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Synthesis of a novel tetrahydroisoquinolino[2,1-*c*][1,4]benzodiazepine ring system with DNA recognition potential

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Abstract—We report the first stereospecific synthesis and reactivity of a novel tetrahydroisoquinolino[2,1-*c*][1,4]benzodiazepine ring system with DNA recognition potential.

The pyrrolo[2,1-*c*][1,4]benzodiazepine antitumor antibiotics[1] are a well known class of sequence-selective DNA binding agents derived from various streptomyces species, collectively known as the anthramycins and represented by anthramycin, tomamycin, chicamycin, neomycin, and DC-81 (**1**). PBDs bind to the guanine in the minor groove of DNA in a sequence-selective covalent binding manner, via an electrophilic imine or carbinolamine functionality at N10-C11. Their structural activity relationships proceeding based upon CPK models have been proposed,[1–3] fluorescence, high field NMR, molecular modeling, and DNA foot printing studies[4–6] have established that the PBDs recognize with a preference of 5′-Pu–G–Pu sequence.[7–9,16] The PBDs differ in the number, type, and position of substituents in both the aromatic A-ring,[10] and also pyrrole C[11] ring. The interest in discovering and developing small molecules, capable of binding to DNA in a sequence-selective manner is growing in the area of molecular recognition. In this context variety of PBD analogues such as linked symmetrical, unsymmetrical dimmers, and also more recently PBD-hybrids[12] has been synthesized mainly with modifications and substitutions in the aromatic A-ring. The investigation of their anticancer activities also necessitates the importance of the involvement to find the modified PBD analogues with better profiles.

The C-ring varies in both the type and nature of unsaturation, which is either fully saturated, unsaturated at either C_2–C_3 (endocyclic) or at C_2 (exocyclic) position,[13] SAR studies suggest that this variation influences the activity. It is apparent from the overall twist of anthramycin (45°) and tomaymycin (9°) that the degree of saturation can greatly affect the shape of the molecule, which is essential for the activity. However, all these studies were totally on monocyclic C-ring systems. After the keen observation and understanding the SAR studies of PBDs, we initiated a program to discover and develop the DNA interactive moieties with better recognition potential. With all these information, our efforts have been directed toward the synthesis of modified novel systems, such as the replacement of pyrrole C-ring of (**1**) by the corresponding 1,2,3,4-tetrahydroisoquinoline ring to produce the novel tetrahydroisoquinolino[2,1-*c*][1,4]benzodiazepine (**2**), with potential binding affinity and sequence selectivity (Fig. 1). Not only this is bicyclic C-ring system, this C-ring modified novel target **2** consists both the saturated and unsaturated rings, which takes care about the shape of the molecule and

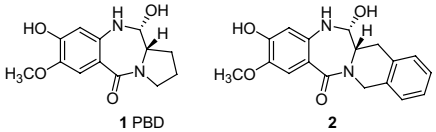

Figure 1. Structures of pyrrolo[2,1-*c*][1,4]benzodiazepine and tetrahydroisoquinolino[2,1-*c*][1,4]benzodiazepine (TBD).

Keywords: Molecular recognition; DNA binding; Sequence-selective; PBDs; Tetrahydroisoquinolino[2,1-*c*][1,4]benzodiazepine.
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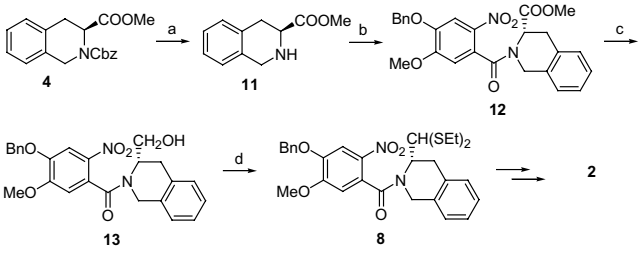
also contains (*S*)-configuration at the chiral C11a position, which provides the molecules with the right-handed twist necessary for a snug fit within the minor groove of DNA like all other biologically active PBDs.

Inspection of the target molecule (**2**) reveals a number of challenges for synthesis that include (a) incorporation of the bicyclic tetrahydroisoquinoline ring with appropriate functionality, which contains both saturated and unsaturated rings, (b) preservation of stereochemical integrity at C11a position, (c) formation of a carbinoalmine or imine moiety in a mild and nonracemizing environment. The synthetic approach described below meets all of these criteria with good yields and also correlated with the alternate approach.

