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Synthesis of 5-/8- Halogenated or Ethynylated Lipophilic Nucleobases as Potential Synthetic Intermediates for Supramolecular Chemistry

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Abstract: A series of lipophilic nucleobases that are substituted at the 5- (pyrimidines) or 8-position (purines) with either a halogen atom or a terminal triple bond have been synthesized. The sequences and reactions studied in this work, which mainly comprise halogenation, alkylation, Sonogashira coupling, and trimethylsilylacetylene deprotection, have been carefully optimized in order to reach the final compounds in the most straightforward, convenient way and with the maximum purity and yield. These compounds include cytosine, *iso*cytosine and uracil as pyrimidine heterocycles, and guanine, *iso*guanine, and 2-aminoadenine as complementary purine bases. Variability was introduced at the *N*-1/*N*-9 positions of these pyrimidine/purine nucleobases, which were functionalized with alkyl or benzyl groups, as well as with protected amine or carboxylic acid substituents. The molecules prepared constitute a useful collection of synthetic intermediates in the field of chemical self-assembly.

Introduction

The design of chemical moieties having specific hydrogen-bonding patterns has been exploited by supramolecular chemists to make interact one or more molecular components and thus create well-defined assemblies with diverse functions.[1] Hydrogen-bonding is employed here as a highly selective and directional noncovalent interaction, whose strength can be tuned as a function of the chemical nature of donor and acceptor functions, as well as on their number and sequence in a particular molecular fragment.[2] These moieties can be seen as "supramolecular directors" that are able to couple specific molecular components in a geometrically defined arrangement, where in many cases hydrogen-bonding interactions cooperate with additional weak non-covalent forces such as π-π stacking, solvophobic or Coulombic interactions. [3]

Among these supramolecular hydrogen-bonding units, naturally occurring DNA bases and synthetic nucleobase analogues are of particular relevance.[4],[5] Besides, nucleobase derivatives play a crucial role in nature and have been found as clinically useful molecules with diverse biological activities. An example of interest is constituted by *N*-9 substituted guanines, such as acyclovir, because of their potential antiviral activity.[6] For these reasons, the development of efficient and reliable synthetic routes to modified nucleobases as versatile building blocks in self-assembly can be of great importance and utility to the supramolecular chemist.[7],[8]

Here, we describe the synthesis of a series of chemically-modified lipophilic natural and non-natural nucleobase derivatives (Figure 1) that are equipped with either an halogen atom or an ethynyl group at the 5-position (for the pyrimidines) or at the 8-position (in the case of the purines). Pyrimidine nucleobases comprise cytosine (C), uridine (U), and *iso*cytosine (iC), whereas the purines prepared in this work are guanine (G), 2,6-diaminopurine or 2-aminoadenine (DAP; hereafter abbreviated as A), and *iso*guanine (iG). Together, these complementary nucleobases constitute a useful collection of synthetic intermediates for supramolecular chemistry. On one hand, the halogenated position can be employed to attach these units to functional molecules with the aim of driving their self-assembly *via* a large battery of metal-catalyzed cross-coupling reactions.[9] On the other, the rich and useful reactivity of the terminal triple bond, either through Sonogashira couplings or "click" cycloaddition reactions, make these six nucleobases convenient "synthons" for the preparation of complex organized systems.[10] These heterocycles have been further substituted with lipophilic alkyl or benzyl groups or with protected amines and carboxylic acids at the *N*-1 (pyrimidines) or *N*-9 (purines). As opposed to related nucleosides,[8] where the bulky ribose unit attached at these position limits aggregation, these simple and planar groups may help in producing hierarchical assemblies where hydrogen-bonding is combined with other non-covalent interactions acting in orthogonal directions, such as π-π stacking with other molecules or with planar substrates.

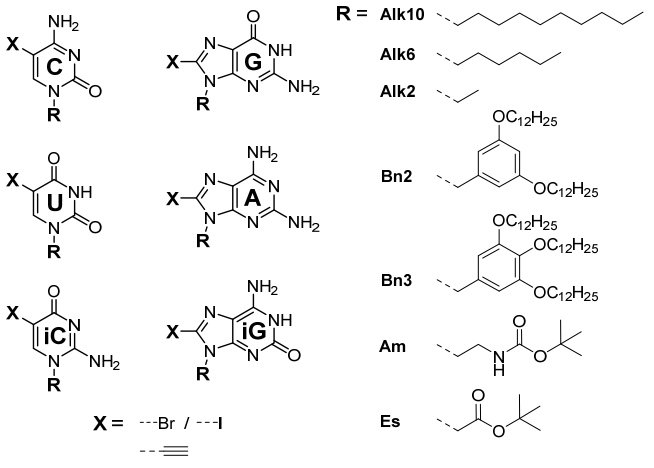

Figure 1. General structure of the pyrimidine (**C**, **U**, **iC**) and purine (**G**, **A**, **iG**) derivatives targeted in this work.

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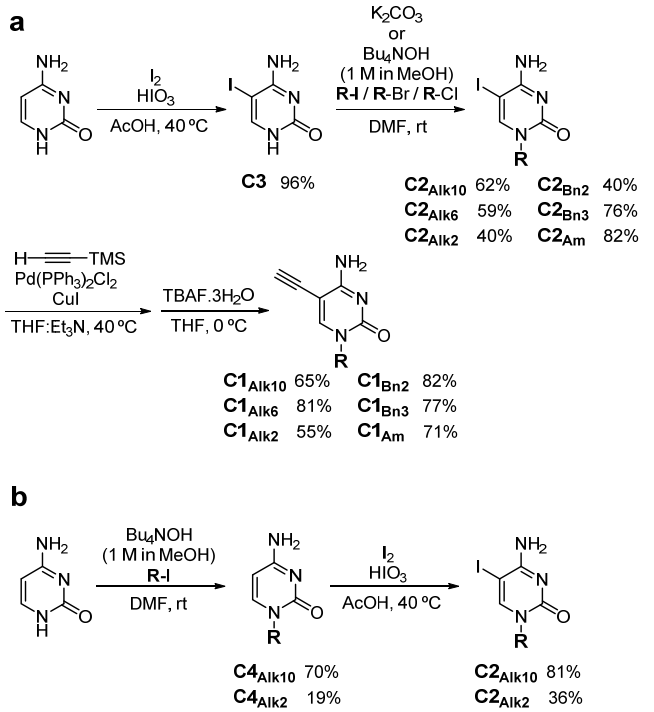
Results and Discussion

As shown in Figure 1, our target nucleobases present common functional groups, such as the halogen atom or the ethynyl group at the 5-position of pyrimidines and the 8-position of purines, as well as variable substituents, such as the diverse lipophilic groups at the 1-position of pyrimidines and the 9-position of purines. Therefore, the ideal, most convergent synthetic route to these derivatives would comprise three consecutive steps: 1. Halogenation (bromination or iodination); 2. Palladium-catalyzed Sonogashira coupling[9] with trimethylsilylacetylene (TMSA), followed by trimethylsilyl (TMS) deprotection and; 3. Nucleophilic substitution with the corresponding alkylating reagent.[11] Since the variability in our compounds is introduced at the level of the alkyl substituents, a lower number of products would need to be synthesized using this sequence. However, as will be explained below for each nucleobase, different problems arose during synthesis that made us deviate from this optimal route. Many intermediates were unreactive in some conditions and/or displayed very low solubility to be properly purified. The sequences and reactions described in this work have been therefore carefully optimized in order to reach the final compounds in the most straightforward and convenient way and with the maximum purity and overall yield.

Synthesis of pyrimidines. With the aim of reaching the most convergent route, iodination of the pyrimidine heterocycles was selected as the first reaction in the synthetic schemes towards lipophilic C, U and *i*C derivatives. The incorporation of iodine was chosen instead of bromine due to the higher reactivity of iodoarenes in metal-catalyzed cross-coupling reactions. Different iodination agents and protocols, such as iodine/iodic acid (I_2/HIO_3), iodine/periodic acid (I_2/H_5IO_6), *N*-iodosuccinimide (NIS), or iodine monochloride (ICl), were essayed. Only the best options for each substrate are reported here. Next, the Sonogashira coupling in different conditions was attempted in each 5-iodopyrimidine. However, none of them (C, U or *i*C) was reactive. We believe that *N*-1 unsubstituted pyrimidines can deactivate the catalytic palladium species thorough chelation *via* one of their different tautomeric forms, as has been suggested for other nucleobase derivatives.[12] 5-iodo-substituted pyrimidines were instead subjected first to an alkylation reaction which is, in most cases, quite selective for the *N*-1 position. The Sonogashira reaction was performed on these alkylated iodopyrimidines, leading in all cases to excellent yields of coupled products. Finally, the TMS protecting group was cleaved in the presence of tetrabutylammonium fluoride (TBAF).

Cytosine (Scheme 1). A total of six 5-iodocytosine and 5-ethynylcytosine derivatives were synthesized, each of them having different alkyl or benzyl groups. Iodination of commercial cytosine (Scheme 1a) was carried out in the presence of I_2 and HIO_3.[13] In these conditions, 5-iodocytosine (**C3**) was obtained in close to quantitative yields by neutralization and straightforward filtration and washing. This product was then subjected to an alkylation reaction in the presence of the corresponding alkyl/benzyl halide. These reactions are typically carried out in the presence of cesium or potassium carbonates but, in the case of our iodoalkanes and benzyl halides, the use of these bases did not afford good yields. Instead, the more soluble Bu_4NOH base in methanol[14] was used to deprotonate **C3** and produce **C2$_{Alk10}$**, **C2$_{Alk6}$**, **C2$_{Alk2}$**, **C2$_{Bn2}$**, and **C2$_{Bn3}$** in acceptable yields. 1-Alkyl-5-iodocytosines were then transformed into the final 5-ethynyl derivatives using standard Sonogashira-TMS deprotection methods.[15]

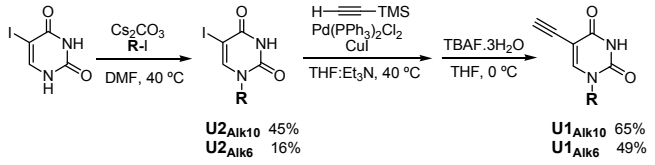


Scheme 1. Synthetic routes to 5-iodo- and 5-ethynyl-cytosines using the (**a**) halogenation-alkylation or (**b**) alkylation-halogenation sequence.

We also tested the inverted reaction order, that is, alkylation of cytosine followed by halogenation (Scheme 1b). Besides being less convergent, this alternative route presented other types of drawbacks. First, the isolation of the halogenated products was more tedious and produced lower yields. Second, the presence of the bulky iodine atom at the C5 position in **C3** was proven effective in directing alkylation selectively at the *N*-1 position.[16] For instance, when carrying out the alkylation reaction with ethyl iodide directly onto commercial cytosine, a triply alkylated byproduct was also obtained, having ethyl chains at the *N*-1 position but also in the amino group. Finally, performing the halogenation after the alkylation reaction is not compatible with the benzyl-substituted derivatives, since they comprise electron-rich aryl groups that would give rise to mixtures of halogenated products.

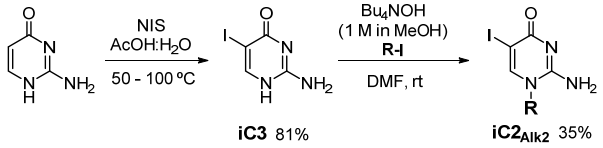
Uridine (Scheme 2). The route to the uridine derivatives started directly from commercial 5-iodouridine, a compound that can also obtained in excellent yields from uridine.[17] 5-iodouridine was alkylated in the presence of Cs_2CO_3, which was proven to be slightly more efficient than K_2CO_3 because of its better solubility in organic solvents. The yields of **U2$_{Alk10}$** and **U2$_{Alk6}$** were not very satisfactory, although they are in the same range of those

reported on similar alkylation reactions with uridine derivatives.[18] One of the reasons for these relatively low yields is the additional formation of *N*-3-substituted products and the corresponding dialkylated products, identified by ^{1}H NMR and MS, which compete with alkylation at *N*-1. Finally, 1-Alkyl-5-iodouracils were then converted to the corresponding 5-ethynyl derivatives via cross-coupling reaction with TMSA. Traces of deiodinated products were detected in this last reaction.



Scheme 2. Optimized synthetic route to 5-iodo- and 5-ethynyl-uracils.

Isocytosine (Scheme 3). The nonnatural isocytosine analog **iC$_{Alk2}$** was also prepared following the halogenation-alkylation sequence. In this case, iodination was carried out in the presence of *N*-iodosuccinimide (NIS),[19] since it afforded better results than other methods. Alkylation was then performed using the same procedure as with the cytosine derivatives. The base was equipped with a simple ethyl group for subsequent sublimation studies under ultrahigh vacuum. This reaction led as well to the *N*-3-substituted product in minor amounts, which could be separated by chromatography from the target *N*-1-alkylated derivative. Product **iC$_{Alk2}$** is the only one in this work that was not transformed into the corresponding 5-ethynyl derivative.



Scheme 3. Synthetic route to 5-iodo-*iso*cytosine **iC$_{Alk2}$**.

