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Structure−Function Studies on a Synthetic Guanosine Receptor That Simultaneously Binds Watson−Crick and Hoogsteen Sites

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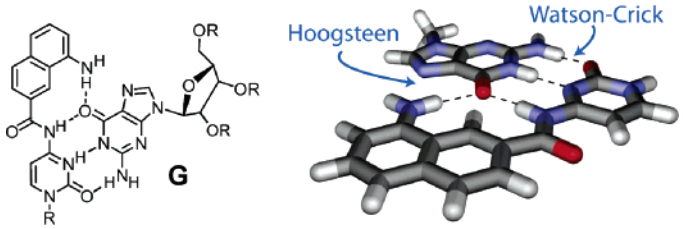

A series of receptors (**11**−**16**) designed to simultaneously bind the Watson−Crick and Hoogsteen sites of guanosine were synthesized, and their binding of guanosine tri-*O*-pentanoate (**32**) was probed via ^{1}H NMR complexation studies in 5% DMSO-d_6−chloroform-*d*. The guanosine receptors were synthesized with aminonaphthalene or aminoquinoline auxiliary groups tethered to *N*-4 of cytosine via a methylene or carbonyl group. A structure−function relationship was established allowing energetic contributions made by components of nucleoside analogues to be probed and more general design rules formulated that may guide the development of more efficacious DNA bases.

Introduction

The high specificity with which oligonucleotides form duplexes has been exploited in areas ranging from nanotechnology[1] to genetic medicines.[2] In an effort to improve the performance of some of these DNA- and RNA-based systems, considerable effort has focused on novel nucleotides with enhanced hydrogen-bonding and base-stacking abilities.[3] Considerably more attention has been given to increasing base stacking especially through a dangling-end base. In contrast, many synthetic receptors for nucleobases[4] have expanded their hydrogen-bonding contacts beyond the Watson−Crick edge.[5] By forming multiple hydrogen-bonding contacts, a number of these receptors are able to complex nucleobases in competitive media, including some in water. However, there are few accounts of nucleoside analogues, particularly those incorporated into oligonucleotides, having enhanced hydrogen-bonding capabilities.[6]

Umezawa et al.[7] reported that **1**, a cytosine analogue with an 8-ureido-2-naphthoyl group attached at *N*-4, complexes guanine (**G**) with five hydrogen bonds and

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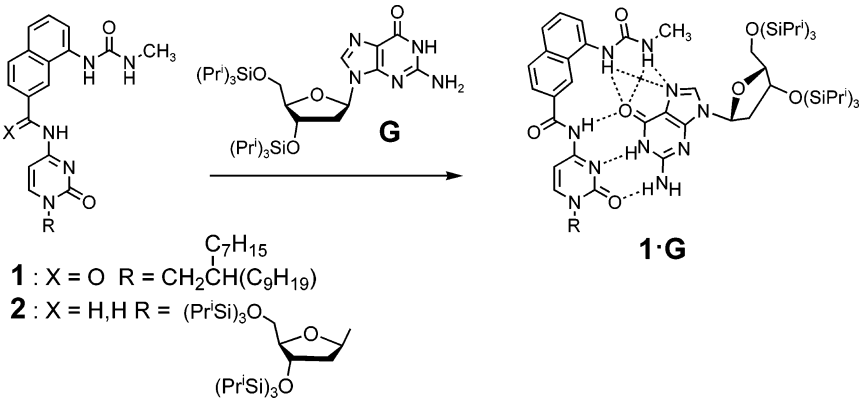
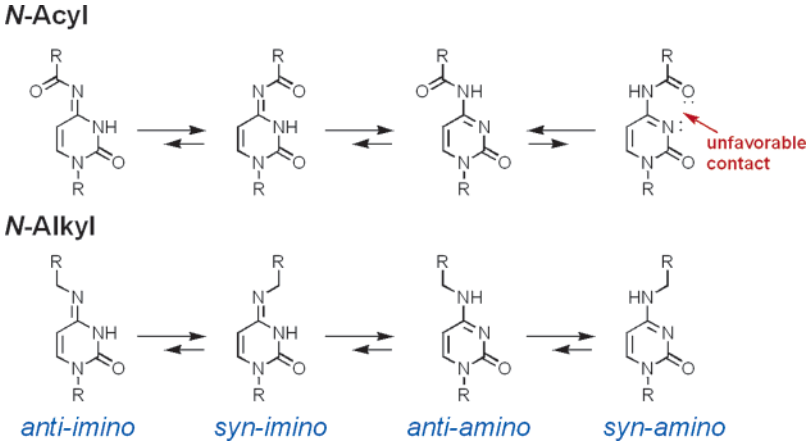
SCHEME 1



SCHEME 2



an association constant (K_{assoc}) = 170 M^{-1} in 4:1 (v/v) $CDCl_3$/DMSO-d_6 (Scheme 1). To our knowledge, this nucleoside analogue has not been incorporated into oligonucleotides. In this regard, the *N*-4 amido group presents a special challenge because it may lack sufficient stability to withstand the standard DNA deprotection conditions. Herein, we explore analogues of Umezawa's receptor designed both to be more stable to hydrolysis and to probe the importance of the various associated structural features in **1**. By examining the effect of structural modifications on complex stability within nucleoside−synthetic receptor complexes it was hoped that the energetic contributions made by components of nucleoside analogues would be probed and ultimately more general design rules formulated.

Results and Discussion

Receptor Design. As noted above, one of the appealing features of **1** is the tethering of the cytosine nucleus to a recognition unit capable of hydrogen bonding to the Hoogsteen site of guanosine. Modeling of DNA oligonucleotides further suggested that runs of base **1** (amino in place of ureido group, vide infra) in one strand would position the naphthalene units so that they can stack efficiently in the major groove. Modeling also indicated that a similar complex could be formed analogously with **2**. *N*-4-Substituted cytidines exist in either the imino or amino tautomeric form (Scheme 2). Both acetyl and alkyl substitution at *N*-4 produce the amino tautomer exclusively, provided C-5 is unsubstituted.[8,9] In addition, *N*-4 monosubstitution gives rise to syn and anti rotamers.[10,11] In *N*,*N*′-1,4-dimethylcytosine the syn form is energetically favored by 1.6 kcal/mol at −19 °C in DMF-d_7.[10] Steric repulsion between H-5 and the alkyl substituent is proposed to lead to the observed preference for the syn

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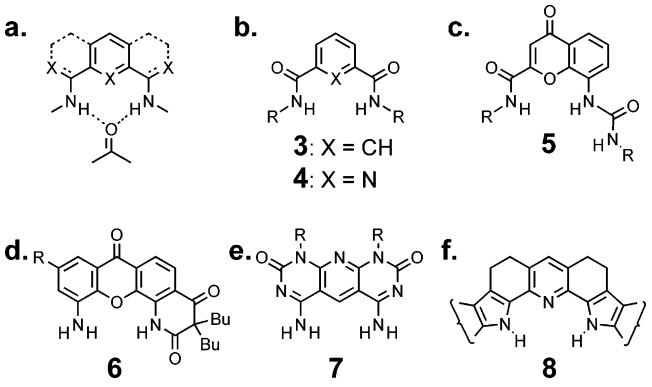

FIGURE 1. Structural diversity in carbonyl complexation units. (a) General motif with NH groups oriented toward carbonyl "rabbit ears." Selected examples: (b) isophthaloyl and pyridine-2,6-dicarboxamide, (c) and (d) chromenone, (e) pyridodipyrimidinedione, (f) pyridobisindole.

rotamer in *N*-4-alkylated cytosines.[11] Syn−anti isomerization has not been reported for *N*-4-acylcytidines which may reflect rapid rotation on the NMR time-scale or more likely a bias toward the anti form as a result of the interaction between the carbonyl group and *N*-3 shown in Scheme 2 and a favorable CH···O contact with H-5.[8b,12]

In considering structural modifications to guanosine receptor **1** attention was focused on: (1) the group linking the cytosine nucleus to the major groove-binding naphthalene unit, (2) the carbonyl binding cleft formed by the amide and urea groups, and (3) the Hoogsteen pairing unit, the urea group itself. As indicated above, there was considerable interest in the methylene linker because of its expected stability during oligonucleotide synthesis.

