Design and Synthesis of 1,2,9,9a-Tetrahydrocyclopropa[*c*]benz[*e*]indole-4-one (CBI) Dimers

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Abstract: Three series of dimers, which contain two racemic 1,2,9,9a-tetrahydrocyclopropa-[*c*]benz[*e*]indol-4-one (CBI) moieties linked by flexible methylene chain of variable length, were synthesized.

CC-1065, a highly cytotoxic antitumor antibiotic, has been shown to bind covalently to the N-3 position of selected adenines located within the minor groove of double stranded B-DNA by using the cyclopropylpyrroloindole (CPI) subunit of the natural product.[1] Studies have shown that cetain structures which contain two CPI moieties, the alkylating subunit of CC-1065, are significantly more potent than CC-1065 both *in vitro* and *in vivo*.[2] Furthermore, many active antitumor agents act by cross-linking DNA.[2b,3] Boger et al. reported that 1,2,9,9a-tetrahydrocyclopropa[*c*]benz-[*e*]indol-4-one (CBI) based agents displayed similar DNA alkylation specificity to those shown for

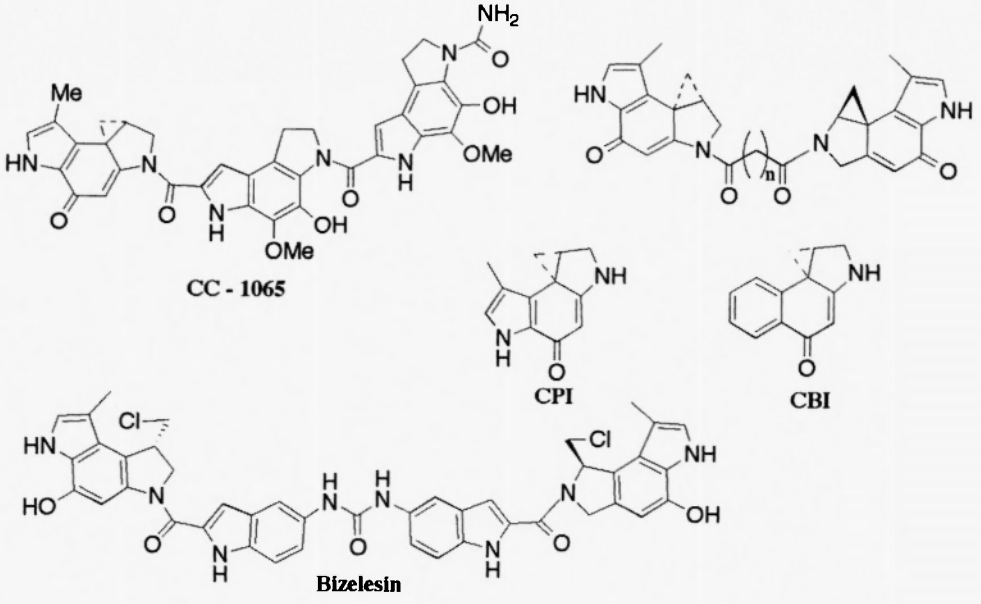
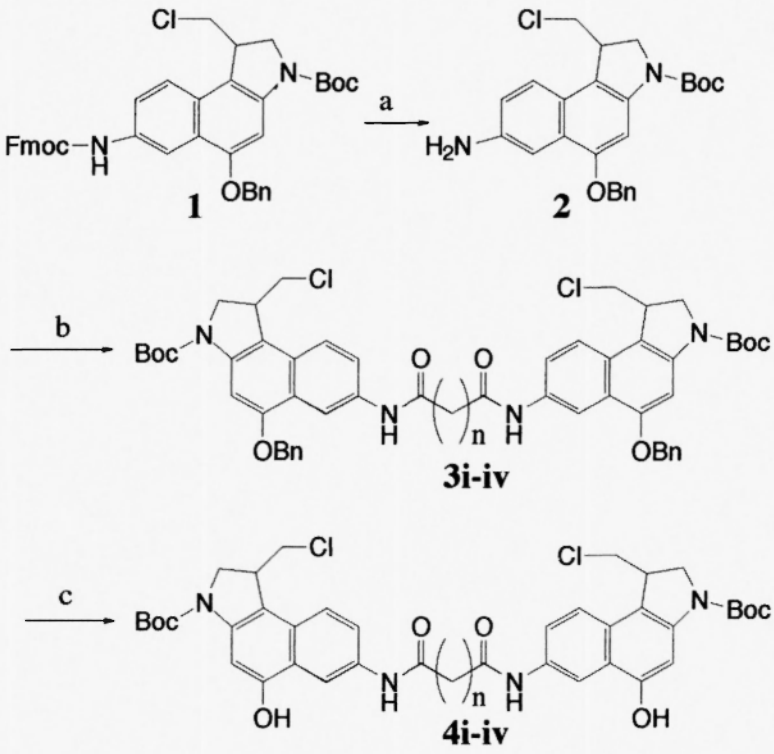