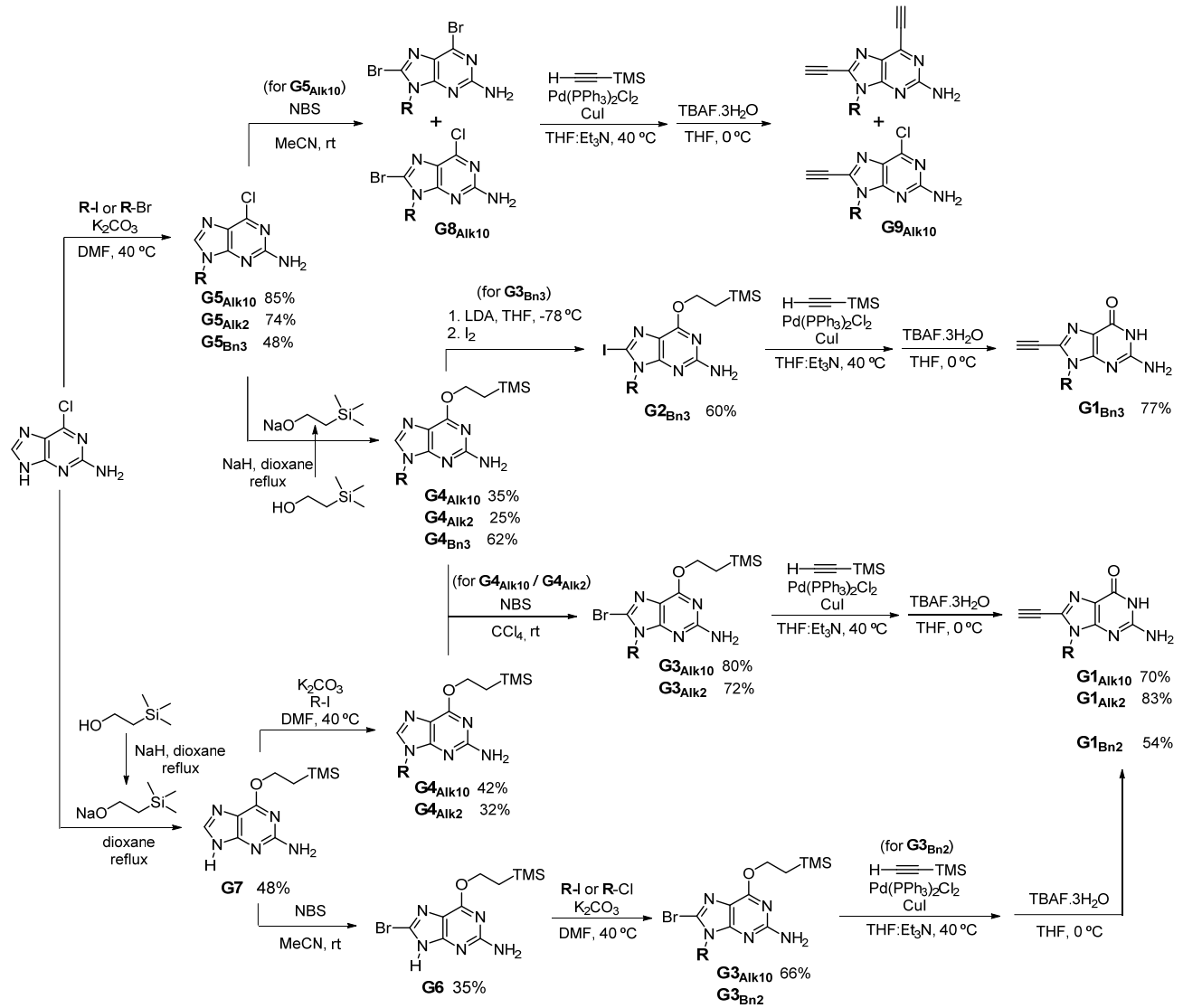
Synthesis of purines. The optimized route to 8-halogenated and 8-ethynylated purines followed a different synthetic sequence to that used with the pyrimidines. We were of course interested in achieving the most convergent path by introducing the halogenation step[20] as soon as possible in the sequence, as we have shown with the pyrimidines. However, although this was accomplished in some cases, the early introduction of the halogen atom resulted in a series of secondary problems during subsequent reactions that reduced the overall yield. Hence, the alkylation reaction was preferably carried out as the first step in the routes to guanine, 2-aminoadenine and *iso*guanine derivatives, despite the higher number of products that needed to be synthesized. Then, the alkylated products were either brominated or iodinated. The preparation of 8-iodopurines was obviously preferred because of their higher reactivity in subsequent palladium-catalyzed couplings, so their synthesis was optimized and studied in more detail using different iodination methods. The iodine substituent could be introduced either by electrophilic aromatic substitution in the presence of diverse reagents (*vide supra*) or by deprotonation at the 8-position followed by quenching with iodine. The first method, together with NBS bromination, was not compatible with the benzyl groups, since they bear electron-rich aromatic rings that are more activated towards electrophilic substitution than the purine ring, as we found out during our tests (see below). As in the case of the pyrimidines, the Sonogashira reaction was left as the last step in the sequence to 8-ethynylpurines. This reaction, as will be explained below, required in some instances previous functional group protection of the purine heterocycles. Similarly to the pyrimidine bases, all our attempts to perform this palladium-catalyzed coupling after halogenation and before alkylation were unsuccessful, probably because of deactivation of the catalytic species due to a higher metal-coordination ability of *N*-9 unsubstituted derivatives.

Guanine (Schemes 4 and 5). The development of an efficient synthetic route to 8-ethynyl lipophilic guanines (**G1$_{Alk10}$**, **G1$_{Alk2}$**, **G1$_{Bn2}$**, **G1$_{Bn3}$**) turned out to be, with a big difference, the most complex task in this work and considerable effort was dedicated to this mission. There are several reasons for this. The low solubility of guanine or 2-amino-6-hydroxypurine in different solvents is one of them. Among all the nucleobases, guanine exhibits the most rich supramolecular chemistry[21],[22] and often self-associate in solution to form highly insoluble products or viscous gels. Also, guanine, and in general purines, are constituted by a mixture of tautomers that can lead to different isomers in the alkylation reactions. The most common of them are the *N*-7 and *N*-9 alkylated products, which are sometimes difficult to separate.[23] But probably the most important reason is the requirement to protect or mask the carbonyl group before palladium-catalyzed cross-couplings. As a matter of fact, the low reactivity of the guanine heterocyle in metal-mediated oxidative addition processes has been reported.[8],[12],[24] The low oxidation potential of this base or its ability to coordinate organometallic catalytic species are cited among the causes that would explain such lack of reactivity.[12] Conversion to different functionalized derivatives like 6-alkoxy-,[8],[24],[25] or 6-halogenopurines, which, at the same time, may exhibit a higher selectivity in the alkylation reaction, is an alternative. Unfortunately, the use of these starting reagents involve higher costs and an increase in the number of reaction steps, which results in poorer overall yields. Furthermore, previous methods reported in the literature for the conversion of 2-amino-6-chloropurine into guanine use vigorous acidic or basic conditions that are not compatible with sensitive functional groups.

We essayed first the use of 2-amino-6-chloropurine as the starting reagent and we evaluated different routes and sequences from this commercial derivative (Scheme 4). Our initial idea was to perform the whole three-step reaction sequence directly on this kind of derivatives. Since our attempts to halogenate this substrate under different conditions were unsuccessful, we started the route by alkylating 2-amino-6-chloropurine with diverse iodoalkanes, to yield **G5$_{Alk10}$** and **G5$_{Alk2}$**, and with the corresponding benzyl bromide, to afford **G5$_{Bn3}$**.[26] Whereas the benzyl halide led mainly to a single *N*-9 alkylation product,[27] 1-iododecane or 1-iodoethane, presumably due to their lower steric

hindrance, produced mixtures of *N*-7 and *N*-9 substituted products in an approximate 1:4 ratio, although the overall yields were still very satisfactory.

Next, we tested halogenation on **G5$_{Alk10}$**. Only NBS-mediated bromination worked properly in our hands. However, treatment of this substrate in the presence of NBS unexpectedly afforded a mixture of brominated products, mainly including our target 2-amino-8-bromo-6-chloropurine and 2-amino-6,8-dibromopurine, in which the 6-chloro atom was replaced by bromine. Unfortunately, this mixture could not be separated and the use of other conditions did not avoid the formation of this dibrominated secondary product. Then, the mixture was subjected to a Sonogashira coupling to see if one of these 6- or 8-positions reacted selectively or if the products could be separated at the last step by chromatography. Despite all our attempts under different conditions and palladium catalysts, both positions seemed to be equally reactive and our target compound could not be separated from the mixture of ethynylated products. On the other hand, the hydrolysis of the mixture of brominated products in acidic conditions[28] led to mixtures of 8- and 6-oxopurines.



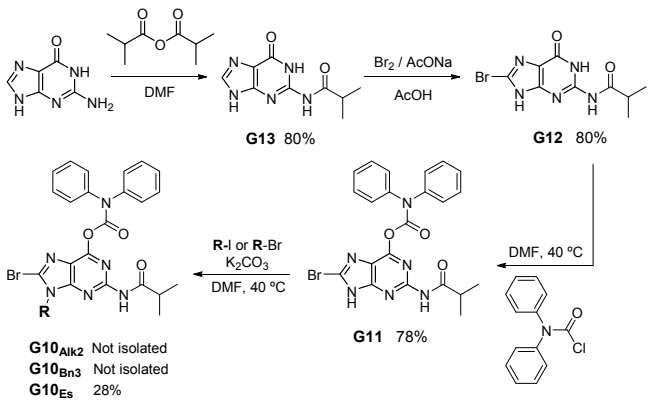
Scheme 4. Synthetic routes to 8-iodo- and 8-ethynyl-guanines from 2-amino-6-chloropurine.

To circumvent these problems, substitution of the 6-chloro atom with a 2-trimethylsilylethoxy group[29] was next considered with the aim of reducing the reactivity of such position in the halogenation step. This particular protecting group was chosen because of several additional advantages in the synthetic route: it imparts solubility to the heterocyclic ring and can be efficiently deprotected in the presence of fluoride at the very last step in the route,[30] along with the TMSA group. Compound **G7**[30] was thus synthesized and subjected then to a halogenation reaction. Electrophilic iodination was first tested with negative results and

the starting material was recovered in all cases. Bromination in the presence of Br_2 did not work properly either. Contrarily, bromination with NBS led to **G6**, which could be subsequently alkylated. It is worth to note that the alkylation reaction on this substrate led to complete regioselectivity at *N*-9, both for alkyl and benzyl halides, affording $\mathbf{G3_{Alk10}}$ and $\mathbf{G3_{Bn2}}$. However, despite its convergence, we were still not very satisfied with this route since the first two reactions (nucleophilic aromatic substitution and bromination) proceeded with low to moderate yields, were not very reproducible, and the products obtained (**G7** and **G6**) could not be easily isolated from traces of impurities. It is also important to note that **G6** was unreactive in palladium-catalyzed couplings, either in Sonogashira reactions with TMSA or in Stille reactions in the presence of ethynyltributylstannane. Altering the sequence by alkylation of **G7** led to more easily isolable products. The use of 1-iododecane or 1-iodoethane in this reaction led now to a *ca.* 1:1 mixture of *N*-7 and *N*-9 products, which is surprising in view of the higher regioselectivities attained in the alkylation reactions on **G6** or on 2-amino-6-chloropurine (see above). Bromination of $\mathbf{G4_{Alk10}}$ or $\mathbf{G4_{Alk2}}$ led to the 8-bromopurines $\mathbf{G3_{Alk10}}$ or $\mathbf{G3_{Alk2}}$ in quite good yields.

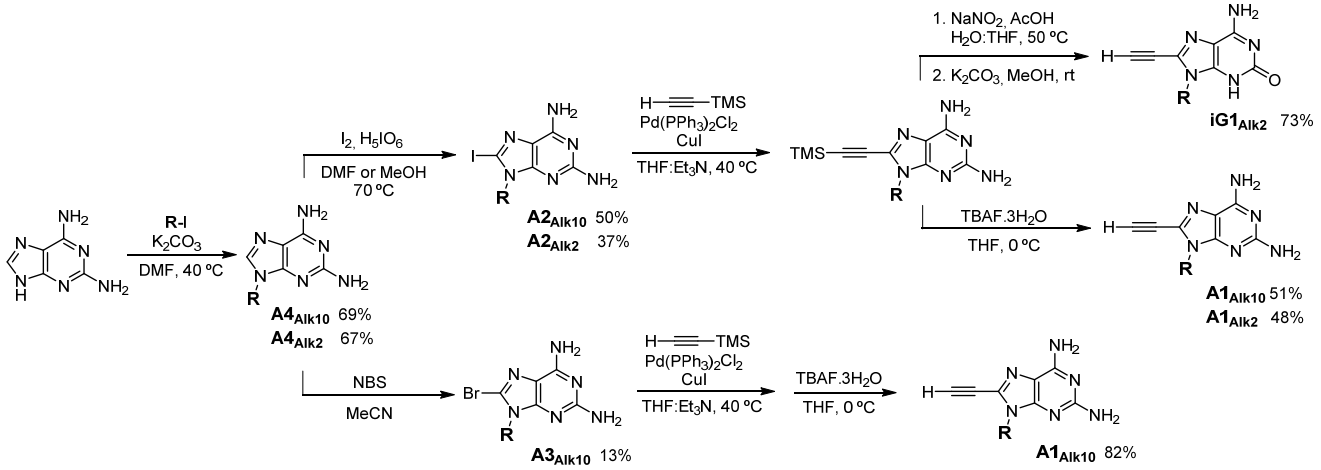
Nevertheless, the best route we found to our target lipophilic guanines is shown in the central region of Scheme 4. Alkylation was first performed on 2-amino-6-chloropurine using K_2CO_3 or Cs_2CO_3 as the base, as has been explained above. This reaction afforded rather soluble products with good yields that could be easily purified and subjected to the aromatic nucleophilic substitution with the 2-trimethylsilylethoxy group, leading to compounds $\mathbf{G4_{Alk10}}$, $\mathbf{G4_{Alk2}}$, and $\mathbf{G4_{Bn3}}$. As just mentioned, the $\mathbf{G4_{Alk10}}$ and $\mathbf{G4_{Alk2}}$ products could be brominated at the 8-position in the presence of NBS, but reaction of $\mathbf{G4_{Bn3}}$ in the presence of 1 equivalent of NBS led instead to the selective bromination at the aromatic benzyl residue. Instead, iodination was essayed under a different mechanism that involved deprotonation at the guanine 8-position in the presence of LDA and quenching of the resulting anion with iodine.[31] Product $\mathbf{G2_{Bn3}}$ was in this way generated with acceptable yields. This iodination procedure is, of course, also compatible with the alkylated purines. Finally, bromo-derivatives $\mathbf{G3_{Alk10}}$, $\mathbf{G3_{Alk2}}$ and $\mathbf{G3_{Bn2}}$, and iodoguanine $\mathbf{G2_{Bn3}}$ were subjected to a Sonogashira coupling in the usual conditions, followed by deprotection of the alkyne TMS group, to yield $\mathbf{G1_{Alk10}}$, $\mathbf{G1_{Alk2}}$, $\mathbf{G1_{Bn2}}$ and $\mathbf{G1_{Bn3}}$.

