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Design and synthesis of 2,2'-diindolylmethanes to selectively target certain G-quadruplex DNA structures

Madeleine Livendahl[a], Jan Jamroskovic[b], Svetlana Ivanova[a], Peter Demirel[a], Nasim Sabouri[b]*, and Erik Chorell[a]*

Abstract: G-quadruplex (G4) structures carry vital biological functions and compounds that selectively target certain G4 structures have both therapeutic potential and value as research tools. Along this line, 2,2'-diindolylmethanes have in this work been designed and synthesized based on the condensation of 3,7- or 3,6-substituted indoles with aldehydes**.** The developed class of compounds efficiently stabilizes G4 structures without inducing conformational changes in the G4 structures. Furthermore, the 2,2'-diindolylmethanes target certain G4 structures more efficiently than others and this G4 selectivity can be altered by chemical modifications of the compounds.

G4 structures can form in DNA and RNA sequences with four repeats of two or more guanines bridged by random nucleotides called “loops”. These sequences form stacks of guanine tetrads (G-tetrads) and each G-tetrad is held together by Hoogsteen hydrogen bonding.[1] The G4 structures are stabilized by cations, such as sodium or potassium, placed in the central of the stacks.[2] The number of potential G4 structures is vast in the human genome and they may adopt inter- or intramolecular structures, as well as parallel or antiparallel structures.[3] Several of the predicted G4 sequences also form G4 structures *in vitro* but if they actually form G4 structures *in vivo*, and their biological roles, are still under investigation. So far, G4 structures have proven important to govern central biological processes such as gene transcription, DNA replication, translation, and telomere maintenance.[4] Research in this field is therefore of continuous interest to uncover the details about the biological functions of G4 structures and to discover their potential unknown functions at different genomic locations.

Low molecular weight compounds that interact with G4 structures have potential as drug candidates but also as research tools.[5] One of the biggest challenges in this context is to be able to target and stabilize specific G4 structures and to do so without inducing conformational changes. Reports of compounds with selectivity between G4 structures are rare, and studies of such selective compounds that do not induce conformational changes are even more scarce. Phen-DC3 is one of the most frequently used and most potent G4 DNA stabilizing compounds.[6] It has a central phenanthroline core with two identical quinoline side chains (Figure 1). Detailed NMR studies of Phen-DC3 binding to the Pu24T G4 structure derived from the *c-MYC* promoter have revealed that the compound efficiently binds to the top of the G4 structure.[7] Furthermore, ESI-MS studies using the human telomeric 24TTG G4 structure have shown that Phen-DC3 displace one of the cations in the G4 structure upon binding.[8] In addition, it is known that Phen-DC3, Phen-DC3 analogues, and other well-known compounds that bind to G4 structures, such as 360A and pyridostatin, perturb the structure of human telomeric G4 DNA upon binding.[8-9]

Here, we have designed and synthesized substituted 2,2'-diindolylmethanes based on indole derivatives and evaluated their ability to bind and stabilize different G4 DNA structures. Indoles frequently appear in biologically active compounds and marketed drugs, and are therefore considered to be privileged structures in medicinal chemistry.[10] One class of bis-indoles have been reported to stabilize G4 structures,[11] but the 2,2'-diindolylmethanes have to our knowledge, not been reported in this setting. Previous work on 2,2'-diindolylmethanes is mostly associated with the design of anion receptors, catalysts, and dyes.[12] Although 2,2'-diindolylmethanes are frequently reported in the literature, substitutions in position 6 or 7 on the indoles in the 2,2'-diindolylmethanes are not extensively studied and to the best of our knowledge no studies with amides from 6- or 7-carboxylate indoles have been reported. We used quinoline side chains (see structure of Phen-DC3) attached via an amide to position 6 or 7 on the indoles that constitute the 2,2'-diindolylmethanes (Figure 1).

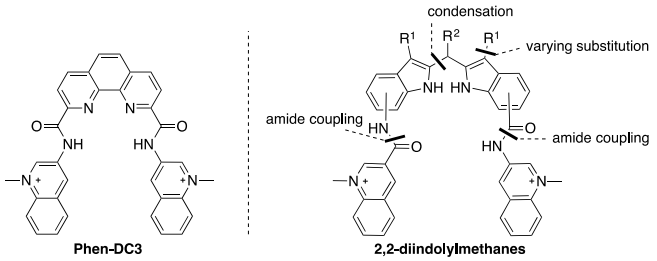

Figure 1. Structure of Phen-DC3 and outline for the synthesis of 2,2'-diindolylmethanes.

