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Pyridyl–Oxazole Oligomers

Linear and Branched Pyridyl–Oxazole Oligomers: Synthesis and Circular Dichroism Detectable Effect on c-Myc G-Quadruplex Helicity

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Abstract: Five unprecedented pyridyl–oxazole oligomers exhibiting either linear or branched connectivity of their subunits were developed as a family of potential G-quadruplex-interacting ligands. Our synthesis employed variations of a key Pd/Cu-mediated C–C cross-coupling/C–H activation reaction to gain access to the oligomer products from a small set of substituted pyridine building blocks. The effect of the compounds on the conformation of a c-myc oncogene promoter G-quadruplex was investigated by circular dichroism under various conditions. Some or all of the compounds induced detectable helicity enhancement in low-cation and Na^+-rich Tris-HCl (pH 7.4) buffers, respectively, in which the helix was only partially prefolded.

Introduction

High-order biomolecular structures are critical in nearly all biological processes, and the complex mechanisms for the dynamic conversion of unfolded primary sequences into folded – and functional – 3D entities have formed the object of numerous investigations aimed at gaining insight into relations between structure and function.[1] Several non-canonical secondary structures have been identified for nucleic acid sequences,[2] some of which are believed to be biologically relevant. Guanine-rich sequences, in particular, have attracted enormous attention,[3] owing to their inherent propensity to self-assemble into tetrastranded helices, termed G-quadruplexes, in the presence of monovalent cations at near-physiological pH. Thermodynamic and kinetic data suggest a relative stability of G-quadruplexes under these conditions, as opposed to other non-B-DNA structures.[4]

About a decade ago, early bioinformatic studies detected that G-rich sequences, with potential to fold into G-quadruplexes, are prevalent in the human genome[5] and most notably in the telomere as well as in promoter regions of several genes. These included powerful oncogenes, such as c-myc, c-kit, and k-ras. The abundance of G-rich tracts in gene promoters led to hypotheses that in nature these sequences might serve as regulatory elements of gene transcription.[6] Furthermore, the observation that stabilization of G-quadruplexes within oncogene promoters causes suppression of the oncogene's expression established these sequences as promising targets for anticancer research.[7] In more recent years, this field has taken giant leaps forward and it is now widely recognized that G-quadruplexes play various roles in both healthy and cancer cells, with impact on chromatin remodeling, genomic instability and repair, telomerase dysfunction, gene expression, and cancer progression.[3a,7,8] High-throughput methods for the detection and mapping of G-quadruplex-forming sequences in the human genome[9] and in cellular transcripts[10] have been reported. Moreover, evidence for the in vivo occurrence of G-quadruplexes has been obtained by the use of G-quadruplex-recognizing antibodies in fixed cells[11] and, very recently, by the use of "smart" small-molecule bioimaging agents in live cells.[12]

Progress in the G-quadruplex field has been chemistry driven, and small molecules have been at the epicenter of many of the aforementioned discoveries, as it was first realized that one of the most effective ways to induce and/or stabilize a G-quadruplex is through its direct interaction with appropriately designed small molecules.[6a,7] Efforts toward the development of improved G-quadruplex stabilizers remain very active, as they are anticipated to yield novel anticancer pharmaceuticals or specialized bioimaging probes for elucidating yet unknown biological functions of G-quadruplexes.

Terminal guanine tetrads, the planar arrangements of four guanines exposed to either end of any G-quadruplex helix, have been the most frequently exploited binding sites for small-molecule interaction. Owing to the planarity of G-tetrads, conventional binder design has focused on polycyclic (hetero)aromatic chromophores that offer the possibility for π–π stacking[13] (Figure 1, a). Whereas such systems may reach sufficiently high affinity in engaging with G-quadruplexes, especially if reinforced with cationic/ionizable functionalities or metal cations, most tend to lack specificity for one particular G-quadruplex. Undesired affinity for duplex DNA, cell membranes, or other hydrophobic biomolecular surfaces may occasionally become limiting

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for their progression to medicinal application. Quarfloxin is the first compound from this class to have progressed to phase II clinical trials.[7,14]

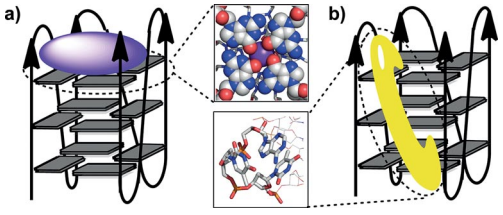


Figure 1. Alternative small-molecule binding modes on a G-quadruplex (gray rectangles represent guanine bases): (a) end stacking (π–π stacking) to terminal guanine tetrads, typical for rigid planar binders; (b) interaction with residues displayed in grooves and loops, believed to occur with conformationally flexible, modular binders.

The realization that the most differentiating element of diverse G-quadruplexes is the shape of their grooves and loops, which are also viewed as their most elusive domains because of their dynamic nature,[15] has turned researchers toward considering longer modular molecules that offer conformational flexibility (Figure 1, b). Studies have demonstrated that the grooves of G-quadruplexes can accommodate diverse natural products such as aminoglycosides[16] and nonplanar alkaloids,[17] and analogous binding should be possible for synthetic ligands. Following this line of thinking, deviations from conventional binder design have delivered few groove/loop binders for G-quadruplexes. For example, the cationic dye 3,3′-diethyloxadicarbocyanine (DODC),[18] BINOL derivatives,[19] helically folded oligoamides,[20] and distamycin A with some of its synthetic derivatives[21] have been reported as such. Prominent work by Teulade-Fichou and co-workers has identified the neutral, symmetric pyridine/oxazole-based oligoheteroaryl system TOxaPy[22] and related cationic oxadiazole compound BOxAzaPy[23] as potential groove binders with the ability to discriminate between two distinct folds of human telomeric G-quadruplex DNA.

These last reports demonstrate that conformationally flexible ligands for G-quadruplexes may offer potential for target-specific interactions. This prompted us to embark on a synthetic effort to expand the available pool of conformationally versatile ligands, the design of which would not pose any limitations as to their possible modes of binding (i.e., not exclude a priori any of the aforementioned binding modes) but would instead allow adaptability to the G-quadruplex DNA target at hand. In particular, we became interested in developing a modular synthetic method to gain access to heteroaryl oligomers with diverse architectures and featuring the "privileged" pyridyl–oxazole unit. Herein, we describe the synthesis of a small library of oligomers and present preliminary circular dichroism data on compound interaction with the c-myc oncogene promoter G-quadruplex under various conditions to determine the ability of some of the compounds to induce favorable conformational changes to the helix.

Results and Discussion

Compound Design and Considerations

The emergence of TOxaPy as a target-specific telomeric G-quadruplex binder, for which spectroscopic data and molecular docking suggested a groove-interaction mode,[22] stressed the marked absence of analogous neutral, modular binders for c-myc and other oncogene promoter sequences. This encouraged us to consider how small heteroaromatic moieties, such as the pyridyl–oxazole fragment, could be employed in a new context to assemble an extended family of oligomeric compounds with variable architectural features (i.e., shape and size). We envisaged that an atom-economic synthesis employing a few common key intermediates to construct all members of this diverse set of oligomers could be employed, in combination with a small number of recurring reaction conditions. In this way a "privileged" chemical moiety could be evaluated as a building unit and incorporated in various architectures to identify convenient ones for interaction with c-myc.

Employing combinations of pyridine and oxazole subunits as building blocks, both of which have been previously validated as part of other successful (including macrocyclic) DNA-binding motifs,[22–24] seemed like a reasonable starting point. Both ring systems are small-size heteroaromatics likely to fit well into DNA cavities. They can serve as H-bond acceptors, which is a desired property in guanine-rich groove environments, whereas they do not exclude the possibility of π–π stacking. The aryl–aryl connectivity of these heteroaromatics was chosen to provide "ribbon-like" compounds that serve as mimics of protein helical structures,[25] owing to the way they "exhibit" their heteroatoms in a helical arrangement around their periphery. This type of connectivity also allows for necessary rotational flexibility, so that the compounds can "sample" potential binding modes before developing the most favorable multivalent interaction with the DNA. Finally, their neutral character differentiates these compounds from the vast majority of previous c-myc quadruplex-interacting molecules that are cationic, which might enhance selectivity.

