tert-Amino Effect at a Coumarin and a 2-Quinolone System: Synthesis of 1,2 Fused 5*H*-Chromeno[4,3-*b*]pyridin-5-ones and a 6*H*-Benzo[*h*][1,6]naphthyridin-5-one

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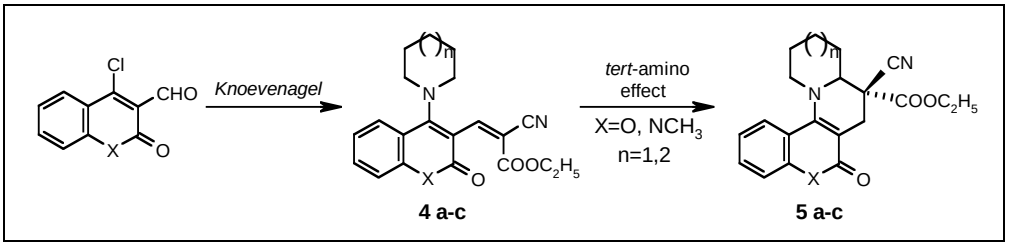

Some novel 1,2-fused 5*H*-chromeno[4,3-*b*]pyridin-5-ones (**5a,b**) and a 6*H*-benzo[*h*][1,6]naphthyridin-5-one (**5c**) have been synthesized starting from the 4-chlorocoumarin-3-carbaldehyde (**1a**) or its *N*-methyl-2-quinolone analogue (**1b**) *via* subsequent Knoevenagel condensation and ring closure reaction known as the '*tert*-amino effect'. These are rare examples of the *tert*-amino effect occurring at 2-pyrone and 2-pyridone ring. An unusual intramolecular redox reaction of the iminium ion **6**, reported earlier, most probably follows analogous mechanism as the *tert*-amino effect reactions leading to **5**.

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INTRODUCTION

The *tert*-amino effect was defined by Meth-Cohn and Suschitzky more than thirty years ago [1a,b] and hundreds of examples have been found since. Most recently, a comprehensive review [2] has been published on the late developments of ring-closure reactions using the *tert*-amino effect. Two further publications appeared afterwards, announcing new applications of this hetero-cyclization principle. Thus, Devi *et al.* used the readily available 2-chloroquinoline-3-carbaldehyde to transform it into some novel quinolizine-, indolizine- and pyrido-1,4-oxazine-fused quinoline derivatives [3a]. Paramonov *et al.* synthesized novel spiro[1,4]thiazino-[4,3-*a*]quino-line-5,5'-pyrimidines starting from 2-thio-morpholino-5-trifluoromethylbenzaldehyde [3b].

Most of the *tert*-amino heterocyclizations reported in the literature employ either ortho-vinyl *N,N*-dialkyl-anilines or their heteroaromatic analogues such as appro-priately substituted pyridine, pyridazine or pyrimidine derivatives as starting compounds [1,2].

One area of our research had to do with the application of selected *N*-substituted 4-amino-3-vinylcoumarins for the synthesis of fused heterocyclic systems, *e.g.* [1]benzo-pyrano[4,3-*b*]pyridines [4a-c]. It was a challenge for us to check whether representatives of this class of compounds, i.e. the 3-vinyl-4-dialkylaminocoumarins and their aza-analogues, the 3-substituted 4-dialkylamino-2-quinolones, would also be able to undergo the *tert*-amino-effect cycli-sations leading to novel fused polycyclic heterocycles. We report here the positive answer to this question.

