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# *N*-(*p*-Ethynylbenzoyl) derivatives of amino acid and dipeptide methyl esters – Synthesis and structural study

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ABSTRACT

A series of *N*-(*p*-ethynylbenzoyl) derivatives (**1–4**) of the amino acids glycine and L-alanine as well as the dipeptides glycylglycine and L-alanylglycine has been synthesized via a two-step reaction sequence including the reaction of an appropriate *N*-(*p*-bromobenzoyl) precursor with trimethylsilylacetylene followed by deprotection of the trimethylsilyl protecting group, respectively. X-ray crystal structures of the amino acid and dipeptide methyl esters **1–4** are reported. The amide and peptide bonds within each molecular structure are planar and adopt the *trans*-configuration. The packing structures are governed by N—H···O interactions leading to the formation of characteristic strand motifs. Further stabilization results from weaker C—H···O and C—H···π contacts.



## 1. Introduction

Amino acids and peptides can be considered as interesting molecular building blocks for the construction of bio-inspired materials or nanotechnological devices [1,2]. The synthesis of those bioconjugate structures demands the linkage of synthetic molecules and amino acid or peptide fragments via covalent bonds [3]. Hence, amino acid or peptide building blocks containing a functional group that ensures a chemoselective covalent bond formation are required in order to build up the intended bioconjugates. Metal-catalyzed coupling or cycloaddition reactions [4] are very promising methods for this kind of bond formation. Regarding these types of reactions, ethynyl substituted compounds are important building units as they serve as excellent coupling components in respective C—C coupling reactions, including the methods originally developed by Sonogashira et al. [5], Cadiot and Chodkiewicz [6] or Eglinton et al. [7]. Ethynyl derivatives are also important for 1,3-dipolar Huisgen type cycloadditions [8], nowadays referred to as "click" reactions [9]. Although in the literature a number of examples of ethynyl-containing derivatives of the simple amino acids glycine and alanine as well as other natural amino acids can be found, research in this field has mainly focused on α-ethynyl [10], α-propargyl [11], propargylic ester [12] and *N*-propargyl derivatives [13]. In extension to our recent study relating to *N*-(*p*-bromobenzoyl) amino acids and peptides as promising building blocks for the construction of bio-inspired hybrid compounds [14], here we present a new method of incorporating a reactive terminal C≡C triple bond into natural amino acids and peptides with the ethynyl moiety being part of an *N*-benzoyl substituent. Using this method, we synthesized a series of four new *N*-(*p*-ethynylbenzoyl) derivatized amino acid and peptide methyl esters (**1–4**, Fig. 1) contributing to an expansion of the pool of non-natural ethynyl-containing amino acids and peptides that offer potential applications in bioconjugate formation. In this connection, the knowledge of the solid state structures of the new compounds is of relevance. Thus, here we describe the synthesis of the respective compounds (Fig. 1) and report their X-ray crystal structures focusing on molecular geometries and characteristic packing motifs.

## 2. Experimental

### 2.1. Materials and methods

The starting materials *N*-(*p*-bromobenzoyl)glycine methyl ester, *N*-(*p*-bromobenzoyl)-L-alanine methyl ester, *N*-(*p*-bromobenzoyl)glycylglycine methyl ester and *N*-(*p*-bromobenzoyl)-L-alanylglycine methyl ester were prepared as described in a previous paper [14]. All other chemicals were purchased from commercial sources and used without further purification. Dry solvents (ethyl acetate, triethylamine and methanol) were obtained using standard drying procedures.

Thin layer chromatography (TLC) was performed using aluminum sheets coated with silica gel 60 $F_{254}$ (MERCK, Darmstadt, Germany). Silica gel 60, 0.040–0.063 mm (MERCK, Darmstadt, Germany) was used for flash column chromatography.

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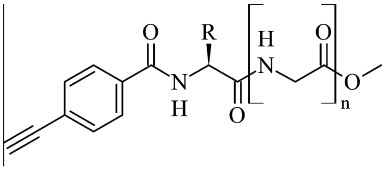


**1**: R = H, n = 0

**2**: R = Me, n = 0

**3**: R = H, n = 1

**4**: R = Me, n = 1

**Fig. 1.** Compound formulas of *N*-(*p*-ethynylbenzoyl) substituted amino acid and dipeptide methyl ester derivatives **1–4** studied in this paper.

Melting points (mp) were determined with a BÜCHI Melting Point B-450 device (BÜCHI Labortechnik AG, Flawil, Switzerland) and are uncorrected. Optical rotation measurements were performed on a Perkin–Elmer 241 polarimeter at 20 °C and with $\lambda = 589.3$ nm ($Na_D$ line). The $[\alpha]_D^{20}$ values are given in $10^{-1}$°cm$^2$ g$^{-1}$ (including the molar concentration and solvent used for the appropriate measurement). $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance III 500 NMR spectrometer at 500.13 MHz and 125.76 MHz, respectively, at 25 °C and with DMSO-$d_6$ as solvent. Chemical shifts ($\delta$) are given in ppm (referring to tetramethylsilane as internal standard) and coupling constants ($^3J_{HH}$, $^2J_{HH}$) in Hz. The multiplicity is given as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quintuplet), m (multiplet) or br s (broad singlet). IR spectra were recorded in the range of $\bar{\nu} = 4000—400$ cm$^{-1}$ using a Nicolet 510-FT-IR spectrometer (KBr pellets). MS spectra were obtained using a GC/MS system Hewlett–Packard 5890 Series II/MS 5989A (electron ionization). The ESI-MS spectrum was measured on a Varian 320-MS LC/MS system in negative (−) scan mode. Elemental analyses (EA) were performed on an Elementar Vario Micro Cube elemental analysator.

### 2.2. General procedure for the preparation of the N-[p-(trimethylsilylethynyl)benzoyl] amino acid and dipeptide methyl esters **5–8**

The corresponding *N*-(*p*-bromobenzoyl) amino acid or dipeptide methyl ester (15 mmol) and trimethylsilylacetylene (6.3 ml, 45 mmol) were added to a mixture of dry ethyl acetate and dry triethylamine (37.5 ml). The resulting mixture was degassed by sonication for 10 min under argon. Bis(triphenylphosphane)palladium(II) chloride (105.3 mg, 0.15 mmol), triphenylphosphane (78.7 mg, 0.3 mmol) and copper(I) iodide (57.1 mg, 0.3 mmol) were added and the reaction mixture was stirred at 60 °C under argon. After completion of the reaction (monitored by TLC) and cooling to room temperature, the mixture was washed twice with saturated $NH_4Cl$ solution and once with saturated NaCl solution. The organic phase was dried over $Na_2SO_4$, the solvent removed in vacuo and the resulting residue subjected to a flash column chromatography. Specific details for each compound are given below.

