Synthesis of an unsymmetrical bis-lexitropsin-1,2,9,9a-tetrahydrocyclopropa[c]benzo[e]indol-4-one (CBI) conjugate

Guofeng Jia, Hirokazu Iida and J. William Lown*

Department of Chemistry, University of Alberta, Edmonton, AB, Canada T6G 2G2. E-mail: annabella.wiseman@ualberta.ca

Received (in Corvallis, OR, USA) 8th October 1998, Accepted 23rd November 1998

A practical synthesis of a novel bis-functionalized precursor of 1,2,9,9a-tetrahydrocyclopropa[c]benzo[e]indol-4-one (CBI) is described; the first unsymmetrical bis-lexitropsin– CBI precursor conjugate was thereby synthesized.

CC-1065, an antitumor antibiotic isolated from the culture of *Streptomyces zelensis*,¹ is one of the most potent cytotoxic agents ever discovered and has a wide spectrum of activity against tumor cells *in vitro* and *in vivo* as well as against microbial organisms.² However, CC-1065 cannot be used in humans because it was found that it caused delayed death in experimental animals.³ In the search for compounds with better antitumor selectivity and DNA sequence specific binding



properties, many CC-1065 analogs have been synthesized in attempts to avoid the undesired side effects while retaining its potency against tumor cells.⁴ As a successful example of modification of 1,2,8,8a-tetrahydro-7-methylcyclopropa[*c*]-pyrrolo[3,2-*e*]indol-4-one (CPI), the DNA alkylating moiety of CC-1065, Boger first reported that the simplified moiety, 1,2,9,9a-tetrahydrocyclopropa[*c*]benzo[*e*]indol-4-one (CBI), and its analogs were more stable and more potent than the CPI counterparts.⁵

In our group, attempts have been made to link CPI with lexitropsins, the well-established DNA minor groove binders. It was found that some optimized CPI–lexitropsin conjugates exhibit up to 10000 times higher potency than CC-1065 against KB human cancer cells.³ Molecular modeling studies predicted that a CBI moiety bearing a lexitropsin carrier on both sides should be more firmly bound to its DNA target sequence and might therefore show enhanced potency. This strategy is designed to exploit binding-driven bonding of the alkylating moiety. We have already reported the synthesis of conjugates of CBI bearing two identical lexitropsins which containing pyrrole units.⁶ Studies on lexitropsins or information reading molecules show that replacement of pyrrole units by imidazoles in lexitropsins may cause a change in the base site recognition



Scheme 1 Reagents and conditions: i, NaH; ii, ClCH=CHCH₂Cl, Bu₄NI; iii, hydrazine hydrate, FeCl₃, C; iv, FmocCl, Et₃N; v, Bu₃SnH, AIBN; vi, TBAF; vii, 5; viii, HCO₂NH₄, Pd/C; ix, HCl; x; 8.

from AT to GC in minor groove of B-DNA.⁷ In order to permit targeting of mixed DNA sequences and to thereby investigate

the effects of DNA sequence selective ability, we herein

describe the synthesis of an unsymmetrical bis-lexitropsin–CBI conjugate, which contains two different lexitropsins. In our previous work,⁶ the CBI moiety was obtained by an *in situ* primary radical trap with TEMPO. Here, the CBI moiety was synthesized by using a more concise and shorter route which was recently developed by Patel and co-workers.⁸

Deprotonation of carbamate 1^6 using NaH, followed by alkylation of the resulting anion with 1,3-dichloropropene in the presence of the phase transfer catalyst Bu₄NI gave an mixture of Z and E isomers of vinyl chloride 2. Selective reduction of the nitro group of 2 using hydrazine,⁹ followed by protection of the amino group, provided 3, the desired precursor for the intramolecular aryl radical cyclization on to a tethered vinyl chloride.⁸ A deoxygenated solution of 3 in dry benzene was heated at reflux for 15 h in the presence of 2 equiv. of Bu₃SnH and a catalytic amount of AIBN to give the fully protected bifunctionalized CBI prodrug form, racemic 4.† Although not investigated in detail, no reaction occurred when nitro compound 2 was treated under the same conditions as amine 3.

Detachment¹⁰ of the Fmoc group from **4**, followed by coupling with polypyrrole carboxamide **5**¹¹ using HOBt and EDCI as the coupling agents^{11b,c} afforded the hybrid **6**. Hydrogenolysis^{8a} of **6** served to remove the benzyl ether almost quantitatively and provided **7**. Acid-mediated deprotection of **7**, followed by coupling with polyimidazole carboxamide **8**¹¹ using EDCI provided the final bis-lexitropsin–CBI precursor conjugate **9**[‡] in fair yield.

In summary, we have described a synthesis of the bisfunctionalized CBI precursor containing two different protective groups and obtained the corresponding unsymmetrical bis-lexitropsin conjugate. Results on the DNA sequence preferences and biological evaluation will be reported in due course.

We are grateful for a research grant (to J. W. L.) from the Natural Sciences and Engineering Research Council of Canada.

