Abstract: A combined structural and quantitative biophysical profile of the DNA binding affinity, kinetics and sequence-selectivity of hairpin polyamide analogues is described. DNA duplexes containing either target polyamide binding sites or mismatch sequences are immobilized on a microelectrode surface. Quantitation of the DNA binding profile of polyamides containing N-terminal 1-alkylimidazole (Im) units exhibit picomolar binding affinities for their target sequences, whereas 5-alkylthiazole (Nt) units are an order of magnitude lower (low nanomolar). Comparative NMR structural analyses of the polyamide series show that the steric bulk distal to the DNA-binding face of the hairpin pPr-Nt polyamide plays an influential role in the allosteric modulation of the overall DNA duplex structure. This combined kinetic and structural study provides a foundation to develop next-generation hairpin designs where the DNA-binding profile of polyamides is reconciled with their physicochemical properties.

Introduction

DNA-binding polyamides (PAs) are cell-permeable transcriptional modulators which function by inhibiting RNA polymerase-mediated elongation and/or transcription factor binding to its target double-stranded DNA (dsDNA) consensus sequence.[1] Of the various designs reported,[2] hairpin PAs are the most widely used[3] where the primary sequence of N-methyl pyrrole (Py) and N-methyl imidazole (Im) heterocyclic amino acids defines the selectivity of dsDNA binding ranging from 7 up to 24 base-pairs in length (e.g., PA1, Figure 1).[1b, 4] At present, an unmet challenge in their further development as a general tool to modulate gene-selective transcription is an in-depth understanding of the interplay between the dsDNA binding profile of PAs determined in vitro, with their overall...
physicochemical properties which impact cell uptake, and ultimately target engagement in vivo.\(^6\)

We have recently expanded the heterocyclic repertoire of current Py-Im hairpin PA designs to include N-terminal thiazole-4-carboxylic acid units (Nt).\(^6\) Nt-building blocks (e.g., PA2–3) direct a hydrogen-bond-acceptor (N3) atom towards the floor of the minor groove and forms a hydrogen bond with the exocyclic hydrogen bond donor amine (N2) of G. A key structural difference with the incorporation of an Nt-unit in the N-terminal position of a hairpin PA is the endocyclic sulfur atom which changes both the geometry and hydrophobicity (logD) of this heterocycle (Figure 1).\(^7\) Furthermore, when a bulky isopropyl substituent is installed in the 5-position (i.e., iPr-Nt, PA3), a more pronounced compression of the major groove is observed relative to the archetypical hairpin PA1·dsDNA complex.\(^6\) These results imply that allosteric modulation of the DNA duplex imparted by PAs is influenced by both the nature of the N-terminal heterocycle pairing with the N2 of G, and the steric bulk of substituents not directly involved in selective minor groove recognition.\(^8\) What is unclear at present is how these changes to the N-terminus influence the kinetics of target versus mismatch binding to dsDNA sequences.

In this manuscript, we report a label-free biophysical assay to profile the affinity, sequence-selectivity and binding kinetics of PA·dsDNA interactions where the N-terminal heterocycle is systematically altered (PA1–4). PAs containing N-terminal Im units (i.e., PA1 and PA4) exhibit enhanced selectivity for their target sequences relative to cognate Nt units (i.e., PA2–3). Whilst increasing the steric bulk of the iPr-Im unit (PA4) does not impact DNA binding affinity for its target sequence, NMR structural analysis reveals the larger iPr-Im unit does induce more pronounced structural perturbation of the target dsDNA duplex relative to PA1, which contains an N-terminal Me-Im unit.

### Results

#### Design and synthesis of hairpin polyamides (PA1–4)

The heterocyclic core of a known hairpin PA sequence (PA1) was chosen as our exemplar scaffold to explore the dsDNA binding profile as a function of four different N-terminal heterocycles.\(^4\) PA1 has an established high affinity binding profile for the general sequence 5′-WWGGWWCW (where W = A/T), for which we used 5′-ATGTACT as the target sequence in an immobilized DNA duplex (ODN1).\(^6,9\) Compounds PA1–4 were prepared using Boc-based solid phase synthesis on a β-Ala PAM resin via amide coupling of the corresponding heterocyclic carboxylic acid (Scheme S1).\(^6,10\)

Polyamides incorporating N-terminal imidazole units exhibit picomolar binding affinity for their target dsDNA sequence

A schematic of the experimental setup is shown in Figure 2. DNA duplexes (ODN1–3, Table 1) were immobilized on a gold surface and contained a fluorophore reporter positioned in close proximity to the proposed PA binding site. PA binding to an immobilized DNA duplex containing the target binding sequence (ODN1)\(^11\) results in fluorophore quenching, which is then restored upon dissociation. This provides an isothermal reporter of the binding kinetics (i.e., \(k_{on}\) and \(k_{off}\)) and the equilibrium dissociation constant (\(K_D\)).\(^12\) The same fluorescence reporter setup was also used to determine the duplex stabilization profile (i.e., \(ΔT_m\)) of PA-ODN complexes as a function of a temperature gradient.