With regard to the carbonyl binding cleft, there is a remarkable diversity in the units designed to spatially position two N−H groups to hydrogen bond the "rabbit ear" lone pairs of a carbonyl group. As seen in Figure 1, the simplest is **3** and **4**, pioneered by Hamilton and coworkers in the context of receptors for barbiturates,[13] and extended to hosts for quinone,[14] diamides,[15] and urea[16] and a variety of other applications.[17] More rigid analogues of **3** and **4** that provide a similar spatial arrangement of two NH groups are seen in Morán's chromenone-based receptors **5** (**6**),[18] our dimethylacetamide complexing tecton **7**,[19] and Thummel's urea binder **8**.[20] Integrating a highly preorganized unit such as **6**−**8** into a receptor such as **1** would represent a significant synthetic challenge, but there was interest in the quinoline analogue of **1**. Hunter and co-workers reported a *p*-quinone receptor with a binding pocket containing **4** that was superior to its analogue with **3**.[14c] The increased stability may originate in a degree of preorganization owing to the intramolecular hydrogen bonding between the amido NH groups and pyridine nitrogen of **4**.[13,21] However, electrostatic repulsion of the pyridine nitrogen with the guanosine carbonyl oxygen might offset the energy gains from preorganization.[15]

Considering the design issues outlined above and the goal of establishing a structure activity relationship that would produce design rules for tethered bases such as **1**, synthetic receptors **9**−**16** were synthesized and model complexation studies performed with cytosine in chloroform solution.

Synthesis of Nucleoside Receptors. Cytidine analogues with *N*-4-amido and alkyl substituents are shown in Chart 1. Acetylcytosine **9** was prepared by treating 2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (**17**) with acetic anhydride, whereas the corresponding benzoyl derivative **10** was prepared by treating **17** with benzoyl chloride. Analogous to the procedure reported by Umezawa,[7b] amido cytidines **11**−**13** were synthesized by coupling of TBDMS-protected deoxycytidine **17** with carboxylic acids **18**, **19**, and **20**,[7b] respectively, using 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (Scheme 3). Naphthalene carboxylic acids **19** and **20** were available from 2-naphthalene carboxylic acid in three and four steps, respectively.[7b] Quinoline carboxylic acid **18** was prepared from commercially available 2-methylquinoline by tribromination and hydrolysis.[22] Thus, coupling of **17** and **20** directly gave **13** in 81% yield, whereas **17** coupled with **18** and **19** to give

(9) Gas-phase calculations by Wallis et al. suggest that *N*-4 benzoyl cytosine (C^{Bz}) prefers the intramolecularly hydrogen bonded *syn*-imino form (Wallis, M. P.; Schwalbe, C. H.; Fraser, W. *Nucleosides Nucleotides* **1997**, *16*, 2053−2068); however, solution data (ref 8a) and solid-state structures indicate that the *anti*-amino form dominates. Selected examples of crystal structures of C^{Bz} derivatives: Schöning, K.-U.; Scholz, P.; Wu, X.; Guntha, S.; Delgado, G.; Krishnamurthy, R.; Eschenmoser, A. *Helv. Chim. Acta* **2002**, *85*, 4111−4153. Rennenberg, D.; Leumann, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5993−6002. Woźniak, L. A.; Wieczorek, M.; Pyzowski, J.; Majzner, W.; Stec, W. J. *J. Org. Chem*. **1998**, *63*, 5395−5402.

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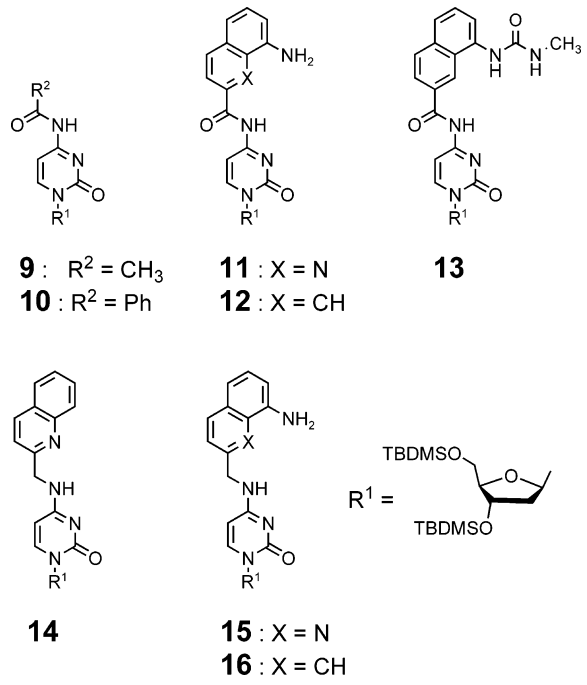
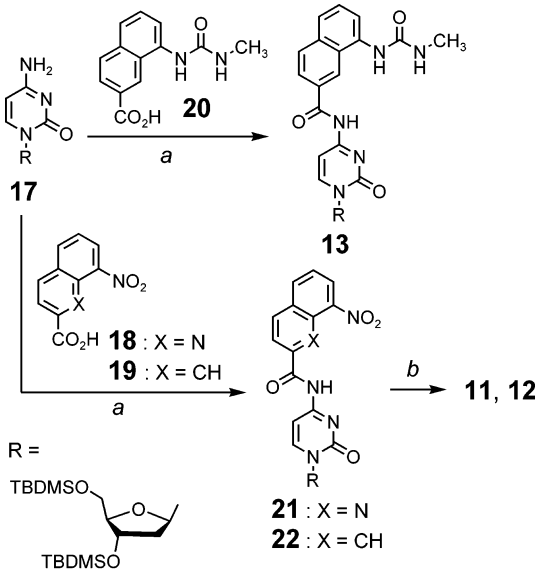
(22) Hammick, D. L. *J. Chem. Soc.* **1926**, 1302−1304. Roth, R.; Erlenmeyer, H. *Helv. Chim. Acta* **1954**, *37*, 1064−1068.

CHART 1



SCHEME 3

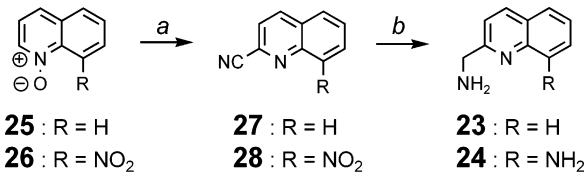


a. EDCI, HOBt, THF (**21**: 83%, **22**: 96%, **13**: 81%), b. H_2, Pd/C, MeOH, EtOAc (**11**: 52%, **12**:100%)

nitro intermediates **21** and **22**, which were then reduced to **11** and **12**, respectively.