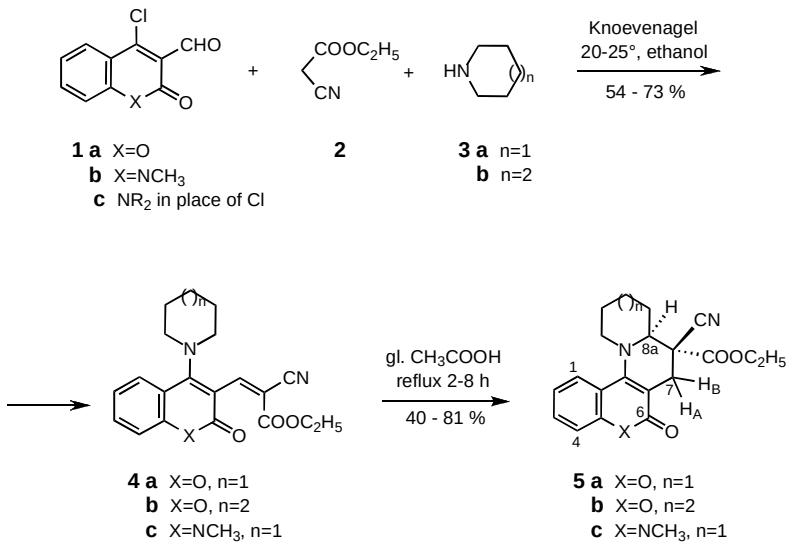
RESULTS AND DISCUSSION

Initially, we attempted to obtain the necessary Knoevenagel products of type **4** directly starting from 4-dialkylaminocoumarin-3-carbaldehydes **1c** [4a] and CH-acids of type **2** but all these trials failed. This is obviously due to the lower reactivity of the 3-formyl group, which is a part of the conjugated enamino push-pull system of **1c**. Fortunately, we succeeded in carrying out the Knoevenagel reaction starting from 4-chlorocoumarin-3-carbaldehyde **1a** and its aza-analogue **1b** with ethyl cyanoacetate (**2**) (Scheme 1). The secondary amines piperidine (**3a**) and hexamethylene imine (azepane, **3b**) served as catalysts and, at the same time, replaced the chlorine atom. The resulting 4-(*tert*-amino)-3-vinyl substituted derivatives **4a-c** were isolated in 54-73% yield.

After refluxing **4a-c** for several hours in glacial acetic acid the tetracyclic products **5a-c** were obtained (yield 40-81%). Another solvent, toluene, frequently used in the iterature, was also examined as a nonpolar reaction medium but none of the desired products were detected by means of tlc. The constitution of the products **5a-c** was deduced mainly from their spectral properties. For example, in the ^{1}H nmr spectra of **5a-c**, typical AB-quartet for the non-equivalent 7-methylene protons was observed at δ 2.9-3.3. The signal of the 8a-methine proton appeared as a triplet at δ 3.04 (compound **5a**). Their ir spectra are characteristic for the two carbonyl groups only, whereas the CN-band is either weak or absent.

Scheme 1

Synthetic pathway for the title compounds **5a-c**.



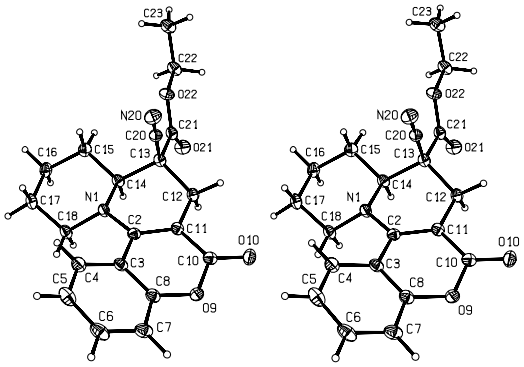


Figure 1. ORTEP stereo view of the X-ray structure of **5a** at the 50% probability level (crystallographic atom numeration).

The structure of the final products **5a,b** was indisputably confirmed by means of X-ray crystallographic analysis (Figure 1). According to it, the cyano group and the methine hydrogen in position 8a (α to the ring nitrogen) are in antiperiplanar configuration while the ethoxycarbonyl group takes an equatorial position.

When malononitrile was used in place of the CH-acidic component **2**, under the Knoevenagel conditions, a product completely different from **5a,b** was isolated [7].

More than ten years ago we reported [4b] an unusual intramolecular redox reaction of the iminium ion **6** (Scheme 2), derived from 4-(monoalkylamino)coumarin-3-carbaldehydes. The 4-amino-3-dialkylaminomethyl-coumarins of type **8** are formed *via* intermediate 1,5-hydride shift **6→7** and subsequent hydrolysis. On the grounds of the similarity between the substrates **4** and **6** as well as the analogy with the occurring chemical transformations, it could be assumed that both reactions most probably follow analogous mechanistic sequences. Sigmatropic rearrangement, hydride transfer or a mixed mechanism has been suggested till now for the *tert*-amino cyclization reactions [5]. The mechanism of the lower oxidation-reduction reaction in Scheme 2 may be regarded as a variant of the *tert*-amino effect, that is, a *tert*-amino effect working in a *sec*-amino compound.

On the other hand, the *tert*-amino effect cyclization found by us is a first example of this effect operative at a coumarin or 2-quinolone system.

