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Studies toward the construction of substituted piperidine-2-ones and pyridine-2-ones from Baylis–Hillman adducts: discovery of a facile synthesis of 5-methyl-4-oxo-6-aryl-3-aza-bicyclo[3.1.0]hexane-1-carboxylates☆

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Abstract—Studies toward the construction of functionalized piperidone derivatives from derivatives of Baylis–Hillman adducts are described. Interestingly the 6-oxo-4-aryl-piperidine-3-carboxylates generated during the study serve as precursor for the facile synthesis of 4-oxo-6-aryl-3-aza-bicyclo[3.1.0]hexane-1-carboxylates.

1. Introduction

The multifunctional nature of the backbone of Baylis–Hillman adducts provides an excellent opportunity to generate a variety of heterocycles employing simple synthetic manipulations. Notably, the last decade has witnessed an extraordinary growth in the number of reports describing different approaches to achieve the syntheses of an array of cyclic compounds using Baylis–Hillman chemistry.[1] Recently, we too have reported the synthesis of a variety of heterocycles in solution and on solid phase utilizing Baylis–Hillman chemistry.[2] In our continuing efforts aimed at this objective, we describe herein the results of our studies toward the synthesis of substituted piperidine-2-ones and pyridine-2-ones from the nucleophilic substitution reaction products afforded by the reaction between the acetyl derivatives of Baylis–Hillman adducts and ethyl cyanoacetate. We have discovered that the substituted piperidine-2-one generated during the endeavor may serve as precursor for the efficient synthesis of 5-methyl-4-oxo-6-aryl-3-aza-bicyclo[3.1.0]-hexane-1-carboxylates.

The piperidine ring system is a structural component of numerous naturally occurring alkaloids, biologically active synthetic molecules, and organic chemicals. The syntheses of piperidones and piperidines have been exhaustively reviewed recently by Sabol and co-workers.[3] We envisaged the synthesis of piperidine-2-ones from the nucleophilic addition products afforded by reactions between acetates of the Baylis–Hillman adducts and ethyl cyanoacetate by reduction of the cyano group and subsequent intramolecular cyclization between the amino group and the ester moiety. On the other hand, the conversion of the cyano group to an amide in the same substrate should lead to 3-methylene-piperidine-2,6-diones (Fig. 1). The substituted piperidine-2,6-diones are structural component of several natural products and biologically active molecules.[4]

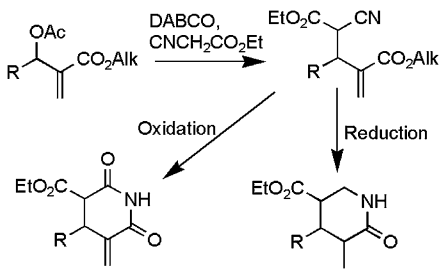

Figure 1. Strategy for the synthesis of substituted piperidine-2-ones and piperidine-2,6-diones.

2. Results and discussion

The preparation of the starting materials in our synthetic sequence (Scheme 1, acetates **3a**–**g**) was accomplished by

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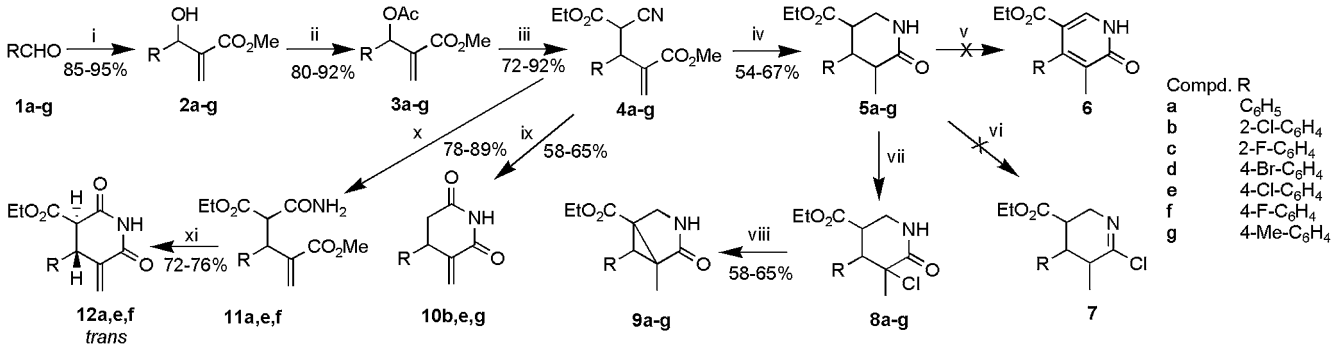

Scheme 1. Reagents and conditions: (i) $CH_2{=}CHCO_2Me$, DABCO, rt, 2–5 days; (ii) AcCl, pyridine, CH_2Cl_2, rt, 4–6 h; (iii) $CNCH_2CO_2Et$, DABCO, THF:H_2O, rt, 2 h; (iv) Raney-Ni, H_2, 40 psi, rt, 3 h; (v) DDQ, dioxane, reflux, 24 h; (vi) $POCl_3$, neat, reflux, 24 h; (vii) PCl_5, $POCl_3$, reflux, 2 h; (viii) DBU, CH_3CN, reflux, 14 h; (ix) $FeCl_3{\cdot}6H_2O$, propionic acid, reflux, 2 h; (x) TFA:H_2SO_4, neat, rt, 3 h; (xi) NaH, toluene, rt, 30 min.

acetylating the Baylis–Hillman adducts **2a**–**g**, which in turn were obtained from substituted benzaldehydes (**1a**–**g**) following the literature procedure.[5] The nucleophilic substitution of the acetates **3a**–**g** with ethyl cyanoacetate in the presence of DABCO in a THF:water system following a standard procedure yielded the substituted 1,5-dipentanoate derivatives **4a**–**g** as diastereoisomeric mixture in excellent yields.[2a] As would be expected, the reduction of these compounds in the presence of Raney-nickel under hydrogenation conditions yielded 5-methyl-6-oxo-4-aryl-piperidine-3-carboxylic acid ethyl esters **5a**–**g** in 54–67% yields. These compounds were obtained as mixtures of diastereoisomers. In principle, oxidation of these piperidinones with a suitable reagent should furnish pyridine-2-one derivatives **6**. Accordingly, the aromatization of these compounds was investigated in the presence of DDQ.[6] However, in our hands, the desired oxidation did not take place and only the starting material was recovered.

At this point, we envisaged that if compound **5** was converted to its chloro-derivative **7** with $POCl_3$ it would easily afford the desired pyridinone through oxidation.[7] Unfortunately, chlorination in the presence of $POCl_3$ under several conditions failed to afford the chloro-derivative **7**. Subsequently, the chlorination of compound **5** was attempted with a mixture of PCl_5 and $POCl_3$. Interestingly, this reaction yielded a less polar product **8**, the structure of which was established on the basis of spectroscopic analysis. The general nature of halogenation was confirmed by the synthesis of compounds **8a**–**g**. In principle, the tertiary nature of the chloro-group in compound **8** should make it an appropriate substrate for dehydrohalogenation followed by oxidation. In order to achieve the envisaged product, several reactions were attempted. It was gratifying to note that compounds **8a**–**g** undergo reaction in the presence of DBU to furnish products in good yields. On the basis of spectroscopic evidence the structure of these compounds was identified as 5-methyl-4-oxo-6-aryl-3-aza-bicyclo[3.1.0]hexane-1-carboxylates **9a**–**g**. The structure of these products was ascertained unambiguously via X-ray analysis of a representative compound **9e** (Fig. 2).[8] The formation of these products could be explained on the basis of the fact that the hydrogen atom on the carbon bearing the alkoxycarbonyl group being more acidic participates in the elimination of the chloride ion.

