C^{2'}H_2$, pip), 24.27 (C, $C^{3'}H_2$, pip), 14.28–13.77 (2C, $2OCH_2CH_3$); SM (IE): Calc. $[M]^+$ $C_{20}H_{29}N_1O_4$: 347.44. Found: $[M+H]^{+\cdot}$ ($m/z$) = 348; $[M-CH(CO_2Et)_2]^{+\cdot}$ ($m/z$) = 188 (100%); Element. analysis: Calc. $C_{20}H_{29}N_1O_4$: %C = 69.14; %H = 8.41; %N = 4.03. Found: %C = 69.05; %H = 8.39; %N = 4.01.

*4.3.24. 2-[(3,5-Dimethyl-pyrazol-1-yl)-4-methoxylphenyl-methyl]-malonic acid diethyl (**34**)*

White crystals; Yield: 85%; $R_f$ = 0.63 (ether/hexane: 1/1); mp: 89 °C; IR (KBr, $\nu$ $cm^{-1}$): 2834–2987 (C–H), 1732 (C=O), 1534–15345 (C=C), 1223–1317 (C–O), 1148, 1027; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.12 (d, $2H_{ortho}$, $^3J$ = 7.88 Hz), 7.26 (d, $2H_{meta}$, $^3J$ = 8.76 Hz), 5.67 (s, 1H, $C^{4'}$, Pz), 5.78 (d, 1H, Ph–$C^3H$, $^3J$ = 11.32 Hz), 4.82 (d, 1H, $C^2H$–$(CO_2Et)_2$, $^3J$ = 11.32 Hz), 4.18 (dq, $2H_{AB}$, $OCH_2CH_3$, $^2J_{AB}$ = 14.29 Hz, $^3J$ = 7.1 Hz), 3.98 (dq, $2H_{AB}$, $OCH_2CH_3$, $^2J_{AB}$ = 14.32 Hz, $^3J$ = 7.1 Hz), 2.24 (s, 3H, $CH_3$, Pz), 2.19 (s, 3H, $CH_3$, Pz), 1.12 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.1 Hz), 1.03 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.1 Hz), 2.22 (s, 3H, $CH_3$Ph); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 166.65 (2C=O), 137.9 ($C_{quat}$, Pz), 144 ($C_{quat}$, Pz), 136 ($C_{quat}$, $COCH_3$, Ph), 130.05 ($C_{quat}$, $pOCH_3$–Ph), 129.12 ($C_{tert}$, $2C_{meta}$, Ph), 127.73 ($C_{tert}$, $2C_{ortho}$, Ph), 105.20 ($C_{tert}$, $C^{4'}H$, Pz), 61.55 ($C_{sec}$, $2OCH_2CH_3$), 60.02 ($C_{tert}$, $C^3H$–Ph), 57.48 ($C_{tert}$, $C^2H$–$(CO_2Et)_2$), 13.8–13.70 ($2C_{sec}$, $2OCH_2CH_3$), 21.09 ($C_{tert}$, $CH_3$–Ph), 11.23–12.13 ($C_{tert}$, $2CH_3$, Pz).

*4.3.25. 2-[(3,5-Dimethyl-pyrazol-1-yl)-4-methoxylphenyl-methyl]-malonic acid diethyl (**35**)*

White crystals; Yield: 81%; $R_f$ = 0.65 (ether/hexane: 1/1); mp: 92 °C; IR (KBr, $\nu$ $cm^{-1}$): 2823–2898 (C–H), 1752 (C=O), 1534–1554 (C=C), 1254–1319 (C–O), 1148, 1027; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 7.17 (d, $2H_{ortho}$, $^3J$ = 7.67 Hz), 7.28 (d, $2H_{meta}$, $^3J$ = 8.67 Hz), 5.68 (s, 1H, $C^{4'}$, Pz), 5.74 (d, 1H, Ph–$C^3H$, $^3J$ = 11.3 Hz), 4.83 (d, 1H, $C^2H$–$(CO_2Et)_2$, $^3J$ = 11.3 Hz), 4.12 (dq, $2H_{AB}$, $OCH_2CH_3$, $^2J_{AB}$ = 14.28 Hz, $^3J$ = 7.2 Hz), 3.97 (dq, $2H_{AB}$, $OCH_2CH_3$, $^2J_{AB}$ = 14.28 Hz, $^3J$ = 7.2 Hz), 2.24 (s, 3H, $CH_3$, Pz), 2.19 (s, 3H, $CH_3$, Pz), 1.13 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.2 Hz), 1.00 (t, 3H, $OCH_2CH_3$, $^3J$ = 7.2 Hz), 2.29 (s, 3H, $CH_3$Ph); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ ppm: 167.13 (2C=O), 137.9 ($C_{quat}$, Pz), 144 ($C_{quat}$, Pz), 130.05 ($C_{quat}$, para-$NO_2$–Ph), 129.01 ($C_{tert}$, $2C_{meta}$, Ph), 127.77 ($C_{tert}$, $2C_{ortho}$, Ph), 105.20 ($C_{tert}$, $C^{4'}H$, Pz), 61.55 ($C_{sec}$, $2OCH_2CH_3$), 60.05 ($C_{tert}$, $C^3H$–Ph), 57.55 ($C_{tert}$, $C^2H$–$(CO_2Et)_2$), 13.8–13.70 ($2C_{sec}$, $2OCH_2CH_3$), 21.09 ($C_{tert}$, $CH_3$–Ph), 10.97–12.20 ($C_{tert}$, $2CH_3$, Pz).

*4.3.26. Synthesis of complex $[Cu_2(CH_3COO^-)4(H_2O)_2]$ (**36**)*

The KOH (0.058 g; 1.05 mmol) was added to a solution of 2-[(4-chlorophenyl)-3,5-dimethyl-pyrazol-1-yl-methyl]-malonic acid diethyl (**25**) (0.2 g; 0.52 mmol) in ethanol (15 mL) and the stirring was continued under reflux in ethanol (4 h), until the complete saponification of the starting material. After addition of $Cu(NO_3)\cdot 3H_2O$, the color changed from blue to purple. The stirring was further continued for additional 6 h. The organic solvent was evaporated slowly over a period of 2 days to give a pure paramagnetic compound as purple crystals (**36**). Purple crystals; Yield: 55%; Decomposition > 260 °C; IR (KBr, $\nu$ $cm^{-1}$): 2934–2988 (CH), 1595 (C=O), 1416 (C=O), 3269–3466 (OH, $H_2O$), 1354, 1092, 830. The ORTEP view of (**36**) is given in Fig. 3.

## 5. Conclusion

In spite of having prolonged reaction time, this aza-Michael addition protocol led to higher yields in an aqueous medium at room temperature, and consequently, would appear to be a simple and useful synthetic protocol. Considering its high efficiency to run at gram-scale level and especially high purity of the final products, this protocol is thus of great usefulness for the synthesis of potentially new drug candidates. The X-ray crystal structures of (**17**) and (**24**) were studied first time and found in complete agreement with the proposed one than in solution.

## 6. Supplementary data

Supplementary crystallographic data for the reported compounds (**17**) and (**24**) are available from the CCDC, 12 Union-Road, Cambridge CB2 1EZ, UK on request, quoting the deposition number CCDC 734201 and CCDC 734199.

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