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Synthesis and noncovalent DNA-binding properties of thiazole derivatives related to leinamycin

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Abstract—A series of compounds related to the macrocyclic portion of the DNA-damaging antitumor agent leinamycin were prepared as tools to characterize noncovalent DNA binding by this natural product. Acyclic (*Z*,*E*)-dienes were assembled via a Sonogashira coupling followed by partial hydrogenation. A Stille coupling was used in the cyclization step leading to a macrocyclic thiazole–diene analogue. Results obtained using the synthetic analogues reported here indicate that the extended π-system on the 'left-hand side' of leinamycin is required for noncovalent association of the natural product with duplex DNA.

Leinamycin (**1**) is a DNA-damaging natural product with potent antitumor activity (IC_{50} of 27 nM against HeLa S3 tumor cells).[1–6] This *Streptomyces* metabolite possesses several unique structural features including an 1,2-dithiolan-3-one 1-oxide heterocycle connected by a spiro linkage to an 18-membered macrocycle that contains a novel *Z*,*E*-5-(thiazol-4-yl)-penta-2,4-dienone assembly.[6] Recent studies indicate that efficient DNA alkylation by leinamycin is driven by noncovalent association of the natural product with the DNA double helix.[3,5,7] This observation is especially interesting because leinamycin does not contain any classical DNA-binding functional groups[8] such as a polycyclic aromatic intercalator, a positively charged functional group, or a polyamide-type groove binder. Thus, it appears that leinamycin may represent a novel type of noncovalent DNA-binding structure (Fig. 1).

Structural elements on the 'upper rim' (the C6–C7 alkene) and 'right-hand side' of leinamycin (the 1,2-dithiolan-3-one 1-oxide heterocycle) constitute the DNA-damaging 'core' of the natural product.[3,9] In a process that is initiated by attack of cellular thiols, these functional groups participate in a rearrangement reaction that generates an episulfonium ion alkylating agent along with a hydrodisulfide residue that causes oxidative stress.[6] On the other hand, we suspected that structural elements on the 'left-hand side' of leinamycin's macrocycle might represent the noncovalent DNA-binding domain of the natural product.[10] To test this hypothesis we prepared a series of compounds (**3**–**9**) containing various portions of leinamycin's *Z*,*E*-5-(thiazol-4-yl)-penta-2,4-dienone fragment and characterized their ability to associate noncovalently with duplex DNA.

Our syntheses started from (*R*)-*N*-Boc alanine, which was converted to the aldehyde **10**[11,12] over five steps in 28% overall yield. This aldehyde was transformed to a dibromo olefin using the Corey–Fuchs procedure (CBr_4, Ph_3P),[13] followed by regiospecific reduction to the *Z*-bromide **11** with Bu_3SnH in the presence of $Pd(PPh_3)_4$.[14] Heck reaction of **11** and methyl acrylate yielded a poorly separable ~1:1 mixture of (*Z*,*E*)- and (*E*,*E*)-dienes **14** and **21** in 40% yield. This result was unsatisfactory, so we examined the possibility of using a Sonogashira coupling,[15] followed by partial hydrogenation of the resulting enyne to prepare the desired thiazole-(*Z*,*E*)-dienone system (Scheme 1).

Accordingly, aldehyde **10** was converted to the alkyne **12** using Gilbert's reagent[16,17] in 72% yield. For synthesis of dienes **3** and **4**, this alkyne (**12**) was coupled to methyl iodoacrylate under Sonogashira conditions[15] to yield the enyne **13** (84%), which was hydrogenated using Lindlar's catalyst to give the >95% pure (*Z*,*E*)-diene **14** in 80% yield.[18] Observed coupling constants of the alkene protons in **14** are consistent with a (*Z*,*E*)-diene