In a different strategy it was envisaged that the conversion of the cyano group to an amide would lead to an intermediate, which should undergo intramolecular cyclization resulting in 3-methylene-piperidine-2,6-dione. Recently Wang et al. have described an interesting $FeCl_3$-mediated highly efficient synthesis of 1,2-dihydro-2-oxo-3-pyridine-carboxylate

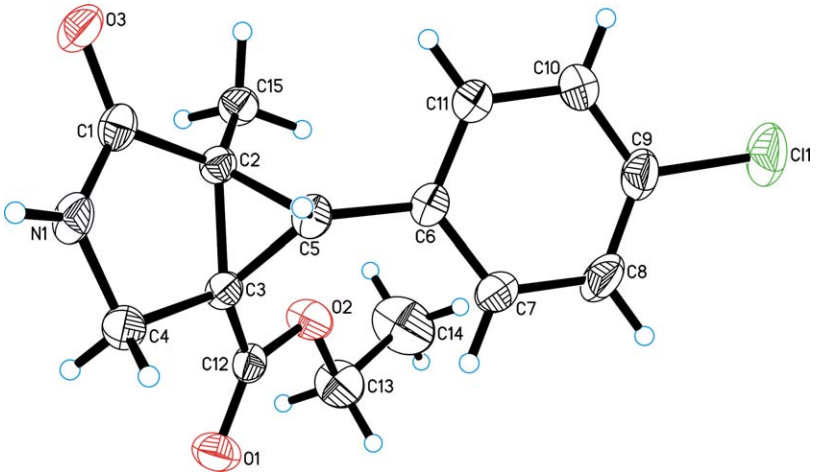

Figure 2. ORTEP diagram showing the crystal structure of **9e** with atomic numbering scheme for non-H atoms only at 30% probability level.

starting from enones and ethyl cyanoacetate.[9] Following their strategy, treatment of compounds **4b**,**e**,**g** with 3 equiv of $FeCl_3 \cdot 6H_2O$ in propionic acid at reflux for 2 h afforded 3-methylene-4-substituted phenyl-piperidine-2,6-diones **10b**,**e**,**g** in 60–65% yields. However, in contrast to their results, we observed that the carboxylate group was lost during the reaction and dehydrogenation did not occurred. In order to investigate the scope of our substrates for the generation of the carboxylate group containing piperidine-2,6-dione derivative, **4a**,**e**,**f** were hydrolyzed in the presence of TFA:H_2SO_4 mixture to afford the products **11a**,**e**,**f** in good yields. Subsequent treatment of the amides **11a**,**e**,**f** with NaH at room temperature furnished the desired 5-methylene-2,6-dioxo-4-phenyl-piperidine-3-carboxylic acid ethyl esters **12a**,**e**,**f** in good yields. Interestingly, the formation of compounds **12a**,**e**,**f** was highly stereoselective in favor of the *trans*-isomer. The stereochemistry was assigned on the basis of selective 1D NOESY experiment with compound **12a**. During the progress of this work, Kim et al. reported the synthesis of 3,5-dimethylene-4-phenyl-piperidine-2,6-dione and mono-alkylidene glutarimide by hydrolysis of the cyano group with sulfuric acid in methanol followed by cyclization in the presence of sodium bicarbonate.[10] However, in our hand, the sodium bicarbonate-mediated cyclization of substrates **11a**,**e**,**f** led to a complex mixture of product from which the corresponding 3-methylene-piperidine-2,6-diones **12a**,**e**,**f** were isolated in only low yields.

3. Conclusions

In summary, we have demonstrated a convenient and general process for the synthesis of 5-methyl-4-oxo-6-aryl-3-aza-bicyclo[3.1.0]hexane-1-carboxylates via products afforded by the nucleophilic addition reaction of ethyl cyanoacetate with acetyl derivatives of the Baylis–Hillman adducts. Additionally these products have been readily hydrolyzed and subsequently cyclized to yield new substituted piperidine-2,6-diones in good yields.

4. Experimental

4.1. General

Melting points were uncorrected and determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using a Perkin–Elmer RX I FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on either 300 or 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts in δ values, J in hertz). The FABMS were recorded on a JEOL/SX-102 spectrometer and ESMS were recorded in a Micromass LCMS system. Elemental analyses as performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL *III* microanalyzer. All compounds were obtained in the powder form unless otherwise stated.

4.2. General procedure for the synthesis of compounds 4a–c, as exemplified for compound 4a

To a stirred solution of compound **3a** (2.0 g, 8.5 mmol) in THF:H_2O (20 mL, 50:50, v/v) was added DABCO (1.5 g, 12.8 mmol) at room temperature and the reaction was allowed to continue for 20 min. Thereafter, ethyl cyanoacetate (1.1 mL, 10.3 mmol) was added to the reaction mixture and the reaction was allowed to proceed at room temperature for 2 h. Then THF was removed from the reaction mixture via rotary evaporation and the residue was diluted with water (100 mL) and extracted with EtOAc (3×40 mL). The organic layers were pooled, washed with brine (50 mL), dried (Na_2SO_4), and evaporated in vacuo to yield a residue, which was purified by silica gel chromatography employing hexane:EtOAc (80:20, v/v) to afford 2.0 g (82%) of product **4a** as colorless oil.

4.2.1. 2-Cyano-4-methylene-3-phenyl-pentanedioic acid-1-ethyl ester-5-methyl ester (4a). ν_{max} (neat) 1747 (CO_2Me and CO_2Et), 2255 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.15 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.33 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.71 (s, 3H, CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 4.10–4.30 (m, 6H, 2×CH_2CH_3 and 2×CHAr), 4.45 (d, 1H, J=8.2 Hz, CHCN), 4.64 (d, 1H, J=8.2 Hz, CHCN), 5.75 (d, 1H, J=1.2 Hz, =CH), 5.99 (d, 1H, J=0.9 Hz, =CH), 6.49 (s, 1H, =CH), 6.51 (s, 1H, =CH), 7.29–7.37 (m, 10H, 2×5ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=14.2, 14.3, 42.3, 42.6, 47.0, 47.6, 52.6, 52.7, 61.8, 63.3, 113.5, 116.0, 127.7, 128.5, 128.6, 128.9, 129.2, 136.9, 137.4, 139.0, 139.3, 163.4, 165.2, 166.4, 166.5; mass (FAB+) m/z 288 (M^++1); Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.08; H, 5.76; N, 4.98.

4.2.2. 3-(2-Chloro-phenyl)-2-cyano-4-methylene-pentanedioic acid-1-ethyl ester-5-methyl ester (4b). Yield 84% (2.3 g from 2.3 g) as a colorless oil; ν_{max} (neat) 1746 (CO_2Me and CO_2Et), 2253 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.13 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.24 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.69 (s, 3H, CO_2CH_3), 3.80 (s, 3H, CO_2CH_3), 4.13–4.25 (m, 4H, 2×CH_2CH_3), 4.33 (d, 1H, J=7.2 Hz, CHAr), 4.61 (d, 1H, J=7.2 Hz, CHAr), 5.08–5.02 (m, 2H, 2×CHCN), 5.61 (d, 1H, J=0.9 Hz, =CH), 6.15 (s, 1H, =CH), 5.50 (s, 1H, =CH), 6.60 (s, 1H, =CH), 7.28–7.63 (m, 8H, 2×4ArH); mass (ES+) m/z 322.0 (M^++1); Anal. Calcd for $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; N, 4.35. Found: C, 59.79; H, 4.87; N, 4.51.

4.2.3. 2-Cyano-3-(2-fluoro-phenyl)-4-methylene-pentanedioic acid-1-ethyl ester-5-methyl ester (4c). Yield 92% (1.1 g from 1.0 g) as a pale yellow oil; ν_{max} (neat) 1744 (CO_2Me and CO_2Et), 2259 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.13–1.33 (m, 6H, 2×CH_3CH_2), 3.71 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 4.13–4.23 (m, 5H, 2×CH_2CH_3 and CHAr), 4.39 (d, 1H, J=7.3 Hz, CHAr), 4.93 (d, 2H, J=7.1 Hz, 2×CHCN), 5.75 (s, 1H, =CH), 6.00 (s, 1H, =CH), 6.50 (s, 1H, =CH), 6.58 (s, 1H, =CH), 7.11–7.30 (m, 6H, 2×3ArH), 7.53–7.56 (m, 2H, 2×1ArH); mass (ES+) m/z 306.1 (M^++1); Anal. Calcd for $C_{16}H_{16}FNO_4$: C, 62.94; H, 5.28; N, 4.59. Found: C, 63.01; H, 5.22; N, 4.58.