EXPERIMENTAL

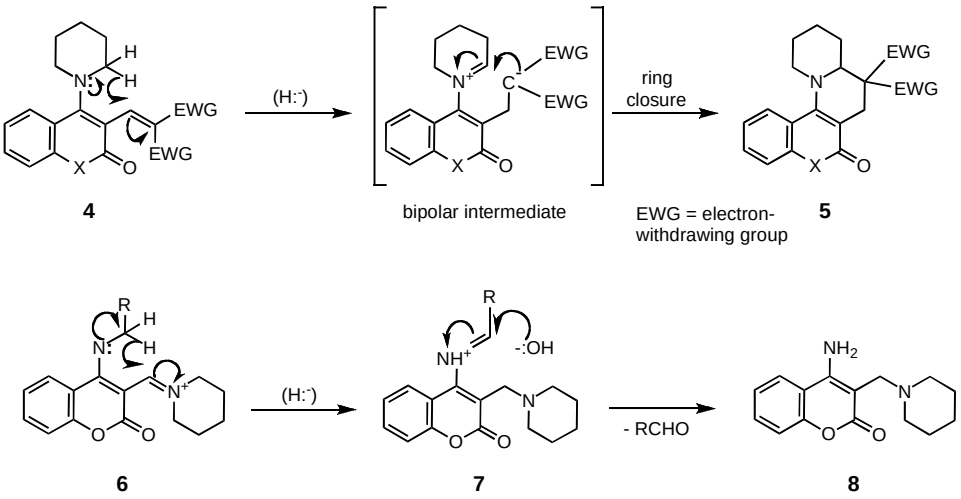
General. The ir spectra were recorded in nujol on a Shimadzu 8001 FTIR spectrometer. ^{1}H and ^{13}C nmr spectra were registered on a Bruker ARX 300 or Bruker AMX 360 spectrometer. Chemical shifts are expressed in δ (ppm) downfield from TMS as an internal reference. Tlc monitoring was carried out on silica gel Merck GF_{254} pre-coated aluminium sheets, eluted with (A) hexane-acetone 2:1 for compounds **4**, and (B) hexane-chloroform-acetone 5:3:2 for compounds **5**.

X-Ray crystal structure analyses. Atomic coordinates, bond lengths [Å] and angles [deg], anisotropic displacement parameters, hydrogen coordinates, torsion angles [deg] have been deposited at Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, under deposition numbers CCDC 232852 for **5a**, CCDC 232853 for **5b** (Fax: +44 1223 336033; Home page: http://www.ccdc.cam.ac.uk).

X-Ray diffraction data of 5a (ORTEP view [8], s. Figure 1). All the measurements were performed using graphite-monochromatized Mo K_{α} radiation at 95K: $C_{20}H_{20}N_2O_4$, M_r 352.38, tri-

Scheme 2

tert-Amino cyclization reaction of compounds **4** compared to the intramolecular hydride transfer in the iminium ion **6** [4b].



clinic, space group P -1, a = 8.764(3) Å, b = 9.883(4) Å, c = 11.258(3) Å, α = 67.10(2)°, β = 86.61(2)°, γ = 71.37(2)°, V = 848.8(5) Å^3, Z = 2, d_{calc} = 1.379 g cm^{-3}, μ = 0.097 mm^{-1}. A total of 3860 reflections were collected (Θ_{max} = 26.0°), from which 3328 were unique (R_{int} = 0.0254), with 2710 having I > 2σ(I). The structure was solved by direct methods (SHELXS-97) [9] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97) [10]. The non-hydrogen atoms were refined with anisotropic displacement parameters without any constraints. The H atoms were put at the external bisector of the C-C-C angle at a C-H distance of 0.95 Å and one common isotropic displacement parameter was refined for these H atoms. The H atom of the tertiary C-H group was refined with all X-C-H angles equal at a C-H distance of 1.00 Å. The H atoms of the CH_2 groups were refined with common isotropic displacement parameters for the H atoms of the same group and idealized geometry with approximately tetrahedral angles and C-H distances of 0.99 Å. The H atoms of the CH_3 group were refined with common isotropic displacement parameters and idealized geometry with tetrahedral angles, enabling rotation around the X-C bond, and C-H distances of 0.98 Å. For 245 parameters final R indices of R = 0.0425 and wR^2 = 0.0963 (GOF = 1.041) were obtained. The largest peak in a difference Fourier map was 0.261eÅ^{-3}.