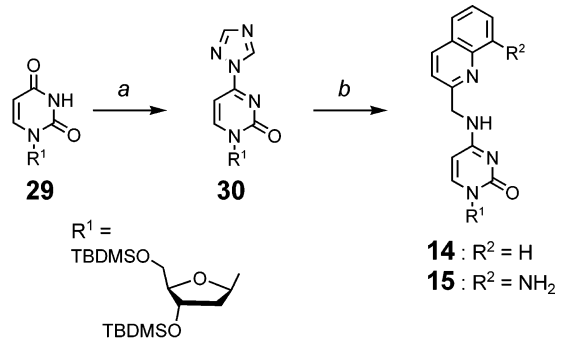
N-4-Alkylated cytidines shown in Chart 1 were prepared either by nucleophilic substitution of an activated uracil with the appropriate amine or by reduction of an *N*-4-amidocytidine (vide infra). The synthesis of the aminomethylquinoline auxiliary groups **23** and **24** is outlined in Scheme 4. Both began with oxidation of quinoline to quinoline *N*-oxide (**25**) followed by nitration according to Yokoyama et al.[23] to give **26** and the 5-nitro (minor) regioisomer. Treatment of **25** and **26** with potassium cyanide and benzoyl chloride gave quinoline-2-carbonitrile **27** and 8-nitroquinoline-2-carbonitrile **28**. The 2,8-substitution of carbonitrile **28** was confirmed by single-crystal X-ray analysis (see the Supporting Information). Reduction of the cyano group in **27** and **28** produced amines **23** and **24**, respectively. Uracil **29** was activated for nucleophilic substitution by conversion into triazolylpyrimidinone **30**.[24] Reaction with amines **23** and **24** at 100 °C in DMF produced nucleoside analogues **14** and **15** (Scheme 5). Because of the difficulty in preparing differentially substituted 1,7-naphthalenes, compound **16** was synthesized by reduction of **22**. Thus, the amide group was reduced with borane−diisopropylethylamine and the nitro group subsequently reduced by hydrogenation (Scheme 6).

SCHEME 4



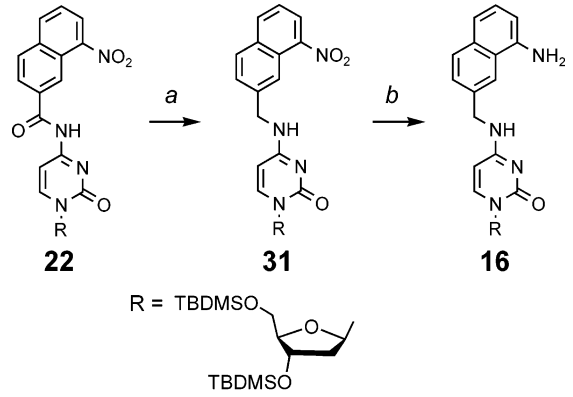
a. KCN, BzCl (**27**: 99%, **28**: 40%), b. H_2, Pd/C (**23**: 76%, **24**: 77%)

SCHEME 5



a. 1,2,4-triazole, $POCl_3$ (98%), b. **23** or **24**, DMF (**14**: 84%, **15**: 95%)

SCHEME 6



a. BH_3-DIPEA, BSA, THF (74%), b. H_2, Pd/C (48%)

Complexation Studies in Organic Solvents. Initial studies focused on establishing intermolecular contact between receptors **11**−**16** and guanosine tri-*O*-pentanoate (**32**). It is well established that NH protons experience large downfield shifts in their ^{1}H NMR spectra

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(24) For related derivatives, see: Sung, W. L. *J. Org. Chem*. **1982**, *47*, 3623−3628.

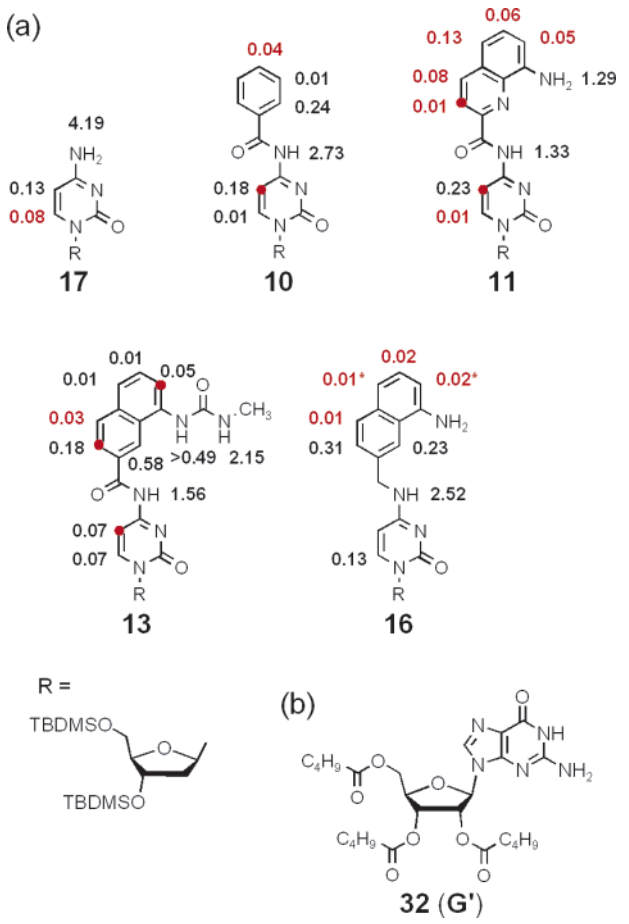

FIGURE 2. (a) Chemical shift change (red: upfield, black: downfield) for protons observed for 0.3 mM solution of receptor in the presence of 5 equiv of **32** (**G′**). In the case of **16**, shifts represent $\Delta\delta_{max}$ values from a titration with **32** (0–19.2 mM). Protons without shifts listed were obscured. An asterisk (*) indicates protons whose assignments might be switched. See text for an explanation of the red dot. (b) Structure of guanosine derivative **32**. All measurements were made in $CDCl_3$ at 20 °C.

when engaged in hydrogen bonds. For example, upon addition of 5 equiv of **32** to a 0.3 mM solution of cytosine derivative **17**, its NH_2 group shifted downfield by ca. 4.2 ppm (Figure 2 shows representative examples). Under the same conditions, similar although less dramatic shifts were seen in the 4-NH groups of 4-benzoylcytosine **10**, Umezawa's receptor **1**, and its simpler analogues **11** and **16**. The amino group on the quinoline unit in **11** and both urea NH groups on receptor **1** showed significant downfield shifts consistent with hydrogen bonding to the Hoogsteen side of **32**. The amino group in **16** was obscured during its titration and could not be followed.

In general, most of the protons not engaged in hydrogen bonding showed only small upfield or downfield shifts. Protons residing in positions labeled with a red dot in Figure 1 become localized in the deshielding cone of a carbonyl if complexes such as **1·G** are formed. If alternative conformations are significantly populated prior to complexation, then significant (ca. 0.1–0.4 ppm) downfield shifts can be expected after binding to **32**.[25] In a few cases, downfield shifts of this magnitude are seen but in others it appears that the receptor is largely preorganized. In comparing receptors, small differences

TABLE 1. Association Constants (K_{assoc}) Measured for Receptor Complexes with G′[a]

complex	K_{assoc} (M^{-1})	$-\Delta G^{\circ}_{298}$ (kcal mol^{-1})	$-\Delta\Delta G^{\circ}_{298}$ (kcal mol^{-1})
9·G′	1610	4.3	0.1
10·G′	210	3.1	1.3
11·G′	230	3.2	1.2
12·G′	2530	4.6	−0.2
13·G′	4070	4.8	−0.4
14·G′	170	3.0	1.4
15·G′	250	3.2	1.2
16·G′	440	3.5	0.9
17·G′	2040	4.4	0.0

[a] The association constants are typically averages of two experiments in 5% DMSO-d_6/$CDCl_3$ at 20 °C in which the values agreed within 15%.

in the magnitude of the complexation shifts in Figure 2 may reflect differences both in the uncomplexed and complexed receptor structures. A reverse titration was performed by holding guanosine at a fixed concentration between 0.1 and 0.3 mM in 5% (v/v) DMSO-d_6/chloroform-d and adding receptors **11**–**16**. Each receptor induced downfield shifts in NH-1 and CH-8 of **G′**. These resonances were often visible throughout the titration; however, the NH-2 group usually broadened into the baseline with relatively few equivalents of added receptor. Overall, the chemical shift changes observed in both **G′** and receptors **10**–**16** indicate Watson–Crick hydrogen bonding and, minimally, one or two additional hydrogen bonds to the Hoogsteen edge of **G′** from the pendant amino or ureido group, respectively.