Kinetic analyses of the binding profile of PA1–4 to ODN1 show all four PAs exhibit high-affinity binding (Table 1). Whilst the Im-containing PAs (PA1 and PA4) exhibit \(K_D\) values in the picomolar range, the Nt-containing PAs (PA2–3) exhibited a binding affinity that is approximately an order of magnitude lower (i.e., in the low nanomolar range). Rate maps of PA1–4 targeting ODN1 provided deeper insight into the origin of the differences in the \(K_D\) values of our PA set (Figure 3). Although the dissociation rate (\(k_{off}\)) for each PA was similar, the rate of...
association ($k_{on}$) of PA2–3 was approximately an order of magnitude slower relative to PA1 and PA4.

**G-selective dsDNA binding observed for all four polyamides**

The sequence selectivity profile of PA1–4 was explored using duplexes where the target binding sequence in ODN1 was replaced with mismatched sequences (ODN2–3). Analyses of the binding kinetics show that Im-containing PAs (PA1 and PA4) are more G-selective relative to Nt-containing PAs (PA2–3, Figure 4). Whilst the rates of association ($k_{on}$) of PA4 for all sequences ODN1–3 were similar, the dissociation rates ($k_{off}$) were significantly faster for mismatched sequences (ODN2–3). A less pronounced $k_{on}/k_{off}$ trend was observed for PA1 binding to ODN2, while no interaction was measured with ODN3.

Consistent with our previous DNA-foot-printing data, the most promiscuous dsDNA binding profile observed was PA2 (Figure 4b) where the $K_D$ was virtually the same for the target (ODN1) and the mismatch (ODN2) sequence. Out of the PA series, PA3 displayed the most unique binding profile (Figure 4c). In this case, a decrease in both $k_{on}$ and $k_{off}$ was observed for the binding profile of PA3 for ODN3, while no interaction was observed for ODN3.

This experimental setup was also used to determine duplex stabilization of PA·dsDNA complexes compared to the free DNA duplex melts. A global Boltzmann fit over three independent runs was used to determine the mid-points of the melting transitions ($T_m$) for free ODN1–3 and in complex with 20 nM PA1–4. The UV/Vis melting profiles of the PA·dsDNA complexes confirm a similar trend in dsDNA sequence selectivity (i.e., higher $ΔT_m$) observed in the fluorescence experiments (Figure S3). Of particular note was the melting stabilization of PA4, which displayed excellent G-selectivity relative to PA1–3. Consistent with our kinetics profiling (Figure 4) and previous DNA-foot-printing work, PA2 exhibited limited sequence selectivity as highlighted by duplex stabilization observed for all three ODNs. Taken collectively, the kinetic and melting analyses show that the sequence selectivity of Im-containing PAs (i.e., PA1 and PA4) is superior to Nt-containing analogues (i.e., PA2–3). Furthermore, whilst enhancing steric bulk on the 5-position of the Nt-series enhanced G-selectivity, this had little effect on the Im-series (i.e., PA1/PA4).

**NMR structural analysis of the PA4·dsDNA complex**

In order to gain insight into the influence of the iPr-Im unit incorporated in PA4 when in complex with its target dsDNA sequence, NMR studies were undertaken using the self-complementary dodecamer sequence d(CGATGTACATCG)$_2$ (ODN4). Titration experiments of PA4 into a solution of ODN4 confirmed the formation of a 1:1 PA4·ODN4 complex. 2D NOESY studies at 4 different mixing times identified a suite of strong NOE cross-correlations from H4 of the iPr-Im building block to G5H1 and the G5N2 exocyclic amine, which implies that the iPr-Im N3 is directed towards the floor of the minor groove (Figure 5; Figure S9). NOE cross-peaks from H4 and H5 of the iPr-Im building block to Py1 and the β-alanine tail in the PA4·ODN4 complex is indicative of the PA binding to its target sequence in the hairpin conformation.