Synthesis of the 2,2'-diindolylmethanes started from the commercially available indoles **1a** and **1b** with methyl esters in position 6 or 7 for subsequent side chain introduction. A methyl substituent was first introduced to **1a** and **1b** using a Vilsmeier-Haack formylation followed by a reduction using $Pd(OH)_2/C$ and hydrogen gas to give **2a** and **2b** in high yields (Scheme 1). Condensation of **2a** or **2b** using previously described procedures with hydrochloric acid and heat[13] resulted in low conversion and complex reaction mixtures, probably as a result of the electron withdrawing methyl ester substituents. After evaluation of various reaction conditions, stirring of **2a** and **2b** with benzaldeyde and trifluoroacetic acid (TFA) at room temperature over night generated the best results giving 2,2'-

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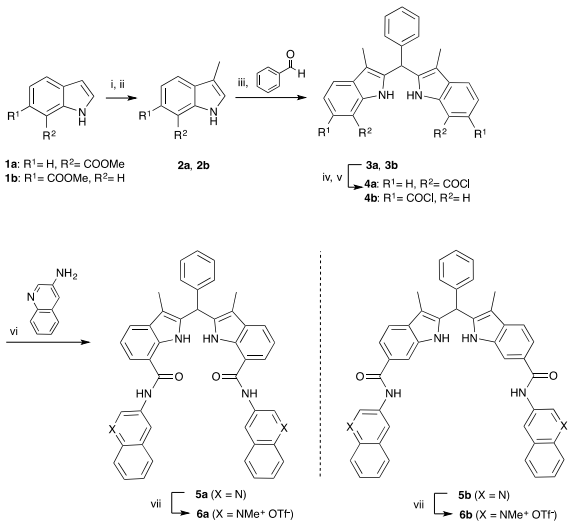
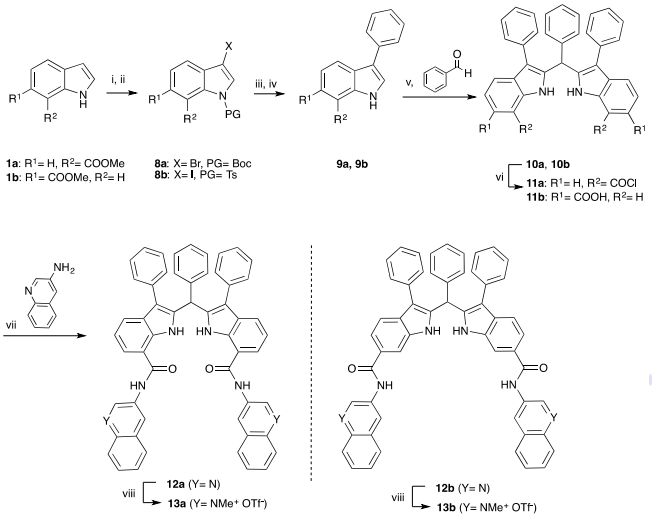
diindolylmethanes **3a** and **3b** in 80% and 88% yield, respectively. Introduction of the side chains to **3a** and **3b** was first attempted using 3-aminoquinoline with different bases and solvents without success. Next, a two-step process with hydrolysis of the methyl ester followed by an amide coupling using different coupling reagents was tested, but unfortunately also this method proved difficult with no or only traces of product observed. Finally, the conversion of the acid to the acid chloride **4a** followed by addition of deprotonated 3-aminoquinoline gave **5a** in 60% yield. Unfortunately, the same procedure only gave **5b** in 7% yield. The reason for these coupling problems was found to be due to the low nucleophilicity of 3-aminoquinoline because other more nucleophilic amines readily formed the amide bond using the same conditions. Quarternarization of the quinoline nitrogens using MeOTf in dichloromethane gave the target compounds **6a** and **6b** in 66% and 81% yield, respectively.