The synthesis of 9-alkyl-8-ethynylguanines was as well attempted using guanine as a convenient starting material due principally to its low cost (Scheme 5). However, the extremely low solubility of this heterocyclic reagent has to be overcome first. The literature offers different methods to transiently transform guanine into products that display enough solubility to carry out several synthetic transformations.[32] Among the different methods we tested, we chose 2-amine protection as an *iso*butyryl amide due to the acceptable solubility and ease in isolation of the product. Compound **G13** was thus synthesized in 80% yield in the presence of *iso*butyric anhydride.[33] This product could be halogenated in the presence of bromine and sodium acetate[34] leading to **G12** in good yields. Direct attempts to perform a Sonogashira reaction with TMSA on compound **G12** were unsuccessful in our hands, despite a related procedure was reported recently from similar substrates,[35] and the starting material was recovered instead. We thought that protection of the 6-carbonyl group in **G12** could increase its reactivity in palladium-catalyzed couplings.[12] A diphenylcarbamoyl protecting group[36] was selected among diverse options, but compound **G11** was still unreactive in any Pd-catalyzed Sonogashira or Stille reaction conditions we tried. Therefore, **G11** was subjected first to an alkylation reaction either with ethyliodide, 3,4,5-tris(dodecyloxy)benzyl bromide or with *tert*butyl bromoacetate. Unexpectedly, in all cases this nucleophilic substitution reaction displayed very low regioselectivity, leading to a mixture of mono- and dialkylated products that complicated the purification process. **G11** was alkylated at both the imidazole ring and at the amide protecting group. Not only that, despite the high steric hindrance of the diphenylcarbamoyl group, the *N*-7 substituted product turned out to be one of the major byproducts in this reaction. Only the target compound $\mathbf{G10_{Es}}$ could be isolated in pure form in 28% yield from this mixture.



Scheme 5. Attempted synthetic route to 8-bromo- and 8-ethynyl-guanines from guanine.

2-Aminoadenine (Scheme 6). Two alkylated adenine derivatives were prepared from commercial 2,6-diaminopurine. All our attempts to either iodinate or brominate this starting material were unsuccessful. Instead, the alkylation reaction[37] was carried out as the first step of the synthetic route. K_2CO_3 proved to be the best base for such reaction due to handling conditions, price and yield reasons. Compounds $\mathbf{A4_{Alk10}}$ and $\mathbf{A4_{Alk2}}$ were prepared in this way. Next, the halogenation reaction was optimized. Iodination in the presence of periodic acid[38] was chosen over bromination reaction with NBS, not only due to the reasons stated above, but also because of the poor yields and reliability of the latter reaction, even with recrystallized NBS. It is worth to mention that none of the guanine derivatives tested could be iodinated under these conditions. Compounds $\mathbf{A2_{Alk10}}$, $\mathbf{A2_{Alk2}}$, and $\mathbf{A3_{Alk10}}$ were then subjected to the Sonogashira-TMS cleavage protocol, leading to $\mathbf{A1_{Alk10}}$ and $\mathbf{A1_{Alk2}}$ in good yields.



Scheme 6. Optimized synthetic route to 8-iodo- and 8-ethynyl-diaminopurine and 8-ethynyl-*iso*guanine.

Isoguanine (Scheme 6). The *iso*guanine non-natural nucleobase could be obtained from 2,6-diaminopurine in a single step by selective hydrolysis at C-2 *via* a diazonium intermediate.[39] For the sake of simplicity and convergence, we performed this process after the cross-coupling reaction of the iodinated **A2** derivatives and before TMS deprotection, since the terminal ethynyl group was found to interfere in this reaction. Compound **iG1$_{Alk2}$** was isolated in 73% overall yield from **A2$_{Alk2}$** after TMS-cleavage in the presence of K_2CO_3.

Conclusions

In this work we have prepared a series of lipophilic nucleobases, comprising natural and non-natural derivatives, that are substituted at the 5- (pyrimidines) or 8-position (purines) with either a halogen atom or a terminal triple bond. These include cytosine, *iso*cytosine and uracil as pyrimidine heterocycles, and guanine, *iso*guanine, and 2-aminoadenine as complementary purine bases. The *N*-1 / *N*-9 position of these compounds was functionalized with alkyl or benzyl groups, as well as with amine or carboxylic acid precursors. This kind of functional groups are suited to afford solubility and direct nucleobase assembly in organic solvents or onto surfaces, as we are studying in our group at the moment. The synthetic sequences leading to the final ethynylated compounds have been optimized for each base attending to convergence, convenience, ease of purification and overall yields. Our results indicate that the choice of reaction conditions and the order in which the halogenation, alkylation and Sonogashira steps are performed is not always trivial and each base requires a particular optimized protocol.

The molecules prepared in this work can be regarded as a relevant collection of “supramolecular synthons” to which a wide diversity of functional units may be attached by means of metal-catalyzed cross-coupling or “click” reactions, in order to guide their organization.

Experimental Section

General Information.

Chemicals were purchased from commercial suppliers and used without further purification. Solid, hygroscopic reagents were dried in a vacuum oven before use. *N*-Bromosuccinimide (NBS) was recrystallized twice from water. Reaction solvents were thoroughly dried before use using standard methods. Column chromatography was carried out on silica gel *Merck-60* (230-400 mesh, 60 Å), and TLC on aluminium sheets precoated with silica gel 60 F254 (Merck). LSI-MS and HR-MS spectra were determined on a *VG AutoSpec* apparatus (FAB) or an *Applied Biosystems QSTAR* equipment (ESI) in the positive mode. MALDI-TOF-MS spectra were obtained from a BRUKER ULTRAFLEX III instrument equipped with a nitrogen laser operating at 337 nm. NMR spectra were recorded with a *BRUKER AC-300* (300 MHz) instrument. The temperature was actively controlled at 298 K. Chemical shifts are measured in ppm using the signals of the deuterated solvent as the internal standard [$CHCl_3$, calibrated at 7.26 ppm (^{1}H) and 77.0 ppm (^{13}C); DMSO calibrated at 2.50 ppm (^{1}H) and 39.5 ppm (^{13}C)].

Compounds **G8$_{Alk10}$**, **G9$_{Alk10}$** and **G3$_{Bn2}$** were not isolated. The synthesis and characterization of compounds 5-iodocytosine **C3**,[40] 5-iodo-*iso*cytosine **iC3**,[19] guanine **G13**,[33] 3,5-bis(dodecyloxy)benzyl chloride,[41] and 3,4,5-tris(dodecyloxy)benzyl bromide[42] has been reported elsewhere.

Synthesis of the cytosine derivatives.

5-iodocytosine (C3): C3 was synthesized according to a literature procedure[13] adapted to our molecule. Cytosine (10.0 g, 90.0 mmol), iodine (34.3 g, 135.0 mmol) and iodic acid (22.2 g, 126.0 mmol) were stirred in acetic acid (300 mL) at 40 °C overnight. Once completed, the reaction mixture was cooled and treated with $Na_2S_2O_3$ (sat) (200 mL) until a white suspension was obtained. The mixture was then neutralized with NaOH 6M (900 mL). The resulting white solid was filtered and washed with slightly basified water until the filtered water had neutral pH. **C3** was dried under reduced pressure affording 20.6 g (96% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.76 (bs, 2H, N^1*H*), 7.76 (s, 1H, *H*^{6}), 6.48 (bs, 2H, NH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4, 155.8, 149.4, 55.2 ppm. HRMS

(ESI+): Calculated for $C_4H_5N_3OI$: 237.9471 $[M+H]^+$. Found: 237.9464 $[M+H]^+$.

***Standard Procedure A* for the Nucleobase alkylation reaction.** To a suspension of the nucleobase starting material (1 eq) and a base (1.2 eq) (indicated in each case) in dry DMF (volume indicated in each case) was added dropwise the corresponding iodoalkane or benzyl bromide/chloride (1.2 eq) (indicated in each case). The mixture was stirred under argon at 40 ^{0}C for a period of time (indicated in each case) until completion, which was monitored by TLC. Work-up and purification methods are indicated in each case.

1-decyl-5-iodocytosine ($C2_{Alk10}$): $C2_{Alk10}$ was synthesized according to a literature procedure[14] adapted to our molecule. **$C2_{Alk10}$** can be obtained following *Standard Procedure A* using **C3** (10.0 g, 42.2 mmol), a 1.0 M solution in MeOH of Bu_4NOH (50.6 mL, 50.6 mmol), 1-iododecane (11.0 mL, 50.6 mmol) and DMF (150 mL). The reaction was completed in 12 h. Then, the reaction mixture was poured into 150 mL of water and the precipitated solid was filtered, washed with water and dried. The resulting solid was washed with acetonitrile affording 9.8 g of **$C2_{Alk10}$** (62% yield). **$C2_{Alk10}$** can also be obtained by stirring **$C4_{Alk10}$** (15.7 g, 62.5 mmol), iodine (10.1 g, 40.5 mmol) and iodic acid (13.2 g, 76.0 mmol) in 400 mL acetic acid at 40 °C overnight. Once completed, the reaction mixture was cooled and the unsoluble iodic acid was filtered away. The resulting mixture was extracted with ethylacetate and washed with water (3 x 400 mL), $NaHCO_3$ (sat) (3 x 400 mL), $Na_2S_2O_3$ (sat) (400 mL) and brine (400 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was washed with ether affording **$C2_{Alk10}$** as a bright beige solid; m. p. 163-165 ºC (15.8 g, 81%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.07 (s, 1H, H^6), 7.58 (bs, 1H, NH_2), 6.43 (bs, 1H, NH_2), 3.7-3.6 (m, 2H, $N^1CH_2C_9H_{19}$), 1.6-1.4 (m, 2H, $N^1CH_2CH_2C_8H_{17}$), 1.4-1.1 (m, 14H, $N^1C_2H_4C_7H_{14}CH_3$), 0.85 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 155.4, 150.9, 55.0, 50.5, 31.8, 29.5, 29.4, 29.3, 29.23, 29.17, 26.5, 22.6, 14.1 ppm. HRMS (ESI+): Calculated for $C_{14}H_{25}N_3OI$: 378.1036 $[M+H]^+$. Found: 378.1028 $[M+H]^+$.

1-hexyl-5-iodocytosine ($C2_{Alk6}$): $C2_{Alk6}$ can be obtained following *Standard Procedure A* using **C3** (5.0 g, 21.1 mmol), a 1.0 M solution in MeOH of Bu_4NOH (25 mL, 25.3 mmol), 1-iodohexane (4 mL, 25.3 mmol) and DMF (75 mL). The reaction was completed in 8 h. The reaction mixture was then poured into 75 mL of water and the precipitated solid was filtered, washed with water and dried. The resulting solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH; (50:1), affording 4.0 g of **$C2_{Alk6}$** (59% yield) as a pale solid; m. p. 165-166 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39 (bs, 1H, NH_2), 7.54 (s, 1H, H^6), 5.54 (bs, 1H, NH_2), 3.73 (m, 2H, $N^1CH_2C_5H_{11}$), 1.8-1.6 (m, 2H, $N^1CH_2CH_2C_4H_9$), 1.4-1.2 (m, 6H, $N^1C_2H_4C_3H_6CH_3$), 0.87 (t, J = 6.6 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.9, 154.6, 151.9, 55.0, 48.6, 30.8, 28.6, 25.5, 21.9, 13.8 ppm. HRMS (ESI+): Calculated for $C_{10}H_{17}N_3OI$: 322.0410 $[M+H]^+$. Found: 322.0405 $[M+H]^+$.

1-ethyl-5-iodocytosine ($C2_{Alk2}$): $C2_{Alk2}$ can be obtained following *Standard Procedure A* using **C3** (10.0 g, 42.2 mmol), a 1.0 M solution in MeOH of Bu_4NOH (50.6 mL, 50.6 mmol), 1-iododecane (11 mL, 50.6 mmol) and DMF (150 mL). The reaction was completed in 5 h. After solvent evaporation, the crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH; (20:1). A final recrystallization using acetonitrile yielded **$C2_{Alk2}$** as a white solid (2.2 g, 40%). **$C2_{Alk2}$** can also be obtained by stirring **$C4_{Alk2}$** (1.0 g, 7.2 mmol), iodine (2.8 g, 11.1 mmol) and iodic acid (1.5 g, 8.8 mmol) in 20 mL acetic acid at 40 °C. The reaction was completed in 4h. Then, the reaction mixture was cooled to room temperature and the unsoluble iodic acid was filtered away. The mixture was extracted with $CHCl_3$ and washed with water (3 x 10 mL), $NaHCO_3$ (sat) (3 x 10 mL), $Na_2S_2O_3$ (sat) (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH; (20:1), affording **$C2_{Alk2}$** as a white solid; m. p. 203-204 ºC (0.7 g, 36%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.09 (s, 1H, H^6), 7.61 (bs, 1H, NH_2), 6.46 (bs, 1H, NH_2), 3.67 (q, J = 7.0 Hz, 2H, $N^1CH_2CH_3$), 1.13 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.9, 154.4, 151.6, 55.2, 43.8, 14.5 ppm. HRMS (ESI+): Calculated for $C_6H_9N_3OI$: 265.9784 $[M+H]^+$. Found: 265.9781 $[M+H]^+$.

1-(3,5-bis(dodecyloxy)benzyl)-5-iodocytosine ($C2_{Bn2}$): Following *Standard Procedure A* for the alkylation reaction, to a suspension of **C3** (500 mg, 2.26 mmol) in dry DMF (25 mL), a 1.0 M solution of Bu_4NOH in MeOH (2.26 mL, 2.26 mmol) was added. The resulting mixture was stirred at 40 ºC for 1 h. Then 1-(chloromethyl)-3,5-bis(dodecyloxy)benzene (1.34 g, 2.72 mmol) was added and the resulting solution was stirred at 40 ºC for 16 h. Once the reaction was completed, the solvent was evaporated under reduced pressure. The crude was dissolved in CH_2Cl_2 (10 mL), washed with water (3 x 10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purificated by column cromatography eluted with $CHCl_3$/MeOH (50:1). **$C2_{Bn2}$** was obtained as a white solid; m. p. 125-127 ºC (234 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, 1H, H^6), 6.42 (d, J = 2.1 Hz, 3H, Ar-*2,4,6*), 4.89 (s, 2H, N^1CH_2), 3.91 (t, J = 6.5 Hz, 4H, OCH_2), 1.75 (p, J = 6.8 Hz, 6H, OCH_2CH_2), 1.61-1.06 (m, 36H, $OCH_2CH_2(CH_2)_9CH_3$), 1.06-0.78 (m, 6H, $O(CH_2)_{11}CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 161.0, 155.7, 150.6, 137.9, 106.9, 101.2, 77.2, 68.4, 55.8, 52.6, 32.1, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 26.2, 22.8, 14.3 ppm. HRMS (ESI+): Calculated for $C_{35}H_{59}N_3O_3I$: 696.3595 $[M+H]^+$. Found: 696.3581 $[M+H]^+$.

