POLYAMIDES CONTAINING C-TERMINUS β-ALANINE-CARBOXYLIC ACIDS AS INTERMEDIATES FOR DIVERGENT SYNTHESIS

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Abstract : The synthesis of eight imidazole- and pyrrole-containing polyamides contain an N-terminal pyrrole unit and C-terminal β-alanine carboxylic acid moiety is described. These heterocyclic polyamides are important synthons for the preparation of sequence selective DNA binding agents.

Keywords: β-alanine, polyamide, DNA, distamycin, acid

Introduction

The aliphatic amino acid β-alanine (β) has proved useful in the synthesis of extended minor groove-binding polyamide molecules. Synthetic derivatives of the naturally occurring polyamide distamycin containing the aromatic heterocycles pyrrole (Py) and/or imizadole (Im) form complexes in the minor groove of DNA.[1, 2] However, it has been shown that Py-Im containing polyamides are slightly more curved compared to the DNA helix.[3-5] Polyamides containing more than five heterocycles experience a large drop in binding affinity as the shape of the polyamide no longer fully complements the DNA helix due to over curvature. It has been demonstrated that the incorporation of the β-alanine moiety into a polyamide relaxes the curvature of the molecule, allowing for the synthesis of larger ligands that retain affinity for the DNA helix .[6-8]

Polyamides containing a β-alanine carboxylic acid moiety at the C-terminus have the potential to be coupled to amine-containing intermediates. Therefore, C-terminal-β-polyamides are useful synthons for the preparation of a range of different polyamide derivatives.[9] Moieties with specific functionalities, such as intercalators, can be coupled to these C-terminal-β polyamides, or the group can be used as a spacer between other polyamides. Consequently the availability of the C-terminal polyamides as intermediates will greatly aid in the future design of DNA binding agents. This paper describes the synthesis of eight C-terminal-β-polyamides (Figure-1): Four triheterocyclic polyamides (**1-4**) and four tetraheterocyclic polyamides (**5-8**). Each compound contains an Im and/or Py heterocyclic core, an N-terminal pyrrole moiety, and the C-terminal β-alanine-acid moiety.

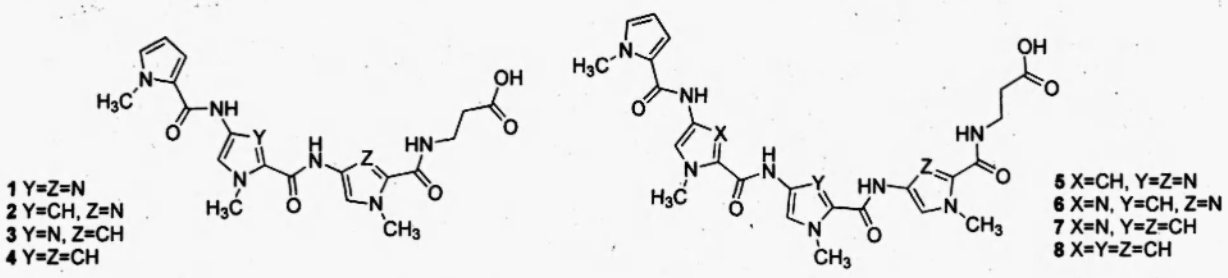
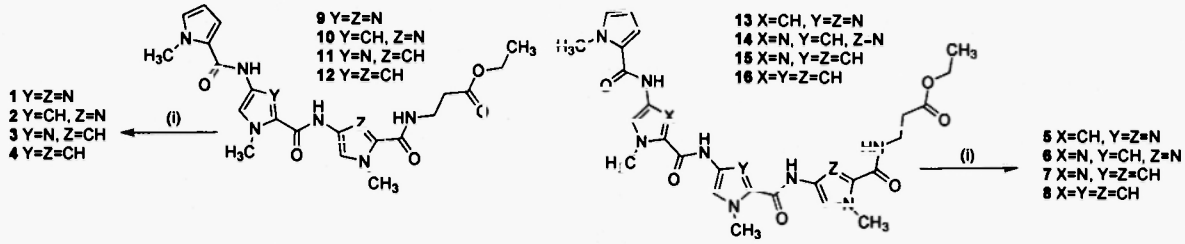


Figure-1 : Structures of the triheterocyclic (**1-4**) and tetraheterocyclic polyamides (**5-8**).