Scheme 1. 1a, **1b**: i. $POCl_3$, DMF, 35 °C, 1h, 93%, 66% respectively ii. $Pd(OH)_2/C$, H_2, MeOH:THF (1:1), rt, 4h, 83%, 65% respectively. **2a**, **2b**: iii. TFA, PhCHO, DCE, rt, o.n, 80%, 88% respectively. **3a**, **3b**: iv. LiOH (4M), MeOH, reflux, 6h, 90%, 93% respectively v. Oxalyl chloride, DMF, MeCN, rt, 2h, quant., quant. **4a**, **4b**: vi. NaH, 3-aminoquinoline, THF, rt, o.n. 60%, 7% respectively. **5a**, **5b**: vii. MeOTf, DCE, reflux, o.n. 66%, 81% respectively.

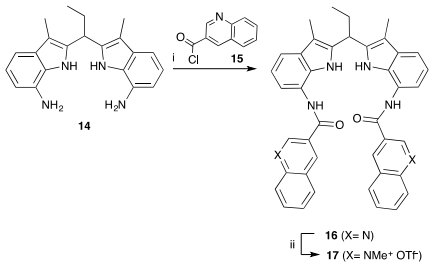
After completing the synthetic route based on 3-methyl substituted indoles, we also investigated the difference in reactivity and also potential G4 structure stabilization when the 3-methyl substituents were replaced with larger phenyl substituents. To reach these derivatives the 6- and 7-methylester substituted indoles **1a** and **1b** were first halogenated using *N*-bromosuccinimide (NBS) or iodine in high yields. Subsequent Suzuki-Miyaura couplings to introduce the desired phenyl substituent gave low conversion and a mixture of products. As a consequence, the indole nitrogens were protected using $(Boc)_2O$ or Ts-Cl to give **8a** and **8b** (Scheme 2). With substrate **8b**, the coupling reaction was next performed using a previously published procedure[12c] followed by deprotection using NaOMe in MeOH that quickly and cleanly removed the tosyl protective group without hydrolyzing the methyl ester, to give product **9b**. However, this sequence did not work for **8a**. Instead, $PdCl_2$ and dppf in a tetrahydrofuran (THF)-water mixture[14] was used to achieve the coupling reaction and the Boc protective group was removed by standard conditions to give **9a** in high yield. Condensation of **9a** and **9b** using the method developed for **2a** and **2b** gave **10a** and **10b** in 91% and 67% yield, respectively, albeit after longer reaction times. As expected, the following introduction of the side chains proved to be problematic also for **10a** and **10b**. For **10a**, the hydrolysis followed by conversion into the acid chloride was the preferred route, which gave **11a** in quantitative yield. Subsequent addition of **11a** to deprotonated 3-aminoquinoline in dichloroethane (DCE) gave **12a** in 18% yield. The same method was not applicable to **10b**, for which instead a hydrolysis to give **11b** in 96% yield followed by a coupling reaction was used. After extensive testing of different coupling reagents, the use of EDC and HOBt in dimethylformamide (DMF) worked best and gave **12b** in 25% yield. Methylation of the quinoline nitrogens gave the target compounds **13a** and **13b** in 71% and quantitative yield, respectively.



Scheme 2. 1a: i. NBS, DCE, -20 °C, 3 min, 90% ii. $(Boc)_2O$, NEt_3, DMAP, rt, o.n., 99% **1b**: i. I_2, NaOH, DMF, rt, o.n., 95%. ii. Ts-Cl, NaOH, DCM, rt, o.n., 90% **8a**: iii. $PdCl_2$, dppf, $PhB(OH)_2$, Na_2CO_3, $THF:H_2O$ (3:1), 70 °C, o.n., 73% iv. 10% TFA, DCM, 0°C, 3h, 90% **8b**: iii. $Pd(PPh_3)_4$, $PhB(OH)_2$, Na_2CO_3 (aq), Toluene, 120 °C, o.n., 99%. iv. NaOMe, MeOH, reflux, o.n., 84% **9a**, **9b**: v. TFA, PhCHO, DCE, rt, 48-72h, 92%, 67% respectively **10a**: vi. 1) LiOH (4M), MeOH, reflux, o.n., 95%, 2) Oxalyl chloride, DMF, MeCN, rt, 2h, quant. **10b**: vi. LiOH (4M), MeOH, reflux, o.n., 96% **11a**: vii. NaH, 3-aminoquinoline, DCE, rt, o.n., 18%. **11b**: vii. EDC, HOBt, DMF, rt, o.n., 25%. **12a**: viii. MeOTf, DCE, rt, o.n., 71%. **12b**: viii. MeOTf, DCE, rt, o.n., quant.