1-(3,4,5-tris(dodecyloxy)benzyl)-5-iodocytosine ($C2_{Bn3}$): Following *Standard Procedure A*, to a solution of **C3** (1.0 g, 4.22 mmol) in dry DMF (100 mL), a 1.0 M solution of Bu_4NOH in MeOH was added (4.22 mL, 4.22 mmol) and the mixture was stirred for 30 minutes at 50 ºC. Then, 1-(bromomethyl)-3,4,5-tris(dodecyloxy)benzene (3.36 g, 4.64 mmol) was dissolved in dry DMF (50 mL) and added *via cannula* to the solution. This solution was stirred for 12 h. After completion, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography eluted with $CHCl_3$/MeOH (20:1) to afford **$C2_{Bn3}$** as a white solid; m. p. 115-117 ºC (2.8 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.10 (bs, 1H, C^4NH-*H*), 7.48 (s, 1H, H^6), 6.46 (s, 2H, Ar-*2,4,6*), 5.65 (s, 1H, C^4NH-*H*), 4.82 (s, 2H, N^1CH_2), 3.92 (t, J = 6.3 Hz, 6H, OCH_2), 1.75 (m, 6H, OCH_2CH_2), 1.24 (m, 34H, $OCH_2CH_2(CH_2)_9CH_3$), 0.86 (m, 9H, $O(CH_2)_{11}CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.0, 155.1, 153.6, 148.3, 138.4, 130.6, 107.1, 90.2, 84.0, 77.3, 75.0, 73.4, 69.3, 52.7, 32.0, 30.4, 29.8, 29.7, 29.5, 26.17, 22.74, 14.2 ppm. HRMS (ESI$^+$) Calculated for $C_{47}H_{82}IN_3O_4$: 880.5422 $[M+H]^+$. Found: 880.5454 $[M+H]^+$.

1-(2-(tert-butylcarbamate)ethyl)-5-iodocytosine ($C2_{Am}$): A suspension of **C3** (3.0 g, 12.65 mmol) and Cs_2CO_3 (4.9 g, 15.19 mmol) in dry DMF (75 mL) was stirred at room temperature for 1.5 h. Then 2-(Boc-amino)ethylbromide (3.4 g, 15.19 mmol) diluted in dry DMF (5 mL) was added *via cannula* and the resulting suspension was stirred at room temperature for 12 h. Once the reaction was completed, the resulting solid was filtered, washed with water and dried under vacuum to afford **$C2_{Am}$** as a white solid; m. p. 231-233 ^{0}C (3.92 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (s, 1H, H^6), 7.60 (s, 1H, C^4NH-*H*), 6.85 (bs, 1H, $N^1CH_2CH_2$-N*H*),

6.43 (bs, 1H, C^4NH-*H*), 3.66 (d, *J* = 5.8 Hz, 2H, $N^1CH_2CH_2$), 3.14 (d, *J* = 5.8 Hz, 2H, $N^1CH_2CH_2$), 1.35 (s, 9H, $OC(CH_3)_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.0, 155.6, 154.6, 152.1, 55.0, 48.7, 39.5, 38.5, 28.2 ppm. HRMS (ESI$^+$) Calculated for $C_{11}H_{18}IN_4O_3$: 381.0418 [M+H]$^+$. Found: 381.0403 [M+H]$^+$.

***Standard Procedure B* for the Sonogashira coupling[41] with TMSA and subsequent alkyne-TMS group deprotection.** A dry THF/NEt_3 (4:1) solvent mixture was subjected to deoxygenation by three freeze-pump-thaw cycles with argon. Then, this solvent was added over the system containing the corresponding halogenated base (1 eq), CuI (0.01 eq) and $Pd(PPh_3)_2Cl_2$ (0.02 eq). The mixture was stirred at room temperature during a few minutes. Then, trimethylsilylacetylene (TMSA; 2 eq) was added dropwise. The reaction was stirred under argon at a given temperature for a period of time (indicated in each case) until completion, which was monitored by TLC. Then, the mixture was filtrated over celite and the solvent evaporated under vacuum. The resulting crude was placed in a round-bottomed flask equipped with a magnetic stirrer, THF was added and the mixture was stirred at room temperature until the solid was dissolved. Then, hydrated tetrabutylammonium fluoride (TBAF·$3H_2O$; 1 eq) was slowly added at 0 ºC, and the mixture was stirred at room temperature until reaction completion, which was monitored by TLC (approximately 1 hour in all cases). The solvent was evaporated at reduced pressure and the product was purified by column chromatography (eluent indicated in each case). The resulting solid was finally washed with cold acetonitrile.

1-decyl-5-ethynyl-cytosine ($C1_{Alk10}$): $C1_{Alk10}$ was prepared following *Standard Procedure B*. $C2_{Alk10}$ (10.0 g, 26.5 mmol), $Pd(PPh_3)_2Cl_2$ (372.1 mg, 0.53 mmol) and CuI (50.4 mg, 0.27 mmol) were dissolved in the THF/NEt_3 mixture (125 mL). Then TMSA (9.8 mL, 53.0 mmol) was added. The reaction was completed in 12 h. Then, TBAF·$3H_2O$ (9.2 g, 29.2 mmol) was added over a THF (130 mL) solution of the crude mixture. $C1_{Alk10}$ was purified by column chromatography on silica gel eluted with $CHCl_3$/AcOEt (20:1). A final recrystallization using acetonitrile yielded $C1_{Alk10}$ as a brown solid; m. p. 139-141 ºC (4.7 g, 65%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.05 (s, 1H, H^6), 7.50 (bs, 1H, NH_2), 6.66 (bs, 1H, NH_2), 4.30 (s, 1H, C≡C*H*), 3.7-3.6 (m, 2H, $N^1CH_2C_9H_{19}$), 1.6-1.4 (m, 2H, $N^1CH_2CH_2C_8H_{17}$), 1.3-1.1 (m, 14H, $N^1C_2H_4C_7H_{14}CH_3$), 0.85 (t, *J* = 6.6 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.9, 154.8, 148.8, 89.5, 83.7, 74.9, 50.6, 31.8, 29.4, 29.3, 29.2, 29.12, 29.10, 26.4, 22.6, 14.0 ppm. HRMS (ESI+): Calculated for $C_{16}H_{26}N_3O$: 276.2070 [M+H]$^+$. Found: 276.2079 [M+H]$^+$.

1-hexyl-5-ethynyl-cytosine ($C1_{Alk6}$): $C1_{Alk6}$ was prepared following *Standard Procedure B*. $C2_{Alk6}$ (3.7 g, 11.6 mmol), $Pd(PPh_3)_2Cl_2$ (162 mg, 0.23 mmol) and CuI (22 mg, 0.12 mmol) were dissolved in the THF/NEt_3 mixture (70 mL). Then TMSA (3.3 mL, 23.1 mmol) was added. The reaction was completed in 12 h. Then, TBAF·$3H_2O$ (3.7 g, 11.6 mmol) was added over a THF (60 mL) solution of the crude mixture. $C1_{Alk6}$ was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH; (50:1). A final recrystallization using acetonitrile yielded $C1_{Alk6}$ as an ochre solid; m. p. 163-164 ºC (2.1 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (s, 1H, H^6), 6.89 (bs, 1H, NH_2), 5.64 (bs, 1H, NH_2), 3.77 (m, 2H, $N^1CH_2C_5H_{11}$), 3.35 (s, 1H, C≡C*H*), 1.8-1.6 (m, 2H, $N^1CH_2CH_2C_4H_9$), 1.4-1.2 (m, 6H, $N^1C_2H_4C_3H_6CH_3$), 0.88 (t, *J* = 6.6 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 154.8, 149.1, 89.2, 83.7, 75.0, 50.7, 31.4, 29.2, 26.2, 22.5, 14.0 ppm. HRMS (FAB+): Calculated for $C_{12}H_{18}N_3O$: 220.1450 [M+H]$^+$. Found: 220.1445 [M+H]$^+$.

1-ethyl-5-ethynyl-cytosine ($C1_{Alk2}$): $C1_{Alk2}$ was prepared following *Standard Procedure B*. $C2_{Alk2}$ (1.5 g, 5.7 mmol), $Pd(PPh_3)_2Cl_2$ (79.5 mg, 0.11 mmol) and CuI (10.8 mg, 0.06 mmol) were dissolved in the THF/NEt_3 mixture (15 mL). Then TMSA (2 mL, 11.3 mmol) was added. The reaction was completed in 12 h. Then, TBAF·$3H_2O$ (1.8 g, 5.7 mmol) was added over a THF (50 mL) solution of the crude mixture. $C1_{Alk2}$ was purified by column chromatography on silica gel eluted with $CHCl_3$/AcOEt; (20:1). A final recrystallization using acetonitrile yielded $C1_{Alk2}$ as a white solid; m. p. 196-197 ºC (0.51 g, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (bs, 1H, NH_2), 7.55 (s, 1H, H^6), 5.76 (bs, 1H, NH_2), 3.84 (q, *J* = 7.2 Hz, 2H, $N^1CH_2CH_3$), 3.35 (s, 1H, C≡C*H*), 1.32 (t, *J* = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 154.6, 148.6, 89.7, 83.8, 74.9, 45.6, 14.6 ppm. HRMS (ESI+): Calculated for $C_8H_{10}N_3O$: 164.0818 [M+H]$^+$. Found: 164.0822 [M+H]$^+$.

1-(3,5-bis(dodecyloxy)benzyl) 5-ethynylcytosine ($C1_{Bn2}$): Following *Standard Procedure B,* $C2_{Bn2}$ (1.1 g, 1.58 mmol), CuI (0.03 mg, 0.0158 mmol) and $Pd(Ph_3)_2Cl_2$ (22 mg, 0.032 mmol) were dissolved in the THF/NEt_3 mixture (15 mL). Then, TMSA (0.6 mL, 4.74 mmol) was added and the mixture was stirred at 40 ºC overnight. Once the reaction was completed, the solvent was evaporated under reduced pressure. The residue was dissolved in THF (15 mL) and TBAF·$3H_2O$ (553 mg, 1.58 mmol) was added. Once the deprotection was completed, the solvent was removed under reduced pressure. The crude was purified by column chromatography eluted with $CHCl_3$/MeOH (100:1) and recrystallized from $CHCl_3$/MeCN. A light brown solid was obtained; m. p. 103-105 ºC (902 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (bs, 1H, C^4NH-*H*), 7.51 (s, 1H, H^{6C}), 6.40 (s, 3H, Ar-*2,4,6*), 6.20 (s, 1H, C^4NH-*H*), 4.89 (s, 2H, N^1CH_2), 3.91 (t, *J* = 6.5 Hz, 4H, OCH_2), 3.36 (s, 1H, C≡C*H*), 1.74 (dt, *J* = 8.3, 6.5 Hz, 6H, OCH_2CH_2), 1.62-1.11 (m, 36H, $OCH_2CH_2(CH_2)_9CH_3$), 1.00-0.75 (m, 6H, $O(CH_2)_{11}CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8, 161.1, 148.9, 137.1, 107.1, 101.3, 84.9, 77.3, 74.1, 68.4, 52.8, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 26.2, 22.84, 14.3 ppm. HRMS (ESI+): Calculated for $C_{37}H_{60}N_3O_3$: 594.4629 [M+H]$^+$. Found: 594.4667 [M+H]$^+$.

1-(3,4,5-tris(dodecyloxy)benzyl)-5-ethynylcytosine ($C1_{Bn3}$): Following *Standard Procedure B*, to a solution of $C2_{Bn3}$ (500 mg, 0.568 mmol), $Pd(Ph_3)_2)Cl_2$ (7.71 mg, 0.011 mmol), and CuI (1.07 mg, 0.006 mmol) in THF/NEt_3 (5 mL), TMSA (1.4 mL, 2.27 mmol) was added and the mixture stirred at 40ºC overnight. Once the reaction was completed, the solvent was evaporated, the resulting crude was suspended in THF (10 mL) and TBAF·$3H_2O$ (625 mg, 0.625 mmol) was added. After completion the solvent was evaporated and the resulting residue was purified by column chromatography eluted with $CHCl_3$/MeOH (50:1), affording $C1_{Bn3}$ (340 mg, 77%) as a pale solid; m. p. 94-96 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (s, 1H, H^6), 6.87 (bs, 1H, C^4NH-*H*), 6.49 (s, 2H, Ar-*2,6*), 5.67 (bs, 1H, C^4NH-*H*), 4.87 (s, 2H, N^1CH_2), 3.93 (td, *J* = 6.5, 2.2 Hz, 6H, OCH_2), 3.32 (s, 1H, C≡C*H*), 1.89-1.52 (m, 8H, OCH_2CH_2), 1.28 (m, 64H, $OCH_2CH_2(CH_2)_9CH_3$), 1.03-0.67 (m, 9H, $O(CH_2)_{11}CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 155.1, 153.6, 148.3, 138.4, 130.6, 107.1, 90.2, 84.0, 77.3, 75.0, 73.4, 69.3, 52.7, 32.0, 30.4, 29.8, 29.7, 29.5, 26.2, 22.7, 14.2 ppm. HRMS (ESI$^+$) Calculated for $C_{49}H_{84}N_3O_4$: 778.6456 [M+H]$^+$. Found: 778.6464 [M+H]$^+$.