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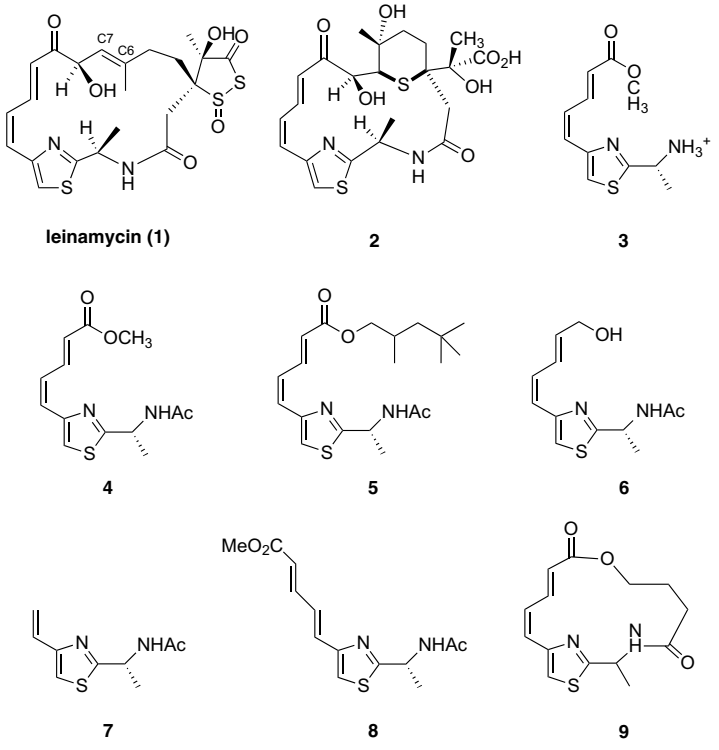
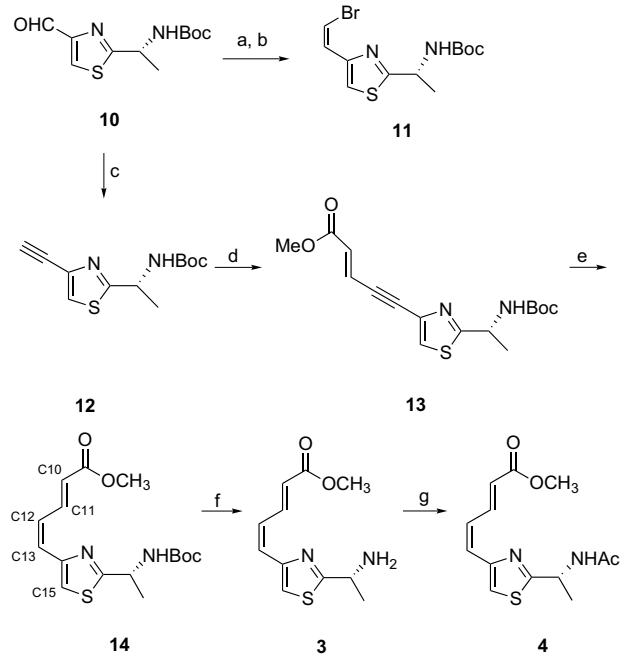


Figure 1. Leinamycin (**1**) and its analogues.



Scheme 1. Reagents and conditions: (a) CBr_4 (1.4 equiv), Ph_3P (3 equiv), Et_3N (3 equiv), 0 °C, 15 min, 56%; (b) Bu_3SnH (2 equiv), $Pd(Ph_3P)_4$ (0.01 equiv), 24 °C, benzene, 3 h, 61%; (c) Gilbert's reagent (1.6 equiv), K_2CO_3 (2.7 equiv), MeOH, 24 °C, 6 h, 72%; (d) methyl iodoacrylate (1.5 equiv), CuI (0.03 equiv), $Pd(Ph_3P)_4$ (0.01 equiv), Et_3N (3 equiv), 24 °C, 6 h, 84%; (e) H_2 (1 atm), Lindlar catalyst, quinoline (1 equiv), EtOAc/MeOH/Et_3N (6:1:1), 48 h, 80%; (f) AcCl, MeOH, 0 °C, 5 min, 91%; (g) Ac_2O (20 equiv), DMAP (2 equiv), 12h, 24 °C, 45%.