#### 2.2.1. N-[p-(Trimethylsilylethynyl)benzoyl]glycine methyl ester (**5**)

*N*-(*p*-Bromobenzoyl)glycine methyl ester (4.08 g, 15 mmol) and ethyl acetate (60 ml) were used (reaction time: 5 h). Purification by flash column chromatography (*n*-hexane/ethyl acetate 1:1 *v*/*v*) yielded **5** as a colorless solid (3.84 g, 88%), mp 108–110 °C. $R_f$: 0.52 (*n*-hexane/ethyl acetate 1:1 *v*/*v*). $^1$H NMR: $\delta_H = 0.25$ (9H, s, Si—(C*H*$_3$)$_3$); 3.66 (3H, s, O—C*H*$_3$); 4.02 (2H, d, $^3J_{HH} = 5.85$, C*H*$_2$); 7.57 (2H, d, $^3J_{HH} = 8.35$, Ar—*H*); 7.87 (2H, d, $^3J_{HH} = 8.40$, Ar—*H*); 9.05 (1H, t, $^3J_{HH} = 5.85$, N*H*). $^{13}$C NMR: $\delta_C = -0.15$ (Si—(*C*H$_3$)$_3$); 41.29 (*C*H$_2$); 51.81 (O—*C*H$_3$); 96.70 (C≡*C*—Si—(CH$_3$)$_3$); 104.43 (Ph—*C*≡C); 125.20, 127.62, 131.69, 133.60 (Ar—*C*); 165.81 (Ph—*C*O—NH); 170.31 (*C*O—O—CH$_3$). IR: $\bar{\nu} = 3281$; 3088; 2958; 2895; 2157; 1755; 1651; 1606; 1546; 1499; 1442; 1404; 1372; 1328; 1306; 1283; 1255; 1207; 1185; 1021; 1008; 875; 859; 840; 758; 698; 666; 634; 561. MS: *m*/*z* calcd for $C_{15}H_{19}NO_3Si$: 289.11, found: 289 [M]$^{+\cdot}$. EA: % calcd: C, 62.25, H, 6.62, N, 4.84, found: C, 61.88, H, 6.67, N, 4.78.

#### 2.2.2. N-[p-(Trimethylsilylethynyl)benzoyl]-L-alanine methyl ester (**6**)

*N*-(*p*-Bromobenzoyl)-L-alanine methyl ester (4.29 g, 15 mmol) and ethyl acetate (40 ml) were used (reaction time: 4.5 h). Purification by flash column chromatography (*n*-hexane/ethyl acetate 2:1 *v*/*v*) afforded **6** as a colorless solid (3.91 g, 86%), mp 126–128 °C. $[\alpha]_D^{20}$: +13.3 (0.05 M, methanol). $R_f$: 0.49 (*n*-hexane/ethyl acetate 2:1 *v*/*v*). $^1$H NMR: $\delta_H = 0.26$ (9H, s, Si—(C*H*$_3$)$_3$); 1.41 (3H, d, $^3J_{HH} = 7.30$, CH—C*H*$_3$); 3.65 (3H, s, O—C*H*$_3$); 4.49 (1H, qui, $^3J_{HH} = 7.20$, C*H*); 7.57 (2H, d, $^3J_{HH} = 8.50$, Ar—*H*); 7.90 (2H, d, $^3J_{HH} = 8.55$, Ar—*H*); 8.90 (1H, d, $^3J_{HH} = 6.90$, N*H*). $^{13}$C NMR: $\delta_C = -0.16$ (Si—(*C*H$_3$)$_3$); 16.73 (CH—*C*H$_3$); 48.36 (*C*H); 51.94 (O—*C*H$_3$); 96.62 (C≡*C*—Si—(CH$_3$)$_3$); 104.45 (Ph—*C*≡C); 125.12, 127.79, 131.56, 133.65 (Ar—*C*); 165.40 (Ph—*C*O—NH); 173.31 (*C*O—O—CH$_3$). IR: $\bar{\nu} = 3294$; 3066; 2993; 2955; 2895; 2157; 1755; 1739; 1632; 1606; 1543; 1499; 1448; 1435; 1337; 1274; 1252; 1211; 1185; 1166; 1119; 865; 843; 767; 672; 631. MS: *m*/*z* calcd for $C_{16}H_{21}NO_3Si$: 303.13; found: 303 [M]$^{+\cdot}$. EA: % calcd: C, 63.33, H, 6.97, N, 4.62, found: C, 63.50, H, 7.23, N, 4.64.

#### 2.2.3. N-[p-(Trimethylsilylethynyl)benzoyl]glycylglycine methyl ester (**7**)

*N*-(*p*-Bromobenzoyl)glycylglycine methyl ester (4.95 g, 15 mmol) and ethyl acetate (120 ml) were used (reaction time: 5 h). Purification by flash column chromatography (*n*-hexane/ethyl acetate 1:3 *v*/*v*) yielded **7** as a colorless solid (4.74 g, 91%), mp 135–137 °C. $R_f$: 0.31 (*n*-hexane/ethyl acetate 1:3 *v*/*v*). $^1$H NMR: $\delta_H = 0.25$ (9H, s, Si—(C*H*$_3$)$_3$); 3.63 (3H, s, O—C*H*$_3$); 3.86 (2H, d, $^3J_{HH} = 5.85$, C*H*$_2$); 3.91 (2H, d, $^3J_{HH} = 5.90$, C*H*$_2$); 7.56 (2H, d, $^3J_{HH} = 8.25$, Ar—*H*); 7.89 (2H, d, $^3J_{HH} = 8.30$, Ar—*H*); 8.36 (1H, t, $^3J_{HH} = 5.80$, N*H*); 8.89 (1H, t, $^3J_{HH} = 5.90$, N*H*). $^{13}$C NMR: $\delta_C = -0.14$ (Si—(*C*H$_3$)$_3$); 40.63, 42.48 (*C*H$_2$); 51.73 (O—*C*H$_3$); 96.56 (C≡*C*—Si—(CH$_3$)$_3$); 104.50 (Ph—*C*≡C); 124.99, 127.75, 131.57, 134.04 (Ar—*C*); 165.71 (Ph—*C*O—NH); 169.49, 170.30 (CH$_2$—*C*O—NH, *C*O—O—CH$_3$). IR: $\bar{\nu} = 3297$; 3079; 2958; 2930; 2895; 2854; 2160; 1739; 1676; 1641; 1606; 1546; 1496; 1442; 1410; 1382; 1306; 1280; 1252; 1217; 1182; 1119; 1033; 1017; 998; 865; 843; 764; 701; 666; 618; 549. MS: *m*/*z* calcd for $C_{17}H_{22}N_2O_4Si$: 346.13, found: 346 [M]$^{+\cdot}$. EA: % calcd: C, 58.93, H, 6.40, N, 8.09, found: C, 59.18, H, 6.55, N, 7.92.