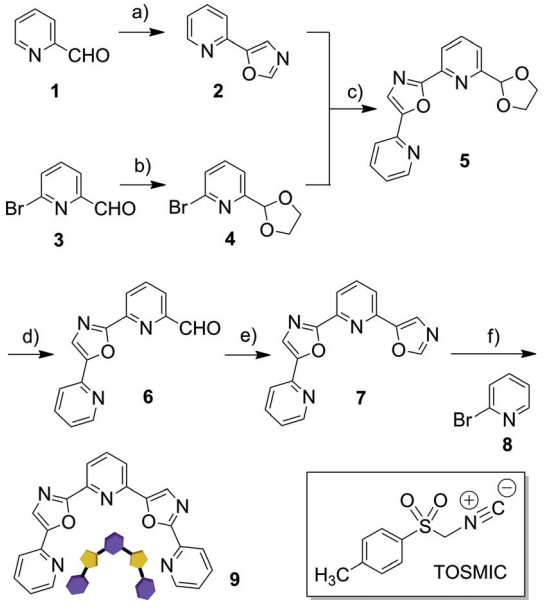
We anticipated that the size and shape of the oligomers would be two critical parameters for association to the target, as G-quadruplexes have very specific spatial and conformational requisites. Thus, a range of linear oligomers from 5–7 constituent units (rings) was deemed ideal. G-quadruplex asymmetry and twist helicity creates nonsymmetric environments in the grooves and loops; therefore, to increase the probability of binding, our synthetic scheme for the linear oligomers relied on nonsymmetric, directional ("head-to-tail") connectivity of the subunits. Branched counterparts were also included in our compound design to test the impact of nonlinear architectures on c-myc interaction, although these were symmetric compounds to simplify their synthesis. Their molecular weights were chosen to be comparable to those of their linear relatives.

Compound Synthesis

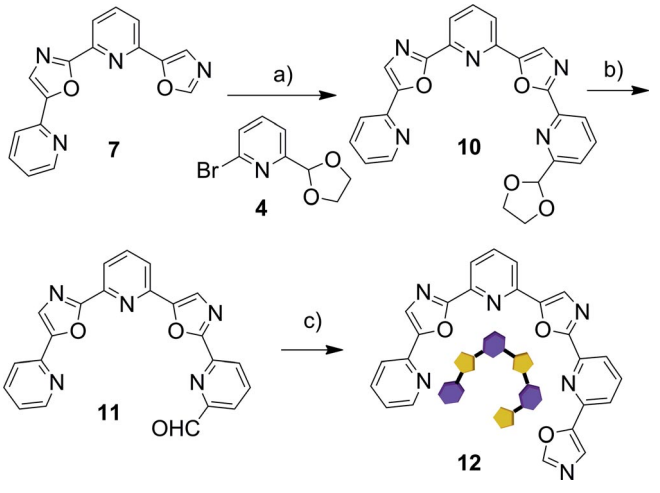
Our synthetic route for constructing a nonsymmetric pentaaryl oligomer in which alternating pyridines and oxazoles are con-

nected in a linear "head-to-tail" fashion (i.e., Pyr-Oxa-Pyr-Oxa-Pyr) is outlined in Scheme 1. This synthesis relied on the use of two key substituted pyridine building blocks in its initial stages, from which all subsequent intermediates were derived. The first, 2-pyridinecarbaldehyde (**1**) was submitted to 1,3-dipolar cycloaddition with the carbenoid reagent *p*-toluenesulfonylmethyl isocyanide (TOSMIC)[26] under deprotonating conditions, which led to the formation of oxazole heterocycle **2** in 98 % yield. The second, 6-bromo-2-pyridinecarbaldehyde (**3**) was converted into dioxolane **4** under standard conditions[27] in 96 % yield. The availability of intermediates **2** and **4** enabled their direct cross-coupling under Pd^{II}/Cu^{I} co-catalysis to furnish extended intermediate **5**. This step, which involves C–H activation of the 2-position of oxazole **2** and its C–C connection to the 2-position of bromide **4** (with loss of HBr), is a key reaction for the rapid assembly of oligomers of this type. It was demonstrated by Hamon et al. in the synthesis of TOxaPy[22] and by us in the construction of a "propeller-like" counterpart.[28] The current work further extends the applicability of this reaction and demonstrates its tolerance for certain chemical functionalities (e.g., dioxolanes and esters). The moderate yield in this case (53 %) was due to the competing formation of homocoupling byproducts from the bromide, which appeared to be a general limitation in all the examples we investigated. Compound **5** was subsequently deprotected to regenerate the aldehyde moiety. This step proved problematic if aqueous 2 M HCl was applied under reflux conditions, in which case we observed conversion of the dioxolane into a stable hydrate derivative of the aldehyde. Therefore, we devised an alternative set of conditions based on a modification of a pre-existing procedure[29] involving extended heating with an excess amount of LiCl (10 equiv.) in a mixed DMSO/H_2O (1:1) solvent. In this case, satisfactory conversion into the aldehyde (67 %) was observed, with no starting material degradation. The TOSMIC reaction proved useful once more in the conversion of aldehyde **6** into tetraaryl intermediate **7** in 68 % yield. Next, another C–H activation–Pd^{II}/Cu^{I} co-catalyzed cross-coupling reaction was performed to pair compound **7** with a third key building block, 2-bromopyridine (**8**), to obtain pentaaryl product **9** (46 % yield). Compound **7** represents a critical synthetic intermediate in our overall scheme that was essential for assembling not only pentameric compound **9** but also all larger linear oligomers in this study.

By employing a similar reaction set, the preparation of a hexaaryl counterpart was possible (Scheme 2). In this case, we made use of pre-existing intermediate **7**, which was cross-coupled directly to bromopyridine **4** to afford pentaaryl dioxolane **10** (43 % yield). The dioxolane offers a handle for further extension, and this took place after its deprotection to aldehyde **11** (80 % yield); submission of the aldehyde to TOSMIC cycloaddition affords hexaaryl product **12** (42 % yield). In contrast to its 5-aryl and 7-aryl counterparts, the 6-aryl compound, which "terminates" with an oxazole ring instead of a pyridine ring, offers the possibility for further elongation by means of repeating the last three synthetic steps. This could potentially provide access to larger even-numbered polyaryl counterparts (i.e., 8-aryl, 10-aryl, etc.). Longer "head-to-tail" counterparts might be useful in targeting the high-order G-quadruplex DNA structures and will form the focus of a future investigation.



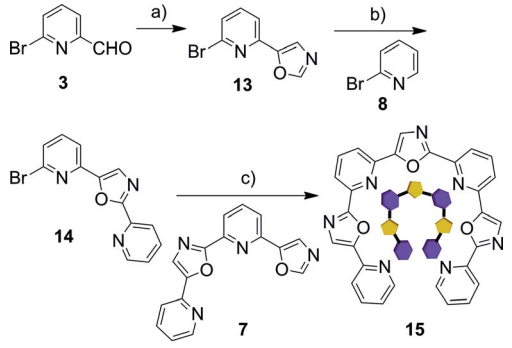
Scheme 1. Synthesis of the linear 5-aryl oligomer. Reagents and conditions: (a) MeOH, TOSMIC, K_2CO_3, 65 °C, 4 h, 98 % yield; (b) benzene, ethylene glycol, *p*-toluenesulfonic acid (TsOH, cat.), 100 °C, 24 h, 96 % yield; (c) 1,4-dioxane, Cs_2CO_3, $Pd(OAc)_2$, CuI, $Cy_3P{\cdot}HBF_4$ (Cy = cyclohexyl), 130 °C, 24 h, 53 % yield; (d) DMSO/H_2O (1:1), LiCl, 150 °C, 48 h, 67 % yield; (e) MeOH, TOSMIC, K_2CO_3, 65 °C, 4 h, 68 % yield; (f) 1,4-dioxane, Cs_2CO_3, $Pd(OAc)_2$, CuI, $Cy_3P{\cdot}HBF_4$, 130 °C, 24 h, 46 % yield. Inset: structure of the TOSMIC reagent used in several steps in this study.