4.2.4. 3-(4-Bromo-phenyl)-2-cyano-4-methylene-pentanedioic acid-1-ethyl ester-5-methyl ester (4d). Yield 82% (2.2 g from 2.3 g) as a colorless oil; ν_{max} (neat) 1748 (CO_2Me and CO_2Et), 2254 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.18 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.32 (t, 3H,

J=7.1 Hz, CH_3CH$_2$), 3.71 (s, 3H, CO$_2$CH$_3$), 3.75 (s, 3H, CO$_2$CH$_3$), 4.13–4.41 (m, 6H, 2×CH_2CH$_3$ and 2×CHAr), 4.55–4.58 (m, 2H, 2×CHCN), 5.75 (s, 1H, =CH), 6.00 (s, 1H, =CH), 6.50 (s, 1H, =CH), 6.52 (s, 1H, =CH), 7.15–7.27 (m, 4H, 2×2ArH), 7.43–7.51 (m, 4H, 2×2ArH); mass (FAB+) m/z 366 (M$^+$+1); Anal. Calcd for $C_{16}H_{16}BrNO_4$: C, 52.48; H, 4.40; N, 3.82. Found: C, 52.63; H, 4.54; N, 3.77.

4.2.5. 3-(4-Chloro-phenyl)-2-cyano-4-methylene-pentanedioic acid-1-ethyl ester-5-methyl ester (4e). Yield 76% (1.8 g from 2.0 g) as a colorless oil; ν_{max} (neat) 1747 (CO$_2$Me and CO$_2$Et), 2255 (CN) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=1.18 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.33 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 3.71 (s, 3H, CO$_2$CH$_3$), 3.75 (s, 3H, CO$_2$CH$_3$), 4.09–4.30 (m, 5H, 2×CH_2CH$_3$ and CHAr), 4.39 (d, 1H, J=7.3 Hz, CHAr), 4.56–4.63 (m, 2H, 2×CHCN), 5.76 (d, 1H, J=1.1 Hz, =CH), 6.00 (s, 1H, =CH), 6.50 (s, 1H, =CH), 6.52 (s, 1H, =CH), 7.25–7.32 (m, 8H, 2×4ArH); mass (ES+) m/z 344 (M$^+$+Na); Anal. Calcd for $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; N, 4.35. Found: C, 59.89; H, 4.78; N, 4.31.

4.2.6. 2-Cyano-3-(4-fluoro-phenyl)-4-methylene-pentanedioic acid-1-ethyl ester-5-methyl ester (4f). Yield 72% (1.3 g from 1.5 g) as a colorless oil; ν_{max} (neat) 1746 (CO$_2$Me and CO$_2$Et), 2254 (CN) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=1.16 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.33 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 3.71 (s, 3H, CO$_2$CH$_3$), 3.76 (s, 3H, CO$_2$CH$_3$), 4.12–4.22 (m, 4H, 2×CH_2CH$_3$), 4.28 (d, 1H, J=7.1 Hz, CHAr), 4.39 (d, 1H, J=7.3 Hz, CHAr), 4.58–4.60 (m, 2H, 2×CHCN), 5.75 (s, 1H, =CH), 6.00 (s, 1H, =CH), 6.49 (s, 1H, =CH), 6.51 (s, 1H, =CH), 7.00–7.09 (m, 4H, 2×2ArH), 7.23–7.39 (m, 4H, 2×2ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ=14.2, 14.3, 42.3, 42.6, 46.3, 47.1, 52.7, 52.8, 63.4, 116.0, 116.4, 127.7, 128.7, 130.2, 130.4, 130.6, 130.8, 132.6, 133.1, 138.8, 139.2, 165.0, 165.3, 166.3, 166.4; mass (ES+) m/z 306.2 (M$^+$+1); Anal. Calcd for $C_{16}H_{16}FNO_4$: C, 62.94; H, 5.28; N, 4.59. Found: C, 63.11; H, 5.41; N, 4.67.

4.2.7. 2-Cyano-4-methylene-3-*p*-tolyl-pentanedioic acid-1-ethyl ester-5-methyl ester (4g). Yield 78% (1.89 g from 2.0 g) as a colorless oil; ν_{max} (neat) 1742 (CO$_2$Me and CO$_2$Et), 2256 (CN) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=1.16 (t, 3H, J=7.2 Hz, CH_3CH$_2$), 1.29 (t, 3H, J=7.2 Hz, CH_3CH$_2$), 2.31 (s, 3H, ArCH$_3$), 2.32 (s, 3H, ArCH$_3$), 3.71 (s, 3H, CO$_2$CH$_3$), 3.75 (s, 3H, CO$_2$CH$_3$), 4.11–4.22 (m, 5H, 2×CH_2CH$_3$ and CHAr), 4.40 (d, 1H, J=7.6 Hz, CHAr), 4.57–4.61 (m, 2H, 2×CHCN), 5.75 (d, 1H, J=1.0 Hz, =CH), 5.97 (s, 1H, =CH), 6.47 (s, 1H, =CH), 6.49 (s, 1H, =CH), 7.09–7.23 (m, 8H, 2×4ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ=14.2, 14.5, 21.5, 42.4, 42.7, 46.7, 47.4, 52.6, 52.7, 61.9, 63.3, 116.1, 127.4, 128.3, 128.8, 129.9, 133.7, 134.3, 138.3, 139.1, 139.4, 165.3, 166.5, 166.6; mass (ES+) m/z 302.1 (M$^+$+1); Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.49; H, 6.51; N, 4.67.

4.3. General procedure for the synthesis of compounds 5a–g, as exemplified for compound 5a

A mixture of compound **4a** (1.2 g, 4.18 mmol) and Raney-Ni (0.3 g, wet) in MeOH (20 mL) was hydrogenated at 40 psi in the hydrogenation assembly (Parr) at room temperature. After completion, the catalyst was filtered over a bed of Celite and the filtrate was evaporated in vacuo to yield the crude product. Purification via silica gel column chromatography (hexane:EtOAc, 40:60, v/v) gave 0.65 g (60%) of product **5a** as a white solid.

4.3.1. 5-Methyl-6-oxo-4-phenyl-piperidine-3-carboxylic acid ethyl ester (5a). Mp 102–104 °C; ν_{max} (KBr) 1661 (CONH), 1730 (CO$_2$Et), 3402 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=0.86 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.00–1.18 (m, 9H, CH_3CH$_2$ and 2×CH_3CH), 2.43–2.61 (m, 1H, CHCH$_3$), 2.71–2.78 (m, 1H, CHCH$_3$), 2.81–3.00 (m, 1H, CHCH$_2$), 3.07–3.22 (m, 1H, CHCH$_2$), 3.31–3.64 (m, 6H, 2×CH_2NH and 2×CHAr), 3.83 (q, 2H, J=7.1 Hz, CH_2CH$_3$), 4.08 (q, 2H, J=7.1 Hz, CH_2CH$_3$), 6.27 (s, 2H, 2×NH), 7.17–7.36 (m, 10H, 2×5ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ=13.6, 14.0, 14.4, 15.2, 38.9, 42.2, 42.5, 43.9, 44.0, 45.7, 47.4, 50.2, 61.0, 61.5, 127.04, 127.7, 128.3, 128.6, 129.0, 140.4, 140.9, 172.2, 172.7, 175.2, 176.4; mass (ES+) m/z 262.1 (M$^+$+1); Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.08; H, 7.55; N, 5.57.

4.3.2. 4-(2-Chloro-phenyl)-5-methyl-6-oxo-piperidine-3-carboxylic acid ethyl ester (5b). Yield 67% (0.98 g from 1.6 g) as a pale yellow oil; ν_{max} (neat) 1667 (CONH), 1731 (CO$_2$Et), 3222 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=0.93 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.01–1.18 (m, 9H, CH_3CH$_2$ and 2×CH_3CH), 2.80–2.98 (m, 1H, CHCH$_3$), 3.17–3.20 (m, 2H, CHCH$_3$ and CHCH$_2$), 3.59–3.60 (m, 1H, CHCH$_2$), 3.63–3.66 (m, 4H, 2×CH_2NH), 3.87–3.92 (m, 2H, 2×CHAr), 4.09–4.24 (m, 4H, 2×CH_2CH$_3$), 6.19 (s, 2H, 2×NH), 7.14–7.21 (m, 6H, 2×3ArH), 7.32–7.42 (m, 2H, 2×1ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ=13.7, 14.0, 14.3, 14.6, 37.2, 37.6, 41.5, 41.8, 42.6, 42.8, 43.4, 43.5, 61.2, 61.6, 127.1, 127.7, 128.6, 129.0, 130.2, 130.4, 134.7, 135.0, 137.4, 138.8, 171.7, 172.3, 174.9, 176.0; mass (FAB+) m/z 296 (M$^+$+1); Anal. Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; N, 4.74. Found: 60.82; H, 5.94; N, 4.89.