**Table 1.** Equilibrium dissociation constant ($K_D$ [pm]) data for PA1–4 binding to the target sequence (ODN1) versus mismatched sequences (ODN2–3).

|       | PA1   | PA2  | PA3   | PA4   |
|-------|-------|------|-------|-------|
| ODN1  | 254 ± 8 | 1170 ± 70 | 1970 ± 240 | 188 ± 5 |
| ODN2  | 1320 ± 70 | 1250 ± 110 | 2880 ± 440 | 967 ± 35 |
| ODN3  | ND    | 15400 ± 7700 | ND       | 1100 ± 100 |
Comparative NMR structural analyses of polyamide-dsDNA complexes

Previous NMR structural work highlighted an increased propensity of PA3 to compress the major groove when in complex with its target DNA sequence (PA3·ODN4) relative to PA1·ODN4. A similar trend in enhanced major groove compression was also observed with PA4·ODN4 relative to PA1·ODN4 (Figure 6). However, the extent of major groove compression was not as pronounced as that observed for the PA3·ODN4 complex.

The origins of these differences become apparent when comparing the extent of minor groove penetration of the three complexes (Figure 7). NMR-restrained molecular dynamics of the PA1·ODN4 complex reveal PA1 penetrating deep within the minor groove, exemplified by a hydrogen bond distance of 2.01 Å between Me-Im N3 and the exocyclic amine G5N2 (Figure 7a). In contrast, the PA3·ODN4 complex shows a reduced level of minor groove penetration with an average distance of 2.36 Å between the iPr-Nt N3 and the exocyclic amine G5N2 (Figure 7b). The PA4·ODN4 complex on the other hand shows a significant level of minor groove penetration (2.10 Å) relative to PA3·ODN4 but it is not as extensive as...
that observed for the PA1·ODN4 complex (2.01 Å). We therefore conclude that both the nature of the N-terminal heterocycle and the steric bulk distal to the DNA-binding face of a PA scaffold influences the allosteric modulation of a target dsDNA sequence.

Figure 6. (a) Major groove width of ODN4 (grey), PA1·ODN4 (green), PA3·ODN4 (blue), and PA4·ODN4 (red). NMR-derived molecular model of (b) the PA4·ODN4 complex.

Discussion

This combined kinetic and structural study has shown that the type of N-terminal heterocycle and its substituents influences the dsDNA binding profile and the overall structure of the duplex. We discuss here several conclusions that emerged from our results.

N-terminal heterocycle of a hairpin polyamide influences rate of association to target dsDNA sequence

Firstly, all four PAs exhibit high affinity (low nanomolar-picomolar) for its target dsDNA sequence. However, the two N-terminal Im-containing PAs (PA1/PA4) showed a higher binding affinity relative to the Nt-containing PA2–3 via an increase in the rate of association. Although there has not been a study dedicated to evaluating the influence of the hairpin PA N-terminus, a previous SPR-based study by Sugiyama et al. has shown that

Figure 7. Comparative analysis of the minor groove penetration of (a) PA1·ODN4, PA3·ODN4, and PA4·ODN4 (PAA-ODN4 structure produced from average of ensemble of clusters from last 800 ps of 1 ns MD simulations; PA1·ODN4 and PA3·ODN4 structures produced through Chimera from averaged clusters from PDB deposition IDs 5OE1 and 5ODM, respectively).
the number of Me-Im and their positioning in a hairpin PA scaffold can have a disproportionate impact on the $k_b$ and $k_o$ relative to only small changes in the $k_i$.[14] In contrast, replacing internal Py/Im heterocycles with more flexible $\beta$-alanine units influences both $k_b$ and $k_o$ parameters.[15] Extensive work by Dervan et al. has investigated heterocyclic changes to the internal positions of hairpin PA structures.[16] However, our results highlight the N-terminal position can be used as a convenient site to tune parameters of dsDNA binding and overall physicochemical properties.

The N-terminal heterocycle position of hairpin polyamides influence DNA structural perturbations

Our structural and binding analyses show that whilst an increase in the steric bulk of the iPr-Im unit does not impact dsDNA binding affinity to its target binding site (i.e., PA4-ODN4 complex), an improvement in G-selectivity relative to the iPr-Nt unit (i.e., PA3-ODN4 complex) is likely due to a greater level of minor groove penetration (see Figure 7), and in turn improved recognition of the N2 amine of G. However, the extent of major groove compression of the PA4-ODN4 complex (Figure 6a) is less than in PA3-ODN4 (Figure 7). This suggests a fine interplay between minor groove penetration versus major groove compression, with enhanced major groove compression occurring if the hydrogen-bond between the N-terminal building block and the N2 of G is weaker as in PA3-ODN4, thereby reducing penetration of the minor groove.

