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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, isoctosine and uracil as pyrimidine heterocycles, and guanine, isoguanine, 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 isoctosine (iC), whereas the purines prepared in this work are guanine (G), 2,6-diaminopurine or 2-aminoadenine (DAP; hereafter abbreviated as A), and isoguanine (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,¹¹ 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.
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 with trimethylsilylacetylene (TMSA), followed by trimethylsilyl (TMS) deprotection; and, 3. Nucleophilic substitution with the corresponding alkylation reagent. 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 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 (I₂/HIO₃), iodine/periodic acid (I₂/H₅IO₆), N-iodosuccinimide (NIS), or iodine monochloride (ICl), were assayed. 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) was reactive. We believe that N-1 unsubstituted pyrimidines can deactivate the catalytic palladium species through chelation via one of their different tautomer forms, as has been suggested for other nucleobase derivatives. 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 iodoypyrimidines, 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 I₂ and HIO₃. 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 Bu₄NOH base in methanol was used to deprotonate C3 and produce C2A₁₈R₉, C2A₁₈S, C2A₂₈, C2B₉R₂, and C2B₉S in acceptable yields. 1-Alkyl-5-iodocytosines were then transformed into the final 5-ethynyl derivatives using standard Sonogashira-TMS deprotection methods.

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. 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. 5-Iodouridine was alkylated in the presence of Cs₂CO₃, which was proven to be slightly more efficient than K₂CO₃ because of its better solubility in organic solvents. The yields of U₂A₁₈R₉ and U₂A₁₈S were not very satisfactory, although they are in the same range of those
reported on similar alkylation reactions with uridine derivatives. 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.

Isocytosine (Scheme 3). The nonnatural isocytosine analog iCAlk2 was also prepared following the halogenation-alkylation sequence. In this case, iodination was carried out in the presence of N-iodosuccinimide (NIS), 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 iCAlk2 is the only one in this work that was not transformed into the corresponding 5-ethyl derivative.

Synthesis of purines. The optimized route to 8-halogenated and 8-ethylated 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 as soon as possible in the sequence, as we have shown with the pyrimidines. However, 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-ethylpurines. 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-ethyl lipophilic guanines (G1Alk10, G1Alk2, G1Bn2, G1Bn3) 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-hydroxy purine in different solvents is one of them. Among all the nucleobases, guanine exhibits the most rich supramolecular chemistry 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. 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 heterocycle in metal-mediated oxidative addition processes has been reported. 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. Conversion to different functionalized derivatives like 8-alkoxyl- or 8-amino or 6-halogenpurines, which, at the same time, may exhibit a higher selectivity in the alkylation reaction, is an alternative. Unfortunately, the use of these starting reagents involves 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 alkylation of 2-amino-6-chloropurine with diverse iodoalkanes, to yield G5Alk10 and G5Alk2, and with the corresponding benzyl bromide, to afford G5Bn2. Whereas the benzyl halide led mainly to a single $N$-9 alkylation product, 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 \( \text{G5}_{\text{alk10}} \). 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 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-trimethylsilyloethoxy group 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, along with the TMSA group. Compound \( \text{G7} \) 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 Br₂ 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 G3Alk10 and G3Bn2. 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-idoethane 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 G4Alk10 or G4Bn2 led to the 8-bromopurines G3Alk10 or G3Bn2 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 K₂CO₃ or Cs₂CO₃ 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-trimethylsilylthiophenoxide group, leading to compounds G4Alk10, G4Alk2, and G4Bn2. As just mentioned, the G4Alk2 and G4Bn2 products could be brominated at the 8-position in the presence of NBS, but reaction of G4Bn3 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.₇¹ Product G2Bn2 was in this way generated with acceptable yields. This iodination procedure is, of course, also compatible with the alkylated purines. Finally, bromo-derivatives G3Alk10, G3Alk2, and G3Bn2, and iodoguanine G2Bn2 were subjected to a Sonogashira coupling in the usual conditions, followed by deprotection of the alkyne TMS group, to yield G1Alk10, G1Alk2, G1Bn2, and G1Bn3.