4.3.3. 4-(2-Fluoro-phenyl)-5-methyl-6-oxo-piperidine-3-carboxylic acid ethyl ester (5c). Yield 57% (0.47 g from 0.9 g) as a colorless oil; ν_{max} (neat) 1652 (CONH), 1723 (CO$_2$Et), 3436 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=0.90 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.02–1.29 (m, 9H, CH_3CH$_2$ and 2×CH_3CH), 2.62–2.93 (m, 2H, 2×CHCH$_3$), 3.24–3.26 (m, 2H, 2×CHCH$_2$), 3.58–3.61 (m, 4H, 2×CH_2NH), 3.87–3.91 (m, 2H, 2×CHAr), 4.06–4.13 (m, 4H, 2×CH_2CH$_3$), 6.37 (s, 2H, 2×NH), 7.00–7.22 (m, 8H, 2×4ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ=13.6, 14.0, 14.3, 15.2, 37.9, 38.5, 41.2, 42.8, 43.1, 43.9, 44.7, 45.8, 61.3, 61.5, 115.9, 116.4, 124.5, 124.7, 127.2, 127.5, 127.8, 128.0, 128.9, 129.2, 129.5, 130.1, 172.0, 172.4, 174.8, 176.0; mass (FAB+) m/z 280 (M$^+$+1); Anal. Calcd for $C_{15}H_{18}FNO_3$: C, 64.50; H, 6.50; N, 5.01. Found: C, 64.55; H, 6.41; N, 5.09.

4.3.4. 4-(4-Bromo-phenyl)-5-methyl-6-oxo-piperidine-3-carboxylic acid ethyl ester (5d). Yield 58% (0.7 g from 1.3 g) as a white solid, mp 126–128 °C; ν_{max} (KBr) 1667 (CONH), 1724 (CO$_2$Et), 3313 (NH) cm^{-1}; ^{1}H NMR

($CDCl_3$, 200 MHz) δ=0.93 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.00 (d, 3H, J=7.3 Hz, CH_3CH), 1.08 (d, 3H, J=6.9 Hz, CH_3CH), 1.17 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 2.38–2.60 (m, 1H, CHCH$_3$), 2.68–2.82 (m, 1H, CHCH$_3$), 2.75–3.10 (m, 2H, 2×CHCH$_2$), 3.45–3.68 (m, 6H, 2×CH_2NH and 2×CHAr), 3.85 (q, 2H, J=7.1 Hz, CH_2CH$_3$), 4.10 (q, 2H, J=7.2 Hz, CH_2CH$_3$), 6.21 (s, 2H, 2×NH), 7.07–7.10 (m, 4H, 2×2ArH), 7.44–7.54 (m, 4H, 2×2ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=13.6, 14.2, 14.4, 15.2, 38.8, 42.2, 42.4, 44.0, 44.1, 45.3, 47.2, 49.7, 61.2, 61.7, 121.4, 121.5, 130.0, 130.3, 132.2, 139.6, 140.0, 171.9, 172.4, 174.7, 176.0; mass (FAB+) m/z 340 (M^++1); Anal. Calcd for $C_{15}H_{18}BrNO_3$: C, 52.96; H, 5.33; N, 4.12. Found: C, 52.58; H, 5.49; N, 3.97.

4.3.5. 4-(4-Chloro-phenyl)-5-methyl-6-oxo-piperidine-3-carboxylic acid ethyl ester (5e). Yield 62% (0.45 g from 0.79 g) as a white solid, mp 118–120 °C; ν_{max} (KBr) 1665 (CONH), 1733 (CO_2Et), 3303 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=0.92 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.00 (d, 3H, J=7.2 Hz, CH_3CH), 1.08 (d, 3H, J=7.0 Hz, CH_3CH), 1.17 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 2.40–2.58 (m, 1H, CHCH$_3$), 2.66–2.78 (m, 1H, CHCH$_3$), 2.93–3.10 (m, 2H, 2×CHCH$_2$), 3.57–3.69 (m, 6H, 2×CH_2NH and 2×CHAr), 3.85 (q, 2H, J=7.1 Hz, CH_2CH$_3$), 4.09 (q, 2H, J=7.1 Hz, CH_2CH$_3$), 6.23 (s, 2H, 2×NH), 7.09–7.15 (m, 4H, 2×2ArH), 7.29–7.33 (m, 4H, 2×2ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=13.5, 14.1, 14.4, 15.2, 38.9, 42.3, 42.5, 44.0, 44.2, 45.2, 47.3, 49.7, 61.2, 61.6, 129.1, 129.2, 129.6, 130.0, 133.3, 133.5, 139.1, 139.5, 171.9, 172.5, 174.7, 176.2; mass (FAB+) m/z 296 (M^++1); Anal. Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; N, 4.74. Found: C, 61.15; H, 5.85; N, 4.88.

4.3.6. 4-(4-Fluoro-phenyl)-5-methyl-6-oxo-piperidine-3-carboxylic acid ethyl ester (5f). Yield 54% (0.26 g from 0.53 g) as a yellow solid, mp 125–127 °C; ν_{max} (KBr) 1663 (CONH), 1729 (CO_2Et), 3407 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=0.90 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.02–1.29 (m, 9H, CH_3CH$_2$ and 2×CH_3CH), 2.38–2.76 (m, 2H, 2×CHCH$_3$), 2.80–3.18 (m, 2H, CHCH$_2$), 3.53–3.63 (m, 6H, 2×CH$_2$NH and 2×CHAr), 3.85 (q, 2H, J=7.0 Hz, CH_2CH$_3$), 4.11 (q, 2H, J=7.1 Hz, CH_2CH$_3$), 6.15 (s, 2H, 2×NH), 6.96–7.06 (m, 4H, 2×2ArH), 7.11–7.20 (m, 4H, 2×2ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=13.6, 14.1, 14.4, 15.1, 39.0, 42.5, 44.0, 44.2, 45.0, 47.5, 49.6, 61.1, 61.6, 115.6, 116.0, 129.7, 129.8. 130.0, 130.2, 136.2, 136.7, 159.8, 164.6, 172.0, 172.6, 174.8, 176.2; mass (FAB+) m/z 280 (M^++1); Anal. Calcd for $C_{15}H_{18}FNO_3$: C, 64.50; H, 6.50; N, 5.01. Found: C, 64.80; H, 6.36; N, 4.88.

4.3.7. 5-Methyl-6-oxo-4-*p*-tolyl-piperidine-3-carboxylic acid ethyl ester (5g). Yield 56% (0.56 g from 1.1 g) as a white solid, mp 105–107 °C; ν_{max} (KBr) 1663 (CONH), 1726 (CO_2Et), 3233 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=0.89 (t, 3H, J=7.2 Hz, CH_3CH$_2$), 1.01 (d, 3H, J=7.2 Hz, CH_3CH), 1.08 (d, 3H, J=7.2 Hz, CH_3CH), 1.17 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 2.32 (s, 6H, 2×ArCH$_3$), 2.46–2.58 (m, 1H, CHCH$_3$), 2.68–2.76 (m, 1H, CHCH$_3$), 2.89–3.11 (m, 2H, 2×CHCH$_2$), 3.55–3.63 (m, 6H, 2×CH_2NH and 2×CHAr), 3.84 (q, 2H, J=7.1 Hz, CH_2CH$_3$), 4.09 (q, 2H, J=7.1 Hz, CH_2CH$_3$), 6.10 (s, 2H, 2×NH), 7.04–7.14 (m, 8H, 2×4ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=13.6, 14.1, 14.4, 15.2, 21.4, 38.9, 41.6, 42.4, 44.0, 44.1, 45.4, 47.5, 49.9, 61.0, 61.5, 128.1, 128.5, 129.6, 137.0, 137.2, 137.3, 137.9, 171.8, 172.2, 172.8, 175.3, 176.5; mass (FAB+) m/z 276 (M^++1); Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.98; H, 7.54; N, 4.89.