Reversing the amides on the side chains of flexible Phen-DC3 analogues can affect their binding to G4 structures.[6, 15] Therefore, we decided to synthesize one such analogue based on previously developed conditions to generate intermediate **14**.[12d] The 3-methyl-7-nitro substituted indole was thus synthesized and condensed with propionaldehyde followed by reduction of the nitro groups using Pd/C and H_2 to get **14**. Introduction of the side chains to 2,2'-diindolylmethane **14** was achieved by using acid chloride **15,** which gave **16** in 22% yield

accompanied by monoaddition and unreacted starting material that had to be separated by preparative HPLC. Attempts to improve the yield by different bases, reaction times, and heat were unsuccessful. Methylation of the quinoline nitrogens was also low yielding (23%) mainly due to low reactivity and problematic purifications, but still gave **17** in sufficient amounts for further evaluations of its ability to bind G4 structures.



Scheme 3. i.1) NEt_3, DCM, rt, 15 min. 2) **15**, DCM, rt, o.n., 22% ii. MeOTf, DCE, rt, o.n., 23%

To probe the target compounds ability to bind G4 structures, we used an assay based on Thioflavin T (ThT) fluorescence.[16] ThT is a known fluorescent probe that, upon binding to G4 structures, gives a distinct fluorescence at 480 nm when excited at 435 nm. A compound that binds the G4 structure and thus out competes ThT can be detected by reduced fluorescence intensity. To test the newly synthesized compound's ability to bind G4 structures, three well-studied oligonucleotides that adopt different G4 structures were examined; the Pu24T *c-MYC* promoter sequence[7, 17] (forming a parallel-stranded G4 structure), the human telomeric sequence 24TTG[18] (forming a hybrid G4 structure), and a ribosomal DNA sequence from *Schizosaccharomyces pombe* genome (forming a parallel-stranded G4 structure)[19] (Figure 2A). The latter sequence was chosen because *S. pombe* closely resembles higher eukaryotes in terms of the high conservation of genome organization, G4 motifs (potential sequences that can form G4 structures), heterochromatin, and RNA interference pathways and is thus considered as a good model organism.[20] The target compounds were tested at a range of different concentrations using the different oligonucleotide templates and Phen-DC3 as a positive control (Figure 2B and supporting information Figure 1A and 1B). Phen-DC3 analogues have previously been shown to display a reduced binding to G4 structures when increasing the flexibility of the core structure of the compound as shown by bis-pyridine derivatives.[6] In addition, reversing the amide has also shown to reduce the activity.[15] Our 2,2'-diindolylmethanes are more flexible than Phen-DC3 and **17** also has a reversed amide. It was therefore interesting to observe that the 2,2'-diindolylmethanes **6a-b, 13a-b,** and **17** bound both the Pu24T *c-MYC* G4 structure, the telomeric G4 structure, and the ribosomal DNA G4 structure in a dose-dependent manner. **6a**, **6b**, and **17** were significantly more active on the Pu24T *c-MYC* G4 structure compared to the telomeric G4 structure, 4-fold, 7-fold, and 11-fold respectively (e.g. half maximum displacement concentration (DC_{50}) for **17** with Pu24T *c-MYC*: 0.20 μM vs DC_{50} for **17** with telomeric: 2.2 μM (Figure 2B). In fact, in this assay **6a**, **6b**, and **17** displayed similar or even improved DC_{50} values with the Pu24T *c-MYC* G4 structure compared to Phen-DC3 (Figure 2B). The larger phenyl substituents in **13a** and **13b**, originating from the corresponding 3-phenyl substituted indoles, induced a substantial drop in affinity compared to the smaller methyl substituents in **6a** and **6b** (Figure 2B and supporting information Figure 1A and 1B). Interestingly, the preference for the Pu24T *c-MYC* G4 structure observed for **6a**, **6b**, and **17**, can be modified by changing the substitution pattern on the 2,2'-diindolylmethanes as **13a** and **13b** showed a higher affinity for the ribosomal DNA G4 structure compared to both the Pu24T *c-MYC* and telomeric G4 structures (e.g. DC_{50} for **13b** with ribosomal DNA: 2.7 μM vs DC_{50} for **13b** with Pu24T *c-MYC*: 8.3 μM and DC_{50} for **13b** with telomeric: 10.3 μM). There was no clear difference between the anchoring position of the side chains to the 2,2'-diindolylmethanes as **6a** and **6b** as well as **13a** and **13b** showed similar activities.