Figure 1. Structures of CC-1065 and CPI Dimers

the CPI counterparts. These compounds have the beneficial attribute of improved chemical stabilities and greater biological activities.[2b,4] While to date some CPI dimers have been prepared to examine inter strand cross-linking of DNA (Figure 1), to our knowledge, no attempt has been made to synthesized CBI dimers. Previously, we reported the synthesis of fully protected bifunctional CBI.[5] In order to investigate the structure-activity relationships systematically, we have designed and synthesized three series of dimers which contain two racemic CBI moieties linked from two positions by a flexible methylene chain of variable length.

Synthesis of C7-C7 Dimers. The synthetic approach began with fully protected racemic CBI **1**.[5b] Deprotection of the Fmoc group followed by reaction with 0.5 equiv of di-acid chloride (glutaryl dichloride, adipoyl chloride, pimeloyl chloride, or suberoyl chloride) produced benzyl protected CBI dimers **3i-iv** in high yield (80-86%). Treatment of **3i-iv** with 3.6 equiv of ammonium formate in the presence of Pd-C[6] for about 15 minutes provided C7-C7 CBI dimers **4i-iv**[7] in 86-97% yield.

Scheme 1

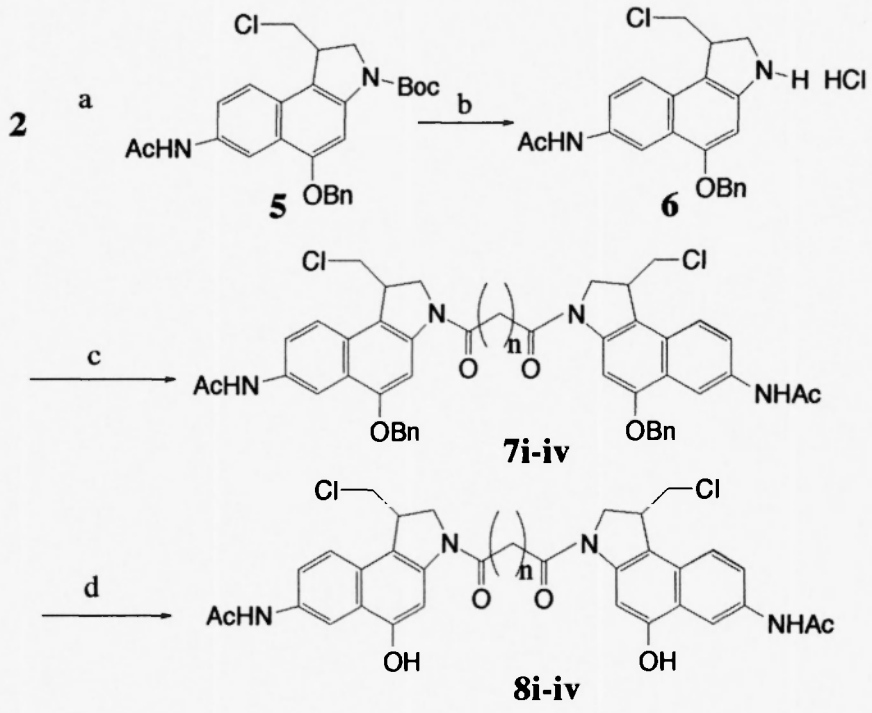


i: n=3, ii: n=4, iii: n=5, iv: n=6

Reagents and conditions: a, n-Bu_4NF; b, $ClCO(CH_2)_3COCl$, $ClCO(CH_2)_4COCl$, $ClCO(CH_2)_5COCl$ or $ClCO(CH_2)_6COCl$, Et_3N; c, HCO_2NH_4, Pd/C.