#### 2.2.4. N-[p-(Trimethylsilylethynyl)benzoyl-L-alanylglycine methyl ester (**8**)

*N*-(*p*-Bromobenzoyl)-L-alanylglycine methyl ester (5.16 g, 15 mmol) and ethyl acetate (150 ml) were used (reaction time: 3.5 h). Purification by flash column chromatography (*n*-hexane/ethyl acetate 1:2 *v*/*v*) afforded **8** as a colorless solid (3.75 g, 69%), mp 128–130 °C. $[\alpha]_D^{20}$: +30.7 (0.02 M, acetone). $R_f$: 0.35 (*n*-hexane/ethyl acetate 1:2 *v*/*v*). $^1$H NMR: $\delta_H = 0.24$ (9H, s, Si—(C*H*$_3$)$_3$); 1.35 (3H, d, $^3J_{HH} = 7.25$, CH—C*H*$_3$); 3.62 (3H, s, O—C*H*$_3$); 3.82 (1H, dd, $^2J_{HH} = 17.35$, $^3J_{HH} = 5.85$, C*H*$_2$); 3.88 (1H, dd, $^2J_{HH} = 17.35$, $^3J_{HH} = 6.00$, C*H*$_2$); 4.52 (1H, qui, $^3J_{HH} = 7.25$, C*H*); 7.55 (2H, d, $^3J_{HH} = 8.45$, Ar—*H*); 7.91 (2H, d, $^3J_{HH} = 8.45$, Ar—*H*); 8.34 (1H, t, $^3J_{HH} = 5.90$, CH$_2$—N*H*); 8.66 (1H, d, $^3J_{HH} = 7.50$, CH—N*H*). $^{13}$C NMR: $\delta_C = -0.14$ (Si—(*C*H$_3$)$_3$); 17.83 (CH—*C*H$_3$); 40.69 (*C*H$_2$); 48.88 (*C*H); 51.74 (O—*C*H$_3$); 96.51 (C≡*C*—Si—(CH$_3$)$_3$); 104.56 (Ph—*C*≡C); 124.96, 127.97, 131.49, 134.10 (Ar—*C*); 165.31 (Ph—*C*O—NH); 170.33, 172.95 (CH—*C*O—NH, *C*O—O—CH$_3$). IR: $\bar{\nu} = 3351$; 3291;

3088; 2955; 2895; 2164; 1755; 1673; 1647; 1609; 1537; 1496; 1451; 1410; 1375; 1252; 1217; 1182; 1014; 869; 843; 761; 701; 669. MS: *m*/*z* calcd for $C_{18}H_{24}N_2O_4Si$: 360.15, found: 360 $[M]^{+\cdot}$. EA: % calcd: C, 59.97, H, 6.71, N, 7.77, found: C, 59.59, H, 7.10, N, 7.82.

### 2.3. General procedure for the preparation of the N-(p-ethynylbenzoyl) amino acid and dipeptide methyl esters **1–4**

The corresponding *N*-[*p*-(trimethylsilylethynyl)benzoyl] amino acid or dipeptide methyl ester (8 mmol) was dissolved in dry methanol. Finely powdered $K_2CO_3$ (0.11 g, 0.8 mmol) was added and the mixture was stirred at room temperature. After completion of the reaction (monitored by TLC), the mixture was diluted with 65 ml of ethyl acetate, washed with diluted $NaHCO_3$ solution (2 × 30 ml) and 25 ml of water. After drying over $Na_2SO_4$, the solvent was removed in vacuo and the resulting residue purified by flash column chromatography or recrystallization. Specific details for each compound are given below.

#### 2.3.1. N-(p-Ethynylbenzoyl)glycine methyl ester (**1**)

Compound **5** (2.32 g, 8 mmol) and methanol (25 ml) were used (reaction time: 3 h). Purification by flash column chromatography (*n*-hexane/ethyl acetate 1:1 *v*/*v*) yielded **1** as a colorless solid (1.42 g, 82%), mp 116–118 °C. $R_f$: 0.39 (*n*-hexane/ethyl acetate 1:1 *v*/*v*). $^1$H NMR: $\delta_H$ = 3.66 (3H, s, C*H*$_3$); 4.03 (2H, d, $^3J_{HH}$ = 5.85, C*H*$_2$); 4.39 (1H, s, C≡C—*H*); 7.61 (2H, d, $^3J_{HH}$ = 8.35, Ar—*H*); 7.89 (2H, d, $^3J_{HH}$ = 8.40, Ar—*H*); 9.06 (1H, t, $^3J_{HH}$ = 5.80, N*H*). $^{13}$C NMR: $\delta_C$ = 41.32 (*C*H$_2$); 51.84 (*C*H$_3$); 82.89, 83.06 (*C*≡*C*); 124.85, 127.63, 131.84, 133.70 (Ar—*C*); 165.90 (Ph—*C*O—NH); 170.35 (*C*O—O—CH$_3$). IR: $\bar{\nu}$ = 3265; 3085; 3072; 3028; 2955; 2857; 2110; 1749; 1625; 1546; 1499; 1432; 1416; 1369; 1328; 1309; 1283; 1217; 1182; 1112; 1071; 1024; 998; 976; 862; 777; 720; 650; 637; 542. MS: *m*/*z* calcd for $C_{12}H_{11}NO_3$: 217.07, found: 217 $[M]^{+\cdot}$. EA: % calcd: C, 66.35, H, 5.10, N, 6.45, found: C, 66.00, H, 5.27, N, 6.23.

#### 2.3.2. N-(p-Ethynylbenzoyl)-L-alanine methyl ester (**2**)

Compound **6** (2.42 g, 8 mmol) and methanol (25 ml) were used (reaction time: 4 h). Purification by flash column chromatography (*n*-hexane/ethyl acetate 2:1 *v*/*v*) afforded **2** as a colorless solid (1.58 g, 85%), mp 113–115 °C. $[\alpha]_D^{20}$: +4.8 (0.05 M, methanol). $R_f$: 0.33 (*n*-hexane/ethyl acetate 2:1 *v*/*v*). $^1$H NMR: $\delta_H$ = 1.41 (3H, d, $^3J_{HH}$ = 7.30, CH—C*H*$_3$); 3.65 (3H, s, O—C*H*$_3$); 4.39 (1H, s, C≡C—*H*); 4.49 (1H, qui, $^3J_{HH}$ = 7.20, C*H*); 7.59 (2H, d, $^3J_{HH}$ = 8.40, Ar—*H*); 7.90 (2H, d, $^3J_{HH}$ = 8.55, Ar—*H*); 8.89 (1H, d, $^3J_{HH}$ = 6.90, N*H*). $^{13}$C NMR: $\delta_C$ = 16.76 (CH—*C*H$_3$); 48.39 (*C*H); 51.97 (O—*C*H$_3$); 82.91, 83.01 (*C*≡*C*); 124.76, 127.80, 131.71, 133.76 (Ar—*C*); 165.50 (Ph—*C*O—NH); 173.12 (*C*O—O—CH$_3$). IR: $\bar{\nu}$ = 3332; 3246; 3006; 2952; 2923; 2851; 2107; 1739; 1641; 1609; 1530; 1496; 1461; 1363; 1318; 1271; 1220; 1169; 856; 774; 701; 653; 628. MS: *m*/*z* calcd for $C_{13}H_{13}NO_3$: 231.09, found: 231 $[M]^{+\cdot}$. EA: % calcd: C, 67.52, H, 5.67, N, 6.06, found: C, 67.32, H, 5.76, N, 6.04.