1-(2-(tert-butylcarbamate)ethyl)-5-ethynylcytosine ($C1_{Am}$): Following *Standard Procedure B*, $C2_{Am}$ (3.0 g, 7.9 mmol), $Pd(PPh_3)_2Cl_2$ (140 mg, 0.2 mmol) and CuI (20 mg, 0.1 mmol) were dissolved in the THF/NEt_3 mixture. TMSA (3.4 mL, 23.9 mmol) was added and the mixture heated at 40 ºC for 12 h. After completion, the solvent was evaporated. The resulting crude and TBAF·$3H_2O$ (2.7 g, 8.9 mmol) were dissolved in a 1:1 CH_2Cl_2/THF

mixture and stirred at room temperature for 1 h until the reaction was completed. The solvent was then evaporated under reduced pressure. The resulting solid was purified by column chromatography eluted with $CHCl_3$/MeOH (20:1) to afford **C1$_{Am}$** as a light brown solid; m. p. 205-206 ^{0}C (1.57 g, 71%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.77 (s, 1H, H^6), 7.51 (bs, 1H, C^{4}NH-H), 6.85 (bs, 1H, N^{1}CH$_2$CH$_2$-NH), 6.64 (bs, 1H, C^{4}NH-H), 4.30 (s, 1H, C≡CH), 3.69 (m, 2H, N^{1}CH_2CH$_2$), 3.16 (m, 3H, N^{1}CH$_2$CH_2), 1.34 (s, 9H, OC(CH_3)$_3$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.6, 155.6, 154.0, 150.5, 87.7, 85.6, 77.8, 75.9, 49.1, 28.1, 1.9 ppm. HRMS (FAB$^+$): Calculated for $C_{13}H_{18}N_4O_3$: 279.1457 [M+H]$^+$. Found: 279.1457 [M+H]$^+$.

1-decyl-cytosine (C4$_{Alk10}$): C4$_{Alk10}$ was synthesized according to a literature procedure[14] adapted to our molecule. **C4$_{Alk10}$** was obtained following *Standard Procedure A* using cytosine (10.0 g, 90 mmol), a 1.0 M solution in MeOH of Bu_4NOH (108 mL, 108 mmol), 1-iododecane (19 mL, 108 mmol) and DMF (500 mL). The reaction was completed in 12 h. Then, the reaction mixture was poured into 150 mL of water and the precipitated solid was filtered, washed with water and dried. The resulting solid was washed with acetonitrile affording 15.8 g (70% yield) of a pale solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.54 (d, J = 7.0 Hz, 1H, H^6), 6.91 (bs, 2H, NH_2), 5.61 (d, J = 7.0 Hz, 1H, H^5), 3.59 (m, 2H, N^{1}CH_2C$_9$H$_{19}$), 1.53 (m, 2H, N^{1}CH$_2$CH_2C$_8$H$_{17}$), 1.3-1.1 (m, 14H, N^{1}C$_2$H$_4$C$_7$$H_{14}CH_3$), 0.85 (t, 3H, C$H_3$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.8, 155.8, 146.0, 93.0, 48.6, 38.5, 31.2, 28.9, 28.6, 25.9, 22.0, 13.9 ppm. HRMS (ESI+): Calculated for $C_{14}H_{26}N_3O$: 252.2070 [M+H]$^+$. Found: 252.2082 [M+H]$^+$.

1-ethyl-cytosine (C4$_{Alk2}$): C4$_{Alk2}$ was obtained following *Standard Procedure A* using cytosine (5.0 g, 45 mmol), a 1.0 M solution in MeOH of Bu_4NOH (54 mL, 54 mmol), 1-iodoethane (4.5 mL, 54 mmol) and DMF (150 mL). The reaction was completed in 12 h. After solvent evaporation, the crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (20:1). A final recrystallization using acetonitrile yielded **C4$_{Alk2}$** as a white solid (1.2 g, 19%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.59 (d, J = 7.0 Hz, 1H, H^6), 7.02 (bs, 2H, NH_2), 5.64 (d, J = 7.0 Hz, 1H, H^5), 3.65 (q, J = 7.0 Hz, 2H, N^{1}CH_2CH$_3$), 1.13 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.5, 155.2, 145.9, 93.3, 43.7, 14.5 ppm. HRMS (ESI+): Calculated for $C_6H_{10}N_3O$: 140.0818 [M+H]$^+$. Found: 140.0813 [M+H]$^+$.

Synthesis of the uracil derivatives.

1-decyl-5-iodouracil (U2$_{Alk10}$): U2$_{Alk10}$ was obtained following *Standard Procedure A* using 5-iodouracil (5.0 g, 21 mmol), Cs_2CO_3 (8.2 g, 25.2 mmol), 1-iododecane (5.4 mL, 25.2 mmol) and DMF (100 mL). The reaction was completed in 4 h. After solvent evaporation, the crude was dissolved in $CHCl_3$ (200 mL) and washed with water (3 x 100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (200:1). **U2$_{Alk10}$** was obtained as a white solid; m. p. 148-149 ºC (3.6 g, 45%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.58 (bs, 1H, N^3H), 8.20 (s, 1H, H^6), 3.64 (t, J = 6.9 Hz, 2H, N^{1}CH_2C$_9$H$_{19}$), 1.55 (m, 2H, N^{1}CH$_2$CH_2C$_8$H$_{17}$), 1.3-1.1 (m, 14H, N^{1}C$_2$H$_4$C$_7$$H_{14}CH_3$), 0.85 (t, J = 6.9 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.8, 150.7, 150.0, 67.5, 49.1, 31.7, 29.3, 29.2, 29.1, 29.00, 28.96, 26.2, 22.5, 13.5 ppm. HRMS (FAB+): Calculated for $C_{14}H_{24}N_2O_2I$: 379.0883 [M+H]$^+$. Found: 379.0881 [M+H]$^+$.

1-hexyl-5-iodouracil (U2$_{Alk6}$): U2$_{Alk6}$ was obtained following *Standard Procedure A* using 5-iodouracil (3.0 g, 12.6 mmol), Cs_2CO_3 (4.9 g, 15.1 mmol), 1-iodohexane (2.2 mL, 15.1 mmol) and DMF (200 mL). The reaction was completed in 4 h. After solvent evaporation, the crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (200:1). **U2$_{Alk6}$** was obtained as a white solid (0.64 g, 16%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (bs, 1H, N^3H), 7.60 (s, 1H, H^6), 3.73 (t, J = 7.4 Hz, 2H, N^{1}CH_2C$_5$H$_{11}$), 1.7-1.6 (m, 2H, N^{1}CH$_2$CH_2C$_4$H$_9$), 1.3-1.2 (m, 6H, N^{1}C$_2$H$_4$C$_3$$H_6CH_3$), 0.90 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 154.3, 148.9, 67.3, 49.2, 31.2, 29.1, 26.0, 22.4, 13.9 ppm. HRMS (ESI+): Calculated for $C_{10}H_{16}N_2O_2I$: 323.0251 [M+H]$^+$. Found: 323.0249 [M+H]$^+$.

1-decyl-5-ethynyl-uracil (U1$_{Alk10}$): U1$_{Alk10}$ was prepared following *Standard Procedure B*. **U2$_{Alk10}$** (3.2 g, 8.4 mmol), $Pd(PPh_3)_2Cl_2$ (117.6 mg, 0.17 mmol) and CuI (15.9 mg, 0.08 mmol) were dissolved in the THF/NEt_3 mixture (60 mL). Then TMSA (3.1 mL, 16.8 mmol) was added. The reaction was completed in 12 h. Then, TBAF·3H_2O (2.7 g, 8.4 mmol) was added over a THF (60 mL) solution of the crude mixture. **U1$_{Alk10}$** was purified by column chromatography on silica gel eluted with hexane/AcOEt; (4:1) affording **U1$_{Alk10}$** as a white solid (461 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (bs, 1H, N^3H), 7.49 (s, 1H, H^6), 3.74 (t, J = 6.7 Hz, 2H, N^{1}CH_2C$_9$H$_{19}$), 3.21 (s, 1H, C≡CH), 1.8-1.6 (m, 2H, N^{1}CH$_2$CH_2C$_8$H$_{17}$), 1.3-1.2 (m, 14H, N^{1}C$_2$H$_4$C$_7$$H_{14}CH_3$), 0.88 (t, J = 6.7 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.6, 149.5, 148.0, 98.7, 82.1, 74.4, 49.4, 31.8, 29.7, 29.44, 29.37, 29.2, 29.1, 26.3, 22.6, 14.1 ppm. HRMS (ESI+): Calculated for $C_{16}H_{25}N_2O_2$: 277.1910 [M+H]$^+$. Found: 277.1910 [M+H]$^+$. Calculated for $C_{16}H_{24}N_2O_2Na$: 299.1729 [M+H]$^+$. Found: 299.1750 [M+H]$^+$.

1-hexyl-5-ethynyl-uracil (U1$_{Alk6}$): U1$_{Alk6}$ was prepared following *Standard Procedure B*. **U2$_{Alk6}$** (0.64 g, 2.0 mmol), $Pd(PPh_3)_2Cl_2$ (27.9 mg, 0.04 mmol) and CuI (3.8 mg, 0.02 mmol) were dissolved in the THF/NEt_3 mixture (20 mL). Then TMSA (0.6 mL, 4.0 mmol) was added. The reaction was completed in 8 h. Then, TBAF·3H_2O (0.6 g, 2.0 mmol) was added over a THF (15 mL) solution of the crude mixture. **U1$_{Alk6}$** was purified by column chromatography on silica gel eluted with $CHCl_3$/hexane; (100:1) affording **U1$_{Alk6}$** as a white solid; m. p. 149-151 ºC (216 mg, 49%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (bs, 1H, N^3H), 7.49 (s, 1H, H^6), 3.74 (t, J = 7.0 Hz, 2H, N^{1}CH_2C$_5$H$_{11}$), 3.21 (s, 1H, C≡CH), 1.8-1.6 (m, 2H, N^{1}CH$_2$CH_2C$_4$H$_9$), 1.4-1.2 (m, 6H, N^{1}C$_2$H$_4$C$_3$$H_6CH_3$), 0.89 (t, J = 6.7 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.9, 149.8, 148.1, 98.7, 82.1, 74.5, 49.4, 31.2, 29.0, 26.0, 22.4, 13.9 ppm. HRMS (ESI+): Calculated for $C_{12}H_{17}N_2O_2$: 221.1284 [M+H]$^+$. Found: 221.1281 [M+H]$^+$.

Synthesis of the *iso*cytosine derivatives.

5-iodoisocytosine (iC3):[19] Isocytosine (1.0 g, 9.0 mmol) was suspended in a 1:1 AcOH/H_2O mixture (35 mL). The reaction mixture was stirred at 50 ºC for 15 minutes. Then *N*-iodosuccinimide (2.4 g, 10.8 mmol) was added and the mixture was stirred at 100 ºC for 2 hours. Once completed, the reaction mixture was cooled to room temperature and the resulting cream-colored solid was filtered and washed with water, affording 1.7 g of **iC3** (81% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.26 (bs, 1H, N^3H). 7.93 (s, 1H, H^6); 6.71 (bs, 2H, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.5, 159.6, 156.6, 71.0 ppm. HRMS (ESI+): Calculated for $C_4H_5N_3OI$: 237.9471 [M+H]$^+$. Found: 237.9464 [M+H]$^+$.

1-ethyl-5-iodoisocytosine (iC2$_{Alk2}$): iC2$_{Alk2}$ was obtained following *Standard Procedure A* using **iC3** (1.7 g, 7.3 mmol), a 1.0 M solution in MeOH of Bu_4NOH (8.8 mL, 8.8 mmol), 1-iodoethane (0.72 mL, 8.8 mmol) and DMF (30 mL). The resulting solution was stirred at room temperature for 2 hours until completion. After solvent evaporation, the crude was dissolved in $CHCl_3$ (40 mL) and washed with water (3 x 20 mL) and brine

(20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (100:1). A final recrystallization using acetonitrile yielded **iC2$_{Alk2}$** as a white solid; m. p. 181-182 ºC (0.67 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (s, 1H, H^6), 5.19 (bs, 2H, NH_2), 4.06 (q, J = 7.3 Hz, 2H, N^{1}CH_2CH$_3$), 1.35 (t, J = 7.3 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 158.9, 155.2, 38.5, 29.7, 12.1 ppm. HRMS (ESI+): Calculated for $C_6H_9N_3OI$: 265.9784 $[M+H]^+$. Found: 265.9786 $[M+H]^+$.

***Standard Procedure C* for the carbonyl group protection of the guanine derivatives.** In a double neck round-bottomed flask, equipped with a basic reflux set-up and a magnetic stirrer, activated NaH (4 eq) was placed under argon. Dry solvent (indicated in each case) was added and the mixture was stirred. Then, 2-trimethylsilylethanol (2 eq) was added dropwise and the mixture was stirred under reflux for 2.5 hours. The mixture was then allowed to cool down to room temperature and the nucleobase (1 eq) was added carefully. The resulting mixture was stirred under reflux overnight until the reaction was completed, which was monitored by TLC. Work-up and purification methods are indicated in each case.

Synthesis of the guanine derivatives.

2-amino-6-(2-(trimethylsilyl)ethoxy)-purine (G7):[29] **G7** was prepared following *Standard Procedure C* using NaH (118.3 mmol, 2.8 g) and dry dioxane (125 mL). Then, 2-trimethylsilylethanol (8.5 mL, 59.2 mmol) was added dropwise. Later, 2-amino-6-chloropurine (5.0 g, 29.6 mmol) was added. The reaction was completed overnight. The reaction mixture was concentrated in vacuo, dissolved in water (100 mL) and washed with ether (2 x 50 mL). Acetic acid was added to the aqueous phase until pH 6 and the resulting solid was filtered. The crude solid was dried and passed through a silica plug eluted with $CHCl_3$/MeOH (10:1). A final recrystallization in MeOH/water afforded **G7** as a white solid; m. p. 184-185 ^{0}C (2.9 g, 48% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.36 (bs, 1H, N^9*H*), 7.77 (s, 1H, H^8), 6.15 (bs, 2H, NH_2), 4.49 (t, J = 7.0 Hz, 2H, OCH_2CH$_2$TMS), 1.13 (t, J = 7.0 Hz, 2H, OCH$_2$CH_2TMS), 0.07 (s, 9H, Si(CH_3)$_3$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.9, 159.6, 156.0, 138.4, 113.0, 63.3, 17.1, -1.3 ppm. HRMS (ESI+): Calculated for $C_{10}H_{18}N_5OSi$: 252.1275 $[M+H]^+$. Found: 252.1299 $[M+H]^+$.

***Standard Procedure D* for the bromination reaction of the purine derivatives.** To a solution of the nucleobase (1 eq) in a solvent (indicated in each case), NBS (1.1 eq) was added over a period of time (indicated in each case). The reaction mixture was stirred for a period of time (indicated in each case) at room temperature until the reaction was completed, which was monitored by TLC. Work-up and purification methods are indicated in each case.