A

Human Pu24T *c-MYC* DNA (24 bp): TGA**GGG**TGGTGA**GGG**T**GGGG**AA**GG**
Human telomeric DNA (24 bp): TT**GGG**TTA**GGG**TTA**GGG**TTA**GGG**A
S. pombe ribosomal DNA (25 bp): **GGGG**AA**GGG**T**GGGG**CATGTTAT**GGG**

B

DC_{50} values of ThT displacement (μM)

	PhenDC3	6a	6b	13a	13b	17
Human Pu24T_*c-MYC* DNA	0.7	0.9	0.7	7.1	8.3	0.2
Human telomeric DNA	0.8	3.5	5	5.3	10.3	2.2
S. pombe ribosomal DNA	0.5	1.3	1.9	2.7	2.2	0.9

C

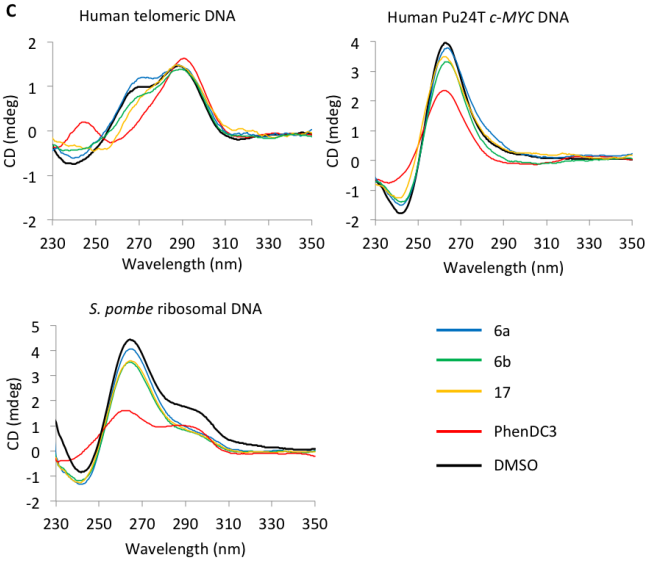


Figure 2. (A) Sequences of G4 forming oligonucleotides used in the study. G4 motif is in bold and underlined. (B) DC_{50} values of ThT displacement from 1 μM Pu24T *c-MYC*, telomeric and ribosomal DNA. Values are shown in μM concentration (see supporting information Figure 1 for error values). (C) CD spectra of 5 μM folded telomeric, Pu24T *c-MYC,* and ribosomal DNA treated with 1.25% DMSO, 40 μM Phen-DC3, **6a**, **6b**, and **17** measured at 25 °C.