Quantitative ^1H NMR complexation studies were initially performed in chloroform-d but ultimately in 5% (v/v) DMSO-d_6/chloroform-d to more readily measure and compare binding constants. Association constants (K_{assoc}) were determined by monitoring the downfield shifts of the NH protons on **32** (**G′**) with an increase in the concentration of the receptor **11**–**16**. Dilution of receptors **11**–**16** monitored by ^1H NMR revealed concentration independent chemical shifts indicating that receptor dimerization could be ignored in determination of K_{assoc} values. Guanosine is well-known to form dimers and higher order aggregates[26,27] but at the concentrations used in this study the K_{assoc} values were negligibly affected.

The K_{assoc} values are collected in Table 1. Perhaps the most striking comparison is between the **17·32** (**C·G′**) base pair and the **13·G′** complex. Despite the latter having as many as four additional hydrogen bonds to the Hoogsteen side of **G′**, it is more stable by only 0.4 kcal mol^{-1}. As indicated above, the amido group could affect the amino–imino tautomeric equilibrium or it might lower the pairing strength if the syn conformation is significantly populated (Figure 1). However, the 4-amido group on the cytosine unit does not by itself present any

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(27) The self-association constant for guanosine could not be determined in this solvent system because nonlinear regression analysis did not converge on a solution.

cost to binding as the **9·G′** complex is just 0.1 kcal mol^{-1} less stable, a value within experimental error. This is consistent with previous work by Sekine and co-workers with oligonucleotides wherein 4-*N*-acetylcytosine paired with guanosine as well as did cytosine. These authors further noted that the imino tautomer is significantly less stable that the amino tautomers. It is also true that the amido group can alter the strength of the hydrogen bond donor and acceptor sites along the Watson−Crick edge. Acylation makes the cytidine N-4-H a better hydrogen bond donor; however, the electron-withdrawing nature of the amido group decreases the hydrogen bond acceptor ability of N3 and O2. Thus, these electronic effects partially offset.

In contrast to the small effect of the acetyl group in **9**, the N-4-benzoyl group in **10** significantly depresses the complex stability (K_{assoc} = 210 M^{-1}, $\Delta\Delta G^{\circ}_{298}$ = 1.3 kcal mol^{-1}). Molecular modeling indicates a close contact between the guanosine carbonyl group and the H2 proton of the phenyl group, but it is unclear if steric repulsion alone can account for the entire drop in stability or whether electronic or conformational effects contribute. In comparing the quinoline system **11** to receptor **10**, the proton in question is no longer present and there is the possibility of additional hydrogen bonding from the pendant amino group. However, the K_{assoc} = 230 M^{-1} for **11·G′** is essentially unchanged, suggesting an unfavorable electrostatic interaction between the quinoline nitrogen lone pair and the guanosine carbonyl group (vide supra).

One of the key goals of this investigation was to determine whether the added flexibility and, particularly, the preferred syn orientation of the more robust methylene linker in **14**−**16** would significantly compromise its complexation efficiency. The stability of their complexes with **G′** suggest that indeed the energy price for adopting the required anti orientation is high. Whatever the origin of the weak binding shown by benzoyl derivative **10**, it is clear that the pendant hydrogen bonding group in **1** (**12** and **13**) compensates to a significant extent. How much do these additional Hoogsteen-side hydrogen bonds contribute? In the series **10** → **12** → **13**, the K_{assoc} values increase from 210 M^{-1} → 2530 M^{-1} → 4070 M^{-1} reflecting the progression from no hydrogen bonding functionality to an amino group to a ureido group. Although the ureido group has been shown to be effective in Hoogsteen-side recognition of guanosine,[26] its advantage in **13** relative to the amino group in **12** is only 0.2 kcal mol^{-1} and just outside of experimental error.

Molecular Modeling. Preliminary molecular modeling provides an explanation for the similar stability of **G′** complexes observed for **12** and **13**. In the **12·G′** complex, the lengths of the Watson−Crick hydrogen bonds (labeled a−c in Figure 3a) are close to those observed in the X-ray structure of GC base pairs.[28] The average difference in heteroatom to heteroatom distance is <3%, and whereas two receptor−ligand hydrogen bonds are longer, one is shorter. This same minimum found in the modeling is very nearly planar. The additional, Hoogsteen-side hydrogen bond is close to being linear (N−H−O angle = 175.9°), and its length (d, 3.06 Å) is only slight longer than the a−c lengths. In contrast, all of the hydrogen bond lengths within the **13·G′** complex are longer and the complex adopts a marked nonplanar conformation to accommodate two additional hydrogen bonds between the ureido group and the Hoogsteen edge of **G**. These hydrogen bonds to *N*-7 and *O*-6 of **G** are long and further bent from linearity with an N−H−N angle = 173.2° and N−H−O angle = 164.9°. More important than the N−H−N bond angle is the fact that the ureido N−H group is directed toward the π-system more than to the *N*-7 lone pair. Thus, this ureido N−H bond is rotated 33.2° out of the plane of the **G** aromatic system. Although each ureido N−H group of **13** may form a bifurcated hydrogen bond to *N*-7 and *O*-6 of **G** for a total of four Hoogsteen-side hydrogen bonds (see Scheme 1), the nonplanar geometry of the complex makes these distances (H···N distance = 3.18 Å, H···O distance = 3.26 Å) too long to be considered as traditional hydrogen bonds. The overall picture that emerges from the modeling, and particularly the data shown in Figure 3, is that significant reorganization is needed for receptor **13** to form five hydrogen bonds to **G**.

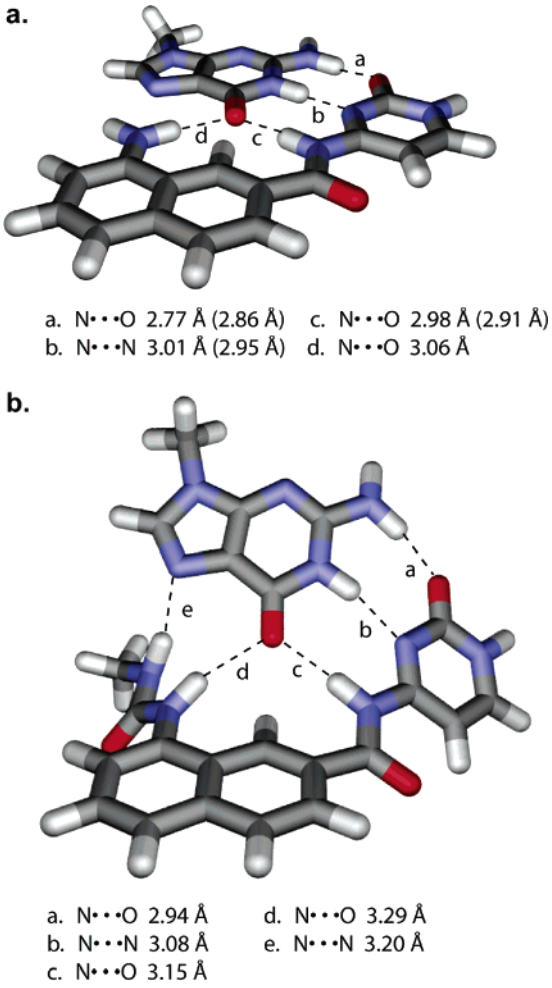

FIGURE 3. MMFF- and HF/3-21G*-minimized structure of (a) complex **12·G** and (b) complex **13·G**. In both cases, the ribose has been replaced by a proton or methyl group. Hydrogen-bonding distances are shown between heteroatoms. Parenthetical values shown in (a) are for the G·C base pair. The program Spartan was used.