Notes and references

† Selected data for 4: δ_H(360 MHz, acetone-d₆) 9.02 (s, NH), 8.38 (s, 1H, C6-H), 7.88–7.30 (m, 16H, Ar-H), 5.30 (s, 2H, PhCH₂O), 4.50 (d, 2H, J 6.9, CH₂ in Fmoc), 4.30 (t, 1H, J 6.9, CH in Fmoc), 4.22–4.05 (m, 3H, C1-H, C2-H), 4.01 (dd, 1H, J3.1, 11.1, CHHCl), 3.70 (dd, 1H, J 8.4, 11.0, CHHCl), 1.58 (s, 9H, Boc-H); Calc. for C₄₀H₃₇N₂O₅Cl: C, 72.66; H, 5.64; N, 4.24. Found C, 72.55; H, 5.74; N, 4.20%.

‡ Selected data for **9**: $\delta_{H}(360 \text{ MHz}, \text{DMSO-}d_6)$ 10.35 (s, 1H), 10.30 (s, 1H), 10.18 (s, 1H), 9.90 (s, 1H), 9.86 (s, 1H), 9.75 (s, 1H), 9.62 (s, 1H), 9.59 (s, 1H), 8.55 (d, 1H, J 2.0, C6-H), 7.97 (s, 1H, C4-H), 7.86 (dd, 1H, J 2.0, 7.5, C8-H), 7.74 (d, 1H, J 7.5, C9-H), 7.64 (s, 1H, Im-H), 7.60 (s, 1H, Im-H), 7.51 (s, 1H, Im-H), 3.31 (d, 1H, J 1.5, Py-H), 7.24 (d, 1H, J 1.5, Py-H), 7.21 (d, 1H, J 1.5, Py-H), 7.16 (d, 1H, J 1.5, Py-H), 7.07 (d, 1H, J 1.5, Py-H), 6.88 (d, 1H, J 1.5, Py-H), 4.7–3.6 (m, 23H, NCH3, ClCH2, C1-H, C2-H), 2.28 (t, 2H, J 7.3, COCH2), 2.20 (t, 2H, J 7.4, COCH2), 1.63–1.53 (m, 4H, COCH2CH2CH2), 0.91–0.86 (m, 6H, COCH2CH2CH3); Calc. for C₅₄H₅₈N₁₇O₉Cl: C, 57.15; N, 21.17. Found C, 57.06; N, 20.97%.

- 1 L. J. Hanka, A. Dietz, S. A. Gerpheide, S. L. Kuentzel and D. G. Martin, *J. Antibiot.*, 1978, **31**, 1211.
- 2 B. K. Bhuyan, K. A. Newell, S. L. Crampton and D. D. Von Hoff, *Cancer Res.*, 1982, **42**, 3532.
- 3 H. Iida and J. W. Lown, *Recent Res. Dev. Synth. Org. Chem.*, 1998, 1, 17 and references cited therein.
- 4 D. L. Boger and R. S. Coleman, J. Am. Chem. Soc, 1988, **110**, 4796; C. H. Lin, D. Sun and L. H. Hurley, Chem. Res. Toxicol., 1991, **4**, 21; M. A. Mitchell, R. C. Kelly, N. A. Wicnienski, N. T. Hatzenbuhler, M. G. Williams, G. L. Petzold, J. L. Slightom and D. R. Siemieniak, J. Am. Chem. Soc., 1991, **113**, 8994; R. C. Kelly, I. Gebhard, N. Wicknienski, P. A. Aristoff, P. D. Johnson and D. G. Martin, J. Am. Chem. Soc., 1987, **109**, 6837; D. L. Boger and D. S. Johnson, Angew. Chem., Int. Ed. Engl., 1996, **35**, 1439.
- 5 D. L. Boger, T. Ishizaki, R. J. Wysocki, Jr., S. A. Munk, P. A. Kitos and O. Suntornwat, J. Am. Chem. Soc., 1989, **111**, 6461; D. L. Boger and T. Ishizaki, J. Org. Chem., 1990, **55**, 5823; D. L. Boger, W. Yun and B. R. Teegarden, J. Org. Chem., 1992, **57**, 2873; D. L. Boger, P. Mesini and C. M. Tarby, J. Am. Chem. Soc., 1994, **116**, 6461; D. L. Boger and J. A. McKie, J. Org. Chem., 1995, **60**, 1271; P. A. Aristoff and P. D. Johnson, J. Org. Chem., 1992, **57**, 6234; K. J. Drost and M. P. Cava, J. Org. Chem., 1991, **56**, 2240.
- 6 G. Jia, H. Iida and J. W. Lown, *Heterocycl. Commun.*, 1998, in the press.
- 7 K. E. Rao and J. W. Lown, *Trends Org. Chem.*, 1992, **3**, 141 and references cited therein.
- 8 (a) 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; (b) D. L. Boger, C. W. Boyce, R. M. Garbaccio and M. Searcey, *Tetrahedron Lett.*, 1998, **39**, 2227.
- 9 D. L. J. Clive, A. G. Angoh and S. M. Bennett, J. Org. Chem., 1987, 52, 1339.
- 10 M. Ueki and M. Amemiya, Tetrahedron Lett., 1987, 28, 6617.
- 11 (a) E. Nishiwaki, S. Tanaka, H. Lee and M. Shibuya, *Heterocycles*, 1988, **27**, 1945; (b) L. Huang, J. C. Quada, Jr. and J. W. Lown, *Bioconjugate Chem.*, 1995, **6**, 21; (c) R. Zhao, N. H. Al-Said, D. L. Sternbach and J. W. Lown, *J. Med. Chem.*, 1997, **40**, 216.

Communication 8/07884J