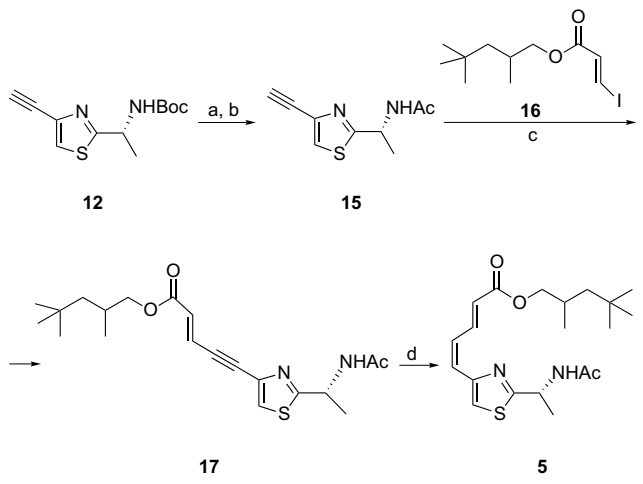
stereochemistry. In addition, the NOE spectrum of **14** shows crosspeaks between the proton at C13 and those on C12 (strong), and C15 (weak), as expected for the (*Z*,*E*)-diene. In contrast, a crosspeak between the protons on C13 and C11 would be expected for the (*E*,*E*)-analogue. Deprotection of **14** (AcCl, MeOH, 91%) provided **3** and subsequent acetylation (Ac_2O, DMAP, 45%) gave **4**.[19]

In a similar sequence, alkyne **12** was converted to **15** by removal of the Boc group followed by acetylation (Scheme 2, 71%). This alkyne was coupled to the iodoacrylate **16**[20] ($Pd(Ph_3P)_4$, CuI, 84%) to afford enyne **17**. This enyne was partially hydrogenated to the desired diene **5**, again using Lindlar conditions (30%).

For synthesis of the alcohol **6**, alkyne **15** was coupled to the methyl iodoacrylate to yield enyne **18**. Reduction of the ester group in **18** with $LiBH_4$ in THF (54%) and subsequent hydrogenation under Lindlar conditions (19%) gave **6**. Alkene **7** was prepared by partial hydrogenation of the alkyne **12** (79%) followed by removal of the Boc group and acetylation (Scheme 3, 68%).

The (*E*,*E*)-diene **8** was prepared from the aldehyde **10** via a Wittig reaction with trimethyl 4-phosphocrotonate in the presence of $NaN(TMS)_2$ in THF at −78 °C, followed by removal of the Boc group and acetylation (Scheme 4). A crystal structure of **21**[10] confirmed that (*E*,*E*)-diene was obtained.

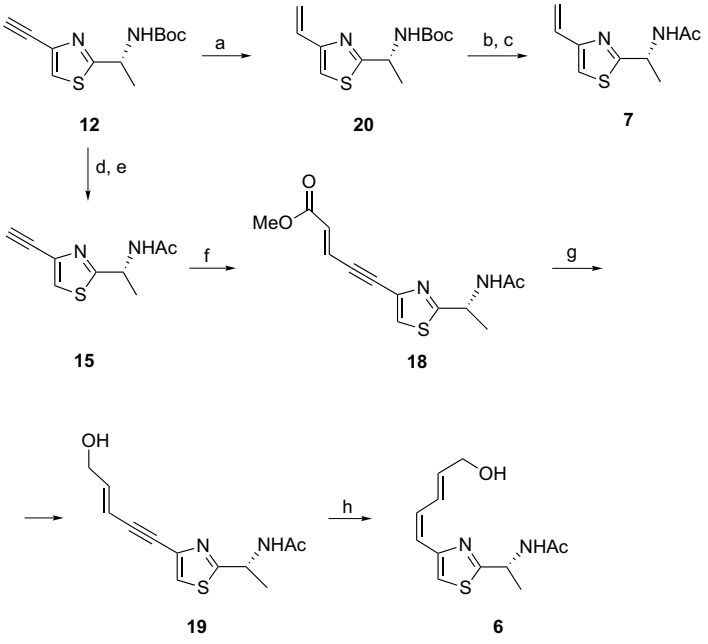
Synthesis of the macrocyclic thiazol-5-yl-penta-2,4-dienone **9** proved somewhat challenging. Initially, we sought to employ a macrolactamization reaction for