4.4. General procedure for the synthesis of compounds 8a–g, as exemplified for compound 8a

A mixture of compound **5a** (0.51 g, 1.95 mmol) and PCl_5 (1.62 g, 7.8 mmol) in $POCl_3$ (4 mL) was refluxed for 3 h. Thereafter, the reaction mixture was poured into ice water, neutralized with $NaHCO_3$, and extracted with EtOAc (2×25 mL). The combined organic layer was washed with brine (50 mL), dried (Na_2SO_4), and the solvent was in vacuo. The crude product obtained was purified by silica gel column chromatography (hexane:EtOAc, 50:50, v/v) to give 0.39 g (68%) of chloro-derivative **8a** as a white solid.

4.4.1. 5-Chloro-5-methyl-6-oxo-4-phenyl-piperidine-3-carboxylic acid ethyl ester (8a). Mp 142–144 °C; ν_{max} (KBr) 1678 (CONH), 1736 (CO_2Et), 3200 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=0.90 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.03 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.56 (s, 3H, CH$_3$), 1.61 (s, 3H, CH$_3$), 3.32–3.38 (m, 2H, 2×CHAr), 3.62–3.72 (m, 4H, 2×CH_2NH), 3.78–4.05 (m, 6H, 2×CHCH$_2$ and 2×CH_2CH$_3$), 6.36 (br s, 1H, NH), 6.74 (br s, 1H, NH), 7.24–7.40 (m, 10H, 2×5ArH);^{13}C NMR ($CDCl_3$, 50 MHz) δ=14.1, 14.2, 26.0, 26.2, 42.4, 43.1, 43.9, 44.5, 52.9, 54.8, 61.4, 61.7, 67.8, 68.1, 128.2, 128.3, 128.4, 128.7, 130.0, 136.1, 138.0, 170.7, 171.3, 171.6, 172.0; mass (FAB+) m/z 296 (M^++1); Anal. Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; N, 4.74. Found: C, 61.19; H, 5.87; N, 4.78.

4.4.2. 5-Chloro-4-(2-chloro-phenyl)-5-methyl-6-oxo-piperidine-3-carboxylic acid ethyl ester (8b). Yield 65% (0.59 g from 0.81 g) as a white crystalline solid, mp 142–144 °C; ν_{max} (KBr) 1685 (CONH), 1735 (CO_2Et), 3250 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=0.93 (t, 3H, J=6.0 Hz, CH_3CH$_2$), 1.17 (t, 3H, J=6.0 Hz, CH_3CH$_2$), 1.58 (s, 3H, CH$_3$), 1.60 (s, 3H, CH$_3$), 3.26–3.40 (m, 2H, 2×CHAr), 3.50–3.61 (m, 4H, 2×CH$_2$N), 3.86–4.03 (m, 6H, 2×CH_2CH$_3$ and 2×CHCO$_2$Et), 6.18 (s, 1H, NH), 6.47 (s, 1H, NH), 7.20–7.30 (m, 6H, 2×3ArH), 7.42–7.46 (m, 2H, 2×1ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=14.2, 14.3, 25.9, 26.0, 41.5, 42.0, 45.6, 45.9, 49.2, 50.1, 61.5, 61.9, 67.0, 68.0, 126.8, 127.4, 127.6, 129.3, 129.4, 129.9, 130.6, 131.5, 135.7, 137.8, 171.2, 171.4, 171.7, 171.9; mass (ES+) m/z 330.0 (M^++1), 332.1 (M^++3); Anal. Calcd for $C_{15}H_{17}Cl_2NO_3$: C, 54.56; H, 5.19; N, 4.24. Found: C, 54.33; H, 5.11; N, 4.52.

4.4.3. 5-Chloro-4-(2-fluoro-phenyl)-5-methyl-6-oxo-piperidine-3-carboxylic acid ethyl ester (8c). Yield 63% (1.39 g from 2.0 g) as a white solid, mp 144–146 °C; ν_{max} (KBr) 1679 (CONH), 1735 (CO_2Et), 3401 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=0.93 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.06 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.62 (s, 3H, CH$_3$), 1.65 (s, 3H, CH$_3$), 3.28–3.41 (m, 2H, 2×CHAr), 3.55–3.63 (m, 4H, 2×CH$_2$N), 3.88–4.07 (m, 6H,

2×C*H*$_2$CH$_3$ and 2×CHCO$_2$Et), 6.52 (s, 1H, NH), 6.83 (s, 1H, NH), 7.03–7.18 (m, 6H, 2×3ArH), 7.27–7.31 (m, 2H, 2×1ArH); mass (ES+) *m*/*z* 314.0 (M$^+$+1); Anal. Calcd for $C_{15}H_{17}ClFNO_3$: C, 57.42; H, 5.46; N, 4.46. Found: C, 57.60; H, 5.64; N, 4.31.

4.4.4. 4-(4-Bromo-phenyl)-5-chloro-5-methyl-6-oxo-piperidine-3-carboxylic acid ethyl ester (8d). Yield 60% (0.13 g from 0.2 g) as a white solid, mp 148–150 °C; ν_{max} (KBr) 1697 (CONH), 1726 (CO$_2$Et), 3439 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=0.93–1.09 (m, 6H, 2×C*H*$_3$CH$_2$), 1.55 (s, 3H, CH$_3$), 1.59 (s, 3H, CH$_3$), 3.28–3.47 (m, 2H, 2×CHAr), 3.58–3.83 (m, 4H, 2×CHCO$_2$Et and 2×C*H*HN), 3.89–4.06 (m, 6H, 2×C*H*$_2$CH$_3$ and 2×CH*H*N), 6.32 (s, 1H, NH), 6.67 (s, 1H, NH), 7.13–7.23 (m, 4H, 2×2ArH), 7.45–7.49 (m, 4H, 2×2ArH); mass (ES+) *m*/*z* 374 (M$^+$+1); Anal. Calcd for $C_{15}H_{17}BrClNO_3$: C, 48.09; H, 4.57; N, 3.74. Found: C, 47.85; H, 4.83; N, 3.78.

4.4.5. 5-Chloro-4-(4-chloro-phenyl)-5-methyl-6-oxo-piperidine-3-carboxylic acid ethyl ester (8e). Yield 54% (1.2 g from 2.0 g) as a white solid, mp 158–160 °C; ν_{max} (KBr) 1690 (CONH), 1728 (CO$_2$Et), 3312 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=0.96 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 1.05 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 1.55 (s, 3H, CH$_3$), 1.59 (s, 3H, CH$_3$), 3.28–3.37 (m, 2H, 2×CHAr), 3.58–3.88 (m, 4H, 2×CHCO$_2$Et and 2×C*H*HN), 3.90–4.06 (m, 6H, 2×C*H*$_2$CH$_3$ and 2×CH*H*N), 6.45 (s, 1H, NH), 6.81 (s, 1H, NH), 7.19–7.34 (m, 8H, 2×4ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ=14.2, 14.3, 25.9, 26.1, 42.4, 43.2, 43.8, 44.3, 52.3, 54.2, 61.6, 61.8, 67.5, 67.8, 128.6, 128.9, 131.3, 131.8, 134.3, 134.5, 134.6, 136.2, 170.3, 170.9, 171.5, 171.8; mass (FAB+) *m*/*z* 330 (M$^+$+1); Anal. Calcd for $C_{15}H_{17}Cl_2NO_3$: C, 54.56; H, 5.19; N, 4.24. Found: C, 54.77; H, 5.02; N, 4.31.

4.4.6. 5-Chloro-4-(4-fluoro-phenyl)-5-methyl-6-oxo-piperidine-3-carboxylic acid ethyl ester (8f). Yield 72% (0.97 g from 1.2 g) as a white solid, mp 110–112 °C; ν_{max} (KBr) 1696 (CONH), 1728 (CO$_2$Et), 3412 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=0.94 (t, 3H, *J*=7.2 Hz, CH$_3$CH$_2$), 1.04 (t, 3H, *J*=7.2 Hz, CH$_3$CH$_2$), 1.56 (s, 3H, CH$_3$), 1.59 (s, 3H, CH$_3$), 3.29–3.44 (m, 2H, 2×CHAr), 3.57–3.67 (m, 4H, 2×CH$_2$N), 3.83–4.01 (m, 6H, 2×CH$_2$CH$_3$ and 2×CHCO$_2$Et), 6.36 (s, 1H, NH), 6.72 (s, 1H, NH), 6.99–7.07 (m, 4H, 2×2ArH), 7.31–7.34 (m, 4H, 2×2ArH), ^{13}C NMR (CDCl$_3$, 50 MHz) δ=14.1, 14.2, 25.9, 26.0, 42.5, 43.2, 43.8, 44.4, 52.2, 54.1, 61.5, 61.8, 67.7, 68.1, 115.1, 115.4, 115.5, 115.8, 131.6, 132.0, 133.4, 170.5, 171.0, 171.7, 171.9; mass (ES+) *m*/*z* 314.0 (M$^+$+1); Anal. Calcd for $C_{15}H_{17}ClFNO_3$: C, 57.42; H, 5.46; N, 4.46. Found: C, 57.71; H, 5.40; N, 4.44.