#### 2.3.3. N-(p-Ethynylbenzoyl)glycylglycine methyl ester (**3**)

Compound **7** (2.77 g, 8 mmol) and methanol (50 ml) were used (reaction time: 2 h). In contrast to the general procedure described above, the precipitated solid was separated and washed with methanol (2 × 20 ml) to yield a first product fraction. The remaining solution was diluted with 150 ml of ethyl acetate, washed with diluted $NaHCO_3$ solution (2 × 50 ml) and 50 ml of water. After drying over $Na_2SO_4$, the solvent was removed in vacuo. The resulting second product fraction was purified by recrystallization from methanol. Both product fractions were combined to yield **3** as an off-white solid (1.74 g, 79%), mp 178–180 °C. $^1$H NMR: $\delta_H$ = 3.63 (3H, s, C*H*$_3$); 3.86 (2H, d, $^3J_{HH}$ = 5.85, C*H*$_2$); 3.92 (2H, d, $^3J_{HH}$ = 5.95, C*H*$_2$); 4.38 (1H, s, C≡C—*H*); 7.59 (2H, d, $^3J_{HH}$ = 8.30, Ar—*H*); 7.90 (2H, d, $^3J_{HH}$ = 8.30, Ar—*H*); 8.37 (1H, t, $^3J_{HH}$ = 5.80, N*H*); 8.90 (1H, t, $^3J_{HH}$ = 5.95, N*H*). $^{13}$C NMR: $\delta_C$ = 40.66, 42.49 (*C*H$_2$); 51.76 (*C*H$_3$); 82.96 (*C*≡*C*); 124.64, 127.76, 131.69, 134.11 (Ar—*C*); 165.76 (Ph—*C*O—NH); 169.53, 170.33 (CH$_2$—*C*O—NH, *C*O—O—CH$_3$). IR: $\bar{\nu}$ = 3332; 3291; 3231; 3079; 2996; 2980; 2952; 2917; 2854; 2103; 1733; 1670; 1641; 1609; 1559; 1505; 1461; 1442; 1423; 1407; 1394; 1372; 1356; 1328; 1309; 1280; 1258; 1236; 1195; 1059; 1040; 1017; 995; 859; 767; 726; 691; 628; 552. MS: *m*/*z* calcd for $C_{14}H_{14}N_2O_4$: 274.10, found: 274 $[M]^{+\cdot}$. EA: % calcd: C, 61.31, H, 5.14, N, 10.21, found: C, 61.13, H, 5.22, N, 10.21.

#### 2.3.4. N-(p-Ethynylbenzoyl)-L-alanylglycine methyl ester (**4**)

Compound **8** (2.89 g, 8 mmol) and methanol (25 ml) were used (reaction time: 3.5 h). Recrystallization from methanol/diethyl ether afforded **4** as an off-white solid (1.61 g, 70%), mp 166–167 °C. $[\alpha]_D^{20}$: +6.7 (0.05 M, methanol). $^1$H NMR: $\delta_H$ = 1.36 (3H, d, $^3J_{HH}$ = 7.25, CH—C*H*$_3$); 3.63 (3H, s, O—C*H*$_3$); 3.83 (1H, dd, $^2J_{HH}$ = 17.35, $^3J_{HH}$ = 5.85, C*H*$_2$); 3.89 (1H, dd, $^2J_{HH}$ = 17.30, $^3J_{HH}$ = 6.00, C*H*$_2$); 4.37 (1H, s, C≡C—*H*); 4.53 (1H, qui, $^3J_{HH}$ = 7.30, C*H*); 7.58 (2H, d, $^3J_{HH}$ = 8.25, Ar—*H*); 7.93 (2H, d, $^3J_{HH}$ = 8.30, Ar—*H*); 8.36 (1H, t, $^3J_{HH}$ = 5.85, CH$_2$—N*H*); 8.67 (1H, d, $^3J_{HH}$ = 7.50, CH—N*H*). $^{13}$C NMR: $\delta_C$ = 17.76 (CH—*C*H$_3$); 40.61 (*C*H$_2$); 48.79 (*C*H); 51.66 (O—*C*H$_3$); 82.80, 82.91 (*C*≡*C*); 124.50, 127.88, 131.49, 134.10 (Ar—*C*); 165.30 (Ph—*C*O—NH); 170.26, 172.87 (CH—*C*O—NH, *C*O—O—CH$_3$). IR: $\bar{\nu}$ = 3297; 3265; 3082; 2984; 2958; 2933; 2107; 1746; 1663; 1625; 1559; 1537; 1499; 1448; 1385; 1366; 1340; 1293; 1277; 1220; 1182; 1166; 1021; 976; 897; 856; 767; 713; 666; 634. ESI(-)-MS: *m*/*z* calcd for $C_{15}H_{16}N_2O_4$: 288.11, found: 287.1 $[M-H]^-$, 322.9 $[M+Cl]^-$. EA: % calcd: C, 62.49, H, 5.59, N, 9.72, found: C, 62.49, H, 5.84, N, 9.57.

### 2.4. X-ray structure determination

Crystals suitable for X-ray crystal structure determination were obtained by slow evaporation of solutions of the respective compounds in ethyl acetate (**1–3**) and methanol (**4**).

The X-ray crystal structure analyses were performed using a Bruker Kappa diffractometer equipped with an APEX II CCD area detector and graphite-monochromatized Mo Kα radiation ($\lambda$ = 0.71073 Å) employing $\varphi$ and $\omega$ scan modes. The data were corrected for Lorentz and polarization effects. Semiempirical absorption corrections were applied using the SADABS program and the SAINT program was utilized for the integration of the diffraction profiles [15]. The crystal structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement against $F^2$ using SHELXL-97 [16]. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were generated at ideal geometrical positions and refined with the appropriate riding model. Geometrical calculations were performed using PLATON [17] and molecular graphics were generated using SHELXTL [16]. The crystallographic data and refinement details of all compounds studied are summarized in Table SUP-1.