2-amino-8-bromo-6-(2-(trimethylsilyl)ethoxy)-purine (G6): G6 was prepared following *Standard Procedure D*. **G7** (0.10 g, 0.4 mmol) was dissolved in acetonitrile (3 mL) and NBS (0.08 g, 0.4 mmol) was added over a period of 30 min. The reaction was completed in 3 h. The mixture was then filtered through a filter paper and the filtrate was concentrated under reduced pressure. The crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (50:1), affording 40 mg of **G6** as a yellow solid (35% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.09 (bs, 1H, N^9*H*), 6.33 (bs, 2H, NH_2), 4.47 (t, J = 7.0 Hz, 2H, OCH_2CH$_2$TMS), 1.11 (t, J = 7.0 Hz, 2H, OCH$_2$CH_2TMS), 0.06 (s, 9H, Si(CH_3)$_3$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.5, 159.8, 156.1, 121.5, 114.7, 63.6, 40.4, 17.0, -1.3 ppm. HRMS (ESI+): Calculated for $C_{10}H_{17}N_5OSiBr$: 330.0380 $[M+H]^+$. Found: 330.0395 $[M+H]^+$.

2-amino-6-chloro-9-decyl-purine (G5$_{Alk10}$): G5$_{Alk10}$ was obtained following *Standard Procedure A* using 2-amino-6-chloropurine (8.0 g, 47 mmol), K_2CO_3 (7.8 g, 56.4 mmol), 1-iododecane (12 mL, 56.4 mmol) and DMF (110 mL). After solvent evaporation, the crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (50:1). **G5$_{Alk10}$** was obtained as a white solid (12.4 g, 85%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.13 (s, 1H, N^8*H*), 6.87 (bs, 2H, C^{2}NH_2), 4.02 (t, J = 7.0 Hz, 2H, N^{9}CH_2C$_9$H$_{19}$), 1.8-1.6 (m, 2H, N^{9}CH$_2$CH_2C$_8$H$_{17}$), 1.3-1.1 (m, 14H, N^{9}C$_2$H$_4$C$_7H_{14}$CH$_3$), 0.84 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.7, 154.0, 149.3, 143.2, 123.4, 43.0, 31.2, 28.9, 28.8, 28.6, 28.4, 25.9, 22.0, 13.9 ppm. HRMS (ESI+): Calculated for $C_{15}H_{25}N_5Cl$: 310.1793 $[M+H]^+$. Found: 310.1801 $[M+H]^+$.

2-amino-6-chloro-9-ethyl-purine (G5$_{Alk2}$):[26] **G5$_{Alk2}$** was obtained following *Standard Procedure A* using 2-amino-6-chloropurine (3.0 g, 17.7 mmol), K_2CO_3 (2.9 g, 21.2 mmol), 1-iodoethane (1.7 mL, 21.2 mmol) and DMF (60 mL). After solvent evaporation, the crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (50:1). **G5$_{Alk2}$** was obtained as a white solid (2.6 g, 74%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.14 (s, 1H, N^8*H*), 6.91 (bs, 2H, C^{2}NH_2), 4.07 (q, J = 7.3 Hz, 2H, N^{9}CH_2CH$_3$), 1.36 (t, J = 7.3 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.7, 153.9, 149.3, 142.9, 123.4, 38.2, 14.9 ppm. HRMS (ESI+): Calculated for $C_7H_9N_5Cl$: 198.0540 $[M+H]^+$. Found: 198.0542 $[M+H]^+$.

2-amino-9-(3,4,5-tris(dodecyloxy)benzyl)-6-chloro-purine (G5$_{Bn3}$): A suspension of 2-amino-6-chloropurine (2.0 g, 11.79 mmol) and K_2CO_3 (1.9 g, 14.15 mmol) in dry DMF (130 mL) was stirred at 40 ºC for 30 min. Then 1-(bromomethyl)-3,4,5-tris(dodecyloxy)benzene (10.3 g, 14.15 mmol) was added and the mixture was heated at 40 ºC overnight. The solvent was removed under reduced pressure and the crude was purified by column chromatography eluted with cyclohexane/AcOEt (4:1), obtaining **G5$_{Bn3}$** as a white solid; m. p. 92-94 ^{0}C (4.6 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (bs, 1H, H^8), 6.43 (s, 2H, Ar-2,6), 5.34 (bs, 2H, C^{2}NH_2), 5.10 (s, 2H, N^{9}CH_2), 3.90 (q, J = 7.0 Hz, 6H, OCH_2), 1.72 (m, 6H, OCH$_2$CH_2), 1.55-1.05 (m, 60H, OCH$_2$CH$_2$(CH_2)$_9$CH$_3$), 0.86 (t, J = 6.6 Hz, 9H, O(CH$_2$)$_{11}$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 154.0, 153.7, 151.4, 142.3, 138.5, 129.9, 125.2, 106.6, 77.2, 73.6, 69.4, 47.6, 32.0, 30.4, 29.84, 29.80, 29.74, 29.52, 29.47, 26.2, 22.8, 14.2 ppm. HRMS (ESI+): Calculated for $C_{48}H_{83}ClN_5O_3$: 812.6178 $[M+H]^+$. Found: 812.6206 $[M+H]^+$.

2-amino-9-decyl-6-(2-(trimethylsilyl)ethoxy)-purine (G4$_{Alk10}$):[30] **G4$_{Alk10}$** can be obtained following *Standard Procedure A* using **G7** (1.5 g, 6.0 mmol), K_2CO_3 (1.0 g, 7.2 mmol), 1-iododecane (1.5 mL, 7.2 mmol) and DMF (20 mL). The reaction was completed in 8 h. After solvent evaporation, the crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (100:1). **G4$_{Alk10}$** was obtained as a white solid (0.97 g, 42%). **G4$_{Alk10}$** can also be obtained following *Standard Procedure C* using NaH (0.19 g, 0.7 mmol) and 2-trimethylsilylethanol (0.15 mL, 1.0 mmol) in dry THF (5 mL). Then, **G5$_{Alk10}$** (0.16 g, 0.5 mmol) was added. The reaction was completed overnight. The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (20 mL) and washed with water (3 x 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/hexane (5:1), affording **G4$_{Alk10}$** as a white solid (71 mg, 35% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.82 (s, 1H, H^8), 6.28 (bs, 2H, NH_2), 4.49 (m, 2H, OCH_2CH$_2$TMS), 3.97 (t, J = 7.2 Hz, 2H, N^{9}CH_2C$_9$H$_{19}$), 1.8-

1.6 (m, 2H, $N^9CH_2CH_2C_8H_{17}$), 1.3-1.1 (m, 2H, $N^9C_2H_4C_7H_{14}CH_3$), 1.1-1.0 (m, 2H, OCH_2CH_2TMS), 0.84 (t, *J* = 7.1 Hz, 3H, CH_3), 0.06 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 161.4, 159.2, 153.9, 139.1, 115.8, 64.8, 43.5, 31.8, 29.8, 29.44, 29.40, 29.2, 29.0, 26.6, 22.6, 17.6, 14.0, 1.41 ppm. HRMS (ESI+): Calculated for $C_{20}H_{38}N_5OSi$: 392.2840 $[M+H]^+$. Found: 392.2849 $[M+H]^+$.

2-amino-6-(2-(trimethylsilyl)ethoxy)-9-ethyl-purine ($G4_{Alk2}$):[30] **$G4_{Alk2}$** can be obtained following *Standard Procedure A* using **G7** (1.0 g, 3.9 mmol), K_2CO_3 (0.6 g, 4.7 mmol), 1-iodoethane (0.4 mL, 4.7 mmol) and DMF (20 mL). The reaction was completed in 8 h. After solvent evaporation, the crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (50:1). **$G4_{Alk2}$** was obtained as a white solid (0.35 g, 32%). **$G4_{Alk2}$** can also be obtained following *Standard Procedure C* using NaH (0.86 g, 35.8 mmol) and 2-trimethylsilylethanol (2.6 mL, 17.9 mmol) in dry THF (50 mL). Then, **$G5_{Alk2}$** (1.77 g, 9.0 mmol) was added. The reaction was completed overnight. The reaction mixture was concentrated *in vacuo*, dissolved in $CHCl_3$ (50 mL), washed with ether (30 mL) and then with water (3 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/hexane (100:1), affording **$G4_{Alk2}$** as a white solid (633 mg, 25% yield). ^1H NMR (300 MHz, $CDCl_3$): *δ* = 7.60 (s, 1H, H^8), 4.77 (bs, 2H, NH_2), 4.6-4.5 (m, 2H, OCH_2CH_2TMS), 4.10 (q, *J* = 7.0 Hz, 2H, $N^9CH_2CH_3$), 1.48 (t, *J* = 7.0 Hz, 3H, CH_3), 1.3-1.2 (m, 2H, OCH_2CH_2TMS), 0.09 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 162.6, 160.9, 155.0, 140.0, 116.8, 66.0, 39.7, 18.9, 16.7, 0.0 ppm. HRMS (ESI+): Calculated for $C_{12}H_{22}N_5OSi$: 280.1588 $[M+H]^+$. Found: 280.1586 $[M+H]^+$.

2-amino-6-(2-(trimethylsilyl)ethoxy)-9-(3,4,5-tris(dodecyloxy)benzyl)-purine ($G4_{Bn3}$): $G4_{Bn3}$ was obtained following *Standard Procedure A* using NaH (800 mg, 33.37 mmol), 2-(trymethylsilyl)ethanol (1.2 mL, 8.14 mmol) and **$G5_{Bn3}$** (3.4 g, 4.17 mmol) in dry dioxane (60 mL). The mixture was refluxed overnight until the reaction was completed. The resulting mixture was concentrated *in vacuo* and purified by column chromatography on silica gel eluted with cyclohexane/AcOEt (4:1), affording **$G4_{Bn3}$** as a white solid (2.23 g, 62%). ^1H NMR (300 MHz, $CDCl_3$): *δ* = 7.55 (s, 1H, H^8), 6.45 (s, 2H, Ar-*2,6*), 5.12 (s, 2H, N^9CH_2), 5.02 (bs, 2H, C^2NH_2), 4.74-4.39 (m, 2H, C^6OCH_2), 4.03-3.68 (m, 6H, OCH_2), 1.88-1.55 (m, 6H, OCH_2CH_2), 1.56-1.11 (m, 62H, $OCH_2CH_2(CH_2)_9CH_3$), 1.01-0.77 (m, 9H, $O(CH_2)_{11}CH_3$), 0.09 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 161.7, 159.6, 139.2, 138.3, 130.8, 115.8, 106.5, 77.2, 73.6, 69.4, 65.1, 47.2, 32.1, 30.5, 29.84, 29.78, 29.5, 26.2, 22.8, 17.8, 14.2, -1.3 ppm. HRMS (ESI+): Calculated for $C_{53}H_{96}N_5O_4Si$: 894.7226 $[M+H]^+$. Found: 894.7217 $[M+H]^+$.

2-amino-8-bromo-9-decyl-6-(2-(trimethylsilyl)ethoxy)-purine ($G3_{Alk10}$): $G3_{Alk10}$ was obtained following *Standard Procedure D* using **$G4_{Alk10}$** (0.63 g, 2.3 mmol) in CCl_4 (10 mL) and NBS (0.44 g, 2.5 mmol), added over a period of 30 min. The reaction mixture was completed 3 h. The crude mixture was filtered through a filter paper and the filtrate was concentrated under reduced pressure. The crude solid was then purified by column chromatography on silica gel eluted with $CHCl_3$/hexane (100:1), affording 0.87 g of **$G3_{Alk10}$** (80% yield). ^1H NMR (300 MHz, DMSO-d_6): *δ* = 6.48 (bs, 2H, NH_2), 4.48 (m, 2H, OCH_2CH_2TMS), 3.97 (t, *J* = 7.2 Hz, 2H, $N^9CH_2C_9H_{19}$), 1.8-1.6 (m, 2H, $OCH_2CH_2C_8H_{17}$), 1.4-1.1 (m, 14H, $OC_2H_4C_7H_{14}CH_3$), 1.1-1.0 (m, 2H, OCH_2CH_2TMS), 0.84 (t, *J* = 6.7 Hz, 3H, $N^9C_9H_{19}CH_3$), 0.06 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 160.1, 159.0, 154.7, 135.2, 116.0, 65.0, 44.1, 31.9, 29.7, 29.5, 29.4, 29.3, 29.1, 26.5, 22.7, 17.6, 14.1, 1.42 ppm. HRMS (ESI+): Calculated for $C_{20}H_{37}N_5OSiBr$: 470.1945 $[M+H]^+$. Found: 470.1941 $[M+H]^+$.

2-amino-8-bromo-6-(2-(trimethylsilyl)ethoxy)-9-ethyl-purine ($G3_{Alk2}$): $G3_{Alk2}$ was obtained following *Standard Procedure D* using **$G4_{Alk2}$** (0.63 g, 2.3 mmol) in CCl_4 (10 mL) and NBS (0.44 g, 2.5 mmol), added over a period of 30 min. The reaction mixture was completed in 4 h. The crude mixture was filtered through a filter paper and the filtrate was concentrated under reduced pressure. The crude solid was then purified by column chromatography on silica gel eluted with $CHCl_3$/hexane (100:1), affording 0.60 g of **$G3_{Alk2}$** as a white solid (72% yield). ^1H NMR (300 MHz, DMSO-d_6): *δ* = 6.48 (bs, 2H, NH_2), 4.48 (m, 2H, OCH_2CH_2TMS), 4.02 (q, *J* = 7.1 Hz, 2H, $N^9CH_2CH_3$), 1.26 (t, *J* = 7.2 Hz, 3H, CH_3), 1.11 (m, 2H, OCH_2CH_2TMS), 0.06 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 159.8, 159.2, 154.5, 123.7, 114.1, 63.8, 55.6, 17.0, 14.4, -1.3 ppm. HRMS (ESI+): Calculated for $C_{12}H_{21}N_5OSiBr$: 358.0693 $[M+H]^+$. Found: 358.0693 $[M+H]^+$.