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.₇₂ Among the different methods we tested, we chose 2-amine protection as an isobutyryl 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 isobutyric anhydride.²³ This product could be halogenated in the presence of bromine and sodium acetate²⁴ 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,²⁵ 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.²⁶ A diphenylcarbamoyl protecting group²⁷ 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 tertbutyl 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 G10es 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.](image-url)

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 reaction²⁷ was carried out as the first step of the synthetic route. K₂CO₃ proved to be the best base for such reaction due to handling conditions, price and yield reasons. Compounds A₄Alk10 and A₄Bn2 were prepared in this way. Next, the halogenation reaction was optimized. Iodination in the presence of periodic acid²⁸ 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 A₄Alk10, A₂Bn2, and A₃Alk10 were then subjected to the Sonogashira-TMS cleavage protocol, leading to A₁Alk10 and A₁Bn2 in good yields.
Isoguanine (Scheme 6). The isoguanine non-natural nucleobase could be obtained from 2,6-diaminopurine in a single step by selective hydrolysis at C-2 via a diazonium intermediate. 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 iG1Alk2 was isolated in 73% overall yield from A2Alk2 after TMS-cleavage in the presence of K2CO3.

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, isoguanine, and 2-aminoadene 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.

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 ULTRA FLEX 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 [CHCl3, calibrated at 7.26 ppm (1H) and 77.0 ppm (13C); DMSO calibrated at 2.50 ppm (1H) and 39.5 ppm (13C)].

Compounds G8Alk10, G9Alk10 and G3Bn2 were not isolated. The synthesis and characterization of compounds 5-iodocytosine C3,5-iodoiso cytosine IC3, guanine G13, 3,5-bis(dodecyloxy)benzyl chloride, and 3,4,5-tris(dodecyloxy)benzyl bromide has been reported elsewhere.

Synthesis of the cytosine derivatives.

5-iodocytosine (C3): C3 was synthesized according to a literature procedure 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 Na2S2O3 (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). 1H NMR (300 MHz, DMSO-d6): δ = 10.76 (bs, 2H, N’H), 7.76 (s, 1H, H’), 6.48 (bs, 2H, NH); ppm. 13C NMR (75 MHz, CDCl3): δ = 164.4, 155.8, 149.4, 55.2 ppm. HRMS
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°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 (C2Am): C2Am was synthesized according to the literature procedure[14] adapted to our molecule. C2Am can be obtained following Standard Procedure A using C3 (10.0 g, 42.2 mmol), a 1.0 M solution in MeOH of Bu4NOH (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 C2Am (62% yield).

C2Am can be also be obtained by stirring C4Am (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 to room temperature for 12 h. The resulting solid was washed with acetonitrile affording 9.8 g of C2Am (62% yield).

C2Am can be obtained following Standard Procedure A using C3 (10.0 g, 42.2 mmol), a 1.0 M solution in MeOH of Bu4NOH (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 C2Am (62% yield).

C2Am can be also be obtained by stirring C4Am (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 to room temperature for 12 h. The resulting solid was washed with acetonitrile affording 9.8 g of C2Am (62% yield).

1-hexyl-5-iodocytosine (C2Bn): C2Bn can be obtained following Standard Procedure A using C3 (5.0 g, 21.1 mmol), a 1.0 M solution in MeOH of Bu4NOH (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 CHCICMeOH (50:1), affording 4.0 g of C2Am (59% yield) as a pale solid; m: p. 163-165 °C (15.8 g, 81%).[14] 1H NMR (300 MHz, DMSO-d6): δ = 8.07 (s, 1H, Hφ), 7.58 (bs, 1H, H6), 6.43 (bs, 1H, H2), 3.7-3.6 (m, 2H, N'CCH2CH3), 1.6-1.4 (m, 2H, N'CCH2CH2CH3), 1.4-1.1 (m, 14H, N'CCH2CH2CH2), 0.85 (t, J = 7.0 Hz, 3H, CH3), ppm. 13C NMR (75 MHz, DMSO-d6): δ = 164.8, 155.4, 150.9, 150.0, 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 C35H59N3O3I: 696.3595 [M+H]^+. Found: 696.3581 [M+H]^+.