4.4.7. 5-Chloro-5-methyl-6-oxo-4-*p*-tolyl-piperidine-3-carboxylic acid ethyl ester (8g). Yield 67% (0.45 g from 0.6 g) as a white solid, mp 134–136 °C; ν_{max} (KBr) 1679 (CONH), 1724 (CO$_2$Et), 3365 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ=0.94 (t, 3H, *J*=7.5 Hz, C*H*$_3$CH$_2$), 1.07 (t, 3H, *J*=7.5 Hz, C*H*$_3$CH$_2$), 1.56 (s, 3H, CH$_3$), 1.61 (s, 3H, CH$_3$), 2.34 (s, 6H, 2×ArCH$_3$), 3.23–3.40 (m, 2H, 2×CHAr), 3.78–3.80 (m, 3H, 2×CHCO$_2$Et and C*H*HN), 3.84–4.06 (m, 7H, 2×C*H*$_2$CH$_3$, C*H*HN and 2×CH*H*N), 6.18 (s, 1H, NH), 6.56 (s, 1H, NH), 7.12–7.14 (m, 4H, 2×2ArH), 7.24–7.27 (m, 4H, 2×2ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ=14.1, 14.2, 21.6, 26.0, 26.2, 42.4, 43.0, 43.9, 44.5, 52.5, 54.4, 61.4, 61.6, 68.0, 68.2, 129.0, 129.4, 129.8, 130.4, 133.0, 135.0, 137.9, 138.1, 170.8, 171.3, 171.9, 172.0; mass (ES+) *m*/*z* 310 (M$^+$+1), 332.0 (M$^+$+Na); Anal. Calcd for $C_{16}H_{20}ClNO_3$: C, 62.03; H, 6.51; N, 4.52. Found: C, 61.86; H, 6.42; N, 4.60.

4.5. General procedure for the synthesis of compounds 9a–g, as exemplified for compound 9a

To the solution of compound **8a** (0.5 g, 1.69 mmol) in anhydrous acetonitrile was added DBU (0.52 mL, 3.39 mmol) and the reaction mixture was heated at reflux for 14 h. Thereafter, the solvent was evaporated in vacuo to yield a residue, which via silica gel column chromatography (hexane: EtOAc, 40:60 v/v) afforded 0.28 g (64%) of compound **9a** as a white solid.

4.5.1. 5-Methyl-4-oxo-6-phenyl-3-aza-bicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (9a). Mp 115–117 °C; ν_{max} (KBr) 1678 (CONH), 1718 (CO$_2$Et), 3413 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=1.02 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 1.52 (s, 3H, CH$_3$), 2.66 (s, 1H, CHAr), 3.66 (d, 1H, *J*=10.4 Hz, C*H*HN), 3.90 (d, 1H, *J*=10.6 Hz, CH*H*NH), 4.05 (q, 2H, *J*=7.2 Hz, C*H*$_2$CH$_3$), 5.98 (s, 1H, NH), 7.15–7.28 (m, 3H, ArH), 7.32–7.40 (m, 2H, ArH); ^{13}C NMR (CDCl$_3$, 75 MHz) δ=9.1, 14.1, 35.0, 35.4, 37.9, 45.1, 61.3, 128.2, 128.4, 129.6, 136.0, 170.1, 178; mass (ES+) *m*/*z* 260.2 (M$^+$+1); Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.42; H, 6.55; N, 5.31.

4.5.2. 6-(2-Chloro-phenyl)-5-methyl-4-oxo-3-aza-bicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (9b). Yield 61% (0.27 g from 0.5 g) as a yellow oil; ν_{max} (neat) 1679 (CONH), 1732 (CO$_2$Et), 3406 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=0.99 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 1.60 (s, 3H, CH$_3$), 2.49 (s, 1H, CHAr), 3.75 (d, 1H, *J*=10.5 Hz, C*H*HNH), 3.93–4.07 (m, 3H, CH*H*NH and C*H*$_2$CH$_3$), 6.11 (s, 1H, NH), 7.21–7.32 (m, 3H, ArH), 7.34–7.40 (m, 1H, ArH); ^{13}C NMR (CDCl$_3$, 75 MHz) δ=9.3, 14.2, 34.5, 35.6, 37.9, 45.2, 52.2, 61.3, 127.2, 128.6, 130.2, 134.6, 137.4, 171.2, 175.4; mass (ES+) *m*/*z* 294.1 (M$^+$+1); Anal. Calcd for $C_{15}H_{16}ClNO_3$: C, 61.31; H, 5.49; N, 4.77. Found: C, 61.59; H, 5.70; N, 4.68.

4.5.3. 6-(2-Fluoro-phenyl)-5-methyl-4-oxo-3-aza-bicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (9c). Yield 65% (0.16 g from 0.28 g) as a white solid, mp 142–144 °C; ν_{max} (KBr) 1657 (CONH), 1729 (CO$_2$Et), 3280 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ=1.04 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 1.52 (s, 3H, CH$_3$), 2.48 (s, 1H, CHAr), 3.65 (d, 1H, *J*=10.8 Hz, C*H*HN), 3.97–4.09 (m, 3H, C*H*$_2$CH$_3$ and CH*H*N), 5.95 (s, 1H, NH), 6.98–7.15 (m, 2H, ArH), 7.23–7.27 (m, 2H, ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ=9.2, 14.2, 34.4, 35.4, 38.0, 45.3, 61.3, 115.4, 115.8, 121.0, 121.3, 124.2, 129.4, 129.6, 131.8, 169.1, 178.5; mass (FAB+) *m*/*z* 278 (M$^+$+1); Anal. Calcd for $C_{15}H_{16}FNO_3$: C, 64.57; H, 5.82; N, 5.05. Found: C, 64.77; H, 5.70; N, 4.86.

4.5.4. 6-(4-Bromo-phenyl)-5-methyl-4-oxo-3-aza-bicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (9d). Yield

58% (0.05 g from 0.1 g) as a white solid, mp 136–138 °C; ν_{max} (KBr) 1704 (CONH), 1728 (CO_2Et), 3268 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=1.08 (t, 3H, J=7.5 Hz, CH_3CH_2), 1.51 (s, 3H, CH_3), 2.59 (s, 1H, CHAr), 3.66 (d, 1H, J=12.0 Hz, C*H*HN), 3.93 (d, 1H, J=12.0 Hz, CH*H*N), 4.08 (q, 2H, J=7.5 Hz, CH_2CH_3), 5.72 (s, 1H, NH), 7.07 (d, 2H, J=8.5 Hz, ArH), 7.45 (d, 2H, J=8.5 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=8.8, 13.9, 32.2, 37.4, 38.5, 44.8, 61.1, 121.4, 131.4, 131.5, 132.0, 168.8, 177.7; mass (ES+) m/z 338.1 (M^++1), 340.1 (M^++3); Anal. Calcd for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.55; H, 4.91; N, 3.86.

4.5.5. 6-(4-Chloro-phenyl)-5-methyl-4-oxo-3-aza-bicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (9e). Yield 60% (0.16 g from 0.3 g) as a white crystalline solid, mp 125–127 °C; ν_{max} (KBr) 1705 (CONH), 1732 (CO_2Et), 3312 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.07 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.50 (s, 3H, CH_3), 2.60 (s, 1H, CHAr), 3.65 (d, 1H, J=10.0 Hz, C*H*HN), 3.98 (d, 1H, J=10.5 Hz, CH*H*N), 4.00 (q, 2H, J=7.1 Hz, CH_2CH_3), 5.69 (s, 1H, NH), 7.10 (d, 2H, J=8.3 Hz, ArH), 7.29 (d, 2H, J=8.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=9.2, 14.3, 35.7, 37.9, 38.8, 45.4, 61.4, 128.9, 131.6, 131.8, 133.6, 169.3, 178.3; mass (FAB+) m/z 294 (M^++1); Anal. Calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.68; H, 5.41; N, 4.49.