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Conclusions

The structure–activity relationship examined here provides a number of general design principles that may be applied to nucleoside recognition as well as some immediate guidance on how to develop novel nucleosides that will show enhanced recognition of guanosine in duplex DNA. Specifically, in considering hydrogen bonding alone it is not easy to surpass the base-pairing ability of the natural bases. Receptor **13**, an analogue of the Umezawa receptor **1**, and receptor **12** bind **G′** in 5% (v/v) DMSO-d_6/chloroform-*d* with free energies that are just 0.4 and 0.2 kcal mol^{-1} more favorable, respectively, than **C (17)**. However, the stability of the duplex DNA is heavily dependent on aromatic stacking, a feature that is absent in these model studies of base pairing.

In considering the possibility of incorporating receptors such as **9**–**16** into oligonucleotides to test the importance of stacking the tethered aromatic system in the DNA major groove, the results above provide the following guidance. The additional hydrogen bonding provided by **12** and **13** should enhance the selectivity of these bases for **G**, however, the highly nonplanar complex seen with **13** suggests that it will not be accommodated well into duplex DNA. In general, the amide linker group appears to be the best candidate despite the difficulty in incorporating such nucleosides into DNA as a result of their hydrolytic lability. Although the more robust methylene linker groups produced very poor binders of **G** it is possible that the energy gained from aromatic stacking might offset the energy price required to shift these bases from the syn to anti form (Scheme 2). Efforts to test some of these novel nucleoside-based receptors in duplex DNA are underway and will be reported in due course.

Experimental Section

^{1}H NMR Binding Studies. $CDCl_3$ was distilled from $CaCl_2$, passed through a column of activated (flame-dried) basic alumina, and stored over 4 Å molecular sieves. DMSO-d_6 was dried over 4 Å molecular sieves. NMR tubes and volumetric flasks were dried in a 110 °C oven and cooled in a desiccator prior to sample preparation. Samples (8–12) were prepared by adding aliquots of stock solutions of guanosine and receptor via syringe directly into NMR tubes and diluting to 0.700 mL. Spectra were acquired with a 500 MHz spectrometer using temperature control at 20 °C. Data were fit to a 1:1 binding isotherm using standard methods.[29]

4-*N*-Acetyl-2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-cytidine (9). A solution of 113 mg (0.249 mmol) of **17** and 0.5 mL (5.3 mmol) of acetic anhydride in 1.5 mL of pyridine was stirred at room temperature for 20 h and then concentrated in vacuo. The residue was dissolved in 25 mL of CH_2Cl_2 and successively washed with 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of brine. The separated organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, R_f = 0.35, 10% MeOH/CH_2Cl_2) to give 120 mg (97%) of a white foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, 1H, J = 7.6), 8.27 (s, 1H), 7.34 (d, 1H, J = 7.6), 6.24 (t, 1H, J = 5.5), 4.38 (q, 1H, J = 5.6), 3.98–3.95 (m, 2H), 3.78 (dd, 1H, J = 12.0, 2.7), 2.53 (dt, 1H, J = 13.4, 6.3), 2.23 (s, 3H), 2.13 (dt, 1H, J = 12.7, 5.9), 0.93 (s, 9H), 0.88 (s, 9H), 0.123 (s, 3H), 0.111 (s, 3H), 0.058 (s, 3H), 0.055 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 162.8, 155.1, 144.7, 96.4, 87.8, 86.7, 69.8, 61.6, 42.2, 25.8, 25.6, 24.8, 18.3, 17.9, −4.7, −5.0, −5.5, −5.6; $[\alpha]^{21}_D$ = +44.9 (c = 0.55, $CHCl_3$); ESI-HRMS calcd for $(C_{23}H_{43}N_3O_5Si_2{\cdot}H)^+$ 498.2820, found 498.2816. Anal. Calcd for $C_{23}H_{43}N_3O_5Si_2$: C, 55.50; H, 8.71; N, 8.44. Found: C, 55.26; H, 8.74; N, 8.41.

4-*N*-Benzoyl-2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (10). To a solution of 104 mg (0.229 mmol) of **17** in 0.5 mL of pyridine was added 50 μL (60 mg, 0.43 mmol) of benzoyl chloride dropwise at room temperature. The resulting suspension was stirred for 10 min and then concentrated in vacuo, dissolved in 25 mL of CH_2Cl_2, and successively washed with 15 mL of saturated aqueous $NaHCO_3$ and 15 mL of brine. The organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo, and purifed by column chromatography (SiO_2, R_f = 0.3, 5% MeOH/CH_2Cl_2) to give 73 mg (57%) of a white foam spectroscopically similar to published data.[30] Anal. Calcd for $C_{28}H_{45}N_3O_5Si_2$: C, 60.07; H, 8.10; N, 7.51. Found: C, 59.97; H, 8.19; N, 7.49.

4-*N*-(8-Aminoquinolin-2-ylformyl)-2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (11). A mixture of 144 mg (0.220 mmol) of **21** and 6 mL of 1:1 (v/v) MeOH/EtOAc was hydrogenated at atmospheric pressure for 4 h over 75 mg of Pd/C. The mixture was filtered through Celite and the Celite washed with 2 × 15 mL of EtOAc. The filtrate was concentrated in vacuo and purified by column chromatography (SiO_2, R_f = 0.35, 5% MeOH/CH_2Cl_2). The product was precipitated from 3 mL of 10:1 pentane/EtOAc to give 71 mg (52%) of an orange powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.67 (s, 1H), 8.35 (d, 1H, J = 8.5), 8.32 (d, 1H, J = 7.6), 8.14 (d, 1H, J = 8.5), 7.53 (d, 1H, J = 7.4), 7.41 (t, 1H, J = 7.8), 7.06 (d, 1H, J = 8.1), 6.88 (d, 1H, J = 7.5), 6.87 (br s, 2H), 6.14 (t, 1H, J = 5.9), 4.40 (dt, 1H, J = 5.0, 4.8), 3.91 (dt, 1H, J = 3.7, 3.4), 3.86 (dd, 1H, J = 11.5, 3.9), 3.76 (dd, 1H, J = 11.5, 3.1), 2.35 (dt, 1H, J = 12.6, 6.0), 2.21 (dt, 1H, J = 13.1, 6.0), 0.90 (s, 9H), 0.87 (s, 9H), 0.104 (s, 3H), 0.098 (s, 3H), 0.082 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.9, 162.6, 154.5, 147.3, 144.6, 144.6, 137.6, 135.5, 130.6, 130.3, 118.9, 112.4, 109.2, 96.1, 87.2, 86.0, 70.8, 61.9, 40.9, 25.8, 25.7, 18.0, 17.7, −4.8, −5.0, −5.5, −5.6; $[\alpha]^{21}_D$ = +53.4 ($CHCl_3$, c = 0.51); ESI-HRMS calcd for $(C_{31}H_{47}N_5O_5Si_2{\cdot}H)^+$ 626.3194, found 626.3164. Anal. Calcd for $C_{31}H_{47}N_5O_5Si_2{\cdot}H_2O$: C, 57.82; H, 7.67; N, 10.88. Found: C, 57.85; H, 7.34; N, 10.62.