1-(3,5-bis(dodecyloxy)benzyl)-5-iodocytosine (C2Bn): 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 Bu4NOH in MeOH (2.26 mL, 2.26 mmol) was added. The resulting mixture was stirred at 40 °C 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 °C for 16 h. Once the reaction was completed, the solvant was evaporated under reduced pressure. The crude was dissolved in CH2Cl2 (10 mL), washed with water (3 x 10 mL) and brine (10 mL). The combined organic layers were dried over MgSO4 and concentrated in vacuo. The residue was purified by column chromatography eluted with CHCICMeOH (50:1).

C2Bn was obtained as a white solid; m. p. 125-127 °C (234 mg, 40%).[14] 1H NMR (300 MHz, CDCl3): δ = 7.51 (s, 1H, Hφ), 6.42 (d, J = 2.1 Hz, 3H, Ar-2, 4, 6), 4.89 (s, 2H, N'C2H5), 3.91 (t, J = 6.5 Hz, 4H, OCH2), 1.75 (p, J = 6.8 Hz, 6H, OCH2CH2), 1.61-0.86 (m, 36H, OCH2CH2(OCH2)CH2(OCH2)CH2), 1.06-0.78 (m, 6H, OCH2(OCH2)CH2), ppm. 13C NMR (75 MHz, CDCl3): δ = 163.7, 161.0, 155.7, 150.6, 137.9, 109.6, 101.2, 77.2, 68.4, 55.8, 52.6, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 26.2, 22.8, 14.3 ppm. HRMS (ESI+): Calculated for C69H59N3O3I: 966.3595 [M+H]^+. Found: 966.3581 [M+H]^+.

1-(3,4,5-tris(dodecyloxy)benzyl)-5-iodocytosine (C2Bn): 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 Bu4NOH in MeOH was added (4.42 mmol, 2.22 mmol) and the mixture was stirred for 30 minutes at 50 °C. 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 solvant was evaporated under reduced pressure. The residue was purified by column chromatography eluted with CHCICMeOH (50:1) to afford C2Bn as a white solid; m. p. 115-117 °C (2.8 g, 76%).[14] 1H NMR (300 MHz, CDCl3): δ = 9.10 (bs, 1H, C'H), 7.48 (s, 1H, Hφ), 6.46 (s, 2H, Ar-2, 4, 6), 5.65 (s, 1H, CH2=CH-N), 4.82 (s, 2H, N'C2H5), 3.92 (t, J = 6.3 Hz, 6H, OCH2), 1.75 (m, 6H, OCH2CH2), 1.24 (m, 34H, OCH2CH2(OCH2)CH2(OCH2)CH2), ppm. 13C NMR (75 MHz, CDCl3): δ = 165.0, 155.1, 153.6, 148.3, 138.4, 130.6, 107.1, 90.2, 84.0, 77.5, 73.0, 69.3, 52.7, 32.0, 30.4, 29.8, 29.7, 29.5, 29.4, 26.2, 22.8, 14.3 ppm. HRMS (ESI+): Calculated for C43H37N3O3I: 880.5422 [M+H]^+. Found: 880.5454 [M+H]^+.