4.5.6. 6-(4-Fluoro-phenyl)-5-methyl-4-oxo-3-aza-bicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (9f). Yield 63% (0.14 g from 0.25 g) as a yellow oil; ν_{max} (neat) 1701 (CONH), 1738 (CO_2Et), 3400 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.06 (t, 3H, J=7.2 Hz, CH_3CH_2), 1.50 (s, 3H, CH_3), 2.61 (s, 1H, CHAr), 3.65 (d, 1H, J=11.2 Hz, C*H*HNH), 3.92 (d, 1H, J=11.0 Hz, CH*H*NH), 3.98–4.13 (m, 2H, CH_2CH_3), 5.89 (s, 1H, NH), 6.98–7.22 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=9.2, 14.3, 35.7, 38.2, 38.8, 45.6, 61.4, 115.4, 115.8, 128.2, 129.2, 131.7, 131.9, 169.4, 178.9; mass (ES+) m/z 278.1 (M^++1); Anal. Calcd for $C_{15}H_{16}FNO_3$: C, 64.97; H, 5.82; N, 5.05. Found: C, 64.90; H, 5.69; N, 4.98.

4.5.7. 5-Methyl-4-oxo-6-*p*-tolyl-3-aza-bicyclo[3.1.0] hexane-1-carboxylic acid ethyl ester (9g). Yield 65% (0.23 g from 0.4 g) as a white solid, mp 156–158 °C; ν_{max} (KBr) 1696 (CONH), 1735 (CO_2Et), 3426 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.05 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.50 (s, 3H, CH_3), 2.33 (s, 3H, $ArCH_3$), 2.62 (s, 1H, CHAr), 3.65 (d, 1H, J=10.5 Hz, C*H*HN), 3.89 (d, 1H, J=10.4 Hz, CH*H*N), 4.08 (q, 2H, J=7.1 Hz, CH_2CH_3), 5.80 (s, 1H, NH), 7.04 (d, 2H, J=8.1 Hz, ArH), 7.12 (d, 2H, J=8.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=9.3, 14.3, 21.6, 35.6, 38.0, 39.5, 42.6, 61.8, 128.5, 129.4, 136.7, 139.6, 168.0, 171.2; mass (ES+) m/z 274.1 (M^++1); Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.10; H, 6.75; N, 4.88.

4.6. General procedure for the synthesis of compounds 10b,e,g, as exemplified for compound 10g

Compound **4g** (0.3 g, 1.0 mmol) and $FeCl_3 \cdot 6H_2O$ (0.80 g, 3.0 mmol) were dissolved in propionic acid (6 mL) and the mixture was heated at reflux for 2 h. After cooling the mixture to room temperature, it was poured into 1 N HCl (20 mL) and extracted with EtOAc (3×30 mL). The organic layers were pooled and washed with $NaHCO_3$ (50 mL), dried over Na_2SO_4, and evaporated to yield a residue, which was purified via silica gel column chromatography. Elution with hexane:EtOAc (60:40, v/v) yielded 0.13 g (60%) of product **10g** as a brown solid.

4.6.1. 4-(2-Chloro-phenyl)-3-methylene-piperidine-2,6-dione (10b). Yield 58% (0.26 g from 0.62 g) as a white solid, 108–110 °C; ν_{max} (KBr) 1701 (CONH), 3408 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=2.94–3.05 (m, 2H, CH_2CH), 4.54–4.59 (m, 1H, CHAr), 5.33 (s, 1H, =CH), 6.52 (d, 1H, J=0.9 Hz, =CH), 7.15–7.32 (m, 3H, ArH), 7.43–7.48 (m, 1H, ArH), 8.24 (s, 1H, NH);^{13}C NMR ($CDCl_3$, 50 MHz) δ=37.7, 39.1, 127.2, 127.9, 128.5, 129.4, 130.6, 137.1, 137.7, 166.2, 171.8; mass (FAB+) m/z 236 (M^++1); Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found: C, 60.80; H, 4.49; N, 6.01.

4.6.2. 4-(4-Chloro-phenyl)-3-methylene-piperidine-2,6-dione (10e). Yield 65% (0.23 g from 0.49 g) as a white solid, 182–184 °C; ν_{max} (KBr) 1699 (CONH), 3404 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=2.96–2.99 (m, 2H, CH_2CH), 4.02–4.12 (m, 1H, CHAr), 5.39 (s, 1H, =CH), 6.50 (s, 1H, =CH), 7.15 (d, 2H, J=8.5 Hz, ArH), 7.36 (d, 2H, J=8.5 Hz, ArH), 8.19 (br s, 1H, NH);^{13}C NMR ($CDCl_3$, 50 MHz) δ=43.3, 46.5, 131.2, 134.2, 134.4, 138.1, 143.3, 144.5, 171.1, 177.0; mass (FAB+) m/z 236 (M^++1); Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found: C, 61.22; H, 4.03; N, 5.78.

4.6.3. 3-Methylene-4-*p*-tolyl-piperidine-2,6-dione (10g). Mp 152–154 °C; ν_{max} (KBr) 1697 (CONH), 3427 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=2.35 (s, 3H, $ArCH_3$), 2.89–3.02 (m, 2H, CH_2CH), 3.99–4.15 (m, 1H, CHAr), 5.39 (s, 1H, =CH), 6.47 (s, 1H, =CH), 7.09 (d, 2H, J=8.0 Hz, ArH), 7.19 (d, 2H, J=8.0 Hz, ArH), 8.18 (s, 1H, NH); mass (FAB+) m/z 216 (M^++1); Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.67; H, 5.85; N, 6.82.

4.7. General procedure for the synthesis of compounds 11a,e,f, as exemplified for compound 11a

To a flask charged with compound **4a** (0.9 g, 3.14 mmol) was added 6 mL mixture of TFA and H_2SO_4 (1: 1) at room temperature and the reaction was continued for 4 h. Thereafter, the reaction mixture was poured into ice cold water (50 mL) and neutralized with $NaHCO_3$ and extracted with EtOAc (2×30 mL). Combined organic layer was dried over Na_2SO_4 and evaporated in vacuo to afford a residue, which was purified via column chromatography over silica gel using hexane:EtOAc (30:70, v/v) to furnish 0.76 g (80%) of amide **11a** as a white solid.

4.7.1. 2-Carbamoyl-4-methylene-3-phenyl-pentanedioic acid-1-ethyl ester-5-methyl ester (11a). Mp 120–122 °C; ν_{max} (KBr) 1666 ($CONH_2$), 1724 (CO_2Me and CO_2Et), 3396 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.01 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.26 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.69 (s, 6H, 2×CO_2CH_3), 3.97 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.10–4.21 (m, 4H, CH_2CH_3 and

2×CHAr), 4.53 (d, 1H, *J*=12.4 Hz, CHCON), 4.62 (d, 1H, *J*=12.4 Hz, CHCON), 5.36 (s, 1H, 1H of NH_2), 5.53 (s, 1H, 1H of NH_2), 5.80 (s, 1H, =CH), 5.94 (s, 1H, =CH), 5.98 (s, 1H, 1H of NH_2), 6.28 (s, 1H, 1H of NH_2), 6.32 (s, 1H, =CH), 6.33 (s, 1H, =CH), 7.14–7.20 (m, 6H, 2×3ArH), 7.38–7.42 (m, 4H, 2×2ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=19.0, 19.3, 50.7, 50.8, 57.1, 61.5, 61.7, 66.4, 66.5, 125.9, 129.6, 130.5, 135.6, 135.9, 136.3, 143.6, 144.0, 145.3, 146.5, 171.4, 173.5, 173.8; mass (FAB+) *m/z* 306 (M^++1); Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.05; H, 6.13; N, 4.83.