4-*N*-(8-Aminonaphthalen-2-ylformyl)-2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (12). A mixture of 36 mg (0.0550 mmol) of **22** in 4 mL of 1:1 (v/v) MeOH/EtOAc was hydrogenated at atmospheric pressure over 30 mg of Pd/C for 15 min. The mixture was filtered through Celite and the Celite washed with 15 mL of EtOAc. The filtrate was concentrated in vacuo and purified by column chromatography (SiO_2, R_f = 0.15, 1:1 $CHCl_3$/EtOAc) to give 34 mg (100%) of a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.95 (s, 1H), 8.30 (d, 1H, J = 7.5), 7.91 (d, 1H, J = 8.8), 7.81 (d, 1H, 8.6), 7.47 (d, 1H, J = 6.9), 7.34 (t, 1H, J = 7.8), 7.11 (d, 1H, J = 7.9), 6.74 (d, 1H, J = 7.6), 6.14 (t, 1H, J = 6.0), 6.07 (br s, 2H), 4.40 (dt, 1H, J = 5.1, 4.6), 3.91 (q, 1H, J = 3.6), 3.86 (dd, 1H, J = 11.5, 3.8), 3.76 (dd, 1H, J = 11.4, 3.0), 2.34 (dt, 1H, J = 12.9, 5.6), 2.20 (dt, 1H, J = 13.4, 5.9), 0.90 (s, 9H), 0.87 (s, 9H), 0.102 (s, 3H), 0.096 (s, 3H), 0.081 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.9, 163.0, 154.4, 146.6, 144.6, 136.1, 129.9, 128.2, 127.2, 124.1, 124.0, 121.1, 114.8, 108.3, 95.8, 87.1, 86.0, 70.8, 61.9, 40.9, 25.7, 25.7, 18.0, 17.7, −4.8, −5.0, −5.6, −5.6; FD-LRMS m/z 624 (M^+). Anal. Calcd for $C_{32}H_{48}N_4O_5Si_2$: C, 61.50; H, 7.74; N, 8.97. Found: C, 61.72; H, 7.78; N, 8.97.

4-*N*-[8-(3-Methylureido)naphthalen-2-ylformyl]-2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (13). To a suspension of 75 mg (0.307 mmol) of **20**, 62 mg (0.323 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 46 mg (0.340 mmol) of 1-hydroxybenzotriazole, and 2 mL of THF was added a solution of 149 mg (0.327 mmol) of **17** in 1 mL of THF at rt. The solution was stirred at rt for 22 h, diluted with 25 mL of CH_2Cl_2, and successively washed

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with 15 mL of saturated aqueous $NaHCO_3$ and 15 mL of brine. The separated organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, $R_f = 0.6$, 10% MeOH/CH_2Cl_2) using 8% MeOH/CH_2Cl_2 to give 170 mg (81%) of a yellow foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.34 (s, 1H), 8.792 (s, 1H), 8.746 (s, 1H), 8.325 (d, 1H, $J = 7.2$), 8.03−7.97 (m, 3H), 7.62 (d, 1H, $J = 8.0$), 7.56 (t, 1H, $J = 7.9$), 7.44 (d, 1H, $J = 7.2$), 6.52 (q, 1H, $J = 4.4$), 6.14 (t, 1H, $J = 5.9$), 4.40 (dt, 1H, $J = 5.1, 4.9$), 3.91 (dt, 1H, $J = 3.8, 3.6$), 3.86 (dd, 1H, $J = 11.3, 4.0$), 3.76 (dd, 1H, $J = 11.4, 2.8$), 2.72 (d, 3H, $J = 4.7$), 2.35 (m, 1H), 2.20 (dt, 1H, $J = 13.1, 6.1$), 0.91 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.105 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.7, 163.1, 156.1, 154.4, 144.6, 136.8, 135.6, 129.7, 128.7, 128.5, 124.4, 124.2, 123.8, 121.6, 117.2, 95.8, 87.1, 86.0, 70.7, 61.9, 40.9, 26.3, 25.7, 25.6, 18.0, 17.7, −4.8, −5.0, −5.6, −5.6; $[\alpha]^{21}_D = +89.2$ ($c = 0.57$, $CHCl_3$); FD-LRMS *m/z* 681 (M^+), 651 (100, −NHMe). Anal. Calcd for $C_{34}H_{51}N_5O_6Si_2$: C, 59.88; H, 7.54; N, 10.27. Found: C, 59.73; H, 7.54; N, 10.25.

4-*N*-(Quinolin-2-ylmethyl)-2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (14). A solution of 1.10 g (2.17 mmol) of **30** and 0.50 g (3.2 mmol) of **23**[31] in 5 mL of DMF was stirred at 100 °C for 23 h. The solvent was removed via vacuum, and the residue was purified by column chromatography using 2% MeOH−CH_2Cl_2 (SiO_2, $R_f = 0.25$, 5% MeOH/CH_2Cl_2) to give 1.22 g (95%) of an off-white foam: ^{1}H NMR (400 MHz, DMSO-d_6) 8.41 (t, 1H, $J = 5.9$), 8.32 (d, 1H, $J = 8.3$), 7.97−7.54 (m, 5H), 7.46 (d, 1H, $J = 8.5$), 6.12 (t, 1H, $J = 6.3$), 5.92 (d, 1H, $J = 7.3$), 4.75 (m, 2H), 4.34 (m, 1H), 3.77−3.67 (m, 3H), 2.11−2.02 (m, 2H), 0.87 (s, 9H), 0.84 (s, 9H), 0.062 (s, 6H), 0.048 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.5, 158.9, 154.8, 147.0, 139.9, 136.7, 129.7, 128.4, 127.9, 127.0, 126.2, 119.9, 94.6, 86.5, 84.6, 71.4, 62.3, 45.7, 40.4, 25.8, 25.7, 18.0, 17.7, −4.8, −5.0, −5.5, −5.6; $[\alpha]^{21}_D = +3.3$ ($c = 1.00$, DMSO); ESI-HRMS calcd for $(C_{31}H_{48}N_4O_4Si_2{\cdot}H)^+$ 597.3292, found 597.3287. Anal. Calcd for $C_{31}H_{48}N_4O_4Si_2$: C, 62.38; H, 8.11; N, 9.39. Found: C, 61.98; H, 8.09; N, 9.30.