Scheme 2. Synthesis of the linear 6-aryl oligomer. Reagents and conditions: (a) 1,4-dioxane, Cs_2CO_3, $Pd(OAc)_2$, CuI, $Cy_3P{\cdot}HBF_4$, 130 °C, 24 h, 43 % yield; (b) DMSO/H_2O (1:1), LiCl, 150 °C, 48 h, 80 % yield; (c) MeOH, TOSMIC, K_2CO_3, 65 °C, 4 h, 42 % yield.

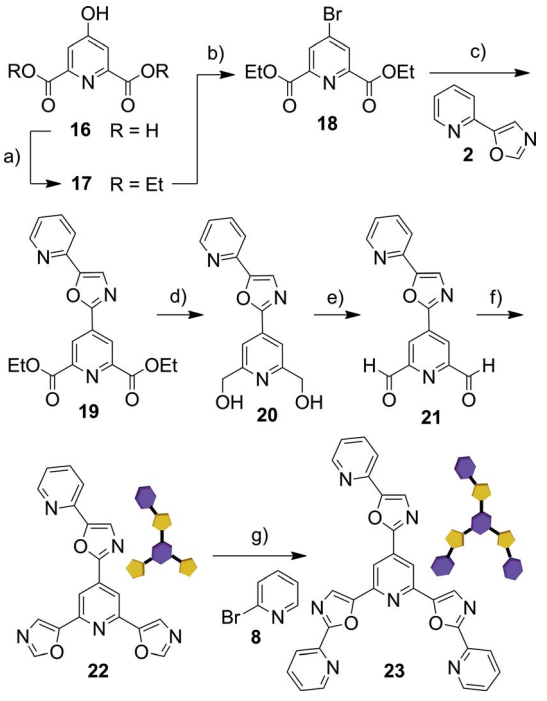
To obtain a nonsymmetric "head-to-tail" 7-aryl compound, a slightly modified route was applied (Scheme 3). A triaryl unit with a bromine handle for cross-coupling was needed. This was obtained in two steps: conversion of key building block **3** into oxazole **13** (82 % yield), followed by cross-coupling of **13** to

2-bromopyridine (**8**). The second step entailed the risk of **13** undergoing "head-to-tail" homocoupling, as it contains both an aryl bromide and an oxazole functionality. Indeed, a competing byproduct was formed in accord with a previous report,[22] which was consistent with a 4-*mer* compound, and this thus limited the yield of desired product **14** to 44 %. With compound **14** in hand, we proceeded to couple it to compound **7**, the result of which was desired 7-*mer* **15** (47 % yield).



Scheme 3. Synthesis of the linear 7-aryl oligomer. Reagents and conditions: (a) MeOH, TOSMIC, K_2CO_3, 65 °C, 4 h, 82 % yield; (b) 1,4-dioxane, Cs_2CO_3, $Pd(OAc)_2$, CuI, $Cy_3P{\cdot}HBF_4$, 130 °C, 24 h, 44 % yield; (c) 1,4-dioxane, Cs_2CO_3, $Pd(OAc)_2$, CuI, $Cy_3P{\cdot}HBF_4$, 130 °C, 24 h, 47 % yield.

To cover a broader range of pyridyl–oxazole architectures with potentially different abilities to interact with c-myc, we extended our synthetic efforts to include branched counterparts. A distinct synthetic scheme was developed (Scheme 4) that was initiated from chelidamic acid (**16**), a pyridine-based building block with three positions for chemical modification. The 2- and 6-carboxylate positions were converted into ethyl ester groups to obtain **17** in excellent yield (98 %) by using thionyl chloride in EtOH.[30] The 4-OH group of **17** was subsequently replaced by a bromine atom in high yield (92 %) upon treatment with PBr_5 (neat) at 95 °C,[30] which afforded pyridyl bromide **18**. We next investigated this bromide as a substrate for Pd^{II}/Cu^{I}-mediated C–C cross-coupling to oxazole **2** to introduce "branching" to the central pyridine ring. The obtained 50 % conversion to compound **19** indicated that 4-bromopyridine **18** has reactivity comparable to that of the 2-bromopyridines used for similar reactions in our previous schemes and that the reaction tolerates ester functionalities as substituents on the bromopyridine coupling partner. A stepwise reduction–reoxidation method was next applied on diethyl ester **19**. Coordinating aluminum-based reducing agents [e.g., diisobutylaluminum hydride (DIBAL-H), sodium bis(2-methoxyethoxy)-aluminum hydride (Red-Al)] led only to partial reduction and loss of material; we, therefore, resorted to $NaBH_4$ in anhydrous MeOH[31] for the full reduction of **19** to diol **20** (76 % yield). Reoxidation of **20** to corresponding dialdehyde **21** was performed with fresh SeO_2 under reflux in 1,4-dioxane (64 % yield).[32] Treatment of dialdehyde **21** with TOSMIC for an extended time period ensured oxazole formation on both reactive positions to furnish branched pyridyl–oxazole **22** in 77 % yield. The synthesis was completed with C–C cross-coupling to 2-bromopyridine (an excess amount was needed) to afford final C_2-symmetric product **23** in 54 % yield.



Scheme 4. Synthesis of the branched 5-aryl and 7-aryl oligomers. Reagents and conditions: (a) EtOH, $SOCl_2$, 0 °C, then r.t. for 18 h, then reflux for 2 h, 98 % yield; (b) PBr_5 (neat), 95 °C, 3.5 h, then $CHCl_3$, EtOH, 0 °C, 3 h, 92 % yield; (c) 1,4-dioxane, Cs_2CO_3, $Pd(OAc)_2$, CuI, $Cy_3P{\cdot}HBF_4$, 130 °C, 24 h, 50 % yield; (d) MeOH, $NaBH_4$, 0 °C, then r.t. for 18 h, 76 % yield; (e) 1,4-dioxane, SeO_2, 100 °C, 5 h, 64 % yield; (f) MeOH, TOSMIC, K_2CO_3, 65 °C, 6 h, 77 % yield; (g) 1,4-dioxane, Cs_2CO_3, $Pd(OAc)_2$, CuI, $Cy_3P{\cdot}HBF_4$, 130 °C, 24 h, 54 %.

Circular Dichroism Titrations

Circular dichroism (CD) may be used to study G-quadruplex helicity and conformational polymorphism.[33] It can indicate conformational changes to the helix brought about by alteration of its environmental conditions or by small-molecule binding. As part of this study, we performed preliminary CD titration experiments to determine whether final oligomeric compounds **9**, **12**, **15**, **22**, and **23** had any effect on the helicity of prefolded c-myc promoter G-quadruplex under various conditions. Any observed effect could serve as an initial indication of interaction. The CD experiments were conducted in 50 mM Tris-HCl buffer (pH 7.4), either in the absence of added salt or in the presence of a monovalent cation (Na^+ or K^+, 100 mM concentration) chloride. Specific cations may affect the topology assumed by G-quadruplexes.[34] Under all three conditions used, the CD spectra exhibited a positive signal around 265 nm and a negative signal around 240 nm. This profile is typical of a unimolecular parallel-stranded G-quadruplex[35] (for a graphical representation see Figure 1) and is consistent with NMR structures for c-myc 2345 (a variation of which is used in this study) under K^+ conditions.[15b,15c] The intensity of the CD signals correlates to helix thermal stability and followed the order $K^+ > Na^+ >$ no added salt.

Control CD measurements (see the Supporting Information) confirm that none of the five compounds exhibit intrinsic helicity on their own within their UV-absorbing region, even in 100 mM cation-containing buffer. This is consistent with their achiral and rotationally flexible nature. Besides, the UV data of the free compounds is not suggestive of any conformational differences in the three different buffer systems (see the Supporting Information). Nonetheless, these are likely to arise upon helix binding.

Table 1. C-myc G-quadruplex helicity enhancement, as per CD data.[a]

Ligand	Type[b]	Tris-HCl/low-salt buffer[c]	Tris-HCl/Na^+ buffer[c]	Tris-HCl/K^+ buffer
9	linear-5	+	+	none
12	linear-6	++	+	none
15	linear-7	++	+	none
22	branched-5	none	+	none
23	branched-7	none	+	none

[a] For the full set of CD spectra, see the Supporting Information. [b] Numbering refers to aromatic rings present in each ligand structure. [c] Increase in CD signal intensity: +: up to 25 %, ++: up to 60 %.