Ethyl 2-cyano-3-[2-oxo-4-(1-piperidinyl)-2H-chromen-3-yl]acrylate (**4a**). To a stirred mixture of chlorocarbaldehyde **1a** (1.04 g, 5.0 mmol) and ethyl cyanoacetate (**2**) (1.0 ml, 10 mmol) in ethanol (20 ml), piperidine (1.1 ml, 11.0 mmol) was added dropwise at 20-25 °C. The mixture changed to a red solution and after 10 min yellow crystals of **4a** separated which were collected by filtration, washed with cold ethanol and recrystallised. Yield 1.28 g (73%) of yellow crystals (ethanol), mp 164-165.5 °C; ir: ν 2224 (CN), 1711 (C=O), 1588, 1516, 1433, 1289, 1244, 1229, 1105, 756 cm^{-1}; ^{1}H nmr ($CDCl_3$; 300 MHz): δ 1.39 (t, 3H, CH_3, J = 7.1 Hz), 1.83 (m, 2H, 4-H_2 of 1-piperidinyl), 2.78 (m, 4H, 3-H_2 and 5-H_2 of 1-piperidinyl), 3.63 (br. s, 4H, 2-H_2 and 6-H_2 of 1-piperidinyl), 4.36 (q, 2H, OCH_2, J = 7.1 Hz), 7.22-7.38 (m, 2Harom., 6-H, 8-H), 7.57 (dd, 1Harom., 7-H), 7.80 (d, 1H, 5-Harom., J =8.1 Hz), 8.26 (s, 1H, β-H); ms (70 eV): m/z (%) = 352 (69; M•+), 323 (3), 307 (5), 279 (77), 251 (10), 240 (100), 223 (4), 196 (6). *Anal*. Calcd. for $C_{20}H_{20}N_2O_4$ (352.38): C, 68.17; H, 5.72; N, 7.95. Found: C, 67.92; H, 5.72; N, 7.74.

Ethyl 3-[4-(1-azepanyl)-2-oxo-2*H*-chromen-3-yl]-2-cyano-acrylate (**4b**). To a stirred mixture of 1.04 g (5.0 mmol) of chloroaldehyde **1a** and 1.0 ml (10 mmol) of ethyl cyanoacetate (**2**) in 20 ml ethanol 1.3 ml (11.0 mmol) of azepane was added dropwise at 20-25 °C. The mixture changed to a red solution and after 60 min yellow crystals of **4b** separated which were collected by filtration, washed with cold ethanol and recrystallised. Yield 0.98 g (54%) of yellow crystals (ethanol), mp 134-135 °C; ir: ν 2215 (CN), 1696 (C=O), 1584, 1549, 1420, 1368, 1296, 1238, 1194, 1117, 1098, 951, 749 cm^{-1}; ^{1}H nmr (DMSO-d_6; 300 MHz): δ 1.26 (t, 3H, CH_3, J = 7.1 Hz), 1.55 (br. s, 4H, 4-H_2 and 5-H_2 of 1-azepanyl), 1.83 (br. s, 4H, 3-H_2 and 6-H_2 of 1-azepanyl), 3.84 (m, 4H, 2-H_2 and 7-H_2 of 1-azepanyl), 4.23 (q, 2H, OCH_2, J = 7.1 Hz), 7.33-7.47 (m, 2$H_{arom.}$, 6-H, 8-H), 7.64 (dd, 1$H_{arom.}$, 7-H), 7.96 (d, 1H, 5-$H_{arom.}$, J =8.0 Hz), 8.34 (s, 1H, β-H); ms (70 eV): *m/z* (%) 366 (77; $M^{\bullet+}$), 339 (4), 321 (6), *293* (100), 265 (8), 254 (48). *Anal*. Calcd. for $C_{21}H_{22}N_2O_4$ (366.41): C, 68.84; H, 6.05; N, 7.65. Found C, 68.75; H, 6.12; N, 7.56.

Ethyl 2-cyano-3-[1,2-dihydro-1-methyl-2-oxo-4-(piperidin-1-yl)quinolin-3-yl]acrylate (**4c**). To a stirred mixture of 0.54 g (0.62 ml; 6.4 mmol) of piperidine (**3a**) and 0.50 g (4.4 mmol) of ethyl cyanoacetate (**2**) in ethanol (5 ml), 700 mg (3.2 mmol) of the 2-oxoquinoline-3-carbaldehyde **1b** (prepared as described in the literature [6]) was added. The mixture was stirred at room temperature for 20 min, then poured onto 50 g of ice-water and stirred for further 20 min. The dark-orange precipitate was filtered and dried at 50 °C to give crude **4c** (936 mg) which was then recrystallised. Yield: 820 mg (70 %) of pure **4c**, yellow crystals (ethanol), mp 165-167 °C. Recrystallisation from methanol gives a purer product, no transesterification takes place; ir (KBr;): ν 2941, 2853 (CN band not observed), 1719 (C=O, ester), 1639 (C=O, lactam), 1606, 1579, 1247, 1246 cm^{-1}; ^{1}H nmr ($CDCl_3$; 360 MHz): δ 1.38 (t, J = 7.00, 3H), 1.77 (s, 6H), 3.41 (s, 4H), 3.68 (s, 3H), 4.37 (q, J = 6.3, 2H), 7.21 (t, J = 7.73,