4-*N*-(8-Aminoquinolin-2-ylmethyl)-2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (15). A solution of 886 mg (1.74 mmol) of **30** and 324 mg (1.87 mg) of **24** in 8 mL of DMF was stirred at 100 °C for 19 h. The mixture was concentrated in vacuo and purified by column chromatography (SiO_2, $R_f = 0.10$, 3% MeOH/CH_2Cl_2) to afford 890 mg (84%) of an orange foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (t, 1H, $J = 5.1$), 8.13 (d, 1H, $J = 8.6$), 7.74 (d, 1H, $J = 7.7$), 7.40 (d, 1H, $J = 8.5$), 7.24 (t, 1H, $J = 7.8$), 7.01 (d, 1H, $J = 7.6$), 6.84 (d, 1H, $J = 7.8$), 6.16 (t, 1H, $J = 6.4$), 6.06 (d, 1H, $J = 7.2$), 6.05 (br s, 2H), 4.76 (m, 2H), 4.35 (m, 1H), 3.81−3.70 (m, 3H), 2.14 (ddd, 1H, $J = 13.2, 6.1, 4.2$), 2.05 (dt, 1H, $J = 13.1, 6.2$), 0.89 (s, 9H), 0.86 (s, 9H), 0.079 (s, 6H), 0.064 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4, 154.9, 154.0, 145.0, 139.6, 136.6, 136.2, 127.5, 127.2, 119.8, 113.4, 108.9, 94.8, 86.5, 84.6, 71.4, 62.3, 45.5, 40.4, 25.8, 25.7, 18.0, 17.7, −4.8, −5.0, −5.5, −5.6; $[\alpha]^{21}_D = +16.7$ ($c = 0.52$, $CHCl_3$); FD-LRMS *m/z* 611 (M^+). Anal. Calcd for $C_{31}H_{49}N_5O_4Si_2$: C, 60.85; H, 8.07; N, 11.44. Found: C, 60.67; H, 8.19; N, 11.40.

4-*N*-(8-Aminonaphthalen-2-ylmethyl)-2′deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (16). A mixture of 64 mg (0.0999 mmol) of **31** and 4 mL of 1:1 (v/v) MeOH/EtOAc was hydrogenated at atmospheric pressure for 14 h over 50 mg of Pd/C. The mixture was filtered through Celite, and the Celite was washed twice with 10 mL of 5% (v/v) MeOH/EtOAc. The filtrate was concentrated in vacuo and purified by column chromatography (SiO_2, $R_f = 0.30$, 100:50:1 EtOAc/$CHCl_3$/Et_3N) to give 29 mg (48%) of an orange foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (t, 1H, $J = 5.3$), 7.97 (s, 1H), 7.70 (d, 1H, $J = 7.6$), 7.69 (d, 1H, $J = 8.6$), 7.34 (d, 1H, $J = 8.2$), 7.16 (t, 1H, $J = 7.8$), 7.04 (d, 1H, $J = 8.1$), 6.65 (d, 1H, $J = 7.1$), 6.16 (t, 1H, $J = 6.5$), 5.82 (d, 1H, $J = 7.4$), 5.66 (br s, 2H), 4.60 (m, 2H), 4.34 (m, 1H), 3.79−3.75 (m, 2H), 3.69 (dd, 1H, $J = 10.9, 2.8$), 2.13 (ddd, 1H, $J = 13.4, 6.4, 4.5$), 2.04 (dt, 1H, $J = 13.1, 6.7$), 0.88 (s, 9H), 0.86 (s, 9H), 0.067 (s, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.3, 155.0, 144.6, 139.6, 133.9, 133.4, 128.2, 126.6, 125.6, 122.5, 121.0, 115.3, 107.8, 94.7, 86.5, 84.6, 71.4, 62.3, 43.9, 40.3, 25.7, 25.7, 17.9, 17.7, −4.8, −5.0, −5.6, −5.6; ESI-HRMS calcd for $(C_{32}H_{50}N_4O_4Si_2{\cdot}H)^+$ 611.3449, found 611.3462.

4-*N*-(8-Nitroquinolin-2-ylformyl)-2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (21). To a suspension of 106 mg (0.509 mmol) of **18**, 102 mg (0.532 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 76 mg (0.562 mmol) of 1-hydroxybenzotriazole, and 3 mL of THF was added a solution of 247 mg (0.542 mmol) of **17** in 2 mL of THF at rt. The mixture was stirred for 21 h at rt and then diluted with 50 mL of CH_2Cl_2 and successively washed with 25 mL of saturated aqueous $NaHCO_3$ and 25 mL of brine. The separated organic layer was dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, $R_f = 0.25$, 3% MeOH/CH_2Cl_2) to give 277 mg (83%) of a yellow foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.55−8.50 (m, 3H), 8.40 (dd, 1H, $J = 8.3, 1.2$), 8.22 (dd, 1H, $J = 7.5, 1.1$), 7.79 (t, 1H, $J = 7.9$), 6.59 (d, 1H, $J = 7.4$), 6.29 (dd, 1H, $J = 6.5, 4.4$), 4.41 (dt, 1H, $J = 6.2, 5.3$), 4.01 (dd, 1H, $J = 11.3, 2.5$), 3.98 (m, 1H), 3.81 (dd, 1H, $J = 11.3, 1.6$), 2.58 (dt, 1H, $J = 13.6, 6.4$), 2.21 (ddd, 1H, $J = 13.5, 6.4, 4.4$), 0.97 (s, 9H), 0.89 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H), 0.074 (s, 3H), 0.067 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 161.4, 155.3, 150.0, 147.9, 145.0, 138.6, 137.7, 132.1, 130.2, 127.7, 125.6, 120.5, 95.8, 87.7, 86.9, 69.7, 61.6, 42.3, 25.9, 25.7, 18.4, 17.9, −4.6, −5.0, −5.5, −5.5; $[\alpha]^{21}_D = +37.2$ ($c = 0.54$, $CHCl_3$); ESI-HRMS calcd for $(C_{31}H_{45}N_5O_7Si_2{\cdot}H)^+$ 656.2936, found 656.2944. Anal. Calcd for $C_{31}H_{45}N_5O_7Si_2$: C, 56.77; H, 6.92; N, 10.68. Found: C, 56.46; H, 6.86; N, 10.61.

4-*N*-(8-Nitronaphthalen-2-ylformyl)-2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (22). To a suspension of 205 mg (0.944 mmol) of **19**, 196 mg (1.02 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 145 mg (1.07 mmol) of 1-hydroxybenzotriazole, and 5 mL of THF was added a solution of 445 mg (0.977 mmol) of **17** in 3 mL of THF at rt. The suspension was stirred at rt for 25 h, diluted with 50 mL of CH_2Cl_2, and successively washed with 25 mL of saturated aqueous $NaHCO_3$ and 25 mL of brine. The separated organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, $R_f = 0.65$, 10% MeOH/CH_2Cl_2) using 8% MeOH/CH_2Cl_2 to give 592 mg (96%) of a yellow foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.67 (s, 1H), 9.03 (s, 1H), 8.45 (d, 1H, $J = 8.2$), 8.40 (d, 1H, $J = 7.5$), 8.34 (d, 1H, $J = 7.5$), 8.30 (d, 1H, $J = 8.7$), 8.18 (d, 1H, $J = 8.6$), 7.86 (t, 1H, $J = 7.9$), 7.43 (d, 1H, $J = 7.3$), 6.13 (t, 1H, $J = 5.9$), 4.40 (q, 1H, $J = 4.9$), 3.92 (m, 1H), 3.87 (dd, 1H, $J = 11.5, 3.6$), 3.77 (dd, 1H, $J = 11.4, 2.8$), 2.36 (m, 1H), 2.21 (dt, 1H, $J = 13.5, 5.6$), 0.91 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.105 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 162.9, 154.1, 147.0, 144.5, 135.3, 134.4, 133.4, 129.1, 127.2, 126.2, 124.7, 123.9, 123.1, 95.9, 87.1, 86.0, 70.6, 61.8, 40.9, 25.7, 25.6, 18.0, 17.7, −4.8, −5.1, −5.6, −5.6; $[\alpha]^{21}_D = +33.3$ ($c = 0.81$, $CHCl_3$); FD-LRMS *m/z* 655 (M^+), 597 (100, −*t*Bu). Anal. Calcd for $C_{32}H_{46}N_4O_7Si_2$: C, 58.69; H, 7.08; N, 8.55. Found: C, 58.70; H, 7.13; N, 8.50.