## 3. Results and discussion

### 3.1. Synthesis of N-(p-ethynylbenzoyl) amino acid and dipeptide methyl esters

Starting from corresponding *N*-(*p*-bromobenzoyl) amino acid and dipeptide methyl esters [14], a series of four *N*-(*p*-ethynylbenzoyl) amino acid and dipeptide methyl ester derivatives (**1–4**) was synthesized via a reaction sequence as shown in Scheme 1, respectively. In a first step, the *N*-(*p*-bromobenzoyl) derivatives

were reacted with trimethylsilylacetylene (TMSA) in a Pd-catalyzed *Sonogashira-Hagihara*-type C—C coupling procedure [5,18] to yield the ethynyl-protected *N*-[(*p*-trimethylsilylethynyl)benzoyl] amino acid and dipeptide methyl esters (intermediates **5–8**). In the second step, the deprotection of the ethynyl group of **5–8** using potassium carbonate in methanol was carried out to afford the target compounds **1–4** used for the crystallographic study.

### 3.2. Crystal structures of the amino acid derivatives *1* and *2*

The molecular structures of compounds **1** and **2** (Fig. 2) are characterized by nearly planar and *trans*-configurated amide bonds being be derived from the torsion angles O1—C7—N1—C8 [**1**: 4.2 (2)°, **2**: 1.5(2)°] and $\omega_{-1*}$ [**1**: −173.8(1)°, **2**: −176.9(2)°], respectively (Table 1). Differences occur in the torsion angle C3—C4—C7—O1 referring to the torsion of the phenyl ring with regard to the amide fragment and to a minor extent in the characteristic torsion angles $\varphi_1$ as well as $\psi_{1*}$ defining the conformation of the amino acid (Table 1). Hence, except for the different torsion of the phenyl ring with reference to the amide bond which could be caused by packing effects, the additional methyl group in the L-alanine derivative **2** does not significantly influence the molecular structure of the amino acid which is illustrated by a structural overlay plot in Fig. 3.

The packing structures of the glycine and L-alanine derivatives **1** and **2** are stabilized by numerous hydrogen bonding interactions including stronger N—H···O [19] and weaker C—H···O contacts [20] (Table 2). In both crystal packings molecular strands are formed due to the N1—H1···O1 interaction involving the amide N atom as donor and the amide O atom as acceptor site (Fig. 4). In the packing of compound **1**, the strand motif is further stabilized by an additional (aryl)C—H···O type contact (C5—H5···O1) resulting in the formation of a bifurcated-acceptor type hydrogen bond [21] which is also the case for the corresponding *N*-(*p*-bromobenzoyl) derivative described in a previous study [14]. The characteristic strands formed by the molecules of compound **1** run along the crystallographic *c* axis and exhibit an alternating arrangement of molecules. In contrast to **1**, the strand formation in the packing of compound **2** is assisted by a C—H···O interaction involving the L-alanine $C_\alpha$ methyl group (C11) as donor and the ester O atom (O3) as acceptor being in agreement with the previously published structure of the corresponding *N*-(*p*-bromobenzoyl)-L-alanine methyl ester [14]. In the packing of compound **2**, the strands are arranged parallel to the crystallographic *a* axis and show a regular, non-alternating molecular arrangement pattern.

The interactions between different strands within the crystal structures of **1** and **2** comprising (methyl)C—H···O and (ethynyl)C—H···O contacts [20] are of a weaker nature. In the packing of **1**, different strands are linked via (ethynyl)C12—H12···O2 interactions on one edge and (methyl)C10—H10C···O1 contacts on the

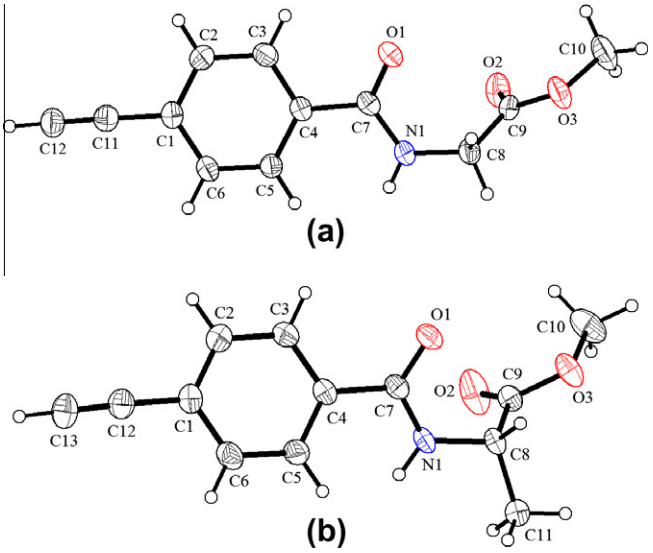



**Fig. 2.** Molecular structures of compounds **1** (a) and **2** (b) including atom numbering schemes. Thermal displacement ellipsoids are drawn at the 50% probability level.

**Table 1**
Selected torsion angles (°) for the compounds **1** and **2**.

| Torsion angle | 1 | 2 |
|---|---|---|
| C3—C4—C7—O1 | 14.5(2) | 30.5(2) |
| C4—C7—N1—C8 ($\omega_{-1*}$) | −173.8(1) | −176.9(2) |
| C7—N1—C8—C9 ($\varphi_1$) | −67.8(2) | −74.9(2) |
| C7—N1—C8—C11 | – | 163.3(2) |
| C8—C9—O3—C10 ($\omega_{1*}$) | 177.0(2) | −178.1(2) |
| N1—C8—C9—O3 ($\psi_{1*}$) | 158.2(1) | 146.5(2) |
| O1—C7—N1—C8 | 4.2(2) | 1.5(2) |

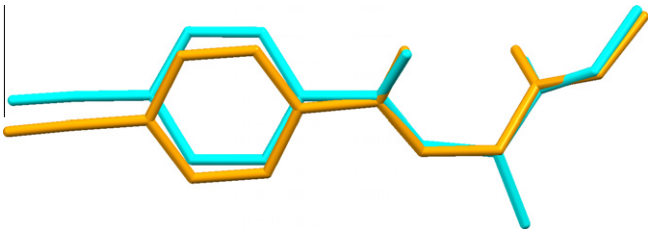
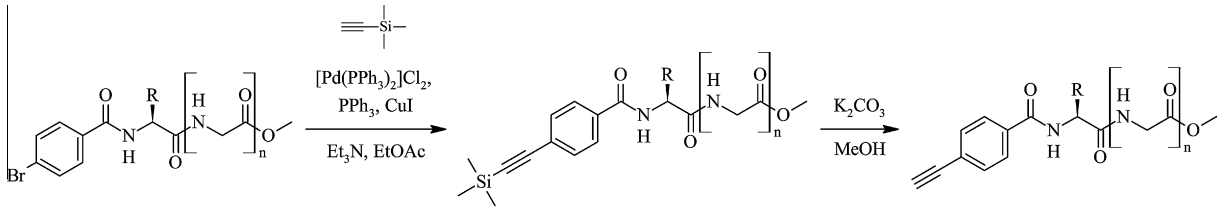