Synthesis of N3-N3 Dimers. To deactivate the amino group at the C7 position, Fmoc was removed from **1** and followed immediately by reaction with acetyl chloride almost quantitatively to afford **5**. Detachment of the Boc group from **5** followed by coupling with 0.5 molar amount of di-acid chloride (glutaryl dichloride, adipoyl chloride, pimeloyl chloride, or suberoyl chloride) afforded **7i-iv** in good yield (66-96%). Hydrogenolysis of **7i-iv** served to remove the benzyl group and provided N3-N3 CBI dimers **8i-iv**[8] (HCO_2NH_4, Pd/C, 71-76%).

Scheme 2

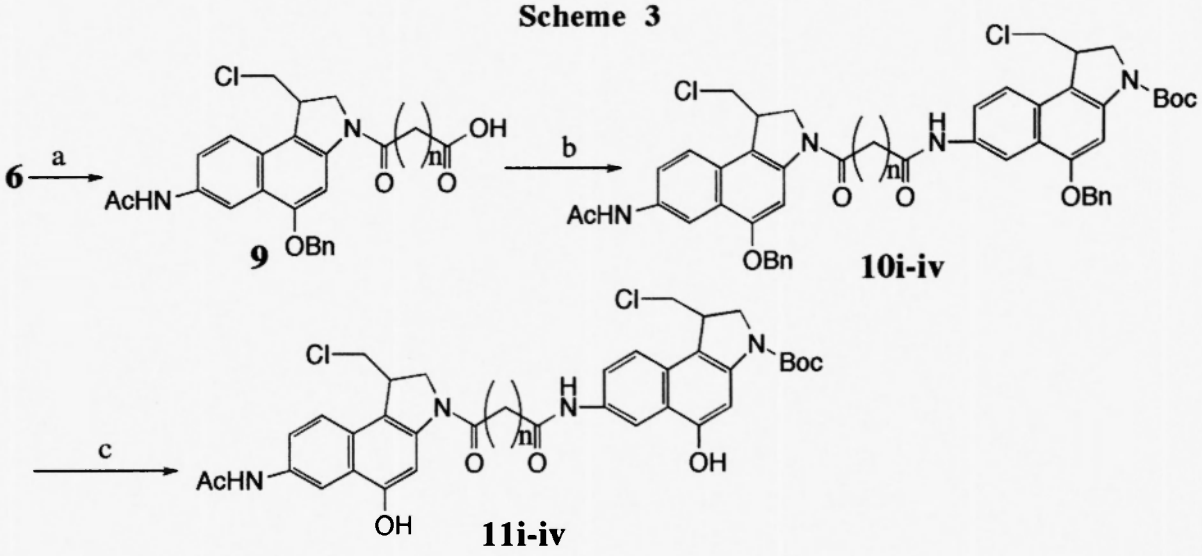


i: n=3, ii: n=4, iii: n=5, iv: n=6

Reagents and conditions: a, CH_3COCl, Et_3N; b, 4M HCl in dioxane; c, $ClCO(CH_2)_3COCl$, $ClCO(CH_2)_4COCl$, $ClCO(CH_2)_5COCl$ or $ClCO(CH_2)_6COCl$, Et_3N; d, HCO_2NH_4, Pd/C.

Synthesis of N3-C7 Dimers. Condensation of agent **6** in the presence of EDCI with excess amount of di-acid (glutaryl acid, adipoyl acid, pimeloyl acid, or suberoyl acid) gave acids **9i-iv** in 66-69% yield. Notably, treatment of **6** with excess di-acid chloride led to a complex mixture, probably arising from the high activity of the acid chlorides. Coupling acids **9i-iv** with **2** (4 equiv of EDCI, DMF, 23°C) produced protected CBI dimers **10i-iv** in fair yield (55-62%). Deprotection of benzyl group from **10i-iv** afforded N3-C7 dimers **11i-iv**[9] in good yield (71-76%).