2-Aminomethylquinolin-8-ylamine (24). A solution of **28** (0.943 g, 4.74 mmol) in 100 mL of 5% (v/v) trifluoroacetic acid/MeOH was hydrogenated (Parr apparatus) at 55 psi for 2.5 h over Pd/C. The mixture was filtered through Celite, concentrated in vacuo, and made slightly basic with 10 mL of water and 7 mL of saturated aqueous Na_2CO_3. The mixture was extracted twice with 70 mL of CH_2Cl_2, and the combined organic layers were successively washed with 15 mL of water and 25 mL of brine. The organic layer was dried over K_2CO_3, filtered, and concentrated in vacuo to afford 630 mg (77%) of a yellow oil that solidified upon standing. The product was of sufficient purity to carry forward without further purification

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(see the Supporting Information): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, 1H, J = 8.4), 7.31 (d, 1H, J = 8.4), 7.29 (dd, 1H, J = 7.9, 7.7), 7.14 (dd, 1H, J = 8.1, 1.3), 6.93 (dd, 1H, J = 7.5, 1.3), 4.98 (br s, 2H), 4.13 (s, 2H), 1.81 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 144.0, 138.0, 137.0, 128.2, 127.2, 120.5, 116.5, 110.8, 48.6; FD-LRMS *m/z* 173 (M^+).

8-Nitroquinoline-2-carbonitrile (28). To a suspension of 15 g (0.23 mol) of KCN and 400 mL of MeOH was added a solution of 22.0 g (0.116 mol) of **26**[32] in 500 mL of CH_3CN. Benzoyl chloride (27 mL, 33 g, 0.23 mol) was added over 5 min. The mixture was stirred for 20 h at rt and then treated with 300 mL of H_2O and 400 mL of CH_2Cl_2. The organic layer was removed, and the aqueous layer was successively extracted with 400 mL and 100 mL of CH_2Cl_2. The combined organic layers were washed with 200 mL of brine, dried over $MgSO_4$, filtered, concentrated in vacuo, purified by column chromatography (SiO_2, R_f = 0.4, 1:1 PE:EtOAc), and recrystallized from $CH_3CN/CHCl_3$ to give 9.3 g (40%) of light brown needles. A total of 8.2 g of **26** was recovered from chromatography. Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation (see the Supporting Information for the CIF file): mp 194–195 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, 1H, J = 8.6), 8.17 (dd, 1H, J = 7.5, 1.3), 8.13 (dd, 1H, J = 8.4, 1.5), 7.87 (d, 1H, J = 8.4), 7.81 (dd, 1H, J = 8.4, 7.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 139.9, 138.4, 136.2, 132.3, 129.5, 128.8, 125.8, 125.7, 117.1; IR (KBr) 3413, 3075, 2245, 1538, 1498, 1378, 1310; FD-LRMS *m/z* 199 (M^+). Anal. Calcd for $C_{10}H_5N_3O_2$: C, 60.31; H, 2.53; N, 21.10. Found: C, 60.25; H, 2.40; N, 20.72.

1-[2-Deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-4-[1,2,4]triazol-1-yl-1*H*-pyrimidin-2-one (30).[33] To a suspension of 3.9 g (56 mmol) of 1,2,4-*1H*-triazole, 1.1 mL (1.8 g, 11.8 mmol) of $POCl_3$, and 32 mL of CH_3CN at 0 °C was added a solution of 1.87 g (4.09 mmol) of **29**[34] in 17 mL of CH_3CN over 15 min. The suspension was stirred at 0 °C for 20 min and then at ambient temperature for 1 h. The reaction was quenched with 4.5 mL of Et_3N and 1.7 mL of water and the mixture concentrated in vacuo. The residue was dissolved in 75 mL of CH_2Cl_2 and washed with 50 mL of 0.5 M aqueous $NaHCO_3$. The organic layer was removed, and the aqueous layer was extracted three times with 75 mL each of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, R_f = 0.40, 5% MeOH/CH_2Cl_2) using 100:1→100:3 CH_2Cl_2/MeOH to give 2.03 g (98%) of a colorless oil that solidifies on standing: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.71 (d, 1H, J = 7.3), 8.11 (s, 1H), 6.97 (d, 1H, J = 7.3), 6.25 (dd, 1H, J = 6.4, 4.3), 4.39 (dt, 1H, J = 6.2, 5.1), 3.99 (m, 2H), 3.80 (m, 1H), 2.58 (dt, 1H, J = 13.7, 6.4), 2.19 (ddd, 1H, J = 13.7, 6.4, 4.5), 0.93 (s, 9H), 0.87 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 154.4, 153.9, 147.0, 143.2, 94.0, 88.0, 87.5, 69.5, 61.5, 42.3, 25.9, 25.6, 18.3, 17.9, −4.6, −5.0, −5.5; $[\alpha]^{21}_D$ = +56.5 (c = 1.00, $CHCl_3$); ESI-HRMS calcd for $(C_{23}H_{41}N_5O_4Si_2{\cdot}H)^+$ 508.2775, found 508.2787. Anal. Calcd for $C_{23}H_{41}N_5O_4Si_2$: C, 54.40; H, 8.14; N, 13.79. Found: C, 54.39; H, 8.25; N, 13.51.

4-*N*-(8-Nitronaphthalen-2-ylmethyl)-2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (31).[35] To a solution of 95 mg (0.145 mmol) of **22** in 2 mL of THF was added 0.177 mL (147 mg, 0.725 mmol) of *N*,*O*-bis(trimethylsilyl)acetamide dropwise at rt. The solution was treated dropwise with 0.252 mL (207 mg, 1.45 mmol) of borane–*N*,*N*-diisopropylethylamine complex and the solution stirred at rt for 15 min. The reaction was quenched with 10 mL of methanol, and the mixture was concentrated in vacuo. The resulting residue was dissolved in 80 mL of a 1:1 (v/v) mixture of methanolic ammonia (17 wt %)/aqueous ammonia (28 wt %) and incubated for 13 h at 50 °C. The mixture was cooled to room temperature, diluted with 100 mL of water, and partially neutralized with 25 mL of 1 N aqueous HCl. The mixture was extracted with chloroform (2 × 50 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, R_f = 0.15, 5% MeOH/CH_2Cl_2) to give 69 mg (74%) of an orange foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (t, 1H, J = 5.9), 8.34 (d, 1H, J = 8.3), 8.31 (d, 1H, J = 7.6), 8.23 (s, 1H), 8.14 (d, 1H, J = 8.5), 7.73 (d, 1H, J = 7.3), 7.67 (t, 1H, J = 7.9), 7.65 (d, 1H, J = 8.5), 6.13 (t, 1H, J = 6.2), 5.85 (d, 1H, J = 7.3), 4.72 (m, 2H), 4.34 (m, 1H), 3.79–3.68 (m, 3H), 2.12 (m, 1H), 2.04 (dt, 1H, J = 12.9, 6.8), 0.88 (s, 9H), 0.85 (s, 9H), 0.067 (s, 6H), 0.58 (s, 6H); ESI-HRMS calcd for $(C_{32}H_{48}N_4O_6Si_2{\cdot}H)^+$ 641.3191, found 641.3174. Anal. Calcd for $C_{32}H_{48}N_4O_6Si_2$: C, 59.97; H, 7.55; N, 8.74. Found: C, 59.87; H, 7.58; N, 8.55.

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Supporting Information Available: General experimental procedures, X-ray analysis data for compound **28** (CIF file), nonlinear regression plots for complexation studies, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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