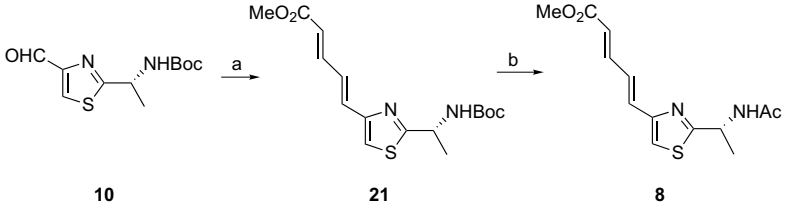
Scheme 2. Reagents and conditions: (a) AcCl (excess), MeOH, 0 °C, 15 min; (b) Ac_2O (9 equiv), DMAP (0.3 equiv), CH_2Cl_2, 24 °C, 10 h, 71%; (c) **16** (1.5 equiv), CuI (0.03 equiv), $Pd(Ph_3P)_4$ (0.01 equiv), Et_3N (3 equiv), 24 °C, 6 h, 84%; (d) H_2 (1 atm), Lindlar catalyst, quinoline (1 equiv), EtOAc/MeOH/Et_3N (6:1:1), 48 h, 24 °C, 30%.

cyclization of this 15-membered ring, as reported previously for this type of system.[21,22] An appropriate precursor was prepared but our attempts to cyclize the ring under a variety of conditions were met with failure. We suspect that the cyclization reaction was unable to compete with isomerization of the (*Z*,*E*)-dienone to the (*E*,*E*)-isomer via reversible Michael addition of the amine substituent to the dienone moiety. Thus, to avoid the presence of a free amino group in the cyclization precursor, we opted to follow a macrolactonization approach to compound **9**, forming the ester bond in the final step. This reaction did provide some product (<5% yield), but it appeared that the cyclization reaction still could not compete favorably against isomerization of the (*Z*,*E*)-diene to (*E*,*E*)-isomer (which cannot cyclize). To avoid this problem we adopted a strategy analogous to that of Pattenden and Thom,[11] where the diene moiety is assembled in the cyclization step using a Stille coupling (Scheme 5, **24** → **9**).

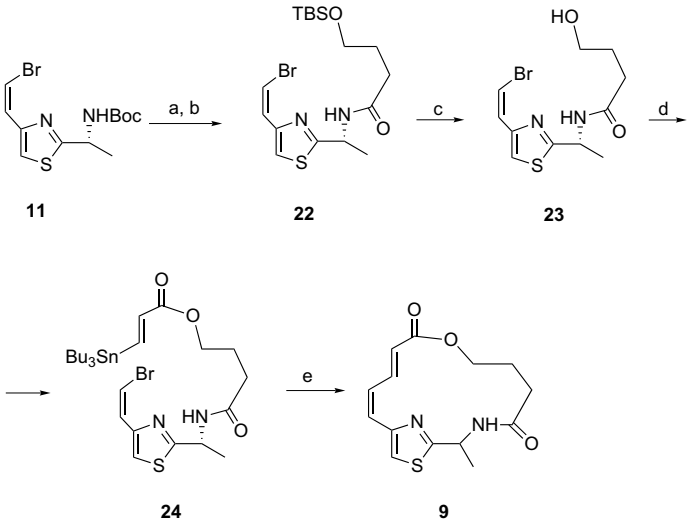
The synthesis of **9** via a Stille coupling started from the *Z*-vinyl bromide **11**. The Boc group was removed



Scheme 3. Reagents and conditions: (a) H_2 (1 atm), Lindlar catalyst, quinoline (4 equiv), MeOH, 4 h, 79%; (b) AcCl (excess), MeOH, 0 °C, 10 min; (c) Ac_2O (excess), DMAP (1.6 equiv), CH_2Cl_2, 24 °C, 10 h, 68%; (d) AcCl (excess), MeOH, 0 °C, 15 min; (e) Ac_2O (9 equiv), DMAP (0.3 equiv), CH_2Cl_2, 24 °C, 10 h, 71%; (f) methyl iodoacrylate (1.1 equiv), CuI (0.025 equiv), $Pd(Ph_3P)_4$ (0.011 equiv), Et_3N (6.7 equiv), 24 °C, 2 h, 87%; (g) $LiBH_4$ (1.1 equiv), 1:1 THF/ether, 24 °C, 10 h, 54%; (h) H_2 (1 atm), Lindlar catalyst, quinoline (3 equiv), EtOAc/MeOH/Et_3N (6:1:1), 24 °C, 24 h, 19%.