1H), 7.36 (d, J = 8.41, 1H), 7.58 (t, J = 7.70, 1H), 7.89 (d, J = 8.12, 1H), 8.30 (s, 1H); ^{13}C nmr ($CDCl_3$; 90.6 MHz): δ 14.0, 23.9, 25.4, 28.1, 29.5, 32.1, 47.5, 54.2, 63.2, 63.4, 106.7, 114.7, 115.6, 116.6, 121.0, 125.4, 129.9, 139.7, 149.7, 161.7 (C=O, lactone), 167.7 (C=O, ester); APCI-ms (70 eV): *m/z* (%) 366 (20, M + 1), *365* (100, M), 319 (48, M – 46), 293 (69, M – 72). *Anal.* Calcd. for $C_{21}H_{23}N_3O_3$ (365.44): C, 69.02; H, 6.34; N, 11.50. Found: C, 68.93; H, 6.31; N, 11.51.

Ethyl 8-cyano-6-oxo-8,8a,9,10,11,12-hexahydro-6*H*,7*H*-chromeno[3,4-*c*]quinolizine-8-carboxylate (**5a**). A solution of 704 mg (2.0 mmol) of the ester **4a** in 5.0 ml glacial acetic acid was refluxed for 8 h. The yellow solution decolorised. On cooling the product **5a** separated in crystalline form and was collected by filtration. Yield: 590 mg (84 %) of tlc homogeneous, colourless crystals (ethanol), mp 194-195 °C; ir: ν 2246 (weak, CN), 1739 (C=O, ester), 1693 (C=O, lactone), 1602, 1558, 1495, 1477, 1425, 1376, 1365, 1320, 1260, 1011, 763, 754, 738, 727 cm^{-1}; ^{1}H nmr (DMSO-d_6; 300 MHz): δ 1.29 (t, 3H, CH_3, J = 7.1 Hz), 1.52-1.72 (m, 2H, γ-CH_2 of piperidine ring), 1.75-2.08 (m, 4H, two β-CH_2 of piperidine ring), 2.96 (d, 1H, H_A of AB-quartet, J = 16.2 Hz), 3.04 (t, 1H, α-C*H*-N, J ≈ 11.5 Hz), 3.21 (d, 1H, H_B of AB-quartet, J = 16.2 Hz), 3.65 (br. d, 1H, α′-C*H*-N, J ≈ 8.7 Hz), 4.19 (br. d, 1H, α′-C*H*-N, J ≈ 14.2 Hz), 4.34 (q, 2H, OCH_2, J = 7.1 Hz), 7.30-7.47 (m, $2H_{arom.}$), 7.56-7.70 (m, $2H_{arom.}$); ^{13}C nmr ($CDCl_3$; 90.6 MHz): δ 14.0 (CH_3), 23.8, 25.1, 28.2, 31.2, 47.6, 53.5, 62.7, 63.7, 98.8, 115.0, 116.0, 117.9, 123.3, 124.9, 131.1, 152.4, 153.4, 161.6 (C=O, lactone), 167.0 (C=O, ester). MS (70 eV): *m/z* (%) 352 (76; $M^{\bullet+}$), 324 (3), 307 (5), *279* (100), 251 (12), 240 (96), 196 (6). *Anal.* Calcd. for $C_{20}H_{20}N_2O_4$ (352.38): C, 68.17; H, 5.72; N, 7.95. Found: C, 68.13; H, 5.72; N, 7.96.