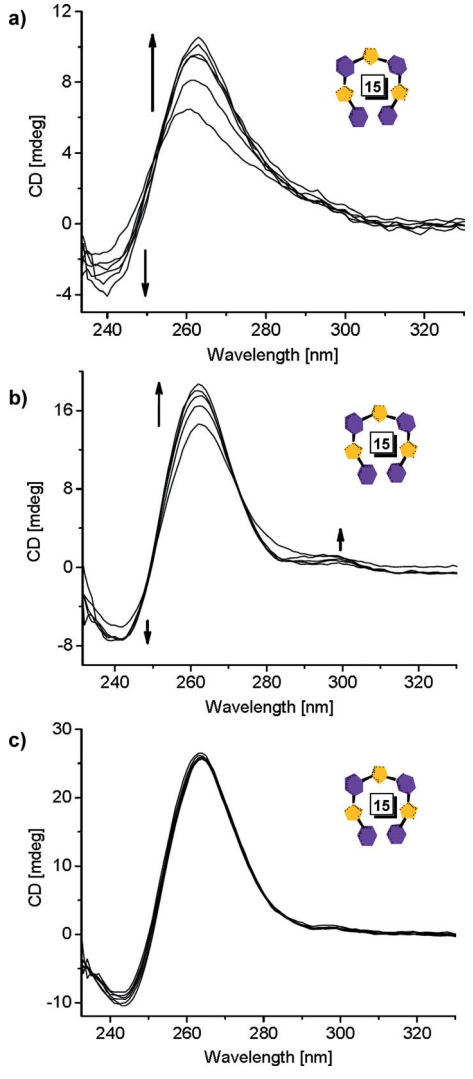


Figure 2. CD titrations of prefolded c-myc promoter G-quadruplexes (3 μM) with increasing amounts of linear oligomer **15** (0–15 μM) in 50 mM Tris-HCl buffer (pH 7.4) (a) without added salt, (b) with 100 mM NaCl, and (c) with 100 mM KCl. Arrows indicate signal intensity changes with increasing ligand.

The preliminary results of CD titrations are summarized in Table 1, whereas a representative data set (for compound **15**) is shown in Figure 2. In the absence of added salt (partially folded helix), significant helicity enhancement was observed with the longest linear members of this compound family (i.e., compounds **12** and **15**) and less so with compound **9**, but no change occurred with their branched counterparts. In Na^+-rich buffer, as would be expected given the higher G-quadruplex stability under these conditions, the helicity enhancement upon compound addition was moderate. Interestingly enough, the observed signal intensity change was comparable for all five compounds in this case, despite their different lengths and architectures. This reinforces our earlier hypothesis that branched pyridyl oxazoles can be potentially as effective as their linear counterparts in inducing G-quadruplex conformational changes under selected conditions.[28] In the CD titrations of the Na^+-induced quadruplex with the longest linear oligomers (i.e., compounds **12** and **15**), a small increase in ellipticity occurred just below 300 nm, in addition to the two main signals. This could be attributed to induced CD of the achiral ligand,[36] as a result of its adapting to the DNA chiral environment during interaction. Finally, none of the five compounds showed any effect on the helicity of the robust K^+-induced quadruplex, which indicates that under these conditions, the interaction – if any – does not lead to CD-detectable conformational change.

Conclusions

In the current work, we implemented a versatile and atom-economic synthetic plan to deliver both nonsymmetric linear and symmetric branched heteroaryl oligomers featuring alternating pyridine and oxazole repetitive units as elements intended for G-quadruplex DNA targeting. These new compounds with diverse lengths and architectures are neutral, modular, and rotationally flexible and were designed with the aim to offer potential for favorable interaction with G-quadruplexes without imposing considerable constraints as to their mode of binding. The synthesized compounds were evaluated by circular dichroism (CD) spectroscopy for their ability to induce conformational changes to a unimolecular parallel G-quadruplex formed from a model c-myc oligonucleotide under three different buffered conditions. CD led to initially identifying conditions under which some or all of the compounds were able to assist in increasing c-myc G-quadruplex helicity. Given that the identified conditions involved partially folded states of the c-myc quadruplex, we are compelled to think of our oligomeric ligands as somewhat comparable to the molecular chaperones employed by nature in the folding of biomolecules.[37] Investigating the mechanisms by which members of this compound family function on G-quadruplexes could prove critical for the development of new improved generations of G-quadruplex binders. Systematic spectroscopic and structural studies are planned by our laboratory to elucidate the possible binding modes for these compounds, and they will be reported in due course.

Experimental Section

General: All reactions were performed under an argon atmosphere and anhydrous solvents were used, unless otherwise stated. In chromatographic purifications, Merck silica gel 60, 0.06–0.2 mm, was used. NMR spectra were obtained with a Bruker Avance III Ultrashield Plus spectrometer (at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR, at 25 °C, chemical shifts relative to tetramethylsilane). MS data were collected with a Bruker Autoflex III Smartbeam MALDI-TOF/TOF instrument. CD and UV spectra were obtained with a Jasco J-815 spectrometer.

5-(Pyridin-2-yl)oxazole (2): In a round-bottomed flask containing dry MeOH (75 mL) were added 2-pyridinecarbaldehyde (**1**; 2.0 mL, 21 mmol, 1 equiv.), TOSMIC (4.51 g, 23.1 mmol, 1.1 equiv.) and K_2CO_3 (6.39 g, 46.2 mmol, 2.2 equiv.), in this order. The flask was fitted with a vertical condenser and the mixture was heated at reflux at 65 °C for 4 h. The solvent was entirely removed under reduced pressure and the residue was resuspended in EtOAc and stirred for 30 min at room temperature Filtration led to removal of insoluble inorganic materials and the solution was concentrated under reduced pressure and applied to a silica column for flash chromatography. Elution took place using a hexane/EtOAc step gradient (from 2:1 to 1:2 to pure EtOAc) and led to isolation of compound **2** (3.01 g, 20.6 mmol, 98 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 7.19 (ddd, J_1 = 7.8 Hz, J_2 = 4.7 Hz, J_3 = 1.0 Hz, 1 H), 7.61 (d, J = 7.8 Hz, 1 H), 7.65 (s, 1 H), 7.71 (dt, J = 7.8 Hz, J_2 = 1.8 Hz, 1 H), 7.93 (s, 1 H), 8.58 (d, J = 5.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 119.0, 122.7, 124.5, 136.6, 146.7, 149.5, 150.7, 150.8 ppm. MS (MALDI-TOF): m/z (%) = 146.22 [M] (calcd. for $C_8H_6N_2O$: 146.05).

2-Bromo-6-(1,3-dioxolan-2-yl)pyridine (4): In a round-bottomed flask, 6-bromo-2-pyridinecarbaldehyde (**3**; 0.93 g, 5 mmol, 1 equiv.), ethylene glycol (0.55 mL, 10 mmol, 2 equiv.), and *p*-toluenesulfonic acid monohydrate (0.047 g, 0.25 mmol, 0.05 equiv.) were dissolved in dry benzene (25 mL). The flask was fitted with a Dean–Stark apparatus and reflux took place at 100 °C for 24 h. The mixture was then cooled to room temperature and 1 % (w/w) aqueous Na_2CO_3 was added to quench. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3×). The combined organic extract was dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was redissolved in CH_2Cl_2 and applied to a silica column for flash chromatography (CH_2Cl_2/MeOH, gradient from 95:5 to 90–10). This led to the isolation of **4** (1.10 g, 4.8 mmol, 96 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 4.07 (m, 2 H), 4.16 (m, 2 H), 5.81 (s, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.59 (t, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 65.6, 102.8, 119.4, 128.5, 139.1, 141.7, 158.5 ppm. MS (MALDI-TOF): m/z (%) = 228.95 $[M]^+$ (calcd. for $C_8H_8BrNO_2$: 228.97).