Scheme 3



i: n=3, ii: n=4, iii: n=5, iv: n=6

Reagents and conditions: a, $ClCO(CH_2)_3COCl$, $ClCO(CH_2)_4COCl$, $ClCO(CH_2)_5COCl$ or $ClCO(CH_2)_6COCl$, Et_3N, EDCI; b, **2**, EDCI; c, HCO_2NH_4, Pd/C.

In summary, three series of dimers containing flexible polymethylene linkages between CBI moieties from two different positions were designed and synthesized. Their biological activity and DNA crosslinking ability are currently under investigation.

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References and Notes:

1 For latest review see: D.L. Boger and D.S. Johnson, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1439.

2 (a) M.A. Mitchell, P.D. Johnson, M.G. Williams and P.A. Aristoff, *J. Am. Chem. Soc.*, 1989, **111**, 6428; (b) S.R. Rajski and R.M. Williams, *Chem. Rev.*, 1998, **98,** 2723 and references cited therein.

3 A. Das, K.S. Tang, S.Gopalakrishnan, M.J. Waring and M. Tomasz, *Chem. Biol.*, 1999, **6**, 461.

4 D.L. Boger, C.W. Boyce, R.M. Genbaccio and J.A. Goldberg, *Chem. Rev.*, 1997, **97**, 787 and references cited therein.

5 (a) G. Jia, H. Iida and J.W. Lown, *Heterocyclic Commun.*, 1998, 4, 557; (b) G. Jia, H. Iida and J.W. Lown, *Chem. Commun.*, 1999, 119.

6 V.F. Patel, S.L. Andis, J.K. Enkema, D.A. Johnson, J.H. Kennedy, F. Mohamadi, R.M. Schultz, D.J. Soose and M.M. Spees, *J. Org. Chem.*,1997, **62**, 8868.

7 **4i**: ^{1}HNMR (DMSO-d$_6$) δ: 10.26(s, OH), 10.01(s, NH), 8.41(s, 2H, 2xC6-H), 7.70-7.62(m, 6H, 2xC4,7,8-H), 4.09-3.65(m, 10H, C1,2-H, 2xClCH$_2$), 2.42(t, 4H, J=7.2Hz, 2xCH$_2$CO), 1.98-1.93(m, 2H, CH$_2$), 1.49(s, 18H, 2xBoc-H). ES-HRMS *m/z* Calcd for $C_{41}H_{47}N_4O_8Cl_2$ 793.2771, found 793.2771 (M^++H).
4ii: ^{1}HNMR (DMSO-d$_6$) δ: 10.25(s, OH), 9.98(s, NH), 8.34(s, 2H, 2xC6-H), 7.70-7.62(m, 6H, 2xC4,7,8-H), 4.07-3.59(m, 10H, C1,2-H, 2xClCH$_2$), 2.41-2.36(m, 4H, 2xCH$_2$CO), 1.69-1.65(m, 4H, CH$_2$CH$_2$), 1.52(s, 18H, 2xBoc-H). ES-HRMS *m/z* Calcd for $C_{42}H_{48}N_4O_8Cl_2Na$ 829.2748, found 829.2755 (M^++Na).
4iii: ^{1}HNMR (DMSO-d$_6$) δ: 10.26(s, OH), 9.96(s, NH), 8.38(s, 2H, 2xC6-H), 7.68-7.61(m, 6H, 2xC4,7,8-H), 4.08-3.65(m, 10H, C1,2-H, 2xClCH$_2$), 2.34(t, 4H, J=7.2Hz, 2xCH$_2$CO), 1.68-1.63(m, 4H, CH$_2$CH$_2$), 1.52(s, 18H, 2xBoc-H), 1.43-1.37(m, 2H, CH$_2$). ES-HRMS *m/z* Calcd for $C_{43}H_{51}N_4O_8Cl_2$ 821.3084, found 821.3082 (M^++H).
4iv: ^{1}HNMR (DMSO-d$_6$) δ: 10.25(s, OH), 9.94(s, NH), 8.38(s, 2H, 2xC6-H), 7.69-7.61(m, 6H, 2xC4,7,8-H), 4.08-3.69(m, 10H, C1,2-H, 2xClCH$_2$), 2.33(t, 4H, J=7.3Hz, 2xCH$_2$CO), 1.68-1.60(m, 4H, 2xCH$_2$), 1.52(s, 18H, 2xBoc-H), 1.38-1.34(m, 4H, CH$_2$CH$_2$). ES-HRMS *m/z* Calcd for $C_{44}H_{53}N_4O_8Cl_2$ 835.3240, found 835.3244 (M^++H).