Ethyl 8-cyano-6-oxo-7,8,8a,9,10,11,12,13-octahydro-6*H*-chromeno[3',4':5,6]pyrido[1,2-*a*]azepine-8-carboxylate (**5b**). A solution of 366 mg (1.0 mmol) of the ester **4b** in 5.0 ml glacial acetic acid was refluxed for 2 h. The yellow solution decolorised. On cooling the product **5b** separated in crystalline form and was collected by filtration. Yield 260 mg (71 %) of TLC homogeneous, colourless crystals (ethanol), mp 146-148 °C; ir: ν 2245 (weak, CN), 1737 (C=O, ester), 1702 (C=O, lactone), 1599, 1558, 1404, 1366, 1255, 1218, 1079, 755 cm^{-1}; ^{1}H nmr (DMSO-d_6; 300 MHz): δ 1.30 (t, 3H, CH_3, J = 7.1 Hz), 1.36-1.64 (m, 2H, CH_2), 1.80-2.15 (m, 6H, three CH_2, azepane ring), 3.03 (d, 1H, H_A of AB-quartet, J = 17.6 Hz), 3.17 (d, 1H, H_B of AB-quartet, J = 17.6 Hz), 3.54-3.66 (m, 1H, α-CH-N of azepane ring), 3.66-3.88 (m, 2H, α′-CH_2-N of azepane ring), 4.22-4.42 (m, 2H, OCH_2), 7.30-7.50 (m, $2H_{arom.}$), 7.80 (d, $1H_{arom.}$, J = 7.9 Hz), 7.62 (m_c, $1H_{arom.}$); ^{13}C nmr ($CDCl_3$; 90.6 MHz): δ 14.1 (CH_3), 25.7, 28.7, 29.7, 31.9, 32.8, 44.6, 49.6, 63.5, 100.8, 115.4, 117.1, 118.1, 123.5, 124.4, 131.0, 152.8, 154.0, 161.6 (C=O, lactone), 168.0 (C=O, ester); ms (70 eV): *m/z* (%) 366 (63; $M^{\bullet+}$), 337 (4), 321 (5), *293* (100), 265 (8), 254 (47), 198 (7). *Anal.* Calcd. for $C_{21}H_{22}N_2O_4$ (366.41): C, 68.84; H, 6.05; N, 7.65. Found C, 68.80; H, 6.07; N, 7.68.

Ethyl 8-cyano-5-methyl-6-oxo-5,7,8,8a,9,10,11,12-octahydro-6*H*-5,12a-diaza-benzo[*c*]phenanthrene-8-carboxylate (**5c**). A stirred solution of 1.0 g (2.74 mmol) of the 2-quinolone derivative **4c** in 10 ml of glacial acetic acid was heated under reflux for 1.5 h. After the reaction was complete (tlc-monitoring) the mixture was poured onto 100 g of crashed ice and stirred for further 30 min. The yellow precipitate was collected by filtration and air-dried to give crude **5c** (0.86 g) which was flash-chromatographed on silica gel Merck 60H (eluted by ethylacetate-petroleum ether 4:1). Yield: 402 mg (40 %) of pure **5c**, pale yellow prisms (acetonitrile), mp 172-173 °C; ir (KBr): ν 2976, 2938, 2850 (CN band not observed), 1743 (C=O, ester), 1622 (C=O, lactam), 1593, 1251 cm^{-1}; ^{1}H nmr (DMSO-d_6; 360 MHz): δ 1.39 (t, J = 7.0, 3H), 1.84 – 2.17 (m, 6H), 2.82 (t, J = 11.9, 1H), 3.01 (d, 1H, H_A of AB-quartet, J = 16.8 Hz), 3.37 – 3. 41 (m, 1H), 3.53 (d, 1H, H_B of AB-quartet, J = 16.8 Hz), 3.67 (s, 3H, N-CH_3), 4.17 (d, 1H, J = 13.2 Hz), 4.37 (q, 2H, J = 6.9 Hz), 7.19 (t, 1H, J = 7.4 Hz), 7.36 (d, 1H, J = 8.4 Hz); 7.5 (t, 1H, J = 7.5 Hz), 7.6 (d, 1H, J = 7.9 Hz). ^{13}C nmr ($CDCl_3$; 90.6 MHz): δ 14.2, 24.1, 27.0, 29.8, 54.3, 62.4, 107.9, 112.7, 115.0, 115.3, 118.6, 121.5, 126.6, 132.0, 140.9, 153.2, 159.5, 160.3 (C=O, lactam), 162.7 (C=O, ester); APCI-ms (70 eV): *m/z* (%) 366 (26, M + 1), 365 (100, M), 293 (43, M – 72). *Anal.* Calcd. for $C_{21}H_{23}N_3O_3$ (365.44): C, 69.02; H, 6.34; N, 11.50. Found C, 68.95; H, 6.34; N, 11.49.

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