Scheme 4. Reagents and conditions: (a) Trimethyl 4-phosphocrotonate (2 equiv), $NaN(TMS)_2$ (2.2 equiv), THF, −70 to 24 °C, 6 h, 49%; (b) AcCl (excess), MeOH, 0 °C, 2 h; (c) Ac_2O (excess), DMAP (2.5 equiv), CH_2Cl_2, 24 °C, 20 h, 20%.



Scheme 5. Reagents and conditions: (a) AcCl (excess), MeOH, 0 °C, 2 h; (b) $TBSO(CH_2)_3CO_2H$ (2.3 equiv), Et_3N (excess), EDCI (2.2 equiv), DMAP (0.5 equiv), −50 to 24 °C, 10 h, 76%; (c) Et_3N/HF (3 equiv), CH_2Cl_2, 24 °C, 12 h, 85%; (d) (*E*)-$Bu_3Sn(CH{=}CH)CO_2H$ (1.3 equiv), EDCI (1.5 equiv), DMAP (2.5 equiv), 24 C, 6 h, 41%; (e) $Ph_2PO_2^-BnNMe_3^+$ (1.5 equiv), Pd_2dba_3 (0.12 equiv), $(PhO)_3P$ (0.5 equiv), *i*-Pr_2NEt (excess), THF, 50–24 °C, 24 h, 52%.

(MeOH, AcCl) and the resulting amine coupled with TBS-protected 4-hydroxybutanoic acid to yield the amide **22** in 76% yield. The TBS group was removed with triethylamine/HF to afford the alcohol **23** in 85% yield. This alcohol was coupled with (*E*)-tributyltin-acrylic acid[23] in the presence of EDCI and DMAP to yield the ester **24** in 41% yield. Initially, we attempted the intramolecular Stille coupling of **24** using conditions reported for a similar cyclization[11] (toluene, $Pd(PPh_3)_4$, Hunig's base, 70 °C, 20 h) but no product was obtained. When less nucleophilic triphenylarsine was substituted for triphenylphosphine (toluene, Pd_2dba_3, Ph_3As, Hunig's base, 110 °C, 20 h), the desired product **9** was obtained, albeit in low yield (~10%). Changes in the reaction solvent, temperature (from 24 to 110 °C) and ratios of Pd_2dba_3 and Ph_3As did not improve the yield of **9**. However, the reaction was more successful in the presence of Pd_2dba_3, triphenylphosphite, and 1.5 equiv of the 'tin scavenger', $Ph_2PO_2^-BnNMe_3^+$,[24,25] and gave **9**[26] in 52% yield. X-ray crystallography confirmed the identity of this product.[10]

We compared the noncovalent DNA-binding properties of analogues **5**, **6**, **7**, and **9** to that of leinamycin and the leinamycin metabolite **2** (Table 1). Association constants of these compounds with mixed-sequence, double-stranded DNA were determined employing a widely-used ethidium displacement assay.[27] The association constant of leinamycin with DNA is modest ($1000\ M^{-1}$). Nonetheless, it is important to point out that leinamycin is a very efficient DNA-alkylating agent and depends absolutely on noncovalent association to drive the alkylation reaction.[3,6,7] Along these lines, it is useful to note that DNA-binding constants of this magnitude are sufficient to confer efficient DNA-alkylating properties on other biologically-active agents.[28,29] The DNA-binding constant measured for the macrocyclic leinamycin analogue **9** is similar to that seen for the natural product. Interestingly, the *acyclic* analogue **5** retains DNA affinity comparable to the natural product (**1**) and the macrocyclic analogue **9**. On the other hand, disruption of the carbonyl moiety in leinamycin's extended π-system, as seen in analogue **6**, completely abolishes noncovalent DNA binding. Similarly, smaller sections of leinamycin's macrocycle, such as the thiazole–alkene construct (**7**), do not show significant affinity for duplex DNA.