8 **8i**: ^{1}HNMR (DMSO-d$_6$) δ: 10.23(s, OH), 10.02(s, NH), 8.36(s, 2H, 2xC6-H), 7.97(s, 2H, 2xC4-H), 7.72-7.66(m, 4H, 2xC9,8-H), 4.34-4.26(m, 2H, 2xC1-H), 4.18-4.08(m, 4H, 2xC2-H), 4.01-3.94(m, 2H, 2xClC*H*H), 3.80-3.72(m, 2H, 2xClCH*H*), 2.70-2.54(m, 4H, 2xCH$_2$CO), 2.06(s, 6H, 2xCH$_3$CON), 1.68-1.60(m, 2H, CH$_2$). ES-MS *m/z* Calcd for $C_{35}H_{35}N_4O_6Cl_2$ 677.2, found 677.2 (M^++H, 95), 679.2(65).
8ii: ^{1}HNMR (DMSO-d$_6$) δ: 10.24(s, OH), 10.02(s, NH), 8.35(s, 2H, 2xC6-H), 7.94(s, 2H, 2xC4-H), 7.72(d, 2H, J=8.9Hz, 2xC9-H), 7.64(d, 2H, J=8.9Hz, 2xC8-H), 4.34-4.29(m, 2H, 2xC1-H), 4.16-4.10(m, 4H, 2xC2-H), 3.98-3.96(m, 2H, 2xClC*H*H), 3.79-3.73(m, 2H, 2xClCH*H*), 2.62-2.53(m, 4H, 2xCH$_2$CO), 2.06(s, 6H, 2xCH$_3$CON), 1.65-1.61(m, 4H, CH$_2$CH$_2$). ES-MS *m/z* Calcd for $C_{36}H_{36}N_4O_6Cl_2Na$ 713.2, found 713.2 (M^++Na, 50), 715.2(36).
8iii: ^{1}HNMR (DMSO-d$_6$) δ: 10.24(s, OH), 10.03(s, NH), 8.35(s, 2H, 2xC6-H), 7.96(s, 2H, 2xC4-H), 7.72(d, 2H, J=9.0Hz, 2xC9-H), 7.65(d, 2H, J=9.0Hz, 2xC8-H), 4.35-4.30(m, 2H, 2xC1-H), 4.15-4.04(m, 4H, 2xC2-H), 3.98-3.95(m, 2H, 2xClC*H*H), 3.74-3.72(m, 2H, 2xClCH*H*), 2.63-2.53(m, 4H, 2xCH$_2$CO), 2.06(s, 6H, 2xCH$_3$CON), 1.60-1.55(m, 4H, 2xCH$_2$), 1.48-1.42(m, 2H, CH$_2$). ES-MS *m/z* Calcd for $C_{37}H_{39}N_4O_6Cl_2$ 705.2, found 705.3 (M^++H, 100), 707.2(66).

8iv: ^{1}HNMR (DMSO-d$_6$) δ: 10.24(s, OH), 10.03(s, NH), 8.35(s, 2H, 2xC6-H), 7.95(s, 2H, 2xC4-H), 7.72(d, 2H, J=8.7Hz, 2xC9-H), 7.64(d, 2H, J=8.7Hz, 2xC8-H), 4.32-4.26(m, 2H, 2xC1-H), 4.14-4.05(m, 4H, 2xC2-H), 3.99-3.94(m, 2H, 2xClC*H*H), 3.76-3.72(m, 2H, 2xClCH*H*), 2.63-2.52(m, 4H, 2xCH_2CO), 2.07(s, 6H, 2xCH_3CON), 1.66-1.62(m, 4H, 2xCH_2), 1.45-1.38(m, 4H, CH_2CH_2).ES-MS *m/z* Calcd for $C_{38}H_{41}N_4O_6Cl_2$ 719.2, found 719.2 (M^++H, 100), 721.2(70).