***Standard Procedure E* for the iodination reaction of the guanine derivatives.** To a solution of the nucleobase (1 eq) in THF (volume indicated in each case) was added a solution of LDA freshly prepared from diisopropylamine (7.5 eq) and *n*BuLi (2,5 M, 5.0 eq) in THF (volume indicated in each case) at -78 °C. After 4 h, a solution of I_2 (3.0 eq) in THF (volume indicated in each case) was added and the mixture was stirred at -78 °C until the reaction was completed, which was monitored by TLC. The mixture was left to warm up to 0 °C, followed by hydrolysis with NH_4Cl (sat). The water phase was separated and extracted with DCM. The combined organic layers were concentrated under reduced pressure, dissolved in DCM and washed with $Na_2S_2O_3$ (sat), $NaHCO_3$ (sat) and brine. The organic layer was then dried over $MgSO_4$ and concentrated in vacuo. Purification methods are indicated in each case.

2-amino-8-iodo-6-(2-(trimethylsilyl)ethoxy)-9-(3,4,5-tris(dodecyloxy)benzyl)-purine ($G2_{Bn3}$): Following *Standard Procedure E*, LDA was prepared from diisopropyl amine (1.6 mL, 11.82 mmol) and a 2.5 M *n*BuLi solution in THF (7.88 mL, 7.88 mmol) in THF (21 mL). The mixture was stirred at 0 ºC for 45 min, cooled at -78 ºC and then, a solution of **$G4_{Bn3}$** (1.41 g, 1.58 mmol) in THF (21 mL) was added *via cannula*. The resulting mixture was stirred at -78 ºC for 5 h. A solution of I_2 (1.19 g, 4.7 mmol) in THF (10 mL) was added. Once the reaction was completed, saturated NH_4Cl (10 mL) was added to the mixture and the system was allowed to slowly reach room temperature. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layer was washed with $Na_2S_2O_3$ (sat) (1 x 30mL), $NaHCO_3$ (sat) (1 x 30 mL) and brine (1 x 30 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The resulting solid was purified by column chromatography eluted with cyclohexane/AcOEt (5:1) to afford **$G2_{Bn3}$** as a white solid; m. p. 77-79 ^{0}C (977 mg, 60%). ^1H NMR (300 MHz $CDCl_3$): *δ* = 6.46 (s, 2H, Ar-*2,6*), 5.07 (s, 2H, N^9CH_2), 5.00 (s, 2H, C^2NH_2), 4.59-4.43 (m, 2H, C^6OCH_2), 4.01-3.72 (m, 6H, OCH_2), 1.70 (q, *J* = 6.9 Hz, 6H, OCH_2CH_2), 1.24 (d, *J* = 5.8 Hz, 63H, $OCH_2CH_2(CH_2)_9CH_3$), 0.99-0.73 (m, 9H, $O(CH_2)_{11}CH_3$), 0.05 (d, *J* = 1.3 Hz, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 160.0, 159.3, 155.0, 153.2, 137.9, 130.5, 118.5, 106.2, 97.0, 73.3, 69.1, 65.0, 48.5, 31.9, 30.3, 29.68, 29.65, 29.62, 29.60, 29.58, 29.59, 29.53, 29.4, 29.3, 26.0, 22.6, 17.6, 14.0, -1.5 ppm. HRMS (ESI+): Calculated for $C_{53}H_{94}IN_5O_4Si$: 1020.6192 $[M^*+H]^+$. Found: 1020.6210 $[M^*+H]^+$.

9-decyl-8-ethynyl-guanine ($G1_{Alk10}$): $G1_{Alk10}$ was prepared following *Standard Procedure B*. **$G3_{Alk10}$** (2.3 g, 4.9 mmol), $Pd(PPh_3)_2Cl_2$ (68.6 mg, 0.10 mmol) and CuI (9.3 mg, 0.05 mmol) were dissolved in the THF/NEt_3 mixture (20 mL). Then TMSA (1.80 mL, 9.8 mmol) was added. The reaction was completed in 12 h. Then, the reaction mixture was

concentrated under reduced pressure, dissolved in THF (30 mL) and TBAF·3H_2O (3.4 g, 10.8 mmol) was added. After solvent evaporation the dark brown oil was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (30:1). **G1$_{Alk10}$** was obtained as a light yellow solid; m. p. > 250 ºC (1.1 g, 70%). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): *δ* = 10.68 (bs, 1H, N^1*H*), 6.59 (bs, 2H, N*H*$_2$), 4.70 (s, 1H, C≡C*H*), 3.97 (t, *J* = 6.9 Hz, 2H, N^{9}C*H*$_2$C$_9$H$_{19}$), 1.8-1.6 (m, 2H, N^{9}CH$_2$C*H*$_2$C$_8$H$_{17}$), 1.3-1.1 (m, 14H, N^{9}C$_2$H$_4$C$_7$*H*$_{14}$CH$_3$), 0.83 (t, *J* = 6.9 Hz, 3H, C*H*$_3$) ppm. ^{13}C NMR (75 MHz, DMSO-*d*$_6$): *δ* = 156.2, 84.8, 73.6, 42.7, 31.2, 28.85, 28.78, 28.6, 28.4, 25.8, 22.0, 13.9 ppm. HRMS (ESI+): Calculated for $C_{17}H_{26}N_5O$: 316.2131 $[M+H]^+$. Found: 316.2146 $[M+H]^+$.

9-ethyl-8-ethynyl-guanine (G1$_{Alk2}$): G1$_{Alk2}$ was prepared following *Standard Procedure B*. **G3$_{Alk2}$** (0.57 g, 1.6 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (22.0 mg, 0.03 mmol) and CuI (3.0 mg, 0.02 mmol) were dissolved in the THF/NEt_3 mixture (15 mL). Then TMSA (0.6 mL, 3.2 mmol) was added. The reaction was completed in 8 h. Then, the reaction mixture was concentrated under reduced pressure, dissolved in THF (20 mL) and TBAF·3H_2O (1.1 g, 3.5 mmol) was added. After solvent evaporation the dark brown oil was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (10:1). **G1$_{Alk2}$** was obtained as a light yellow solid; m. p. > 250 ºC (270 mg, 83%). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): *δ* = 10.71 (bs, 2H, N*H*^{1}), 6.61 (bs, 2H, N*H*$_2$), 4.71 (s, 1H, C≡C*H*), 4.01 (q, *J* = 7.0 Hz, 2H, N^{9}C*H*$_2$CH$_3$), 1.27 (t, *J* = 7.0 Hz, 3H, C*H*$_3$) ppm. ^{13}C NMR (75 MHz, DMSO-*d*$_6$): *δ* = 156.2, 154.2, 150.7, 128.8, 116.5, 84.8, 73.4, 37.7, 14.8. HRMS (ESI+): Calculated for $C_9H_{10}N_5O$: 204.0879 $[M+H]^+$. Found: 204.0878 $[M+H]^+$.

9-(3,4,5-tris(dodecyloxy)benzyl)-8-ethynyl-guanine (G1$_{Bn3}$): G1$_{Bn3}$ was prepared following *Standard Procedure B* for a Sonogashira coupling reaction. **G2$_{Bn3}$** (977 mg, 0.95 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (13.3 mg, 0.019 mmol) and CuI (1.8 mg, 0.0095 mmol) were dissolved in the THF/NEt_3 mixture (10 mL). Then TMSA (0.7 mL, 0.67 mmol) was added and the mixture was stirred at 40 ºC for 24 h. Once the reaction was completed, the solvent was evaporated *in vacuo*. TBAF·3H_2O (659 mg, 2.09 mmol) was added over a solution of the crude in THF (10 mL). The residue was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (100:1). A final recrystallization using $CHCl_3$/MeCN yielded **G1$_{Bn3}$** as a light brown solid; m. p. 148-149 ^{0}C (598 mg,77%). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 11.81 (bs, 1H, N^1*H*), 6.64 (bs, 2H, C^{2}NH-*H*), 6.54 (s, 2H, Ar-*2,6*), 5.13 (s, 2H, N^{9}CH$_2$), 3.89 (t, *J* = 6.4 Hz, 6H, OC*H*$_2$), 3.37 (s, 1H, C≡C*H*), 1.72 (m, 6H, OCH$_2$C*H*$_2$), 1.54-1.07 (m, 60H, OCH$_2$CH$_2$(C*H*$_2$)$_9$CH$_3$), 0.87 (td, *J* = 6.7, 2.1 Hz, 9H, O(CH$_2$)$_{11}$C*H*$_3$) ppm. ^{13}C NMR (76 MHz, CDCl3): δ = 154.6, 153.3, 138.1, 130.9, 106.6, 77.3, 73.5, 69.2, 32.1, 30.5, 29.9, 29.8, 29.7, 29.5, 26.3, 22.8, 14.3 ppm. Calculated for $C_{50}H_{84}N_5O_4$: 818.6517 $[M+H]^+$. Found: 818.6540 $[M+H]^+$.

9-(3,5-bis(dodecyloxy)benzyl)-8-ethynyl-guanine (G1$_{Bn2}$): Following *Standard Procedure A*, **G6** (288 mg, 0.87 mmol), K_2CO_3 (144 mg, 1.044 mmol) and 1-(chloromethyl)-3,5-bis(dodecyloxy)benzene (516 mg, 1.04 mmol) were dissolved in dry DMF (10 mL) and heated at 40 ºC overnight. Once the reaction was completed, the solvent was removed under reduced pressure. The resulting crude was passed through a silica plug eluted with $CHCl_3$/MeOH (100:1). The residue was dissolved in the THF/NEt_3 mixture with Pd(Ph$_3$)$_2$Cl$_2$ (12.3 mg, 0.0175 mmol) and CuI (1.7 mg, 0.009 mmol), following *Standard Procedure B* for a Sonogashira coupling. Then, TMSA (0.3 mL, 2.33 mmol) was added. The resulting mixture was stirred at 40 ºC overnight. Once the reaction was completed, the solvent was removed under reduced pressure. The resulting crude was dissolved in THF (10 mL) and TBAF·3H_2O (548 mg, 1.74 mmol) was added. Once the deprotection was completed, the solvent was removed under reduced pressure and the crude purified by column chromatography eluted with $CHCl_3$/MeOH (100:1). **G1$_{Bn2}$** was obtained as a light brown solid; m. p. 88-89 ^{0}C (219.3 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 11.90 (bs, 1H, N^1*H*), 6.57-6.24 (m, 3H, Ar-*2,4,6*), 5.16 (s, 2H, N^{9}C*H*$_2$), 3.86 (t, *J* = 6.5 Hz, 5H, OC*H*$_2$), 3.35 (s, 1H, C≡C*H*), 1.88-1.58 (m, 6H, OCH$_2$C*H*$_2$), 1.26 (m, 39H, OCH$_2$CH$_2$(C*H*$_2$)$_9$CH$_3$), 0.98-0.72 (m, 6H, O(CH$_2$)$_{11}$C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* =163.9, 162.6, 155.8, 153.7, 150.3, 138.4, 130.7, 107.1, 77.2, 73.5, 69.4, 56.3, 52.6, 36.6, 32.0, 31.5, 30.4, 29.84, 29.82, 29.80, 29.78, 29.75, 29.7, 29.7, 29.5, 29.48, 29.5, 26.2, 22.8, 14.2 ppm. HRMS (ESI+): Calculated for $C_{38}H_{60}N_5O_3$: 634.4690 $[M+H]^+$. Found: 634.4688 $[M+H]^+$.

8-bromo-*N*^{2}*iso*butyrylguanine (G12): To a suspensión of *N*^{2}-***iso*butyryl**guanine[33] (5.85 g, 26.48 mmol) and AcONa (6.29 g, 52.96 mmol) in AcOH (70 mL), Br_2 (2 mL, 52.96 mmol) was added. The mixture was stirred at 80 ºC overnight. Once the reaction was completed, the system was allowed to cool to room temperature and the resulting solid was filtered and washed with H_2O and EtOH. **G12** was obtained as a white solid (6.37 g, 80%). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): *δ* = 13.88 (bs, 1H, N^1*H*), 12.09 (bs, 1H, N^9*H*), 11.60 (s, 1H, N*H*CO^{i}Pr), 2.75 (sep, *J* = 6.8 Hz, 1H, C*H*^{i}Pr), 1.12 (d, *J* = 6.8 Hz, 6H, C*H*$_3$^{i}Pr) ppm. ^{13}C NMR (75 MHz, DMSO-*d*$_6$): *δ* =180.0, 154.3, 153.0, 147.2, 39.5, 34.7, 19.0 ppm. HRMS (FAB$^+$): Calculated for $C_9H_{11}BrN_5O_2$: 300.0096 $[M+H]^+$. Found: 300.0092 $[M+H]^+$.

8-bromo-*O*^{6}-diphenylcarbamoil-*N*^{2}-*iso*butyrylguanine (**G11**): To a suspension of **G12** (6.37 g, 21.22 mmol), DMAP (51.53 mg, 0.42 mmol) and diphenylcarbamoyl chloride (5.89 g, 42.44 mmol) in $CHCl_3$ (300 mL) under argon, DIPEA (5.4 mL, 31.38 mmol) was added. The resulting mixture was stirred at reflux overnight. Then, the mixture was filtered and the solvent was removed under reduced pressure. The crude was purified by column chromatography eluted with $CHCl_3$/MeOH (100:1) obtaining **G11** as a white solid; m. p. 140-141 ^{0}C (8.17 g, 78%). ^{1}H RMN (300 MHz, DMSO-*d*$_6$): *δ* = 12.16 (bs, 1H, N^1*H*), 11.89 (s, 1H, N^9*H*), 7.51-7.28 (m, 10H, Ph), 2.77 (sept, *J* = 6.9 Hz, 1H, C*H*^{i}Pr), 1.16 (d, *J* = 6.9 Hz, 6H, C*H*$_3$^{i}Pr) ppm. ^{13}C RMN (75 MHz, DMSO-*d*$_6$): *δ* = 180.4, 153.2, 150.1, 148.3, 146.8, 141.1, 139.9, 129.6, 129.4, 128.5, 127.9, 127.9, 126.8, 126.0, 119.9, 118.9, 79.1, 34.9, 18.9, 18.7 ppm. HRMS (ESI+): Calculated for $C_{22}H_{20}N_6O_3Br$: 495.0774 $[M+H]^+$. Found: 495.0758 $[M+H]^+$.