1-(2-[2-(tert-butylcarbamate)ethyl]-5-iodocytosine (C2Am): A suspension of C3 (3.0, 12.65 mmol) and Cs2CO3 (4.9 g, 15.19 mmol) in dry DMF (75 mL) was stirred at room temperature for 1.5 h. Then 2-(Boc-amino)ethyrobromide (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 C2Am as a white solid; m. p. 231-233 °C (3.92 g, 82%).[14] 1H NMR (300 MHz, CDCl3): δ = 7.80 (s, 1H, Hφ), 7.60 (s, 1H, C'H), 6.85 (bs, 1H, N'C2H5-NH), 5.65 (s, 2H, C'H2).
1-decyl-5-ethyl-cytosine (C1 Alk10): C1 Alk10 was prepared following Standard Procedure B. C2Alk10 (10.0 g, 26.5 mmol), Pd(PPh3)2Cl2 (372.1 mg, 0.53 mmol) and Cul (50.4 mg, 0.27 mmol) were dissolved in the THF/NEt3 mixture (70 mL). Then TMSA (3.4 mL, 23.9 mmol) was added and the mixture was added at room temperature under argon at a constant pressure of 1 atm. The solvent was evaporated, the resulting crude was suspended in THF (10 mL) and TBAF·3H2O (1.8 g, 5.7 mmol) was added. The reaction was completed in 12 h. Then, TBAF·3H2O (2.7 g, 8.9 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·3H2O (553 mg, 1.58 mmol) was added. Once the preparation was completed, the solvent was removed under reduced pressure. The crude was purified by column chromatography eluted with CHCl3/MEOH (10:1) and recrystallized from CHCl3/MeCN. A light brown solid was obtained; m. p. 103-105 ºC (902 mg, 82%). 1H NMR (300 MHz, CDCl3): δ = 8.41 (bs, 1H, C4NH-), 7.51 (s, 1H, H6), 6.40 (s, 2H, N1C), 4.89 (s, 2H, N1CH2CH2CN), 3.91 (t, J = 6.5 Hz, 4H, OC2H5), 3.18 (s, 1H, C1CH3), 1.74 (dt, J = 8.3, 6.5 Hz, 6H, OCH2CH2(C2H5)2), 1.62-1.11 (m, 36H, OCH2CH2(CH2)2CH3), 1.00-0.75 (m, 6H, O(CH2)2CH3). 13C NMR (75 MHz, CDCl3): δ = 163.8, 161.1, 148.9, 137.3, 107.1, 101.3, 84.9, 77.3, 74.1, 68.4, 52.8, 32.1, 29.7, 29.6, 29.5, 29.4, 26.2, 22.84, 14.3 ppm. HRMS (ESI+): Calculated for C37H60N3O3: 594.4629 [M+H]+. Found: 594.4667 [M+H]+.

1-(3,5-bis(dodecyloxy)benzyl) 5-ethynlycitosine (C1 Bn2): Following Standard Procedure B. C2Alk10 (1.1 g, 1.585 mmol) was dissolved in the THF/NEt3 mixture (15 mL). Then, TMSA (0.6 g, 4.74 mmol) was added and the mixture was heated 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·3H2O (553 mg, 1.58 mmol) was added. Once the preparation was completed, the solvent was removed under reduced pressure. The crude was purified by column chromatography eluted with CHCl3/MEOH (100:1) and recrystallized from CHCl3/MeCN. A light brown solid was obtained; m. p. 103-105 ºC (902 mg, 82%). 1H NMR (300 MHz, CDCl3): δ = 8.41 (bs, 1H, C4NH-), 7.51 (s, 1H, H6), 6.40 (s, 2H, N1C), 4.89 (s, 2H, N1CH2CH2CN), 3.91 (t, J = 6.5 Hz, 4H, OC2H5), 3.18 (s, 1H, C1CH3), 1.74 (dt, J = 8.3, 6.5 Hz, 6H, OCH2CH2(C2H5)2), 1.62-1.11 (m, 36H, OCH2CH2(CH2)2CH3), 1.00-0.75 (m, 6H, O(CH2)2CH3). 13C NMR (75 MHz, CDCl3): δ = 163.8, 161.1, 148.9, 137.3, 107.1, 101.3, 84.9, 77.3, 74.1, 68.4, 52.8, 32.1, 29.7, 29.6, 29.5, 29.4, 26.2, 22.84, 14.3 ppm. HRMS (ESI+): Calculated for C59H92N3O4: 946.6429 [M+H]+. Found: 954.4667 [M+H]+.