**Fig. 3.** Structural overlay of **1** (orange) and **2** (cyan). The overlay was calculated with RMS = 0.168 using pairs of atoms C7—C10, O1—O3 and N1, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)




**5**: R = H, n = 0
**6**: R = Me, n = 0
**7**: R = H, n = 1
**8**: R = Me, n = 1

**1**: R = H, n = 0
**2**: R = Me, n = 0
**3**: R = H, n = 1
**4**: R = Me, n = 1

**Scheme 1.** Two-step synthesis of compounds **1–4** via the respective intermediates **5–8** starting from the appropriate *N*-(*p*-bromobenzoyl) amino acid or peptide methyl ester.

**Table 2**
Interactions in the crystal structures of compounds **1** and **2**.

| Atoms involved | Symmetry | Distance (Å) | | | Angle (°) |
|---|---|---|---|---|---|
| | | *r*(D—H) | *d*(H···A) | *D*(D···A) | *θ*(D—H···A) |
| **1** | | | | | |
| N1—H1···O1 | $x, -y+1/2, z-1/2$ | 0.88 | 2.00 | 2.848(2) | 162.5 |
| C5—H5···O1 | $x, -y+1/2, z-1/2$ | 0.95 | 2.38 | 3.275(2) | 156.5 |
| C10—H10C···O1 | $-x+2, -y+1, -z+1$ | 0.98 | 2.54 | 3.120(2) | 117.8 |
| C12—H12···O2 | $-x+1, -y+1, -z$ | 0.95 | 2.35 | 3.191(2) | 147.0 |
| **2** | | | | | |
| N1—H1···O1 | $x+1, y, z$ | 0.88 | 2.20 | 3.052(2) | 164.1 |
| C11—H11B···O2 | $x, y, z+1$ | 0.98 | 2.43 | 3.293(2) | 146.7 |
| C11—H11C···O3 | $x+1, y, z$ | 0.98 | 2.41 | 3.345(2) | 158.7 |
| C13—H13···O2 | $-x+1, y-1/2, -z+1$ | 0.95 | 2.31 | 3.258(3) | 174.4 |

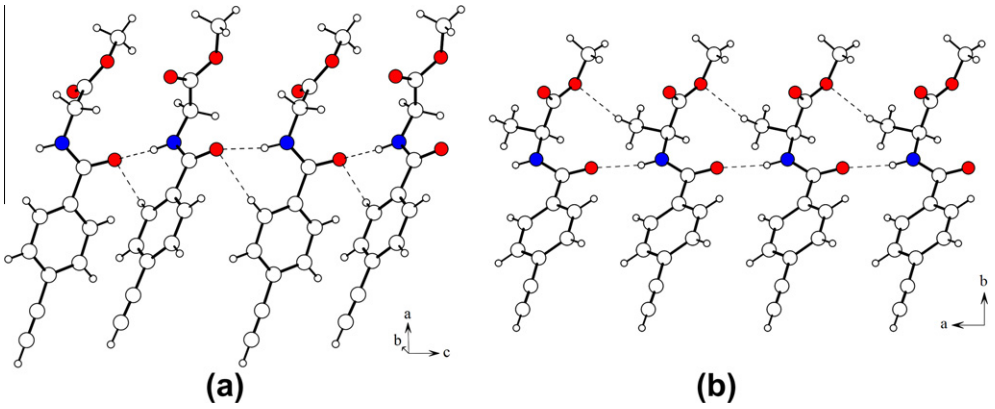



**Fig. 4.** Characteristic strand motifs within the packing structures of **1** (a) and **2** (b). Hydrogen bonding interactions are represented as dashed lines.

other one while for **2** the connection of different strands is realized via (ethynyl) C13—H13···O2 and (methyl)C11—H11B···O2 interactions both contributing to bifurcated-acceptor type hydrogen bonds [21]. Packing diagrams of the crystal structures of the amino acid derivatives **1** and **2** are included in the electronic supplementary material (Figs. 1sup and 2sup).

### 3.3. Crystal structures of the dipeptide derivatives *3* and *4*

The asymmetric units of the dipeptide derivatives consist of one molecule in the case of compound **3** and two molecules (**4′** and **4″**) in the case of compound **4** (Fig. 5). The examination of appropriate torsion angles shows that both the amide and the peptide bond within the respective molecular structures are nearly planar and *trans*-configurated. The planarity of these bonds can be deduced from the torsion angles O1—C7—N1—C8 (**3** and **4′**) and O5—C22—N3—C23 (**4″**) for the amide bonds as well as O2—C9—N2—C10 (**3** and **4′**) and O6—C24—N4—C25 for the peptide bonds, respectively, being approximately 0° (Table 3). The *trans*-configuration is proven by the torsion angles $\omega_{-1*}$ and $\omega_1$ for the amide and peptide bonds, respectively, adopting values of approximately ±180° (Table 3). A maximum deviation for these ideal values is found for the peptide bond in **4′** with torsion angles of 10.3(2)° (O2—C9—N2—C10) and −170.4(2)° ($\omega_1$). As already unveiled in Fig. 5b, the torsion angle $\psi_{2*}$ (N2—C10—C11—O4 for **4′** and N4—C25—C26—O8 for **4″**, respectively) is the major conformative difference between the two independent molecules within the asymmetric unit of **4**. A structural overlay plot, making this difference more obvious, is given in Fig. 6. For **3**, **4′** and **4″**, differences occur in the torsion of the phenyl ring with reference to the amide bond being represented by values of −10.4(2)°, 23.2(2)° and 34.0(2)° for the appropriate torsion angle C3—C4—C7—O1 or C18—C19—C22—O5, respectively.