2-[6-(1,3-Dioxolan-2-yl)pyridin-2-yl]-5-(pyridin-2-yl)oxazole (5): A round-bottomed flask was charged with compound **2** (0.15 g, 1 mmol, 1 equiv.), compound **4** (0.24 g, 1 mmol, 1 equiv.), Cs_2CO_3 (0.72 g, 2.2 mmol, 2.2 equiv.), $Pd(OAc)_2$ (0.045 g, 0.2 mmol, 0.2 equiv.), CuI (0.21 g, 1.1 mmol, 1.1 equiv.), and $Cy_3P{\cdot}HBF_4$ (0.035 g, 0.1 mmol, 0.1 equiv.). The flask was fitted with a vertical condenser and was set under an argon atmosphere. Anhydrous 1,4-dioxane (10 mL) was added by syringe, and the mixture was heated at reflux at 130 °C for 24 h. The mixture was then cooled to room temperature and filtered through a sintered Büchner funnel to remove insoluble inorganic material. The dioxane solution was dried under reduced pressure. The crude residue was redissolved in a small amount of dichloromethane and then applied to a silica gel column for flash chromatography (CH_2Cl_2/MeOH, 95:5), which afforded compound **5** (0.156 g, 0.53 mmol, 53 % yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 4.10 (t, J = 7.0 Hz, 2 H), 4.20 (t, J = 7.0 Hz, 2 H), 5.97 (s, 1 H), 7.22 (t, J = 6.0 Hz, 1 H), 7.63 (d, J = 7.8 Hz, 1 H), 7.76 (t, J = 7.5 Hz, 1 H), 7.85–7.87 (m, 3 H, signals overlapping), 8.18 (d, J = 8.4 Hz, 1 H), 8.62 (d, J = 4.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 65.6, 103.5, 119.7, 121.7, 122.6, 123.1, 127.1, 136.8, 137.7, 145.4, 147.0, 149.9, 151.9, 157.9, 160.5 ppm. MS (MALDI-TOF): m/z (%) = 296.28 $[M + H]^+$ (calcd. for $C_{16}H_{14}N_3O_3$: 296.10).

6-[5-(Pyridin-2-yl)oxazol-2-yl]picolinaldehyde (6): A round-bottomed flask was charged with compound **5** (0.45 g, 1.5 mmol, 1 equiv.) and DMSO (9 mL). A solution of LiCl (0.635 g, 15 mmol, 10 equiv.) in water (9 mL) was added, and a vertical condenser was fitted to the flask. The mixture was heated at reflux at 150 °C for 48 h and then cooled to room temperature, diluted with water, and extracted with CH_2Cl_2 (3×). The organic extracts were combined and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was redissolved in CH_2Cl_2 and applied to a silica gel column for flash chromatography (hexane/EtOAc, gradient from 1:1 to 1:3). This led to the isolation of compound **6** (0.25 g, 1 mmol, 67 % yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 7.28 (ddd, J_1 = 7.6 Hz, J_2 = 4.8 Hz, J_3 = 1.2 Hz, 1 H), 7.81 (dt, J_1 = 7.6 Hz, J_2 = 1.7 Hz, 1 H), 7.87 (td, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1 H), 7.90 (s, 1 H), 8.03 (m, 2 H, signals overlapping), 8.40 (dd, J_1 = 5.7 Hz, J_2 = 3.2 Hz, 1 H), 8.66 (dt, J_1 = 4.9 Hz, J_2 = 1.0 Hz, 1 H), 10.23 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 119.9, 122.2, 123.5, 126.2, 127.4, 137.1, 138.1, 146.4, 146.8, 150.0, 152.3, 153.0, 159.7, 193.0 ppm. MS (MALDI-TOF): m/z (%) = 251.18 $[M]^+$ (calcd. for $C_{14}H_9N_3O_2$: 251.07).

2-[6-(Oxazol-5-yl)pyridin-2-yl]-5-(pyridin-2-yl)oxazole (7): Compound **6** (0.21 g, 0.84 mmol, 1 equiv.), TOSMIC (0.18 g, 0.92 mmol, 1.1 equiv.), and K_2CO_3 (0.26 g, 1.88 mmol, 2.2 equiv.) were sequentially added to a round-bottomed flask containing anhydrous MeOH (10 mL). The flask was fitted with a vertical condenser, and the mixture was heated at reflux at 65 °C for 4 h. The solvent was entirely removed under reduced pressure, and the residue was resuspended in EtOAc and stirred for 30 min. Filtration led to removal of the insoluble inorganic materials, and the solution was concentrated under reduced pressure and applied to a silica gel column for flash chromatography (hexane/EtOAc, gradient from 1:2 to pure EtOAc) and led to the isolation of compound **7** (0.165 g, 0.57 mmol, 68 % yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 7.28 (ddd, J_1 = 7.6 Hz, J_2 = 4.7 Hz, J_3 = 1.0 Hz, 1 H), 7.76 (d, J = 7.8 Hz, 1 H), 7.83 (dt, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 1 H), 7.89 (d, J = 8.1 Hz, 1 H), 7.92 (m, 3 H, signals overlapping), 8.02 (s, 1 H), 8.15 (d, J = 8.1 Hz, 1 H), 8.67 (d, J = 4.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 119.8, 120.3, 121.7, 123.3, 125.9, 127.3, 137.1, 138.0, 146.1, 146.9, 147.6, 149.9, 150.5, 151.4, 152.0, 160.2 ppm. MS (MALDI-TOF): m/z (%) = 290.17 $[M]^+$ (calcd. for $C_{16}H_{10}N_4O_2$: 290.08).

2-(Pyridin-2-yl)-5-{6-[5-(pyridin-2-yl)oxazol-2-yl]pyridin-2-yl}-oxazole (9): A round-bottomed flask was charged with compound **7** (0.070 g, 0.24 mmol, 1 equiv.), 2-bromopyridine (**8**; 0.070 mL, 0.73 mmol, 3 equiv.), Cs_2CO_3 (0.17 g, 0.52 mmol, 2.2 equiv.), $Pd(OAc)_2$ (0.011 g, 0.048 mmol, 0.2 equiv.), CuI (0.050 g, 0.26 mmol, 1.1 equiv.), and $Cy_3P{\cdot}HBF_4$ (0.0085 g, 0.024 mmol, 0.1 equiv.). The flask was fitted with a vertical condenser and was set under an argon atmosphere. Anhydrous 1,4-dioxane (5 mL) was added by syringe, and the mixture was heated at reflux at 130 °C for 24 h, cooled to room temperature, and filtered through a sintered Büchner funnel to remove insoluble inorganic materials. The dioxane solution was dried under reduced pressure, and the crude residue was redissolved in a small amount of dichloromethane. It was applied to a silica gel column for flash chromatography (CH_2Cl_2/MeOH, gradient from 99:1 to 90:10). This afforded compound **9** (0.040 g, 0.11 mmol, 46 % yield) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ =

7.29 (ddd, J_1 = 7.9 Hz, J_2 = 4.7 Hz, J_3 = 1.0 Hz, 1 H), 7.42 (t, J = 6.0 Hz, 1 H), 7.84 (dt, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1 H), 7.87 (t, J = 7.7 Hz, 1 H), 7.92 (s, 1 H), 7.93 (d, J = 7.0 Hz, 1 H), 7.95 (t, J = 7.7 Hz, 1 H), 7.99 (d, J = 7.7 Hz, 1 H), 8.11 (s, 1 H), 8.17 (dd, J_1 = 7.7 Hz, J_2 = 0.9 Hz, 1 H), 8.26 (d, J = 7.7 Hz, 1 H), 8.68 (d, J = 4.7 Hz, 1 H), 8.80 (d, J = 3.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 119.8, 120.6, 121.7, 122.6, 123.3, 125.0, 127.2, 128.3, 136.9, 137.0, 137.9, 145.8, 146.1, 147.0, 147.5, 150.0, 150.1, 151.4, 152.1, 160.2, 160.8 ppm. MS (MALDI-TOF): m/z (%) = 366.99 $[M]^+$ (calcd. for $C_{21}H_{13}N_5O_2$: 367.11). UV (50 mM Tris-HCl aqueous buffer, pH 7.4): λ_{max} = 306 nm.