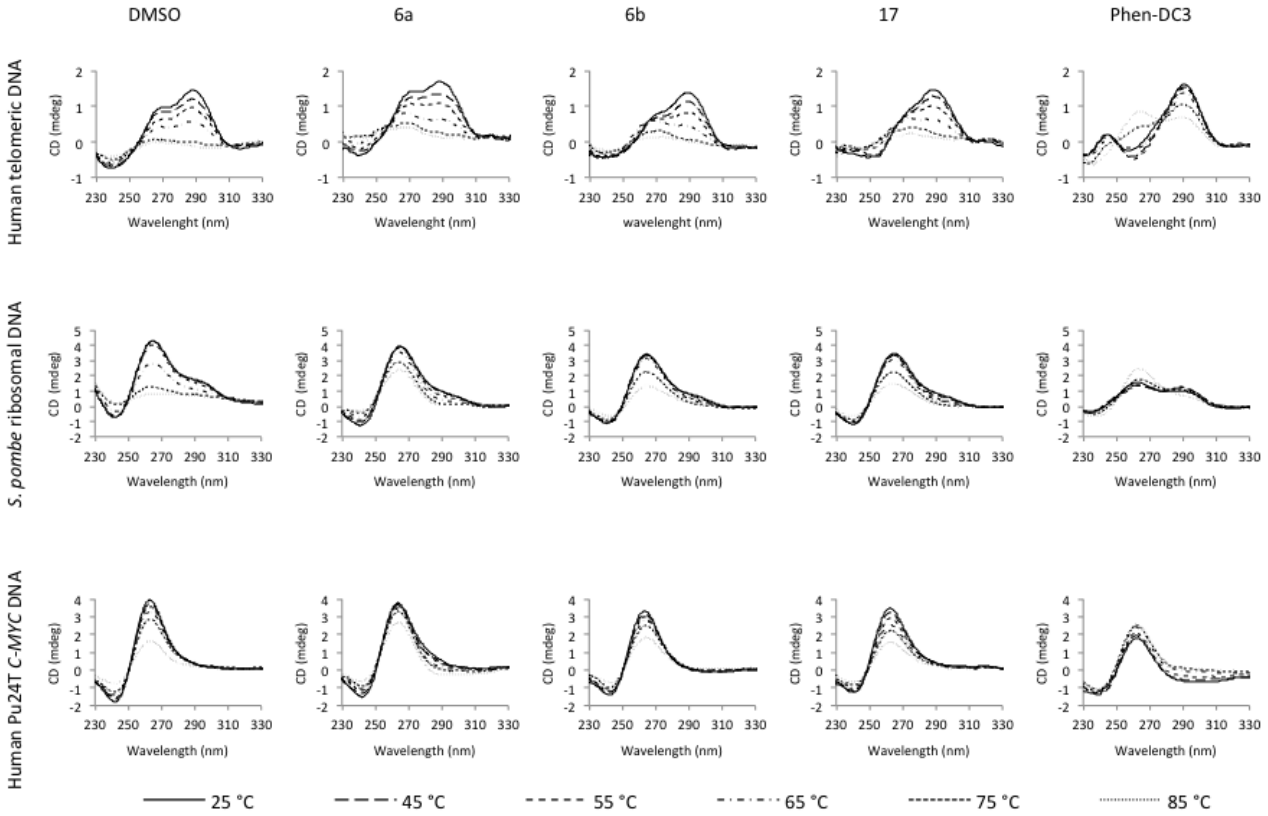


Figure 3. The compounds show selective G4 structure stabilizing without any induction of structural changes. CD spectra for 5 µM human telomeric DNA (left), *S. pombe* ribosomal DNA (middle), and *human Pu24T_C-myc DNA* (right) in 1.25 % v/v DMSO or 40 µM of **6a**, **6b**, **17**, and Phen-DC3, measured at six different temperatures, 25, 45, 55, 65, 75, and 85 °C.

To investigate if the compounds change the G4 structures upon binding, they were evaluated using circular dichroism (CD) spectroscopy. The most active compounds from the ThT displacement assay, **6a**, **6b**, and **17** were evaluated with the Pu24T *c-MYC* G4 structure, the telomeric G4 structure, and the ribosomal DNA G4 structure at 8:1 molar ratios (Figure 2C). None of the tested compounds, including Phen-DC3, induced any significant structural changes in the Pu24T *c-MYC* G4 structure. However, Phen-DC3 not only induced large structural changes in the telomeric G4 structure, as previously reported,[8] but also in the ribosomal DNA G4 structure (Figure 2C). In comparison, all of the 2,2'-diindolylmethanes induced very minor structural changes in the tested G4 structures; **6a** and **6b** induced the least structural changes whereas **17** induced similar but less pronounced changes as Phen-DC3.