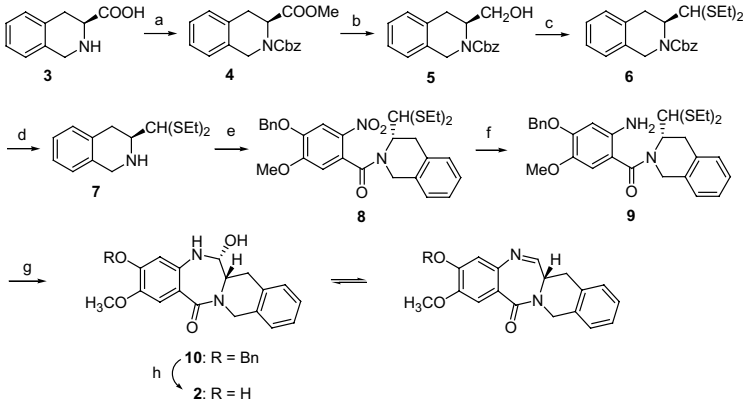
The synthesis was started with commercially available (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**3**), which was protected as *N*-Cbz and methyl ester to give **4**; compound **4** was reduced in presence of $LiBH_4$[14] to obtain **5**. Oxidation of primary alcohol in **5** to the corresponding aldehyde was problematic thus, a variety of oxidizing protocols, such as PCC, Swern etc. were unsatisfactory in terms of yields and isolation. However, oxidation proceeded smoothly in 76% yield upon treatment with IBX in DMSO[15,16] at room temperature to give the aldehyde. Having obtained the desired aldehyde, the next concern was careful protection and deprotection of the aldehyde in a mild and nonracemizing environment. Moreover, the aldehyde was found to be rather unstable and was therefore immediately converted into compound **6** by treating with EtSH in presence of $BF_3{\cdot}Et_2O$ (Scheme 1). Free amine **7** was generated in 83% yield from **6** using TMSI. Compound **7** was treated with the 4-bezyloxy-5-methoxy-2-nitro benzoyl chloride,[17,18] which was obtained from the corresponding acid, to afford the key intermediate amide **8**. Reduction of the nitro group in **8** with $SnCl_2{\cdot}2H_2O$ in methanol under reflux condition gave **9**. Finally, deprotection of the thioacetal group of **9** was performed with $HgCl_2/CaCO_3$ resulting in concomitant ring closure to give the carbinolamine **10** in 79% yield. A significant feature of this compound was the downfield shift of the H11a proton,[19] which was from at δ 4.99, compared to H11a at δ 3.92 for the DC-81. Debenzylation was effected by treatment with 10%Pd–C in 1,4-cyclohaxadiene to afford **2** in 70% yield.

In an alternative approach, the intermediate **8** was prepared from **4** in large quantities via intermediates **11**, **12**, and **13** (Scheme 2). Compound **8** was exactly matching with all the spectral data of the same compound from earlier route. Ultimately, crucial intermediate **8** was converted to obtain the desired system **2**, following the reduction of nitro group, deprotection of thioacetal resulting in concomitant ring closure and debenzylation.

In conclusion, the first stereospecific synthesis of a novel tetrahydroisoquinolino[2,1-*c*][1,4]benzodiazepine ring system has been prepared and also this opened new door for the synthesis of a series of PBD analogues that is both C_7 and C_8 linked dimers and some A-ring modified PBDs for evaluation as potential DNA-binding ligands and cytotoxic agents. The DNA-binding abilities and anticancer activities of **2** under investigation, the detailed mechanistic and molecular modeling studies of **2** along with other analogues of this series will be reported elsewhere.



Scheme 2. Reagents and conditions: (a) TMSI, CH_3CN, 4 h, 75%; (b) 4-benzyloxy-5-methoxy-2-nitrobenzoyl chloride,[17] Et_3N, THF, 4 h, 60%; (c) $LiBH_4$, THF/MeOH, 6 h, 88%; (d) (i) IBX, DMSO, 6 h, 81%; (ii) EtSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 18 h, 89%.



Scheme 1. Reagents and conditions: (a) (i) BnOCOCl, NaOH (aq), 36 h, 94%; (ii) $SOCl_2$, MeOH, reflux, 6 h, 96%; (b) $LiBH_4$, THF/MeOH, 6 h, 70%; (c) (i) IBX, DMSO, 6 h, 76%; (ii) EtSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 18 h, 66%; (d) TMSI, CH_3CN, 4 h, 83%; (e) 4-benzyloxy-5-methoxy-2-nitrobenzoyl chloride,[17] Et_3N, THF, 4 h, 60%; (f) $SnCl_2{\cdot}2H_2O$/MeOH, reflux, 2.5 h, 76%; (g) $HgCl_2$, $CaCO_3$, CH_3CN/H_2O, 2.5 h, 79%; (h) 10%Pd–C, 1,4-cyclohexadiene, EtOH, 6 h, 70%.