In agreement with the amino acid derivatives **1** and **2**, the packing structures of the *N*-substituted dipeptide methyl esters **3** and **4** are characterized by the formation of strands being stabilized by N—H···O hydrogen bonding interactions [19] comprising the peptide group as donor and acceptor site (N2—H2N···O2 for **3**, N2—H2N···O6 and N4—H4N···O2 for **4**, Table 4). As shown in Fig. 7a, the strands in the packing of **3** are orientated in direction of the crystallographic *a* axis while the strands in the crystal structure of **4** are aligned parallel to the [*ac*] face diagonal and consist of the independent molecules **4′**and **4″** arranged in an alternating manner (Fig. 7b). Besides the N—H···O contacts, weaker (alkyl)C—H···O interactions [20] assist the formation of the characteristic strand motifs. For **3**, an additional (methylene)C—H···O interaction (C10—H10···O3) is observed, while in the strand of **4**, the N—H···O contact is assisted by C—H···O interactions comprising methyl, methine and methylene C atoms as donor sites (C12—H12B···O7, C23—H23···O2 and C25—H25A···O3).

In the crystal structures of **3** and **4**, the molecular strands are connected by different interactions with the remaining amide group and the ethynyl substituent being of major importance. In both of the crystal structures, the strands are linked to each other via N—H···O interactions (N1—H1N···O1 for **3**, N1—H1N···O5 and N3—H3N···O1 for **4**) which are slightly weaker than those mediating the linkage within the strands (Table 4). The ethynyl substituent in each crystal structure acts both as hydrogen bonding donor and acceptor. Acting as a donor, C—H···O contacts are formed (**3**: C14—H14···O3, **4**: C15—H15···O3). In the function of an acceptor, the midpoint of the triple bond takes part in different C—H···*Cg* interactions (Table 4). The resulting rather complex packing diagrams caused by the numerous intermolecular interactions are included in the electronic supplementary material (Figs. 3sup and 4sup).

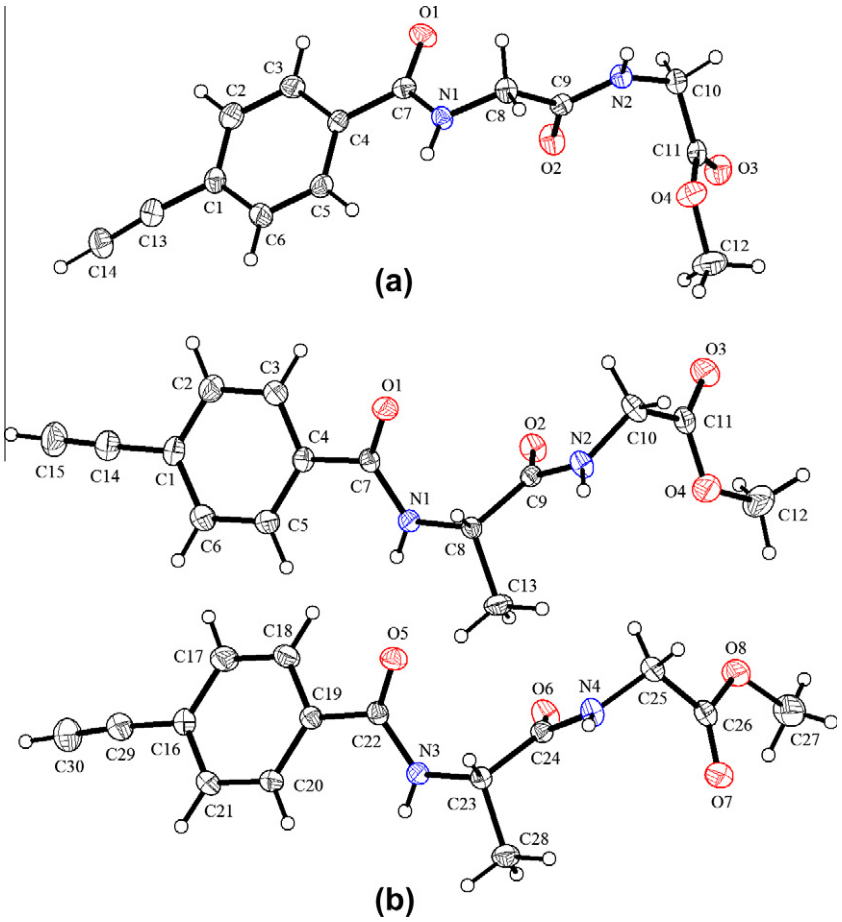



**Fig. 5.** Asymmetric units of the dipeptide derivatives **3** (a) and **4** (b) including atom numbering schemes. The two independent molecules in the asymmetric unit of **4** are **4′** on the top and **4″** at the bottom of (b). Thermal displacement ellipsoids are drawn at the 50% probability level.

**Table 3**
Selected torsion angles (°) for compounds **3** and **4**.

| Torsion angle | **3** | **4** | |
|---|---|---|---|
| | | **4′** | **4″** |
| C3—C4—C7—O1/C18—C19—C22—O5[a] | −10.4(2) | 23.2(2) | 34.0(2) |
| C4—C7—N1—C8/C19—C22—N3—C23[a] ($\omega_{-1*}$) | 179.3(2) | −177.3(2) | −176.4(2) |
| C7—N1—C8—C9/C22—N3—C23—C24[a] ($\varphi_1$) | −77.0(2) | −67.2(2) | −71.4(2) |
| C7—N1—C8—C13/C22—N3—C23—C28[a] | – | 170.5(2) | 167.6(2) |
| C8—C9—N2—C10/C23—C24—N4—C25[a] ($\omega_1$) | −174.7(2) | −170.4(2) | 179.4(2) |
| C9—N2—C10—C11/C24—N4—C25—C26[a] ($\varphi_2$) | −58.9(2) | −65.4(2) | −73.3(2) |
| C10—C11—O4—C12/C25—C26—O8—C27[a] ($\omega_{2*}$) | 179.2(2) | −175.8(2) | 178.0(2) |
| N1—C8—C9—N2/N3—C23—C24—N4[a] ($\psi_1$) | 175.6(2) | 162.2(2) | 157.8(2) |
| N2—C10—C11—O4/N4—C25—C26—O8[a] ($\psi_{2*}$) | −34.9(2) | −40.4(2) | 146.3(2) |
| O1—C7—N1—C8/O5—C22—N3—C23[a] | −0.2(2) | 0.9(2) | 2.0(2) |
| O2—C9—N2—C10/O6—C24—N4—C25[a] | 5.0(2) | 10.3(2) | 1.4(2) |

[a] The first torsion angle refers to **3** and **4′**, the second one to **4″**, respectively.