Conclusions

These experiments were designed to probe how an increase in the steric bulk of heterocyclic building blocks of PA impacts the binding kinetics and the allosteric distortion of dsDNA containing the target binding sequence. Although what super-indicially appears to be a subtle increase in steric bulk at locations within a PA scaffold not directly involved in dsDNA base-read-out, these data suggest that strategic changes in the Im and Nt substitution pattern can be used to fine tune the sequence-selectivity of dsDNA binding as well as the overall physicochemical properties of PA scaffolds.[17] We envisage that the strategic incorporation of modified heterocyclic building blocks within a PA scaffold could be applied more broadly as a strategy to enhance cell uptake and potency of transcriptional modulation in cellulo.

Acknowledgements

G.P. thanks the University of Strathclyde for a University Studentship. G.A.B. thanks the Biotechnology and Biological Sciences Research Council (BBSRC; BB/N016378/1) and the Science and Technology Facilities Council (STFC; ST/M000125/1) for funding this work. We thank the EPSRC U.K. National Mass Spectrometry Facility at Swansea University for HRMS analyses of compounds.

Conflict of interest

The authors declare no conflict of interest.

Keywords: allosterism · binding kinetics · minor groove binder · NMR characterisation · pyrrole-imidazole polyamide

[1] a) G.S. Erwin, M.P. Grieshop, A. Ali, J. Qi, M. Lawlor, D. Kumar, I. Ahmad, A. McNally, N. Teider, K. Worring, R. Sivasankaran, D.N. Syed, A. Eguchi, M. Ashraf, J. Jeffery, M. Xu, P.M. C. Park, H. Mukhtar, A.K. Srivastava, M. Faruq, J. Bradner, A.Z. Ansari, Science 2017, 358, 1617–1622; b) A.A. Kurmis, F. Yang, T.R. Welch, N.G. Nichols, P.B. Dervan, Cancer Res. 2017, 77, 2207–2212; c) F. Yang, N.G. Nichols, B.C. Li, G.K. Marinov, J.W. Said, P.B. Dervan, Proc. Natl. Acad. Sci. USA 2013, 110, 1863–1868; d) J.A. Raskatov, J.L. Meier, J.W. Puckett, F. Yang, P. Ramakrishnan, P.B. Dervan, Proc. Natl. Acad. Sci. USA 2012, 109, 1023–1028; e) T. Hidalca, G.N. Pandian, J. Taniguchi, T. Nobeayama, K. Hashiya, T. Bando, H. Sugiyama, J. Am. Chem. Soc. 2017, 139, 8444–8447; f) K. Hirooka, T. Inoue, R.D. Taylor, T. Watanabe, N. Koshikawa, H. Yoda, K. Shinohara, A. Taka- tori, H. Sugimoto, Y. Maru, T. Denda, K. Fujinara, A. Balmain, T. OZaki, T. Bando, H. Sugiyama, H. Nagase, Nat. Commun. 2015, 6, 6706; g) G.N. Pandian, S. Cato, C. Andhandhakumar, J. Taniguchi, T. Kasahara, T. Kando, L. Han, A. Saha, T. Bando, H. Nagase, H. Sugiyama, ACS Chem. Biol. 2014, 9, 2729–2736.

[2] a) P.B. Dervan, R.M. Doss, M.A. Marques, Curr. Med. Chem. Anticancer Agents 2005, 5, 373–387; b) T.N. Yuan, H. Sugiyama, Y. Harada, Biomater. Sci. 2016, 4, 391–399; c) J.M. Withers, G. Padrón, S.M. Pautf, A.W. Clark, S.P. Mackay, G.A. Burley in Reference Module in Chemistry, Molecular Sciences and Chemical Engineering, Elsevier, Amsterdam, 2017, pp. 149–178; d) L. Pett, J A. Hettlley, K. Kikao, Curr. Top. Med. Chem. 2015, 15, 1293–1322; e) W.D. Wilson, F.A. Taniouis, A. Mathis, D. Tevis, J.E. Hall, D.W. Boykin, Biochimie 2008, 90, 999–1014; f) Y. Kawamoto, T. Bando, H. Sugiyama, Bioorg. Med. Chem. 2018, 26, 1393–1411.