References and notes

1. Thurston, D. E. Advances in the Study of Pyrrolo[2, 1-*c*][1,4]benzodiazepine (PBD) Antitumor Antibiotics In *Molecular Aspects of Anticancer Drug–DNA Interactions*; Neidle, S., Waring, M. J., Eds.; The Macmillan: London, 1993; Vol. 1, p 54.
2. Thurston, D. E.; Hurley, L. H. *Drugs Future* **1983**, *8*, 957.
3. Hurley, L. H.; Thurston, D. E. *Pharm. Res.* **1984**, *2*, 52.
4. Boyd, F. L.; Cheatham, S. F.; Remers, W.; Hill, G. C.; Hurley, L. H. *J. Am. Chem. Soc.* **1990**, *112*, 3279.
5. Farmer, J. D.; Gustafson, G. R., Jr.; Conti, A.; Zimmt, M. B.; Suggs, J. W. *Nucleic Acids Res.* **1991**, *19*, 899.
6. Wang, J. J.; Hill, G. C.; Hurley, L. H. *J. Med. Chem.* **1992**, *35*, 2995.
7. Hurley, L. H.; Reck, T.; Thurston, D. E.; Langley, D. R.; Holden, K. G.; Hertzberg, R. R.; Hoover, J. R. E.; Gallagher, G., Jr.; Faucette, L. F.; Mong, S.-M.; Johnson, R. K. *Chem. Res. Toxicol.* **1998**, *1*, 258.
8. Hertzberg, R. P.; Hecht, S. M.; Reynolds, V. L.; Molineuax, I. J.; Hurley, L. H. *Biochemistry* **1986**, *25*, 1249.
9. Warpehoski, M. A.; Hurley, L. H. *Chem. Res. Toxicol.* **1998**, *1*, 135.
10. Masterson, L. A.; Crocker, S. J.; Jenkins, T. C.; Howard, P. W.; Thurston, D. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 901.
11. Bose, D. S.; Srinivas, P.; Gurjar, M. K. *Tetrahedron Lett.* **1997**, *38*, 5839, and references cited therein.
12. Kamal, A.; Ramesh, G.; Srinivas, O.; Ramulu, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 471.
13. Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433.
14. Peterson, M. L.; Vince, R. *J. Med. Chem.* **1991**, *34*, 2787.
15. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
16. Kiran Kumar, K.; Datta, A. *Tetrahedron* **1999**, *55*, 13899.
17. Kamal, A.; Laxman, N.; Ramesh, G.; Neelima, K.; Kondapi, A. K. *Chem. Commun.* **2001**, *15*, 225.
18. Thurston, D. E.; Murty, V. S.; Langley, D. K.; Jones, G. B. *Synthesis*, **1990**, 81.
19. All new compounds gave satisfactory spectroscopic and analytical data. Data for **10**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53–7.09 (m, 9H), 6.86 (s, 1H), 6.39 (s, 1H), 5.19 (s, 2H), 5.17 (br s, 1H), 5.11–4.85 (m, 1H), 4.65–4.49 (m, 1H), 4.40–4.19 (m, 2H), 3.89 (s, 3H), 3.26–2.94 (m, 2H); FABMS (imine): 399 [M^+]; $[\alpha]_D$ +16.5 (*c* 0.4, $CHCl_3$). Data for **9**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43–6.87 (m, 9H), 6.81 (s, 1H), 6.11 (s, 1H), 5.11 (s, 2H), 4.92 (m, 1H), 4.72–4.47 (m, 2H), 4.39–4.13 (m, 2H, exchangeable with D_2O), 4.07–3.86 (m, 1H), 3.78 (s, 3H), 3.46–3.14 (m, 2H), 2.78–2.44 (m, 4H), 1.21 (t, 6H, J = 6.9 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 150.7, 136.4, 129.2, 128.4, 127.7, 126.9, 126.3, 113.4, 102.5, 70.6, 70.5, 56.6, 52.6, 29.5, 29.4, 14.2, 14.1; FABMS calcd for $C_{29}H_{34}N_2O_3S_2$ (522.2) found 522.7 [M^+]; $[\alpha]_D$ −9.0 (*c* 0.5, $CHCl_3$). Data for **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.01 (m, 9H), 5.26–5.06 (m, 3H), 4.82–4.49 (m, 2H), 3.62–3.57 (2s, 3H), 3.24–3.16 (m, 2H); MS (EI) *m/z* (relative intensity): 325 ([M^+], 100); $[\alpha]_D$ +8.05 (*c* 1, $CHCl_3$).