1-ethyl-5-ethyl-cytosine (C1 Alk12): Following Standard Procedure B. C2Alk10 (1.5 g, 5.7 mmol), Pd(PPh3)2Cl2 (79.5 mg, 0.11 mmol) and Cul (10.8 mg, 0.06 mmol) were dissolved in the THF/NEt3 mixture (15 mL). Then TMSA (2 mL, 11.3 mmol) was added. The reaction was completed in 12 h. Then, TBAF·3H2O (1.8 g, 5.7 mmol) was added and the mixture was stirred at 40 ºC overnight. Once the reaction was completed, the solvent was evaporated. The resulting crude was purified by column chromatography eluted with CHCl3/MEOH (10:1) and recrystallized from CHCl3/MeCN. A light brown solid was obtained; m. p. 103-105 ºC (902 mg, 82%). 1H NMR (300 MHz, CDCl3): δ = 8.28 (bs, 1H, C4NH-), 7.51 (s, 1H, H6), 6.40 (s, 3H, Ar-), 6.20 (s, 1H, C4NH-), 4.89 (s, 2H, N1CH2CH2CN), 3.80 (t, J = 6.5 Hz, 4H, OC2H5), 3.18 (s, 1H, C1CH3), 1.74 (dt, J = 8.3, 6.5 Hz, 6H, OCH2CH2(C2H5)2), 1.62-1.11 (m, 36H, OCH2CH2(CH2)2CH3), 1.00-0.75 (m, 6H, O(CH2)2CH3). 13C NMR (75 MHz, CDCl3): δ = 163.8, 161.1, 148.9, 137.3, 107.1, 101.3, 84.9, 77.3, 74.1, 68.4, 52.8, 32.1, 29.7, 29.6, 29.5, 29.4, 26.2, 22.84, 14.3 ppm. HRMS (ESI+): Calculated for C31H52N3O2: 476.3818 [M+H]+. Found: 476.3818 [M+H]+.

1-ethyl-5-ethyl-cytosine (C1 Alk12): Following Standard Procedure B. C2Alk10 (0.50 g, 0.568 mmol) was dissolved in the THF/NEt3 mixture (70 mL). Then TMSA (0.50 g, 0.050 mmol) and Pd(PPh3)2Cl2 (22 mg, 0.032 mmol) were dissolved in the THF/NEt3 mixture (15 mL). Then, TMSA (0.50 g, 0.050 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·3H2O (553 mg, 1.58 mmol) was added. Once the preparation was completed, the solvent was removed under reduced pressure. The crude was purified by column chromatography eluted with CHCl3/MEOH (100:1) and recrystallized from CHCl3/MeCN. A light brown solid was obtained; m. p. 94-96 ºC (902 mg, 82%). 1H NMR (300 MHz, CDCl3): δ = 8.41 (bs, 1H, C4NH-), 7.51 (s, 1H, H6), 6.40 (s, 2H, N1C), 4.89 (s, 2H, N1CH2CH2CN), 3.91 (t, J = 6.5 Hz, 4H, OC2H5), 3.18 (s, 1H, C1CH3), 1.74 (dt, J = 8.3, 6.5 Hz, 6H, OCH2CH2(C2H5)2), 1.62-1.11 (m, 36H, OCH2CH2(CH2)2CH3), 1.00-0.75 (m, 6H, O(CH2)2CH3). 13C NMR (75 MHz, CDCl3): δ = 163.8, 161.1, 148.9, 137.3, 107.1, 101.3, 84.9, 77.3, 74.1, 68.4, 52.8, 32.1, 29.7, 29.6, 29.5, 29.4, 26.2, 22.84, 14.3 ppm. HRMS (ESI+): Calculated for C31H52N3O2: 476.3818 [M+H]+. Found: 476.3818 [M+H]+.
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 CHCl₃/MeOH (20:1) to afford C₁₄H₂₄N₂O₂I as a white solid (0.64 g, 16%). ¹H NMR (300 MHz, CDCl₃): δ = 8.20 (bs, 1H, N₃), 7.60 (s, 1H, H₆), 3.73 (t, J = 7.4 Hz, 2H, N₃C₆H₅CH₂CH₃), 1.7-1.6 (m, 2H, N₃C₆H₅CH₂CH₃), 1.3-1.2 (m, 6H, N₃C₆H₄C₆H₅CH₃), 0.90 (t, J = 7.0 Hz, 3H, CH₃) ppm. ¹C NMR (75 MHz, CDCl₃): 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 C₁₄H₁₃N₂O₃: 323.0251 [M⁺H⁺]. Found: 323.0249 [M⁺H⁺].