2-[6-(1,3-Dioxolan-2-yl)pyridin-2-yl]-5-{6-[5-(pyridin-2-yl)oxazol-2-yl]pyridin-2-yl}oxazole (10): A round-bottomed flask was charged with compound **7** (0.061 g, 0.21 mmol, 1 equiv.), compound **4** (0.048 g, 0.21 mmol, 1 equiv.), Cs_2CO_3 (0.15 g, 0.46 mmol, 2.2 equiv.), $Pd(OAc)_2$ (0.009 g, 0.042 mmol, 0.2 equiv.), CuI (0.044 g, 0.23 mmol, 1.1 equiv.), and $Cy_3P{\cdot}HBF_4$ (0.007 g, 0.021 mmol, 0.1 equiv.). The flask was fitted with a vertical condenser and was set under an argon atmosphere. Anhydrous 1,4-dioxane (5 mL) was added by syringe, and the mixture was heated at reflux at 130 °C for 24 h, then cooled to room temperature, and filtered through a sintered Büchner funnel to remove insoluble inorganic materials. The dioxane solution was dried under reduced pressure, and the crude residue was redissolved in a small amount of dichloromethane. It was applied to a silica gel column for flash chromatography (EtOAc/MeOH, gradient from 99:1 to 95:5). This afforded compound **10** (0.040 g, 0.09 mmol, 43 % yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 4.14 (t, J = 6.2 Hz, 2 H), 4.24 (t, J = 6.2 Hz, 2 H), 6.02 (s, 1 H), 7.29 (t, J = 6.0 Hz, 1 H), 7.69 (d, J = 7.8 Hz, 1 H), 7.85 (t, J = 7.8 Hz, 1 H), 7.91–7.99 (m, 5 H, signals overlapping), 8.11 (s, 1 H), 8.18 (d, J = 7.5 Hz, 1 H), 8.25 (d, J = 8.0 Hz, 1 H), 8.68 (d, J = 3.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 65.8, 103.5, 119.8, 120.7, 121.7, 121.9, 122.9, 123.3, 127.2, 128.3, 137.0, 137.8, 137.9, 145.4, 146.1, 147.1, 147.5, 150.0, 151.4, 152.1, 157.9, 160.2, 160.6 ppm. MS (MALDI-TOF): m/z (%) = 439.00 $[M]^+$ (calcd. for $C_{24}H_{17}N_5O_4$: 439.13).

6-(5-{6-[5-(Pyridin-2-yl)oxazol-2-yl]pyridin-2-yl}oxazol-2-yl)-picolinaldehyde (11): A round-bottomed flask was charged with compound **10** (0.088 g, 0.20 mmol, 1 equiv.) and then DMSO (1.5 mL) was added. A solution of LiCl (0.085 g, 2 mmol, 10 equiv.) in water (1.5 mL) was added, and a vertical condenser was fit to the flask. The mixture was heated at reflux at 150 °C for 48 h, then cooled down to room temperature, diluted with water, and extracted with CH_2Cl_2 (3×). The organic extracts were combined and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was redissolved in CH_2Cl_2 and applied to a silica gel column for flash chromatography (EtOAc/MeOH, gradient from 99:1 to 95:5). This led to the isolation of **11** as a pale yellow solid (0.063 g, 0.16 mmol, 80 % yield). ^{1}H NMR ($CDCl_3$): δ = 7.35 (t, J = 6.3 Hz, 1 H), 7.91 (t, J = 7.3 Hz, 1 H), 7.96–8.02 (m, 3 H, signals overlapping), 8.03–8.09 (m, 3 H, signals overlapping), 8.13 (s, 1 H), 8.22 (dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 1 H), 8.46 (t, J = 4.4 Hz, 1 H), 8.70 (d, J = 4.4 Hz, 1 H), 10.25 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 120.1, 120.8, 122.0, 122.1, 122.4, 123.5, 125.3, 126.3, 128.4, 138.1, 138.2, 138.3, 146.0, 146.3, 147.2, 149.1, 151.7, 153.0, 155.5, 159.9, 160.4, 192.9 ppm. MS (MALDI-TOF): m/z (%) = 395.12 $[M]^+$ (calcd. for $C_{22}H_{13}N_5O_3$: 395.10).

2-[6-(Oxazol-5-yl)pyridin-2-yl]-5-{6-[5-(pyridin-2-yl)oxazol-2-yl]-pyridine-2-yl}oxazole (12): Compound **11** (0.047 g, 0.12 mmol, 1 equiv.), TOSMIC (0.026 g, 0.13 mmol, 1.1 equiv.), and K_2CO_3 (0.036 g, 0.26 mmol, 2.2 equiv.) were sequentially added to a round-bottomed flask containing anhydrous MeOH (2 mL). The flask was fitted with a vertical condenser, and the mixture was heated at reflux at 65 °C for 4 h. The solvent was entirely removed under reduced pressure, and the residue was resuspended in dichloromethane and directly applied to a silica gel column for flash chromatography (CH_2Cl_2/MeOH, gradient from 99:1 to 90:10), which led to the isolation of compound **12** (0.022 g, 0.05 mmol, 42 % yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 7.32 (dd, J_1 = 5.9 Hz, J_2 = 3.4 Hz, 1 H), 7.80 (d, J = 7.7 Hz, 1 H), 7.92 (t, J = 7.7 Hz, 1 H), 7.96–8.00 (m, 4 H, signals overlapping), 8.02–8.06 (m, 3 H, signals overlapping), 8.11 (s, 1 H), 8.22 (d, J = 7.7 Hz, 1 H), 8.70 (d, J = 4.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 120.0, 120.5, 120.8, 121.8, 121.9, 123.4, 125.7, 126.3, 127.5, 128.8, 130.9, 132.4, 137.4, 137.9, 138.0, 146.0, 146.1, 146.8, 146.9, 147.4, 147.6, 149.7, 160.3, 160.8 ppm. MS (MALDI-TOF): m/z (%) = 435.55 $[M + H]^+$ (calcd. for $C_{24}H_{15}N_6O_3$: 435.12). UV (50 mM Tris-HCl aqueous buffer, pH 7.4): λ_{max} = 319 nm.

5-(6-Bromopyridin-2-yl)oxazole (13): 6-Bromo-2-pyridinecarbaldehyde (**3**; 0.615 g, 3.3 mmol, 1 equiv.), TOSMIC (0.71 g, 3.6 mmol, 1.1 equiv.), and K_2CO_3 (1.02 g, 7.4 mmol, 2.2 equiv.) were sequentially added to a round-bottomed flask containing anhydrous MeOH (15 mL). The flask was fitted with a vertical condenser, and the mixture was heated at reflux at 65 °C for 4 h. The solvent was entirely removed under reduced pressure, and the residue was resuspended in EtOAc and stirred for 30 min. Filtration led to removal of the insoluble inorganic materials, and the solution was concentrated under reduced pressure and applied to a silica gel column for flash chromatography (hexane/EtOAc, gradient from 3:1 to 1:1), which led to the isolation of compound **13** (0.6 g, 2.7 mmol, 82 % yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 7.36 (dd, J_1 = 7.0 Hz, J_2 = 1.9 Hz, 1 H), 7.56 (m, 2 H, signals overlapping), 7.69 (s, 1 H), 7.94 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 117.9, 126.1, 127.4, 139.1, 142.2, 147.8, 149.7, 151.5 ppm. MS (MALDI-TOF): m/z (%) = 223.96 $[M]^+$ (calcd. for $C_8H_5BrN_2O$: 223.96).

5-(6-Bromopyridin-2-yl)-2-(pyridin-2-yl)oxazole (14): A round-bottomed flask was charged with compound **13** (0.43 g, 1.9 mmol, 1 equiv.), 2-bromopyridine (**8**; 0.18 mL, 1.9 mmol, 1 equiv.), Cs_2CO_3 (1.36 g, 4.2 mmol, 2.2 equiv.), $Pd(OAc)_2$ (0.085 g, 0.38 mmol, 0.2 equiv.), CuI (0.40 g, 2.1 mmol, 1.1 equiv.), and $Cy_3P{\cdot}HBF_4$ (0.067 g, 0.19 mmol, 0.1 equiv.). The flask was fitted with a vertical condenser and was set under an argon atmosphere. Anhydrous 1,4-dioxane (20 mL) was added by syringe, and the mixture was heated at reflux at 130 °C for 24 h, then cooled to room temperature, and filtered through a sintered Büchner funnel to remove insoluble inorganic materials. The dioxane solution was dried under reduced pressure, and the crude residue was redissolved in a small amount of dichloromethane. It was applied to a silica gel column for flash chromatography (hexane/EtOAc, gradient from 3:1 to 1:3). This afforded compound **14** (0.25 g, 0.83 mmol, 44 % yield) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ = 7.37 (m, 2 H, signals overlapping), 7.58 (t, J = 7.8 Hz, 1 H), 7.81 (m, 2 H, signals overlapping), 7.86 (s, 1 H), 8.17 (d, J = 8.1 Hz, 1 H), 8.74 (d, J = 4.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 118.2, 122.5, 125.1, 127.4, 128.2, 137.2, 139.1, 142.1, 145.3, 147.7, 149.9, 150.5, 160.6 ppm. MS (MALDI-TOF): m/z (%) = 300.99 $[M]^+$ (calcd. for $C_{13}H_8BrN_3O$: 300.99).