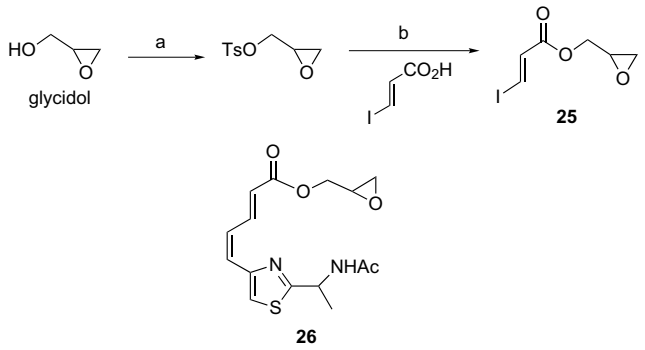
Table 1. Noncovalent DNA binding by leinamycin and its analogues

	C_{50} (μM)[a]	K_B (M^{-1})[b]
Leinamycin (**1**)	125	1000
2	85	1500
5	125	1000
6	—	<100
7	—	<100
9	140	900

[a] In a typical assay, to a solution of ethidium bromide (0.5 μM) in buffer (10 mM Tris, 0.5 mM EDTA, pH 7.0, 10% CH_3CN) at 24 °C was added herring sperm DNA (1 μM bp). To the resulting ethidium–DNA complex small, concentrated (5–50 mM in CH_3CN) aliquots of the putative DNA-binding agents were added as the fluorescence of the solution ($\lambda_{ex} = 545$ nm, $\lambda_{em} = 596$ nm) was measured before and after each addition. C_{50} is the concentration of the compound required to decrease the fluorescence of a DNA–ethidium solution by 50% via displacement of the ethidium bromide from the DNA duplex. (—) Indicates that addition of the compound did not significantly diminish fluorescence in the assay mixture.

[b] Binding constants were calculated as described previously.[27] The standard error in these values is approximately ±10%.

Little is known regarding the detailed structural nature of leinamycin's noncovalent interactions with duplex DNA; however it is clear that the natural product must localize in the major groove because it exclusively alkylates the N7-position of guanine residues.[3] Therefore, it is relevant to ask whether the compounds of the type



Scheme 6. Reagents and conditions: (a) TsCl (0.8 equiv), DMAP (0.05 equiv), Et_3N, CH_2Cl_2, 24 °C, 3 h, 82%; (b) (*E*)-iodoacrylic acid (0.7 equiv), DBU (0.85 equiv), toluene, reflux, 3 h, 39%.

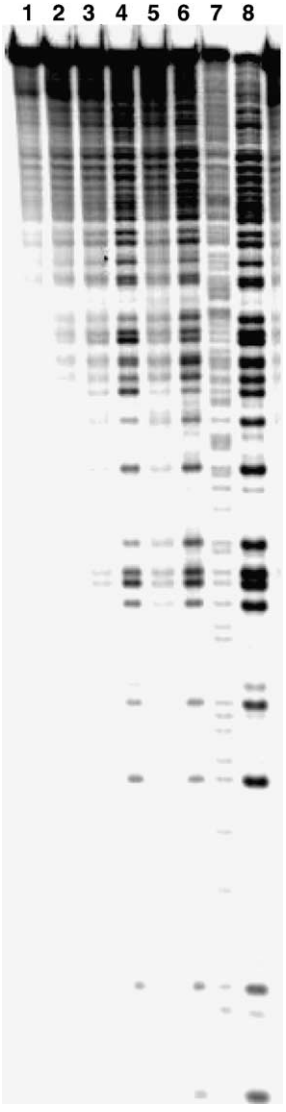


Figure 2. DNA-alkylation of a ^{32}P-labeled restriction fragment by **26** and glycidol. Reactions were conducted using a 377 bp, 5′-end labeled EcoR I–BamH I restriction fragment from pBR322 in 10 mM sodium phosphate buffer, pH 7.0 at 37 °C for 20 h, followed by Maxam–Gilbert workup, and separation of the resulting fragments by denaturing polyacrylamide gel electrophoresis as described in our previous work.[7] Lanes 1–4: **26** (0.75, 7.5, 75, 750 μM); lanes 5–6 glycidol (1, 10 mM); lane 7: A + G sequencing reaction; lane 8: G sequencing reaction.

examined here (Table 1) are able to associate (at least partially) in the major groove of DNA, as seen for the natural product leinamycin. To address this issue we employed the affinity–cleaving approach pioneered by Dervan's group.[30–32] Thus, we prepared compound **26**, with an eye toward determining whether an *acyclic* version of the 5-(thiazol-4-yl)-penta-2,4-dienone unit found in leinamycin can facilitate reaction of a tethered epoxide residue with nucleophilic sites in the major groove of duplex DNA (specifically with the N7-position of guanine residues).