1-decyl-5-ethyl-uracil (U₁Alk₁₀): U₁Alk₁₀ was prepared following Standard Procedure B. U₂Al₉ (3.2 g, 8.4 mmol), Pd(PPh₃)₃Cl₂ (117.6 mg, 0.17 mmol) and Cul (15.9 mg, 0.08 mmol) were dissolved in THF/NET₃ mixture (60 mL). Then TMSA (3.1 mL, 16.8 mmol) was added. The reaction was completed in 12 h. Then, TBAF·3H₂O (2.7 g, 8.4 mmol) was added over a THF (60 mL) solution of the crude mixture. U₁Alk₁₀ was purified by column chromatography on silica gel eluted with hexane/AcOEt (4:1) affording U₁Alk₁₀ as a white solid (461 mg, 65%). ¹H NMR (300 MHz, CDCl₃): δ = 8.16 (bs, 1H, N₃), 7.49 (s, 1H, H₆), 3.74 (t, J = 6.7 Hz, 2H, N₃C₆H₅CH₂CH₃), 3.21 (s, 1H, CHI), 1.8-1.6 (m, 2H, N₃C₆H₅CH₂CH₃), 1.3-1.2 (m, 14H, N₃C₆H₄C₆H₅CH₃), 0.88 (t, J = 6.7 Hz, 3H, CH₃) ppm. ¹C NMR (75 MHz, DMSO-d₆): δ = 165.8, 155.8, 146.0, 93.0, 48.6, 38.5, 31.2, 28.9, 26.8, 25.9, 22.0, 13 ppm. HRMS (ESI⁺): Calculated for C₁₅H₁₃N₂O₃: 252.2070 [M⁺H⁺]. Found: 252.2082 [M⁺H⁺].

Synthesis of the uracil derivatives.

1-decyl-5-iodouracil (U₂Alk₁₀): U₂Alk₁₀ was obtained following Standard Procedure A using cytosine (10.0 g, 90 mmol), 1.0 M solution in MeOH of Bu₄NOH (108 mL, 108 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 solid was purified by column chromatography on silica gel eluted with CHCl₃/MeOH (200:1). U₂Al₉ was obtained as a white solid (216 mg, 49%). ¹H NMR (300 MHz, CDCl₃): δ = 7.93 (s, 1H, H₆), 7.16 (s, 1H, H₇), 3.79-3.73 (m, 2H, N₃C₆H₄C₆H₅CH₃), 1.79-1.69 (m, 2H, N₃C₆H₄C₆H₅CH₃), 0.88 (t, J = 6.9 Hz, 3H, CH₃) ppm. ¹C NMR (75 MHz, DMSO-d₆): δ = 167.1, 154.9, 148.5, 68.2, 81.4, 74.4, 49.4, 31.8, 29.7, 29.4, 29.2, 29.1, 26.3, 22.6, 14.1 ppm. HRMS (ESI⁺): Calculated for C₁₆H₁₃N₂O₃Na: 299.1729 [M⁺H⁺]. Found: 279.1710 [M⁺H⁺].

1-decyl-5-ethyl-uracil (U₁Alk₁₀): U₁Alk₁₀ was prepared following Standard Procedure B. U₂Al₉ (3.2 g, 8.4 mmol), Pd(PPh₃)₃Cl₂ (117.6 mg, 0.17 mmol) and Cul (15.9 mg, 0.08 mmol) were dissolved in THF/NET₃ mixture (60 mL). Then TMSA (3.1 mL, 16.8 mmol) was added. The reaction was completed in 12 h. Then, TBAF·3H₂O (2.7 g, 8.4 mmol) was added over a THF (60 mL) solution of the crude mixture. U₁Alk₁₀ was purified by column chromatography on silica gel eluted with hexane/AcOEt (4:1) affording U₁Alk₁₀ as a white solid (461 mg, 65%). ¹H NMR (300 MHz, CDCl₃): δ = 8.16 (bs, 1H, N₃), 7.49 (s, 1H, H₆), 3.74 (t, J = 6.7 Hz, 2H, N₃C₆H₅CH₂CH₃), 3.21 (s, 1H, CHI), 1.8-1.6 (m, 2H, N₃C₆H₅CH₂CH₃), 1.3-1.2 (m, 14H, N₃C₆H₄C₆H₅CH₃), 0.88 (t, J = 6.7 Hz, 3H, CH₃) ppm. ¹C NMR (75 MHz, DMSO-d₆): δ = 165.8, 155.8, 146.0, 93.0, 48.6, 38.5, 31.2, 28.9, 26.8, 25.9, 22.0, 13 ppm. HRMS (ESI⁺): Calculated for C₁₅H₁₃N₂O₃: 252.2070 [M⁺H⁺]. Found: 252.2082 [M⁺H⁺].