2-(Pyridin-2-yl)-5-[6-(5-{6-[5-(pyridin-2-yl)oxazol-2-yl]pyridin-2-yl}oxazol-2-yl)pyridin-2-yl]oxazole (15): A round-bottomed flask was charged with compound **14** (0.10 g, 0.34 mmol, 1 equiv.), compound **7** (0.10 g, 0.34 mmol, 1 equiv.), Cs_2CO_3 (0.24 g, 0.74 mmol, 2.2 equiv.), $Pd(OAc)_2$ (0.015 g, 0.067 mmol, 0.2 equiv.), CuI (0.071 g, 0.37 mmol, 1.1 equiv.), and $Cy_3P{\cdot}HBF_4$ (0.012 g, 0.034 mmol, 0.1 equiv.). The flask was fitted with a vertical condenser and was set under an argon atmosphere. Anhydrous 1,4-dioxane (7 mL) was added by syringe, and the mixture was heated at reflux at 130 °C for 24 h, then cooled to room temperature, and filtered through a

sintered Büchner funnel to remove insoluble inorganic materials. The dioxane solution was dried under reduced pressure, and the crude residue was redissolved in a small amount of dichloromethane. It was applied to a silica gel column for flash chromatography (CH_2Cl_2/MeOH, gradient from 99:1 to 90:10). This afforded compound **15** (0.082 g, 0.16 mmol, 47 % yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 7.30 (dd, J_1 = 7.8 Hz, J_2 = 5.4 Hz, 1 H), 7.43 (br. s, 1 H), 7.89 (t, J = 7.6 Hz, 2 H), 7.94 (s, 1 H), 7.97–8.03 (m, 5 H, signals overlapping), 8.13 (s, 1 H), 8.17 (br. s, 1 H), 8.21 (m, 2 H, signals overlapping), 8.28 (d, J = 5.4 Hz, 1 H), 8.69 (d, J = 4.6 Hz, 1 H), 8.81 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 119.6, 119.7, 120.2, 121.5, 122.3, 123.1, 123.2, 124.7, 125.9, 127.1, 127.2, 136.8, 136.9, 137.9, 145.9, 146.0, 146.9, 147.0, 147.4, 149.7, 149.8, 149.9, 150.0, 150.4, 151.3, 151.8, 152.0, 160.0, 160.5 ppm. MS (MALDI-TOF): m/z (%) = 512.15 $[M + H]^+$ (calcd. for $C_{29}H_{18}N_7O_3$: 512.14). UV (50 mM Tris-HCl aqueous buffer, pH 7.4): λ_{max} = 306 nm.

Diethyl 4-Hydroxypyridine-2,6-dicarboxylate (17): Thionyl chloride (12.6 mL, 174 mmol, 7 equiv.) and chelidamic acid monohydrate (**16**; 5.01 g, 24.9 mmol, 1 equiv.) were sequentially added to a round-bottomed flask containing absolute EtOH (50 mL) at 0 °C. The resulting mixture was warmed to room temperature, stirred at this temperature for 18 h, and then heated at reflux at 80 °C for 2 h. Subsequently, the solvent was removed under reduced pressure and distilled water was added to the crude product at 0 °C. The mixture was neutralized with 10 % aqueous Na_2CO_3 (5 mL) and 50 % aqueous EtOH (5 mL). The precipitate was filtered, washed with water, and dried under reduced pressure to afford compound **17** (5.84 g, 24.4 mmol, 98 % yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 1.41 (t, J = 7.1 Hz, 6 H), 4.46 (q, J = 7.1 Hz, 4 H), 7.35 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$ with trace [D_6]DMSO): δ = 13.6, 61.7, 115.7, 148.2, 163.9, 167.1 ppm. MS (MALDI-TOF): m/z (%) = 240.23 $[M + H]^+$ (calcd. for $C_{11}H_{14}NO_5$: 240.09).

Diethyl 4-Bromopyridine-2,6-dicarboxylate (18): A round-bottomed flask was charged with compound **17** (1.48 g, 6.2 mmol, 1 equiv.) and phosphorus pentabromide (5.34 g, 12.4 mmol, 2 equiv.). The flask was fitted with a vertical condenser, and the mixture was heated at 95 °C for 3.5 h, then cooled down to room temperature, and $CHCl_3$ (5 mL) was added. The temperature was further reduced to 0 °C and EtOH (10 mL) was added dropwise. The mixture was stirred at 0 °C for another 3 h. The solvent was then removed under reduced pressure, and the crude mixture was redissolved in CH_2Cl_2. The organic phase was washed with 10 % aqueous $NaHCO_3$, aqueous NaCl (satd.), and water and was then dried with Na_2SO_4. The drying agent was removed, and the solution was concentrated under reduced pressure. The sample was applied to a short silica gel column (hexane/EtOAc, 2:1) to afford compound **18** (1.72 g, 5.7 mmol, 92 % yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 1.45 (t, J = 7.2 Hz, 6 H), 4.49 (q, J = 7.2 Hz, 4 H), 8.42 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 62.7, 131.0, 134.9, 149.5, 163.5 ppm. MS (MALDI-TOF): m/z (%) = 301.15 $[M]^+$ (calcd. for $C_{11}H_{12}BrNO_4$: 300.99).

Diethyl 4-[5-(Pyridin-2-yl)oxazol-2-yl]pyridine-2,6-dicarboxylate (19): A round-bottomed flask was charged with compound **18** (0.60 g, 2 mmol, 1 equiv.), compound **2** (0.29 g, 2 mmol, 1 equiv.), Cs_2CO_3 (1.43 g, 4.4 mmol, 2.2 equiv.), $Pd(OAc)_2$ (0.091 g, 0.40 mmol, 0.2 equiv.), CuI (0.42 g, 2.2 mmol, 1.1 equiv.), and $Cy_3P{\cdot}HBF_4$ (0.070 g, 0.20 mmol, 0.1 equiv.). The flask was fitted with a vertical condenser and was set under an argon atmosphere. Anhydrous 1,4-dioxane (20 mL) was added by syringe, and the mixture was heated at reflux at 130 °C for 24 h, then cooled to room temperature, and filtered through a sintered Büchner funnel to remove insoluble inorganic materials. The dioxane solution was dried under reduced pressure, and the crude residue was redissolved in a small amount of dichloromethane. It was applied to a silica gel column for flash chromatography (hexane/EtOAc, gradient from 2:1 to 1:2 to pure EtOAc) to afford compound **19** (0.38 g, 1.0 mmol, 50 % yield) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ = 1.47 (t, J = 7.2 Hz, 6 H), 4.51 (q, J = 7.2 Hz, 4 H), 7.30 (td, J_1 = 5.5 Hz, J_2 = 2.8 Hz, 1 H), 7.82 (br. s, 2 H, signals overlapping), 7.91 (s, 1 H), 8.66 (dt, J_1 = 4.7 Hz, J_2 = 1.5 Hz, 1 H), 8.88 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.3, 62.7, 119.9, 123.8, 123.9, 127.8, 136.7, 137.2, 146.4, 149.8, 150.1, 152.6, 158.2, 164.2 ppm. MS (MALDI-TOF): m/z (%) = 368.19 $[M + H]^+$ (calcd. for $C_{19}H_{18}N_3O_5$: 368.12).