Compound **26** was prepared by the route described for analogue **5**, except using iodoacrylate derivative **25** in the Sonogashira coupling reaction (Scheme 6).[33] The ability of **26** to alkylate a ^{32}P-labeled restriction fragment was compared to the simple epoxide glycidol (Fig. 2). First, the observed base-labile strand cleavage at guanine residues suggests that **26**, like glycidol,[34] alkylates the N7-position of guanine residues. Second, we find that **26** is a more potent DNA-alkylating agent than glycidol, as indicated by the fact that significantly higher concentrations of glycidol are required to achieve a given level of DNA alkylation. Overall, the results indicate that the 5-(thiazol-4-yl)-penta-2,4-dienone assembly does, in fact, associate in the major groove of DNA in a manner that can facilitate reaction of an appended electrophile with the N7-position of guanine residues.

The results presented here represent an important step toward identifying the functional groups that are responsible for noncovalent DNA association by the structurally unique natural product leinamycin. Overall, the results suggest that the 5-(thiazol-4-yl)-penta-2,4-dienone fragment found on the left-hand side of leinamycin may be responsible for the bulk of the noncovalent DNA-binding affinity displayed by this natural product. Studies are currently underway to further characterize noncovalent DNA binding by leinamycin and the synthetic analogues described here.

Acknowledgements

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References and notes

1. Hara, M.; Asano, K.; Kawamoto, I.; Takiguchi, T.; Katsumata, S.; Takahashi, K.-I.; Nakano, H. *J. Antibiot.* **1989**, *42*, 333–335.
2. Hara, M.; Saitoh, Y.; Nakano, H. *Biochemistry* **1990**, *29*, 5676–5681.
3. Asai, A.; Hara, M.; Kakita, S.; Kanda, Y.; Yoshida, M.; Saito, H.; Saitoh, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6802–6803.
4. Mitra, K.; Kim, W.; Daniels, J. S.; Gates, K. S. *J. Am. Chem. Soc.* **1997**, *119*, 11691–11692.