[3] a) N.G. Nickols, J.O. Szabolcs, T.K. Abarvige, J.C. Li, J.A. Raskatov, P.B. Dervan, Mol. Cancer Ther. 2013, 12, 675–684; b) J.D. Syed, G.N. Pandian, S. Cato, J. Taniguchi, A. Chandran, K. Hashiya, T. Bando, H. Sugiyama, Chem. Biol. 2014, 21, 1370–1380; c) A. Yasuda, K. Noguchi, M. Minoshima, G. Kashivazaki, T. Kanda, K. Kayayama, T. Mutsuhashi, T. Bando, H. Sugiyama, Y. Sugimoto, Cancer Sci. 2011, 102, 2221–2230; d) K. Haya-togilakthi, G. Padrón, W.S. Wu, L. Fang, E. Gonzalez-Castaneda, Y.C. Hsieh, L. Jackson, T.L. Holyoake, F. Pellicano, G.A. Burley, H.G. Jorgensen, Blood Cells Mol. Dis. 2018, 69, 119–122.

[4] a) P.B. Dervan, B.S. Edelson, Curr. Opin. Struct. Biol. 2003, 13, 284–299; b) R.S. Edayathumangalam, P. Weyermann, J.M. Gottfeld, P.B. Dervan, K. Luger, Proc. Natl. Acad. Sci. USA 2001, 101, 6864–6869; c) A. Hirata, K. Nokihara, Y. Kawamoto, T. Bando, A. Sasaki, S. Ide, K. Maeshima, T. Kasama, H. Sugiyama, J. Am. Chem. Soc. 2014, 136, 11546–11554; d) G.S. Erwin, M.P. Grieshop, D. Bhimsaria, T. J. Do, J. A. Rodriguez-Martinez, C. Mehta, K. Khanna, S.A. Swanson, R. Stewart, J.A. Thomson, P. Ramanathan, A.Z. Ansari, Proc. Natl. Acad. Sci. USA 2016, 113, E7418–E7427; e) G.S. Erwin, D. Bhimsaria, A. Eguchi, A.Z. Ansari, Angew. Chem. Int. Ed. 2014, 53, 10124–10128; Angew. Chem. 2014, 126, 10288–10292; f) A.E. Hargrove, T.F. Martinez, A. Aare, A. A. Kurmis, J. W. Phillips, S. Sud, K.J. Pienta, P.B. Dervan, PLoS One 2015, 10, e014316; g) X. Wang, H. Nagase, T. Watanabe, H. Nobusuke, T. Suzuki, Y. Asami, Y. Shinjima, H. Kawashima, K. Takagi, R. Mishra, J. Igarashi, M. Kimura, T. Takayama, N. Fukuda, H. Sugiyama, Cancer Sci. 2010, 101, 759–766; h) T.G. Edwards, T.J. Vidmar, K. Koeller, J. K. Bashkin, C. Fisher, PLoS One 2013, 8, e75406; i) Y. Kawamoto, A. Sasaki, A. Chandran, K. Hashiya, S. Ide, T. Bando, K. Maeshima, H. Sugiyama, J. Am. Chem. Soc. 2016, 138, 14100–14107; j) Y. Kawamoto, A. Sasaki, K. Hashiya, S. Ide, T. Bando, K. Maeshima, H. Sugiyama, Chem. Sci. 2015, 6, 2307–2313.

[5] a) A.E. Hargrove, J.A. Raskatov, J.L. Meier, D.C. Montgomery, P.B. Dervan, J. Med. Chem. 2012, 55, 5425–5432; b) C.S. Jacobs, P.B. Dervan, J. Med. Chem. 2009, 52, 7380–7388; c) N.G. Nickols, C.S. Jacobs, M.E. Farkas, P.B. Dervan, Nucleic Acids Res. 2007, 35, 363–370.

[6] G. Padrón, J.A. Parkinson, K.R. Fox, G.A. Burley, Nucleic Acids Res. 2018, 46, 42–53.
[7] a) C. C. O’Hare, D. Mack, M. Tandon, S. K. Sharma, J. W. Lown, M. L. Kopka, R. E. Dickerson, J. A. Hartley, Proc. Natl. Acad. Sci. USA 2002, 99, 72–77; b) N. G. Anthony, B. F. Johnston, A. I. Khalaf, S. P. MacKay, J. A. Parkinson, C. J. Suckling, R. D. Waigh, J. Am. Chem. Soc. 2004, 126, 11338–11349.