4.7.2. 2-Carbamoyl-3-(4-chloro-phenyl)-4-methylene-pentanedioic acid-1-ethyl ester-5-methyl ester (11e). Yield 89% (0.63 g from 0.67 g) as a white solid, mp 102–104 °C; ν_{max} (KBr) 1667 ($CONH_2$), 1725 (CO_2Me and CO_2Et), 3389 (NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.02 (t, 3H, *J*=7.2 Hz, CH_3CH_2), 1.25 (t, 3H, *J*=7.2 Hz, CH_3CH_2), 3.69 (s, 6H, 2×CO_2CH_3), 3.96 (q, 2H, *J*=7.2 Hz, CH_2CH_3), 4.11–4.25 (m, 4H, CH_2CH_3 and 2×CHAr), 4.54 (d, 1H, *J*=12.4 Hz, CHCON), 4.63 (d, 1H, *J*=12.4 Hz, CHCON), 5.62 (s, 1H, 1H of NH_2), 5.73 (s, 1H, 1H of NH_2), 5.81 (s, 1H, =CH), 5.85 (s, 1H, 1H of NH_2), 5.94 (s, 1H, =CH), 5.98 (s, 1H, 1H of NH_2), 6.32 (s, 1H, =CH), 6.33 (s, 1H, =CH), 7.23–7.31 (m, 8H, 2×4ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=19.0, 19.2, 50.8, 51.1, 57.3, 61.7, 61.8, 66.3, 66.5, 129.5, 130.5, 133.4, 135.2, 135.4, 137.7, 142.9, 143.4, 145.4, 146.5, 171.4, 173.6, 173.8; mass (ES+) *m/z* 340.0 (M^++1); 342.0 (M^++3); Anal. Calcd for $C_{16}H_{18}ClNO_5$: C, 56.56; H, 5.34; N, 4.12. Found: C, 56.79; H, 5.22; N, 3.95.

4.7.3. 2-Carbamoyl-3-(4-fluoro-phenyl)-4-methylene-pentanedioic acid-1-ethyl ester-5-methyl ester (11f). Yield 78% (0.68 g from 0.83 g) as a white solid, mp 110–112 °C; ν_{max} (KBr) 1664 ($CONH_2$), 1726 (CO_2Me and CO_2Et), 3403 (NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.02 (t, 3H, *J*=7.5 Hz, CH_3CH_2), 1.27 (t, 3H, *J*=7.5 Hz, CH_3CH_2), 3.70 (s, 3H, CO_2CH_3), 3.71 (s, 3H, CO_2CH_3), 3.94–4.01 (m, 3H, CH_2CH_3 and CHAr), 4.12–4.25 (m, 3H, CH_2CH_3 and CHAr), 4.57 (d, 1H, *J*=12.0 Hz, CHCON), 4.66 (d, 1H, *J*=12.0 Hz, CHCON), 5.28 (s, 1H, 1H of NH_2), 5.43 (s, 1H, 1H of NH_2), 5.81 (s, 1H, =CH), 5.95 (s, 2H, =CH and 1H of NH_2), 6.28 (s, 1H, 1H of NH_2), 6.34 (s, 2H, 2×=CH), 6.94–7.00 (m, 4H, 2×2ArH), 7.26–7.32 (m, 4H, 2×2ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=14.1, 14.3, 46.1, 46.6, 52.3, 57.5, 61.7, 61.8, 115.1, 115.6, 124.5, 125.7, 130.3, 130.5, 130.6, 134.9, 135.2, 140.5, 141.7, 159.6, 164.4, 166.6, 166.7, 168.6, 169.2; mass (ES+) *m/z* 324.1 (M^++1); Anal. Calcd for $C_{16}H_{18}FNO_5$: C, 59.44; H, 5.61; N, 4.33. Found: C, 59.63; H, 5.40; N, 4.47.

4.8. General procedure for the synthesis of compounds 12a,e,f, as exemplified for compound 12a

To the stirred solution of compound **11a** (0.5 g, 1.64 mmol) in anhydrous toluene was added NaH (0.098 g in 60% oil, 2.46 mmol) at ambient temperature. After 30 min reaction mixture was quenched carefully with water and extracted with ethyl acetate (2×25 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo to obtain a residue that was subjected to column chromatography using hexane:EtOAc (40:60 v/v) over silica gel to yield 0.32 g (72%) of compound **12a** as a white solid.

4.8.1. 5-Methylene-2,6-dioxo-4-phenyl-piperidine-3-carboxylic acid ethyl ester (12a). Mp 114–116 °C; ν_{max} (KBr) 1705 (CONH), 1748 (CO_2Et), 3418 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.13 (t, 3H, *J*=7.5 Hz, CH_3CH_2), 3.40 (d, 1H, *J*=9.0 Hz, CHAr), 4.14 (q, 2H, *J*=7.5 Hz, CH_2CH), 4.43 (d, 1H, *J*=9.0 Hz, $CHCO_2Et$), 5.45 (s, 1H, =CH), 6.57 (s, 1H, =CH), 7.21–7.33 (m, 3H, ArH), 7.35–7.41 (m, 2H, ArH), 8.15 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=14.3, 46.2, 55.3, 62.5, 128.3, 128.6, 129.6, 137.2, 137.4, 165.1, 167.5, 168.3; mass (ES+) *m/z* 274.1 (M^++1); Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.52; H, 5.53; N, 5.13. Found: C, 65.59; H, 5.71; N, 4.93.

4.8.2. 4-(4-Chloro-phenyl)-5-methylene-2,6-dioxo-piperidine-3-carboxylic acid ethyl ester (12e). Yield 74% (0.15 g from 0.22 g) as a white solid, mp 108–110 °C; ν_{max} (KBr) 1695 (CONH), 1748 (CO_2Et), 3418 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.14 (t, 3H, *J*=7.1 Hz, CH_3CH_2), 3.40 (d, 1H, *J*=9.5 Hz, CHAr), 4.14 (q, 2H, *J*=7.1 Hz, CH_2CH), 4.38 (d, 1H, *J*=9.2 Hz, $CHCO_2Et$), 5.40 (s, 1H, =CH), 6.58 (s, 1H, =CH), 7.16 (d, 2H, *J*=7.8 Hz, ArH), 7.36 (d, 2H, *J*=8.0 Hz, ArH), 8.21 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=14.3, 45.5, 51.1, 62.6, 129.3, 130.5, 134.5, 135.7, 137.1, 164.8, 167.2, 167.9; mass (FAB+) *m/z* 308 (M^++1); Anal. Calcd for $C_{15}H_{14}ClNO_4$: C, 58.54; H, 4.59; N, 4.55. Found: C, 58.50; H, 4.69; N, 4.58.

4.8.3. 4-(4-Fluoro-phenyl)-5-methylene-2,6-dioxo-piperidine-3-carboxylic acid ethyl ester (12f). Yield 76% (0.25 g from 0.36 g) as a white solid, mp 135–137 °C; ν_{max} (KBr) 1703 (CONH), 1740 (CO_2Et), 3372 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.15 (t, 3H, *J*=7.5 Hz, CH_3CH_2), 3.95 (d, 1H, *J*=9.0 Hz, CHAr), 4.15 (q, 2H, *J*=7.5 Hz, CH_2CH), 4.40 (d, 1H, *J*=9.0 Hz, $CHCO_2Et$), 5.41 (s, 1H, =CH), 6.58 (s, 1H, =CH), 7.06–7.12 (m, 2H, ArH), 7.19–7.24 (m, 2H, ArH), 8.12 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=14.3, 45.4, 55.4, 62.6, 116.3, 116.8, 129.6, 130.0, 130.2, 132.9, 137.4, 165.0, 167.3, 168.1; mass (FAB+) *m/z* 292 (M^++1); Anal. Calcd for $C_{15}H_{14}FNO_4$: C, 61.58; H, 4.85; N, 4.81. Found: C, 61.55; H, 4.56; N, 4.77.

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8. Crystal data of compound **9e**: $C_{15}H_{16}NO_3Cl$, M=293.75, orthorhombic, $P2_12_12_1$, a=6.323(1), b=9.076(2), c=26.253(2) Å, V=1506.5(4) Å^3, Z=4, D_c=1.295 g cm^{-3}, μ(Mo K_α)=0.026 mm^{-1}, F(000)=616.0, colorless block, dimension 0.3×0.25×0.2 mm, 2196 reflections measured (R_{int}=0.0234), 1978 unique, wR_2=0.098, conventional R=0.0401 on F values of 1485 reflections with $I>2\sigma(I)$, $(\Delta/\sigma)_{max}$=000), S=1.02 for all data and 184 parameters. Unit cell determination and intensity data collection (2θ=50°) was performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS (Siemens Analytical X-ray Instrument Inc.: Madison, WI, USA, 1996) for data collection and data processing; SHELXTL-NT (Bruker AXS Inc.: Madison, Wisconsin, USA, 1997) for structure determination, refinements, and molecular graphics. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no. of **9e**: 609070).
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