5. Breydo, L.; Zang, H.; Mitra, K.; Gates, K. S. *J. Am. Chem. Soc.* **2001**, *123*, 2060–2061.
6. Gates, K. S. *Chem. Res. Toxicol.* **2000**, *13*, 953–956.
7. Zang, H.; Gates, K. S. *Chem. Res. Toxicol.* **2003**, *16*, 1539–1546.
8. Suh, D.; Chaires, J. B. *Bioorg. Med. Chem.* **1995**, *3*, 723–728.
9. Chatterji, T.; Kizil, M.; Keerthi, K.; Chowdhury, G.; Pospisil, T.; Gates, K. S. *J. Am. Chem. Soc.* **2003**, *125*, 4996–4997.
10. Breydo, L.; Barnes, C. L.; Gates, K. S. *Acta Crystallograph. C* **2002**, *58*, 447–449.
11. Pattenden, G.; Thom, S. M. *Synlett* **1993**, 215–216.
12. Bredenkamp, M. W.; Holzapfel, C. W.; Van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235–2249.
13. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.
14. Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Wada, A.; Ito, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 320–323.
15. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
16. Callant, P.; D'Haenens, L.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 155–161.
17. Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931–2932.
18. Procedure for **13** → **14**: To a solution of **13** (250 mg, 0.75 mmol) in MeOH (80 mL) was added triethylamine (5 mL), quinoline (freshly distilled, 100 μL) and Lindlar catalyst (150 mg). Solution was flushed with H_2 and left in the atmosphere of H_2 for 48 h. It was necessary to exercise care during the purification of **14** because it easily isomerizes to the (*E*,*E*)-isomer **21** in concentrated solutions or in the presence of bases.
19. 2,4,4-Trimethylpentanyl (*E*)-iodoacrylate **16** was synthesized in good yield (77%) by Fisher esterification of (*E*)-iodoacrylic acid with 2,4,4-trimethylpentan-1-ol (dioxane, reflux, 8 h, cat. H_2SO_4).
20. Analytical data for **4**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.87 (dd, $J = 15.5$, 11.7 Hz, 1H), 7.22 (s, 1H), 6.64 (br d, $J = 7$ Hz, 1H), 6.56 (d, $J = 11.7$ Hz, 1H), 6.31 (t, $J = 11.7$ Hz, 1H), 5.99 (d, $J = 15.5$ Hz, 1H), 5.41 (m, 1H), 3.76 (s, 3H), 2.1 (s, 3H), 1.66 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 172.3, 169.6, 167.5, 152.3, 142.3, 127.9, 127.2, 122.6, 120.5, 51.5, 47.2, 23.1, 21.6; *m*/*z* (EI) 280 (M^+), 237, 221, 136; HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}N_2O_3S$ 280.0882, found 280.0883.
21. Baker, R.; Castro, J. L. *J. Chem. Soc., Chem. Commun.* **1989**, 378–381.
22. Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451–8452.
23. Oda, H.; Kobayashi, T.; Kosugi, M.; Migita, T. *Tetrahedron* **1995**, *51*, 695–702.
24. Zhang, S.; Marshall, D.; Liebeskind, L. S. *J. Org. Chem.* **1999**, *64*, 2796–2804.
25. Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834–4836.
26. Procedure for **24** → **9**: To a solution of **24** (25 mg, 0.04 mmol) in THF (70 mL) at 24 °C under Ar was added $Ph_2PO_2^-BnNMe_3^+$ (30 mg, 0.08 mmol), then $(PhO)_3P$ (5 μL, 0.02 mmol) and Pd_2dba_3 (3 mg, 0.005 mmol). The solution was flushed with Ar for 40 min, then heated to 50 °C for 1.5 h, then stirred at 24 °C for 22 h. Analytical data for **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.28 (ddd, $J = 15.8$, 11.7, 0.6 Hz, 1H), 7.25 (s, 1H), 6.52 (d, $J = 11.7$ Hz, 1H), 6.4 (br d, 1H), 6.35 (t, $J = 11.7$ Hz, 1H), 6.87 (d, $J = 15.8$ Hz, 1H), 5.44 (m, 1H), 4.3 (m, 1H), 2.36 (td, $J = 11$, 2.8 Hz, 1H), 2.67 (m, 1H), 2.38 (m, 2H), 2.03 (m, 1H), 1.64 (d, $J = 7$ Hz, 3H), 1.5 (m, 6H), 1.32 (m, 6H), 0.98 (m, 6H), 0.89 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 167.1, 152.0, 143.4, 127.4, 122.0, 120.7, 64.9, 47.7, 33.1, 22.6, 22.4; HRMS (FAB): *m*/*z* calcd for $C_{14}H_{16}N_2O_3S$ 292.0882, found 292.0882.
27. Baguley, B. C.; Denny, W. A.; Atwell, G. J.; Cain, B. F. *J. Med. Chem.* **1981**, *24*, 170–177.
28. Zang, H.; Gates, K. S. *Biochemistry* **2000**, *39*, 14968–14975.
29. Johnson, W. W.; Guengerich, F. P. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 6121–6125.
30. Dervan, P. B. *Science* **1986**, *232*, 464–471.
31. Baker, B. F.; Dervan, P. B. *J. Am. Chem. Soc.* **1989**, *111*, 2700–2712.
32. Povsic, T. J.; Dervan, P. B. *J. Am. Chem. Soc.* **1990**, *112*, 9428–9430.
33. In the ethidium displacement assay, **26** yields a noncovalent binding constant of approximately 1500 M^{-1}, comparable to compounds **1**, **2**, **5**, and **9**.
34. Hemminki, K.; Paasivirta, J.; Kurkirinne, T.; Virkki, L. *Chem. Biol. Interact.* **1980**, *30*, 259–270.