8-bromo-9-(2-tertbutylacetyl)-*O*^{6}-diphenylcarbamoyl-N^2-*iso*butyrylguanine (G10$_{Es}$): Following *Standard Procedure A,* a solution of **G11** (2.35 g, 4.74 mmol) and K_2CO_3 (0.8 g, 5.8 mmol) in dry DMF (60 mL) was stirred for 30 min. Then, *tert*butyl-bromoacetate (839 µL, 5.68 mmol) was added and the resulting mixture was stirred at 40 ºC for 24 h. The solvent was evaporated after completion and the residue was dissolved in $CHCl_3$ (15 mL). The organic layer was washed with water (2 x 15 mL) and brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, affording **G10$_{Es}$** as a white solid; m. p. 102-104 ^{0}C (0.81 g, 28%). ^{1}H RMN (300 MHz, $CDCl_3$): *δ* = 7.75 (s, 1H, N*H*CO^{i}Pr), 7.49-7.08 (m, 10H, Ph), 4.88 (s, 2H, C*H*$_2$) 3.24 (sep, *J* = 6.8 Hz, 1H, C*H*^{i}Pr), 1.40 (s, 9H, C*H*$_3$^{t}Bu), 1.27 (d, *J* = 6.8 Hz, 6H, C*H*$_3$^{i}Pr) ppm. ^{13}C RMN (75 MHz, DMSO-*d*$_6$): *δ* = 176.1, 166.2, 158.3, 153.4, 151.8, 147.0, 129.1, 127.6, 126.9, 125.6, 124.1, 116.8, 82.3, 63.6, 34.9, 27.7, 19.0 ppm. HRMS (ESI$^+$): Calculated for $C_{28}H_{30}N_6O_5Br$: 609.1455 $[M+H]^+$. Found: 609.1459 $[M+H]^+$.

Synthesis of the adenine derivatives.

2,6-diamino-9-decyl-purine (A4$_{Alk10}$): A4$_{Alk10}$ was obtained following *Standard Procedure A* using 2,6-diaminopurine (5.0 g, 33 mmol), K_2CO_3 (5.5 g, 40 mmol), 1-iododecane (8.6 mL, 40 mmol) and DMF (100 mL).

The reaction was completed overnight. After solvent evaporation, the crude was dissolved in $CHCl_3$ (200 mL) and washed with water (3 x 100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (50:1). **$A4_{Alk10}$** was obtained as a white solid (6.7 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.69 (s, 1H, N^8H), 6.61 (bs, 2H, C^6NH_2), 5.75 (bs, 2H, C^2NH_2), 3.92 (t, J = 6.7 Hz, 2H, $N^9CH_2C_9H_{19}$), 1.8-1.6 (m, 2H, $N^9CH_2CH_2C_8H_{17}$), 1.3-1.1 (m, 14H, $N^9C_2H_4C_7H_{14}CH_3$), 0.84 (t, J = 6.5 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.2, 156.1, 151.2, 137.6, 113.2, 42.4, 31.3, 29.3, 29.0, 28.8, 28.7, 28.6, 26.1, 22.1, 14.0 ppm. HRMS (ESI+): Calculated for $C_{15}H_{27}N_6$: 291.2291 $[M+H]^+$. Found: 291.2302 $[M+H]^+$.

2,6-diamino-9-ethyl-purine ($A4_{Alk2}$): $A4_{Alk2}$ was obtained following *Standard Procedure A* using 2,6-diaminopurine (3.0 g, 20 mmol), K_2CO_3 (3.3 g, 24 mmol), 1-iodoethane (2 mL, 24 mmol) and DMF (150 mL). The reaction was completed overnight. The crude mixture was concentrated under reduced pressure and the crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (10:1), affording 2.4 g of **$A4_{Alk2}$** (67% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.71 (s, 1H, N^8H), 6.64 (bs, 2H, C^6NH_2), 5.77 (bs, 2H, C^2NH_2), 3.97 (q, J = 7.3 Hz, 2H, $N^9CH_2CH_3$), 1.32 (t, J = 7.3 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.2, 156.0, 151.3, 137.0, 113.3, 37.3, 15.3. HRMS (ESI+): Calculated for $C_7H_{11}N_6$: 179.1039 $[M+H]^+$. Found: 179.1038 $[M+H]^+$.

2,6-diamino-8-bromo-9-decyl-purine ($A3_{Alk10}$): $A3_{Alk10}$ was obtained following *Standard Procedure D* using **$A4_{Alk10}$** (4.9 g, 16.9 mmol) in acetonitrile (80 mL) and NBS (3.6 g, 18.6 mmol), which was added over a period of 4 h. The reaction was completed overnight. Then, the crude mixture was concentrated under reduced pressure and the crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (30:1), affording 0.8 g of **$A3_{Alk10}$** as an ochre solid; m. p. 140-142 ºC (13% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.77 (bs, 2H, C^6NH_2), 5.87 (bs, 2H, C^2NH_2), 3.90 (t, J = 7.1 Hz, 2H, $N^9CH_2C_9H_{19}$), 1.68 (m, 2H, $N^9CH_2CH_2C_8H_{17}$), 1.3-1.1 (m, 14H, $N^9C_2H_4C_7H_{14}CH_3$), 0.82 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.3, 155.0, 152.7, 121.0, 113.5, 43.0, 31.2, 28.8, 28.7, 28.6, 28.5, 25.9, 22.0, 13.9 ppm. HRMS (ESI+): Calculated for $C_{15}H_{26}BrN_6$: 369.1396 $[M+H]^+$. Found: 369.1411 $[M+H]^+$.

2,6-diamino-9-decyl-8-iodo-purine ($A2_{Alk10}$):[38] Iodine (2.3 g, 9.3 mmol) was added to a suspension of H_5IO_6 (1.4 g, 6.2 mmol) in MeOH (10 mL) at room temperature. After 10 min, a solution of **$A2_{Alk10}$** (1.8 g, 6.2 mmol) in MeOH (10 mL) was added at room temperature. The reaction mixture was stirred at 70 ºC for 5 h. After completion, the mixture was let to cool down to room temperature and $Na_2S_2O_5$ (sat) (10 mL) was added. The mixture was extracted in CH_2Cl_2 (30 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (50:1). **$A2_{Alk10}$** was obtained as a white solid (1.3 g, 50%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.74 (bs, 2H, C^6NH_2), 5.81 (bs, 2H, C^2NH_2), 3.86 (t, J = 7.3 Hz, 2H, $N^9CH_2C_9H_{19}$), 1.7-1.6 (m, 2H, $N^9CH_2CH_2C_8H_{17}$), 1.3-1.1 (m, 14H, $N^9C_2H_4C_7H_{14}CH_3$), 0.84 (t, J = 6.9 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.2, 154.8, 152.8, 116.2, 95.8, 44.3, 31.3, 29.1, 28.88, 28.87, 28.7, 28.6, 26.0, 22.1, 13.9 ppm. HRMS (ESI+): Calculated for $C_{15}H_{26}IN_6$: 417.1258 $[M+H]^+$. Found: 417.1275 $[M+H]^+$.

2,6-diamino-9-ethyl-8-iodo-purine ($A2_{Alk2}$): $A2_{Alk2}$ (1.0 g, 5.6 mmol), iodine (1.3 g, 2.1 mmol) and H_5IO_6 (1.3 g, 5.6 mmol) were stirred in DMF (30 mL) at 70 ºC for 24 h. After completion, the reaction mixture was concentrated *in vacuo*. The crude was dissolved in $CHCl_3$ (50 mL) and washed with $Na_2S_2O_5$ (sat) (40 mL), water (40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (10:1). **$A2_{Alk2}$** was obtained as a white solid; m. p. 242-243 ºC (0.6 g, 37%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.77 (bs, 2H, C^6NH_2), 5.87 (bs, 2H, C^2NH_2), 3.92 (q, J = 7.4 Hz, 2H, $N^9CH_2CH_3$), 1.23 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.3, 154.9, 152.5, 116.3, 95.4, 38.8, 15.0 ppm. HRMS (ESI+): Calculated for $C_7H_{10}N_6I$: 305.0006 $[M+H]^+$. Found: 305.0001 $[M+H]^+$.

2,6-diamino-9-decyl-8-ethynyl-purine ($A1_{Alk10}$): $A1_{Alk10}$ was prepared following *Standard Procedure B*. **$A2_{Alk10}$** (0.34 g, 0.8 mmol), $Pd(PPh_3)_2Cl_2$ (11.4 mg, 0.02 mmol) and CuI (1.5 mg, 0.01 mmol) were dissolved in the THF/NEt_3 mixture (13 mL). Then TMSA (0.3 mL, 1.6 mmol) was added. The reaction was completed in 12 h. The mixture was concentrated under reduced pressure, dissolved in THF (15 mL) and TBAF·$3H_2O$ (0.3 g, 0.9 mmol) was added. **$A1_{Alk10}$** was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH: (20:1) affording **$A1_{Alk10}$** as a white solid (130 mg, 51%). **$A1_{Alk10}$** can also been obtained following *Standard Procedure B* with **$A3_{Alk10}$** (0.91 g, 2.5 mmol), $Pd(PPh_3)_2Cl_2$ (36.1 mg, 0.05 mmol) and CuI (4.9 mg, 0.02 mmol) were dissolved in the THF/NEt_3 mixture (10 mL). Then TMSA (0.9 mL, 5.0 mmol) was added. The reaction was completed in 12 h. The mixture was concentrated under reduced pressure, dissolved in THF (15 mL) and TBAF·$3H_2O$ (0.9 g, 2.8 mmol) was added. **$A1_{Alk10}$** was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH: (20:1) affording **$A1_{Alk10}$** as a white solid; m. p. 144-145 ºC (130 mg, 82%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.86 (bs, 2H, C^6NH_2), 5.94 (bs, 2H, C^2NH_2), 4.69 (s, 1H, C≡CH), 3.98 (t, J = 6.9 Hz, 2H, $N^9CH_2C_9H_{19}$), 1.71 (m, 2H, $N^9CH_2CH_2C_8H_{17}$), 1.4-1.1 (m, 14H, $N^9C_2H_4C_7H_{14}CH_3$), 0.84 (t, J = 6.9 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.2, 156.1, 151.4, 129.0, 113.1, 84.7, 74.0, 42.4, 31.3, 28.95, 28.90, 28.7, 28.6, 26.0, 22.1, 13.9 ppm. HRMS (ESI+): Calculated for $C_{17}H_{27}N_6$: 315.2291 $[M+H]^+$. Found: 315.2289 $[M+H]^+$.

2,6-diamino-9-ethyl-8-ethynyl purine ($A1_{Alk2}$): $A1_{Alk2}$ was prepared following *Standard Procedure B*. **$A2_{Alk2}$** (0.45 g, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (20.6 mg, 0.03 mmol) and CuI (2.8 mg, 0.01 mmol) were dissolved in the THF/NEt_3 mixture (35 mL). Then, TMSA (0.4 mL, 3.0 mmol) was added. The reaction was completed in 12 h. The mixture was concentrated under reduced pressure, dissolved in THF (35 mL) and TBAF·$3H_2O$ (0.55 g, 1.65 mmol) was added. **$A1_{Alk2}$** was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH: (10:1) affording **$A1_{Alk2}$** as a white solid; m. p. > 250 ºC (146 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.41 (bs, 2H, C^6NH_2), 4.77 (bs, 2H, C^2NH_2), 4.18 (q, J = 7.2 Hz, 2H, $N^9CH_2CH_3$), 3.42 (s, 1H, C≡CH), 1.42 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.2, 156.1, 151.1, 128.4, 113.1, 84.7, 73.9, 37.3, 14.9 ppm. HRMS (ESI+): Calculated for $C_9H_{11}N_6$: 203.1039 $[M+H]^+$. Found: 203.1040 $[M+H]^+$.

Synthesis of the *iso*guanine derivative.

9-ethyl-8-ethynyl-isoguanine ($iG1_{Alk2}$):[39a] **$iG1_{Alk2}$** was prepared from **$A2_{Alk2}$** (0.15 g, 0.5 mmol) following the same procedure than **$A1_{Alk2}$** but, before TMS-deprotection, the crude mixture after the Sonogashira coupling was suspended in a 1:1 THF/H_2O mixture (18 mL). Then, a solution of $NaNO_2$ (0.15 g, 2.2 mmol) in H_2O (2 mL) was added. The mixture was heated at 50 ºC and a 1:1 AcOH/H_2O mixture (0.5 mL) was slowly added. The reaction mixture was stirred at 50 ºC for 2 h. Once

completed, the mixture was let to cool down to room temperature and NH_3 was added until pH 8. The reaction mixture was concentrated under reduced pressure. Then, K_2CO_3 (0.15 g, 1.1 mmol) was added over a MeOH (10 mL) solution of the resulting crude solid. The reaction mixture was stirred at room temperature for 1 h. until completion. After solvent evaporation the crude solid was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (20:1). **iG1$_{Alk2}$** was obtained as a light yellow solid; m. p. > 250 ºC (81 mg, 73%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.0 (bs, 1H, N^3*H*), 7.90 (bs, 2H, N*H*$_2$), 4.80 (s, 1H, C≡C*H*), 3.97 (q, *J* = 7.2 Hz, 2H, N^{9}C*H*$_2$CH$_3$), 1.26 (t, *J* = 7.2 Hz, 3H, C*H*$_3$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 130.3, 85.5, 79.2, 73.2, 56.1, 45.9, 37.5, 14.7, 8.7 ppm. HRMS (ESI+): Calculated for $C_9H_{10}N_5O$: 204.0879 $[M+H]^+$. Found: 204.0879 $[M+H]^+$.

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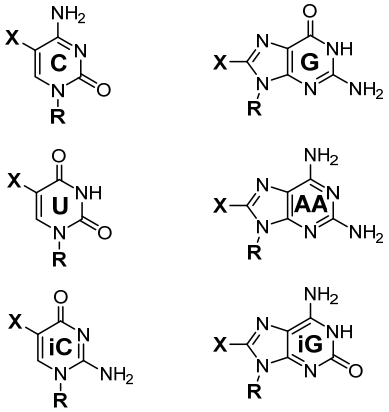
Entry for the Table of Contents

SHORT COMMUNICATION

A series of lipophilic nucleobases that are substituted at the 5- (pyrimidines) or 8-position (purines) with either a halogen atom or a terminal triple bond have been synthesized. These molecules comprise a useful collection of synthetic intermediates in the field of chemical self-assembly.



*5-/8- Ethynylated Nucleobases

Nucleobase Synthesis*

*Nerea Bilbao, Violeta Vázquez-González, M. Teresa Aranda and David González-Rodríguez**

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Synthesis of 5-/8- Halogenated or Ethynylated Lipophilic Nucleobases as Potential Synthetic Intermediates for Supramolecular Chemistry