[8] a) D. M. Chenoweth, P. B. Dervan, J. Am. Chem. Soc. 2010, 132, 14521–14529; b) D. M. Chenoweth, P. B. Dervan, Proc. Natl. Acad. Sci. USA 2009, 106, 13175–13179.

[9] N. G. Nickols, P. B. Dervan, Proc. Natl. Acad. Sci. USA 2007, 104, 10418–10423.

[10] a) E. E. Baird, P. B. Dervan, J. Am. Chem. Soc. 1996, 118, 6141–6146; b) W. Su, S. J. Gray, R. Dondi, G. A. Burley, Org. Lett. 2009, 11, 3910–3913; c) A. J. Fallows, I. Singh, R. Dondi, P. M. Cullis, G. A. Burley, Org. Lett. 2014, 16, 4654–4657; d) L. Fang, Z. Pan, P. M. Cullis, G. A. Burley, W. Su, Curr. Protoc. Nucleic Acid Chem. 2015, 63, 8.11.1–8.11.14; e) S. M. Pauff, A. J. Fallows, S. P. Mackay, W. Su, P. M. Cullis, G. A. Burley, Curr. Protoc. Nucleic Acid Chem. 2015, 63, 8.10.1–8.10.41.

[11] J. Knezevic, A. Langer, P. A. Hampel, W. Kaiser, R. Strasser, U. Rant, J. Am. Chem. Soc. 2012, 134, 15225–15228.

[12] a) A. Cléry, T. J. M. Sahler, T. Welte, A. Langer, F. H. T. Allain, Methods 2017, 118–119, 137–145; b) M. Krepl, M. Blatter, A. Cléry, F. F. Damberger, F. H. T. Allain, J. Sponer, Nucleic Acids Res. 2017, 45, 8046–8063; c) D. Ploschik, F. Rönicke, H. Beike, R. Strasser, H.-A. Wagenknecht, ChemBioChem 2018, 19, 1949–1953.

[13] H. Y. Alniss, M. V. Salvia, M. Sadikov, I. Golovchenko, N. G. Anthony, A. I. Khalaf, S. P. MacKay, C. J. Suckling, J. A. Parkinson, ChemBioChem 2014, 15, 1978–1990.

[14] Y.-W. Han, T. Matsumoto, H. Yokota, G. Kashiwazaki, H. Morinaga, K. Hashiya, T. Bando, Y. Harada, H. Sugiyama, Nucleic Acids Res. 2012, 40, 11510–11517.

[15] a) Y. W. Han, G. Kashiwazaki, H. Morinaga, T. Matsumoto, K. Hashiya, T. Bando, Y. Harada, H. Sugiyama, Bioorg. Med. Chem. 2013, 21, 5436–5441; b) B. B. Liu, S. Wang, K. Aston, K. J. Koeller, S. F. H. Kermani, C. H. Castaneda, M. J. Scuderi, R. S. Luo, J. K. Bashkin, W. D. Wilson, Org. Biomol. Chem. 2015, 15, 9880–9888; c) S. Wang, R. Nanjunda, K. Aston, J. K. Bashkin, W. D. Wilson, Biochemistry 2012, 51, 9796–9806.

[16] a) D. M. Chenoweth, A. Viger, P. B. Dervan, J. Am. Chem. Soc. 2007, 129, 2216–2217; b) D. M. Chenoweth, J. A. Poposki, M. A. Marques, P. B. Dervan, Bioorg. Med. Chem. 2007, 15, 759–770; c) M. A. Marques, R. M. Doss, S. Foister, P. B. Dervan, J. Am. Chem. Soc. 2004, 126, 10339–10349; d) D. Renneberg, P. B. Dervan, J. Am. Chem. Soc. 2003, 125, 5707–5716; e) S. Foister, M. A. Marques, R. M. Doss, P. B. Dervan, Bioorg. Med. Chem. 2003, 11, 4333–4340; f) M. A. Marques, R. M. Doss, A. R. Urbach, P. B. Dervan, Helv. Chim. Acta 2002, 85, 4485–4517.

[17] a) B. Liu, T. Kodadek, J. Med. Chem. 2009, 52, 4604–4612; b) S. Nishijima, K. Shinohara, T. Bando, M. Minoshima, G. Kashiwazaki, H. Sugiyama, Bioorg. Med. Chem. 2010, 18, 978–983.