The 2,2'-diindolylmethanes abilities to stabilize the three G4 structures were further studied by using CD spectroscopy. CD spectra were recorded while stepwise increasing the temperature to study the thermal stability of the G4 structures. Compounds **6a**, **6b**, **17**, Phen-DC3 and DMSO together with the three G4 structures were evaluated using this technique (Figure 3 and melting curves in supporting information Figure 2A-C). From the DMSO experiments it is clear that the Pu24T *c-MYC* G4 structure is most stable and requires high temperatures to unfold. The telomeric G4 structure and the ribosomal DNA G4 structure are less stable and are unfolded already at around 75 °C (Figure 3). Phen-DC3 efficiently stabilize the Pu24T *c-MYC* G4 structure whereas it completely changed the structure of the telomeric and ribosomal DNA G4 structures. The 2,2'-diindolylmethanes **6a**, **6b**, and **17** all strongly stabilized the ribosomal DNA and Pu24T *c-MYC* G4 structures and, in accordance with the ThT assay, this strong stabilization was substantially reduced for the telomeric G4 structure. Unfortunately, we observed that compounds **6b** and **17** were not completely thermally stable as precipitations and colour changes were observed after the thermal CD cycle. This may explain why we do not detect an even stronger G4 stabilization for these compounds. Finally, **6a**, **6b**, and **17** were evaluated for their ability to stabilize dsDNA using CD (supporting information Figure 2D). All compounds displayed selectivity for G4 structures over dsDNA with only minimal stabilization of dsDNA.

In conclusion, we have developed synthetic methods to 2,2'-diindolylmethanes based on the synthesis of 3,7- or 3,6-substituted indoles. These indoles could be condensed with aldehydes followed by introduction of side chains based on the well-known and efficient G4 binding compound Phen-DC3. *In vitro* evaluation of these derivatives in a ThT displacement assay showed that **6a**, **6b**, and **17** have similar or even improved binding activities compared to Phen-DC3. In addition, our results suggest that these compounds bind more efficiently to certain G4 structures than others and that this G4 structure selectivity could be substantially altered by modifications of the substituents on the 2,2'-diindolylmethanes. Analysis of the synthesized 2,2'-diindolylmethanes using CD spectroscopy showed that the compounds stabilize certain G4 structures more efficiently than others, thus supporting the selectivity observed in

the ThT assay. The CD analyses also revealed that the 2,2'-diindolylmethanes only induce subtle structural changes as opposed to the major changes triggered by Phen-DC3 in the human telomeric and ribosomal DNA G4 structures. Taken together, it is clear that the developed 2,2'-diindolylmethanes specifically target defined G4 structures without inducing large conformational changes and that this selectivity can be fine-tuned by chemical modifications. The details of the observed effects by these compounds, with assay conditions closer to physiological settings, as well as their optimizations and use as research tools, both *in vitro* and *in vivo*, are currently on-going in our labs.

Acknowledgements

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Keywords: G-quadruplex • G4 structure • 2,2'-Diindolylmethane • Selectivity • Phen-DC3

[1] a) M. Gellert, M. N. Lipsett, D. R. Davies, *Proc. Natl. Acad. Sci. USA* **1962**, *48*, 2013-8; b) D. Sen, W. Gilbert, *Nature* **1988**, *334*, 364-366.

[2] a) F. B. Howard, H. T. Miles, *Biochemistry* **1982**, *21*, 6736-6745; b) J. R. Williamson, M. K. Raghuraman, T. R. Cech, *Cell* **1989**, *59*, 871-880; c) D. Sen, W. Gilbert, *Nature* **1990**, *344*, 410-414.

[3] a) M. W. Silva, *Chem. Eur. J.* **2007**, *13*, 9738-9745; b) P. Stadlbauer, M. Krepl, T. E. Cheatham, J. Koca, J. Sponer, *Nucleic Acids Res.* **2013**, *41*, 7128-7143; c) A. Guedin, J. Gros, P. Alberti, J.-L. Mergny, *Nucleic Acids Res.* **2010**, *38*, 7858-7868; d) S. Burge, G. N. Parkinson, P. Hazel, A. K. Todd, S. Neidle, *Nucleic Acids Res.* **2006**, *34*, 5402-5415; e) P. Hazel, G. N. Parkinson, S. Neidle, *Nucleic Acids Res.* **2006**, *34*, 2117-2127.

[4] a) M. L. Bochman, K. Paeschke, V. A. Zakian, *Nat. Rev. Genet.* **2012**, *13*, 770-780; b) H. J. Lipps, D. Rhodes, *Trends Cell Biol.* **2009**, *19*, 414-422.

[5] a) D.-L. Ma, Z. Zhang, M. Wang, L. Lu, H.-J. Zhong, C.-H. Leung, *Chem. Biol.* **2015**, *22*, 812-828; b) G. W. Collie, G. N. Parkinson, *Chem. Soc. Rev.* **2011**, *40*, 5867-5892.