{4-[5-(Pyridin-2-yl)oxazol-2-yl]pyridine-2,6-diyl}dimethanol (20): A round-bottomed flask was charged with compound **19** (0.155 g, 0.42 mmol, 1 equiv.) and anhydrous MeOH (3 mL). The mixture was cooled to 0 °C and $NaBH_4$ (0.191 g, 5 mmol, 12 equiv.) was added to the flask in three equal portions under continuous stirring. The mixture was stirred at room temperature for 18 h and then cooled down to 0 °C and quenched with water. The mixture was extracted with CH_2Cl_2 (2×). The pH of the aqueous phase was then adjusted to 7 through the addition of aqueous 1 M HCl, and two more extractions were performed with CH_2Cl_2. All organic extracts were combined together and dried with Na_2SO_4. The drying agent was filtered, and the solvent was removed under reduced pressure to afford compound **20** (0.091 g, 0.32 mmol, 76 % yield) as a white solid. This was used in the next step without further purification. ^{1}H NMR ([D_6]DMSO): δ = 4.63 (br. s, 4 H), 5.64 (br. s, 2 H), 7.44 (t, J = 5.8 Hz, 1 H), 7.96–7.98 (m, 4 H, signals overlapping), 8.07 (s, 1 H), 8.70 (d, J = 5.0 Hz, 1 H) ppm. ^{13}C NMR ([D_6]-DMSO): δ = 64.1, 114.2, 119.9, 123.9, 127.4, 134.4, 137.6, 146.1, 150.1, 151.5, 159.7, 162.8 ppm. MS (MALDI-TOF): m/z (%) = 283.12 $[M]^+$ (calcd. for $C_{15}H_{13}N_3O_3$: 283.10).

4-[5-(Pyridin-2-yl)oxazol-2-yl]pyridine-2,6-dicarbaldehyde (21): A two-necked, round-bottomed flask was charged with fresh SeO_2 (0.235 g, 2.1 mmol, 4 equiv.), and the flask was fitted with a reflux condenser and was set under an argon atmosphere. Anhydrous 1,4-dioxane (10 mL) was added by syringe, and this was followed by the addition of a solution of compound **20** (0.150 g, 0.53 mmol, 1 equiv.) in 1,4-dioxane (5 mL). The mixture was heated at reflux at 100 °C for 5 h, then cooled down to room temperature, and filtered to remove insoluble inorganic materials. The solvent was removed under reduced pressure. The crude residue was redissolved in a small amount of EtOAc and was applied to a silica gel column for flash chromatography (hexane/EtOAc, gradient from 2:1 to 1:3) to afford compound **21** (0.095 g, 0.34 mmol, 64 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 7.34 (dt, J_1 = 5.6 Hz, J_2 = 2.3 Hz, 1 H), 7.86 (m, 2 H, signals overlapping), 7.94 (s, 1 H), 8.70 (d, J = 4.7 Hz, 1 H), 8.80 (s, 2 H), 10.24 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 120.0, 121.4, 123.9, 127.9, 136.9, 137.2, 146.5, 150.3, 153.0, 154.0, 157.9, 191.8 ppm. MS (MALDI-TOF): m/z (%) = 280.24 $[M + H]^+$ (calcd. for $C_{15}H_{10}N_3O_3$: 280.07).

5,5′-{4-[5-(Pyridin-2-yl)oxazol-2-yl]pyridine-2,6-diyl}bis-(oxazole) (22): Compound **21** (0.084 g, 0.30 mmol, 1 equiv.), TOSMIC (0.125 g, 0.65 mmol, 2.2 equiv.), and K_2CO_3 (0.18 g, 1.3 mmol, 4.4 equiv.) were sequentially added to a round-bottomed flask containing dry MeOH (5 mL). The flask was fitted with a vertical condenser, and the mixture was heated at reflux at 65 °C for 6 h. The solvent was entirely removed under reduced pressure, and the residue was resuspended in EtOAc and stirred for 30 min. Filtration led to removal of the insoluble inorganic materials, and the solution was concentrated under reduced pressure and applied to a silica gel column (hexane/EtOAc, gradient from 1:1 to 1:2 to pure EtOAc; then EtOAc/MeOH, gradient from 98:2 to 90:10). Compound **22** (0.082 g, 0.23 mmol, 77 % yield) was isolated as a white solid. ^{1}H

NMR ($CDCl_3$): δ = 7.32 (dt, J_1 = 5.2 Hz, J_2 = 2.9 Hz, 1 H), 7.85 (m, 2 H, signals overlapping), 7.87 (s, 2 H), 7.93 (s, 1 H), 8.05 (s, 2 H), 8.27 (s, 2 H), 8.71 (d, J = 4.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 114.7, 119.8, 123.6, 126.4, 127.6, 136.1, 137.0, 146.7, 148.3, 150.2, 150.4, 151.6, 152.4, 158.9 ppm. MS (MALDI-TOF): m/z (%) = 358.28 $[M + H]^+$ (calcd. for $C_{19}H_{12}N_5O_3$: 358.09). UV (50 mM Tris-HCl aqueous buffer, pH 7.4): λ_{max} = 326 nm.

5,5′-{4-[5-(Pyridin-2-yl)oxazol-2-yl]pyridine-2,6-diyl}bis[2-(pyridin-2-yl)oxazole] (23): A round-bottomed flask was charged with compound **22** (0.080 g, 0.22 mmol, 1 equiv.), 2-bromopyridine (**8**; 0.063 mL, 0.66 mmol, 3 equiv.), Cs_2CO_3 (0.316 g, 0.97 mmol, 4.4 equiv.), $Pd(OAc)_2$ (0.020 g, 0.09 mmol, 0.4 equiv.), CuI (0.092 g, 0.48 mmol, 2.2 equiv.), and $Cy_3P{\cdot}HBF_4$ (0.016 g, 0.045 mmol, 0.2 equiv.). The flask was fitted with a vertical condenser and was set under an argon atmosphere. Anhydrous 1,4-dioxane (5 mL) was added by syringe, and the mixture was heated at reflux at 130 °C for 24 h, then cooled to room temperature, and filtered through a sintered Büchner funnel to remove insoluble inorganic materials. The dioxane solution was dried under reduced pressure, and the crude residue was redissolved in a small amount of dichloromethane. It was applied to a silica gel column for flash chromatography (CH_2Cl_2/MeOH, gradient from 98:2 to 90:10) to afford compound **23** (0.060 g, 0.12 mmol, 54 % yield) as a beige powder. ^1H NMR ($CDCl_3$): δ = 7.33 (dd, J_1 = 7.9 Hz, J_2 = 4.9 Hz, 1 H), 7.45 (dd, J_1 = 7.9 Hz, J_2 = 4.9 Hz, 2 H), 7.85–7.93 (m, 3 H, signals overlapping), 7.95 (d, J = 6.5 Hz, 1 H), 7.96 (s, 1 H), 8.08 (s, 2 H), 8.30 (d, J = 7.9 Hz, 2 H), 8.49 (s, 2 H), 8.72 (d, J = 4.9 Hz, 1 H), 8.83 (d, J = 4.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 115.1, 120.0, 122.7, 123.6, 125.1, 127.6, 128.8, 136.2, 137.0, 137.1, 145.8, 146.7, 148.3, 149.0, 150.2, 151.2, 152.5, 159.1, 161.2 ppm. MS (MALDI-TOF): m/z (%) = 512.41 $[M + H]^+$ (calcd. for $C_{29}H_{18}N_7O_3$: 512.15). UV (50 mM Tris-HCl aqueous buffer, pH 7.4): λ_{max} = 307 nm.

CD Titrations: DNA (c-myc model promoter sequence: 5′-TGAGGGTGGGTAGGGTGGGTAA-3′) was purchased from Microsynth as a synthetic oligonucleotide and was purified by HPLC and dialysis. Stock solutions of 0.1 mM DNA were prepared in 50 mM Tris-HCl buffer (pH 7.4), with added NaCl or KCl at 100 mM concentration or without any added salt. The DNA was annealed at 95 °C for 5 min and then cooled down to room temperature slowly overnight. Appropriate volumes of the aforementioned DNA solutions were mixed with various volumes of 0.4 mM compound in DMSO solution and with buffer (the same as that in which the DNA was dissolved) for 5 min to afford mixtures of fixed total volume, with final DNA concentration of 3 μM and final compound concentrations of 0, 3, 6, 9, 12, and 15 μM. CD spectra for each of the mixtures were obtained at 21 °C by using square quartz cell (1 cm path, 4 mL volume). The scan of the buffer was subtracted from the average scan for each sample. The scans were recorded in the 200–500 nm range, with the following parameters: standard sensitivity, 1 s D.I.T., 2 nm bandwidth, 1 nm data pitch, 50 nm min^{-1} scanning speed, three accumulations.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^1H NMR and ^{13}C NMR spectra of all key intermediates and final products.

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