9 **11i**: ^{1}HNMR (DMSO-d$_6$) δ: 10.26(s, OH), 10.02(s, NH), 10.01(s, NH), 8.40(s, 1H, C6-H), 8.36(s, 1H, C6-H), 7.96(s, 1H, C4-H), 7.73-7.63(m, 5H, C4-H, 2xC8,9-H), 4.33-4.28(m, 1H, C1-H), 4.14-3.90(m, 7H, C1-H, 2xC2-H, 2xClC*H*H), 3.78-3.71(m, 2H, 2xClCH*H*), 2.46-2.43(m, 4H, 2xCH_2CO), 2.06(s, 3H, CH_3CON), 1.98-1.93(m, 2H, CH_2), 1.53(s, 9H, Boc-H). ES-MS *m/z* Calcd for $C_{38}H_{40}N_4O_7Cl_2Na$ 757.2, found 757.2 (M^++Na, 100), 759.2(70).

11ii: ^{1}HNMR (DMSO-d$_6$) δ: 10.25(s, OH), 10.23(s, OH), 10.01(s, NH), 9.98(s, NH), 8.38(s, 1H, C6-H), 8.34(s, 1H, C6-H), 7.94(s, 1H, C4-H), 7.71-7.63(m, 5H, C4-H, 2xC8,9-H), 4.34-4.27(m, 1H, C1-H), 4.14-3.94(m, 7H, C1-H, 2xC2-H, 2xClC*H*H), 3.78-3.72(m, 2H, 2xClCH*H*), 2.45-2.32(m, 4H, 2xCH_2CO), 2.06(s, 3H, CH_3CON), 1.78-1.64(m, 4H, CH_2CH_2), 1.53(s, 9H, Boc-H). ES-MS *m/z* Calcd for $C_{39}H_{42}N_4O_7Cl_2Na$ 771.2, found 771.2 (M^++Na, 50), 773.2(30).

11iii: ^{1}HNMR (DMSO-d$_6$) δ: 10.25(s, OH), 10.23(s, OH), 10.02(s, NH), 9.96(s, NH), 8.38(s, 1H, C6-H), 8.35(s, 1H, C6-H), 7.94(s, 1H, C4-H), 7.72-7.62(m, 5H, C4-H, 2xC8,9-H), 4.33-4.27(m, 1H, C1-H), 4.13-3.95(m, 7H, C1-H, 2xC2-H, 2xClC*H*H), 3.78-3.72(m, 2H, 2xClCH*H*), 2.44-2.33(m, 4H, 2xCH_2CO), 2.06(s, 3H, CH_3CON), 1.70-1.62(m, 4H, 2xCH_2), 1.53(s, 9H, Boc-H), 1.47-1.41(m, 2H, CH_2). ES-MS *m/z* Calcd for $C_{40}H_{45}N_4O_7Cl_2$ 763.3, found 763.3 (M^++H, 100), 765.3(70).

11iv: ^{1}HNMR (DMSO-d$_6$) δ: 10.25(s, OH), 10.22(s, OH), 10.01(s, NH), 9.94(s, NH), 8.38(s, 1H, C6-H), 8.34(s, 1H, C6-H), 7.94(s, 1H, C4-H), 7.72-7.63(m, 5H, C4-H, 2xC8,9-H), 4.30-4.25(m, 1H, C1-H), 4.12-3.93(m, 7H, C1-H, 2xC2-H, 2xClC*H*H), 3.76-3.72(m, 2H, 2xClCH*H*), 2.45-2.32(m, 4H, 2xCH_2CO), 2.06(s, 3H, CH_3CON), 1.66-1.58(m, 4H, 2xCH_2), 1.53(s, 9H, Boc-H), 1.40-1.34(m, 4H, CH_2CH_2). ES-MS *m/z* Calcd for $C_{41}H_{47}N_4O_7Cl_2$ 777.2, found 777.2 (M^++H, 15), 779.2(10).

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