Results and Discussion

The ethyl ester precursors (**9-16**) of all compounds described in this paper were synthesized, using Schotten-Bauman acid chloride coupling reactions, as previously reported for the synthesis of the γ-aminobutyric versions of the compounds.[10] Except, ethyl β-alanine was used instead of ethyl γ-aminobutyrate. The carboxylic acids (**1-4** and **5-8**) were obtained by hydrolysis reactions from the obtained ethyl esters (Scheme-1).



Scheme-1 : (i) aq. NaOH (0.1 *M*), MeOH, THF, reflux, 1-6 h.

The starting materials were dissolved in MeOH and THF, aq. NaOH (0.1 *M*) was added and the solution heated at reflux. Each reaction was followed by TLC (80:20 %v/v $CHCl_3$/MeOH), and upon complete disappearance of the starting material, the non-aqueous solvents in the reaction solutions were removed by rotary evaporation. The remaining aqueous solutions were acidified with aq. HCl (6 M) to pH > 1. These conditions promoted the precipitation of the product from solution, and the resulting solids were filtered and dried under vacuum with P_2O_5 to yield the acids in yields ranging from 39-84%.

Experimental

Compound **1**

P-I-I-β-OEt (9) (0.330 g, 0.701 mmol) was heated at reflux for ~1.5 h with MeOH (2 mL), THF (2 mL), aq. NaOH (0.1 *M*, 8 mL), and H_2O (2 mL). The solvents in the reaction mixture were removed and the resulting aqueous solution was acidified with aq. HCl (6 *M*). The resulting solid was filtered, washed with H_2O, and dried in a vacuum oven for 24 h with P_2O_5 to yield **1** as a yellow solid (120 mg, 39%), mp. decomposed at 250 °C: Rf: 0.5 (20:80 %v/v MeOH:$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 10.44 (s br, 1H); 9.46 (s br, 1H); 8.22 (s br, 1H); 7.62 (s, 1H); 7.52(s, 1H); 7.15-7.13 (m, 1H); 7.00 (s, 1H); 6.08-6.06 (m, 1H); 4.00 (s, 3H); 3.96 (s, 3H); 3.89 (s, 3H); 3.42 (t, 6.4, 2H); 2.47 (t, 6.4, 2H); IR (neat) υ 3410, 2956, 2918, 2848, 1718, 1655, 1536, 1464, 1410, 1372, 1330, 1259, 1180, 1094, 1020 cm^{-1}; MS (ES+) *m/z* (rel. intensity) 885 (2[M+H] 5%), 443 ([M+H] 100%), 145 (20%); Calcd. for $C_{19}H_{22}N_8O_5$ 443.1791, found 443.1791.

Compound **2**[10b]

P-P-I-β-OEt (**10**) (0.221 g, 0.471 mmol) was reacted yield **2** as a yellow/orange solid (142 mg, 69%), mp. decomposed at 269 °C: Rf: 0.4 (80:20 %v/v $CHCl_3$:MeOH); ^{1}H NMR (DMSO-d6) δ 10.36 (s br, 1H); 9.82 (s br, 1H); 7.89 (t, 6.4, 1H); 7.49 (s, 1H); 7.32 (d, 2, 1H); 7.04 (d, 2, 1H); 6.93-6.91 (m, 2H); 6.04 (dd, 1.2, 3.6, 1H); 3.92 (s, 3H); 3.86 (s, 3H); 3.83 (s, 3H); 3.44 (q, 6.4, 2H); IR (neat) υ 3416, 2963, 2849, 2359, 2104, 1656, 1535, 1466, 1447, 1410, 1320, 1260, 1208, 1098, 1618 cm^{-1}; MS (ES+) m/z (rel. intensity) 442 ([M+H] 100%), 464 ([M+Na] 10%); Calcd. for $C_{20}H_{23}N_7O_5$ 442.1839, found 442.1849.