[6] A. De Cian, E. DeLemos, J.-L. Mergny, M.-P. Teulade-Fichou, D. Monchaud, *J. Am. Chem. Soc.* **2007**, *129*, 1856-1857.

[7] W. J. Chung, B. Heddi, F. Hamon, M.-P. Teulade-Fichou, P. Anh Tuan, *Angew. Chem. Int. Ed.* **2014**, *53*, 999-1002.

[8] A. Marchand, A. Granzhan, K. Iida, Y. Tsushima, Y. Ma, K. Nagasawa, M.-P. Teulade-Fichou, V. Gabelica, *J. Am. Chem. Soc.* **2015**, *137*, 750-756.

[9] A. F. Larsen, M. C. Nielsen, T. Ulven, *Chem. Eur. J.* **2012**, *18*, 10892-10902.

[10] M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347-361.

[11] J. Dash, R. N. Das, N. Hegde, G. D. Pantos, P. S. Shirude, S. Balasubramanian, *Chem. Eur. J.* **2012**, *18*, 554-564.

[12] a) J. M. Granda, J. Jurczak, *Chem. Eur. J.* **2015**, *21*, 16585-16592; b) P. Dydio, R. J. Detz, J. N. H. Reek, *J. Am. Chem. Soc.* **2013**, *135*, 10817-10828; c) Y. Ni, W. Zeng, K.-W. Huang, J. Wu, *Chem. Commun.* **2013**, *49*, 1217-1219; d) P. Dydio, T. Zielinski, J. Jurczak, *Chem. Commun.* **2009**, 4560-4562; e) P. Dydio, J. N. H. Reek, *Angew. Chem. Int. Ed.* **2013**, *52*, 3878-3882.

[13] A. Loudet, K. Burgess, *Chem. Rev.* **2007**, *107*, 4891-4932.

[14] P. Shultz, L. Bouchez, *Patent WO 2012129562* **2012**.

[15] P. L. T. Tran, E. Largy, F. Hamon, M.-P. Teulade-Fichou, J.-L. Mergny, *Biochimie* **2011**, *93*, 1288-1296.

[16] a) V. Gabelica, R. Maeda, T. Fujimoto, H. Yaku, T. Murashima, N. Sugimoto, D. Miyoshi, *Biochemistry* **2013**, *52*, 5620-5628; b) J. Mohanty, N. Barooah, V. Dhamodharan, S. Harikrishna, P. I. Pradeepkumar, A. C. Bhasikuttan, *J. Am. Chem. Soc.* **2013**, *135*, 367-376.

[17] A. T. Phan, V. Kuryavyi, H. Y. Gaw, D. J. Patel, *Nat. Chem. Biol.* **2005**, *1*, 167-173.

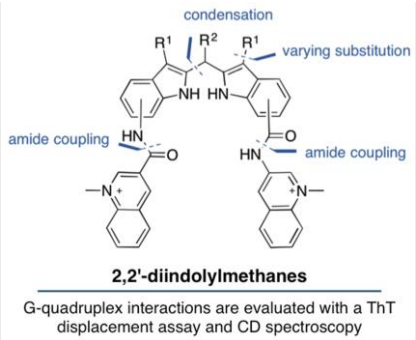
[18] K. N. Luu, A. T. Phan, V. Kuryavyi, L. Lacroix, D. J. Patel, *J. Am. Chem. Soc.* **2006**, *128*, 9963-9970.

[19] M. Wallgren, J. B. Mohammad, K.-P. Yan, P. Pourbozorgi-Langroudi, M. Ebrahimi, N. Sabouri, *Nucleic Acids Res.* **2016**, doi: 10.1093/nar/gkw1349.

[20] N. Sabouri, J. A. Capra, V. A. Zakian, *BMC Biol.* **2014**, *12:101*.

COMMUNICATION

G-quadruplex selectivity: 2,2'-diindolylmethanes have been designed and synthesized. The compounds specifically stabilize defined G-quadruplex structures without inducing large conformational changes and the observed selectivity can be fine-tuned by chemical modifications.



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Design and synthesis of 2,2'-diindolylmethanes to selectively target certain G-quadruplex DNA structures