## 4. Conclusions

Four new amino acid and dipeptide derivatives featuring *N*-(*p*-ethynylbenzoyl) substituents have been prepared and characterized by standard analytical methods. The presented compounds are promising building blocks for the generation of new bioconjugate structures. The synthetic procedure is based on *N*-(*p*-bromobenzoyl) amino acid and dipeptide methyl esters which can be prepared by a previously described protocol [14] and comprises a C—C coupling step of the *Sonogashira-Hagihara*-type using

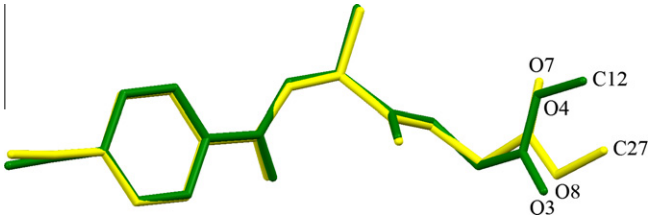



**Fig. 6.** Structural overlay of **4′** (green) and **4″** (yellow). The overlay was calculated with RMS = 0.181 using all pairs of non-hydrogen atoms except those labeled in the figure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 4**
Interactions in the crystal structures of compounds **3** and **4**.

| Atoms involved | Symmetry | Distance (Å) | | | Angle (°) |
|---|---|---|---|---|---|
| | | $r$(D—H) | $d$(H···A) | $D$(D···A) | $\theta$(D—H···A) |
| **3** | | | | | |
| N1—H1N···O1 | $x, -y+1/2, z-1/2$ | 0.88 | 2.05 | 2.865(2) | 154.1 |
| N2—H2N···O2 | $x+1, y, z$ | 0.88 | 1.94 | 2.809(2) | 168.5 |
| C10—H10A···O3 | $x+1, y, z$ | 0.99 | 2.48 | 3.337(2) | 144.2 |
| C10—H10B···*Cg** | $x+1, -y+1/2, z+1/2$ | 0.99 | 2.82 | 3.795(2) | 170.4 |
| C12—H12C···*Cg** | $x+1, -y+1/2, z-1/2$ | 0.98 | 2.74 | 3.718(2) | 176.9 |
| C14—H14···O3 | $-x, y-1/2, -z+3/2$ | 0.95 | 2.33 | 3.282(2) | 174.6 |
| **4** | | | | | |
| N1—H1N···O5 | $x, y, z$ | 0.88 | 2.28 | 3.134(2) | 165.0 |
| N2—H2N···O6 | $x, y, z-1$ | 0.88 | 2.04 | 2.880(2) | 159.8 |
| N3—H3N···O1 | $x-1, y, z+1$ | 0.88 | 2.26 | 3.116(2) | 164.7 |
| N4—H4N···O2 | $x-1, y, z$ | 0.88 | 2.05 | 2.905(2) | 162.3 |
| C10—H10A···O7 | $x+1, y, z-1$ | 0.99 | 2.56 | 3.150(2) | 118.5 |
| C12—H12B···O7 | $x+1, y, z$ | 0.98 | 2.50 | 3.473(3) | 175.8 |
| C12—H12C···*Cg1** | $-x+1, y+1/2, -z+1$ | 0.98 | 2.94 | 3.769(5) | 142.9 |
| C15—H15···O3 | $-x+2, y-1/2, -z+1$ | 0.95 | 2.23 | 3.181(2) | 178.1 |
| C23—H23···O2 | $x-1, y, z$ | 1.00 | 2.54 | 3.188(2) | 122.2 |
| C25—H25A···O3 | $x-1, y, z$ | 0.99 | 2.51 | 3.286(2) | 135.4 |
| C27—H27A···O3 | $x-1, y, z+1$ | 0.98 | 2.58 | 3.555(2) | 173.6 |
| C27—H27B···*Cg2** | $-x, y+1/2, -z+2$ | 0.98 | 2.98 | 3.633(5) | 125.0 |
| C27—H27C···*Cg2** | $-x+1, y+1/2, -z+2$ | 0.98 | 2.91 | 3.708(4) | 139.3 |

* *Cg*, *Cg*1 and *Cg*2 are the midpoints of the triple bonds C13≡C14, C14≡C15 and C29≡C30.

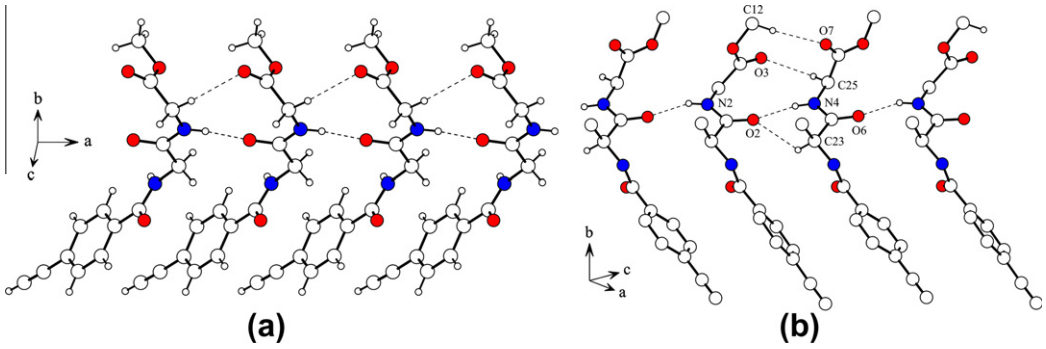



**Fig. 7.** Molecular strands within the crystal structures of **3** (a) and **4** (b). Hydrogen bonds are represented as dashed lines. For (b), only hydrogen atoms involved in hydrogen bonding interactions have been included, others have been omitted for clarity.

trimethylsilylacetylene (TMSA) as a protected acetylene compound, followed by a deprotection step to remove the trimethylsilyl group and to generate the free ethynyl substituent.

X-ray crystal structures of compounds **1–4** show that the amide and peptide bonds within the molecules are all planar and adopt the usually favored *trans*-configuration. In the molecular structures of **1–4**, the *p*-ethynylbenzoyl fragment is distorted towards the neighboring amide bond, with the respective torsion angle varying from −10.4(2)° to 34.0(2)°. The deviation from the ideal coplanar arrangement may be due to sterical hindrance between the amide hydrogen and the aryl hydrogen in *o*-position or caused by packing effects as the amide hydrogen is involved in an N—H···O hydrogen bond, respectively. The packing structures of compounds **1–4** are dominated by N—H···O interactions leading to the formation of molecular strands as characteristic structural motifs. Further stabilization of the packing structures results from weaker C—H···O or C—H···π contacts where – among others – interactions involving the ethynyl substituent either as donor or acceptor site are of major importance.

## Acknowledgement

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## Appendix A. Supplementary data

Table SUP-1 (containing crystallographic data and refinement details for the compounds studied), Fig. 1sup, Fig. 2sup, Fig. 3sup and Fig. 4sup (containing packing diagrams of compounds **1**, **2**, **3** and **4**, respectively). The crystal structure data for this paper have been deposited to the Cambridge Structural Database (CSD) and can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0)1223 336033; e-mail: deposit@ccdc.cam.ac.uk], quoting the CCDC deposition numbers 833948 (**1**), 833949 (**2**), 833950 (**3**) and 833951 (**4**). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2011.08.034.

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