Compound **3**

P-I-P-β-OEt (**11**) (0.225 g, 0.380 mmol) was reacted to yield **3** as a brown/purple solid (39 mg, 42%), mp. 168.5-170.6 °C: Rf: 0.29 (80:20 %v/v $CHCl_3$:MeOH); ^{1}H NMR (DMSO-d6) δ 12.23 (br s, 1H); 10.24 (br s, 1H); 9.92 (br s, 1H); 8.06 (br t, 5.2, 1H); 7.47 (s, 1H); 7.21 (d, 1.6, 1H); 6.99-6.97 (m, 2H); 6.88 (d, 1.6, 1H); 6.08-6.06 (m, 1H); 3.94 (s, 3H); 3.85 (s, 3H); 3.78 (s, 3H); 3.36 (t, 7.2, 2H); 2.47 (t, 7.2, 2H); IR (neat) υ 3477, 2976, 2869, 1657, 1626, 1552, 1536, 1460, 1410, 1365, 1329, 1067, 1033, 908, 803 cm^{-1}; MS (ES+) m/z (rel. intensity) 442 ([M+H] 100%), 115 (40%); Calcd. for $C_{20}H_{24}N_7O_5$ 442.1839, found 442.1847.

Compound **4**[10c]

P-P-P-β-OEt (**12**) (0.276 g, 0.590 mmol) was reacted to yield 4 as a yellow solid (218 mg, 84%), mp. decomposed 130 °C: Rf: 0.28 (80:20 %v/v $CHCl_3$:MeOH); ^{1}H NMR (DMSO-d6) δ 9.90 (s, 1H); 9.83 (s, 1H); 8.03 (br t, 5.6, 1H,); 7.24 (d, 1.6, 1H); 7.19 (d, 1.6, 1H); 7.03 (d, 1.6, 1H); 6.95 (br t, 2.0, 1H); 6.93 (d, 2.0, 1H); 6.92 (d, 1.6, 1H); 6.86 (d, 1.6, 1H); 3.88 (s, 3H); 3.84 (s, 3H); 3.80 (s, 3H); 3.36 (t, 7.2, 2H); 2.47 (t, 7.2, 2H); IR (neat) υ 3307, 2982, 2872, 1637, 1582, 1540, 1460, 1440, 1415, 1260, 1071, 925, 750 cm^{-1}; MS (ES+) m/z (rel. intensity) 463 ([M+Na] 40%), 441 ([M+H] 100%), 115 (40%); Calcd. for $C_{21}H_{25}N_6O_5$ 441.1886, found 441.1897.

Compound **5**

P-P-I-I-β-OEt (**13**) (0.201 g, 0.339 mmol) was reacted to yield **5** as an orange/yellow solid (90 mg, 47%), mp. decomposed at 300 °C: Rf: 0.3 (90:10 %v/v $CHCl_3$:MeOH); ^{1}H NMR (DMSO-d6) δ 10.47 (s br, 1H); 9.86 (s br, 1H); 9.46 (s br, 1H); 9.83 (s br, 1H); 8.19 (t, 6.0, 1H); 7.63 (s, 1H); 7.53 (s, 1H); 7.57 (d, 2.4, 1H); 7.35 (d, 2.4, 1H); 7.10 (d, 1.6, 1H); 6.97-6.94 (m, 1H); 6.06 (dd, 2.4, 4.0, 1H); 4.01 (s, 3H); 3.96 (s, 3H); 3.88 (s, 3H); 3.86 (s, 3H); 3.44 (q, 6.8, 2H); 1.14 (s, 3H); IR (neat) υ 3304, 2958, 2890, 1708, 1638, 1538, 1459, 1441, 1368, 1345, 1322, 1190, 1120, 1065, 1037 cm^{-1}; MS (ES-) m/z (rel. intensity) 563 ([M-H] 100%); Calcd. for $C_{25}H_{28}N_{10}O_6$ 565.2271, found 565.2272.

Compound 6

P-I-P-I-β-OEt (**14**) (0.203 g, 0.343 mmol) was reacted to yield 6 as an orange/yellow solid (161 mg, 82%), mp. decomposed at 300 °C: Rf: 0.5 (80:20 %v/v $CHCl_3$:MeOH); ^{1}H NMR (DMSO-d6) δ 10.37 (s br, 1H); 10.30 (s br, 1H); 10.23 (s br, 1H); 9.78 (s br, 1H); 7.85 (s br, 1H); 7.49 (s, 1H); 7.45 (s, 1H); 7.34 (d, 1.6, 1H); 7.06-7.04 (m, 2H); 6.93 (d, 1.8, 1H); 6.00-5.99 (m, 1H); 3.92 (s, 3H); 3.87 (s, 3H); 3.82 (s, 3H); 3.80 (s, 3H); 1.08 (s, 3H); IR (neat) υ 3372, 2956, 2887, 1720, 1647, 4537, 1444, 1417, 1367, 1346, 1321, 1280, 1187, 1113, 1064 cm^{-1}; MS (ES+) m/z (rel. intensity) 565 ([M+H] 100%); Calcd. for $C_{25}H_{28}N_{10}O_6$ 565.2271, found 565.2264.

Compound 7

P-I-P-P-β-OEt (**15**) (0.134 g, 0.240 mmol) was reacted to yield 7 as a yellow solid (90 mg, 67%), mp. decomposed at 168 °C: Rf: 0.37 (80:20 %v/v $CHCl_3$:MeOH); ^{1}H NMR (DMSO-d6) δ 12.50 (s br, 1H); 10.25 (s br, 1H); 9.99 (s br, 1H); 9.91 (s br, 1H); 8.03 (t, 5.6, 1H); 7.27 (d, 1.6, 1H); 7.19 (d, 1.6, 1H); 7.11 (d, 1.6, 1H); 7.11 (s, 1H); 7.10 (d, 2.0, 1H); 6.99 (t, 2.0, 1H); 6.86 (d, 2.0, 1H); 6.07-6.05 (m, 1H); 3.98 (s, 3H); 3.89 (s, 3H); 3.85 (s, 3H); 3.80 (s, 3H); 3.37 (q, 7.2, 2H); 2.47 (t, 7.2, 2H); IR (neat) υ 3302, 2953, 1715, 1643, 1542, 1467, 1436, 1409, 1253, 1205, 1120, 1065 cm^{-1}; MS (ES+) m/z (rel. intensity) 586 ([M+Na] 10%), 564 ([M+H] 100%), 283 (30%); Calcd. for $C_{26}H_{30}N_9O_6$ 564.2319, found 564.2307.

Compound 8[10d]

P-P-P-P-β-OEt (16) (0.225 g, 0.380 mmol) was reacted to yield 8 as a pink/brown solid (100 mg, 47%), mp. 211-212 °C: Rf: 0.23 (80:20 %v/v $CHCl_3$:MeOH); ^1H NMR (DMSO-d6) δ 9.95 (s, 1H); 9.91 (s, 1H); 9.84 (s, 1H); 8.04 (br t, 5.6, 1H); 7.25 (d, 1.6, 2H); 7.19 (d, 1.6, 1H); 7.05 (br t, 2.4, 2H); 6.95 (br t, 2.4, 1H); 6.93-6.92 (m, 1H); 6.86 (d, 1H, J=1.6 Hz); 6.07-6.06 (m, 1H); 3.88 (s, 3H); 3.86 (s, 3H); 3.85 (s, 3H); 3.80 (s, 3H); 3.36 (t, 7.2, 2H); 2.46 (t, 7.2, 2H); IR (neat) υ 3307, 2960, 2887, 1713, 1638, 1581, 1541, 1461, 1438, 1411, 1067, 1038, 927 cm^{-1}; MS (ES+) m/z (rel. intensity) 585 ([M+Na] 35%), 563 ([M+H] 100%), 322 (35%), 282 (30%); Calcd. for $C_{27}H_{31}N_8O_6$ 563.2366, found 563.2365.

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