Synthesis of the isocytosine derivatives.

5-idoisocytosine (iC₃):[16] Isocytosine (1.0 g, 9.0 mmol) was suspended in a 1:1 AcOH/H₂O mixture (35 mL). The reaction mixture was stirred at 50 °C for 15 minutes. Then Ni-iodosuccinimide (2.4 g, 10.8 mmol) was added and the mixture was stirred at 100 °C 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). ¹H NMR (300 MHz, DMSO-d₆): δ = 8.31 (bs, 1H, NH₂), 7.49 (s, 1H, H₆), 3.74 (t, J = 7.0 Hz, 2H, N₃C₆H₄C₆H₅CH₃), 3.21 (s, 1H, CHI), 1.8-1.6 (m, 2H, N₃C₆H₄C₆H₅CH₃), 1.4-1.2 (m, 6H, N₃C₆H₄C₆H₅CH₃), 0.89 (t, J = 6.7 Hz, 3H, CH₃) ppm. ¹C NMR (75 MHz, DMSO-d₆): δ = 161.9, 149.8, 148.1, 98.7, 82.1, 74.4, 49.4, 31.2, 29.0, 26.0, 22.4, 13.9 ppm. HRMS (ESI⁺): Calculated for C₁₅H₁₃N₂O₃: 237.9471 [M⁺H⁺]. Found: 237.9464 [M⁺H⁺].

1-ethyl-5-iodoscytosine (iC₂Alk₂): iC₂Alk₂ was obtained following Standard Procedure A using 5-iodouracil (1.7 g, 7.3 mmol), 1-iododecane (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 CHCl₃ (40 mL) and washed with water (3 x 20 mL) and brine.
(20 mL). The organic layer was dried over MgSO4 and concentrated in vacuo. The crude solid was purified by column chromatography on silica gel eluted with CHCl3/MeOH (100:1). A final recrystallization using acetonitrile yielded 42 mg as a white solid: m. p. 181-182°C (0.67 g, 35%).

1H NMR (300 MHz, CDCl3): δ = 7.78 (s, 1H, H2), 5.19 (bs, 2H, NH2), 4.06 (q, J = 7.3 Hz, 2H, N9CH2CH3). 1.15 (t, J = 7.3 Hz, 3H, CH3) ppm. 13C NMR (75 MHz, CDCl3): δ = 159.4, 158.9, 155.2, 38.5, 29.7, 12.1 ppm. HRMS (ESI+): For C12H14N3O2S: 252.1275 [M+H]+. Found: 252.1299 [M+H]+.

2-amino-6-chloro-9-decyl-purine (G5Alk10): G5Alk10 was obtained following Standard Procedure A using 2-amino-6-chloropurine (8.0 g, 47 mmol), K2CO3 (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 CHCl3/MeOH (50:1). G5Alk10 was obtained as a white solid (12.4 g, 85%). 1H NMR (300 MHz, DMSO-d6): δ = 8.13 (s, 1H, NH), 6.87 (bs, 2H, C=NH2), 4.02 (t, J = 7.0 Hz, 2H, N9CH2CH3), 1.8-1.6 (m, 2H, N9CH2CH2CH2NH), 1.3-1.1 (m, 14H, N9C2H2CH3), 0.84 (t, J = 7.0 Hz, 3H, CH3) ppm. 13C NMR (75 MHz, DMSO-d6): δ = 159.7, 154.0, 149.3, 143.2, 123.4, 43.0, 31.2, 28.9, 28.8, 28.6, 24.8, 25.9, 22.0, 13.9 ppm. HRMS (ESI+): For C18H12N6Cl: 310.1793 [M+H]+. Found: 310.1801 [M+H]+.

2-amino-6-chloro-9-ethyl-purine (G5Alk12)[30] G5Alk12 was obtained following Standard Procedure A using 2-amino-6-chloropurine (3.0 g, 17.7 mmol), K2CO3 (2.9 g, 21.2 mmol), 1-idoethane (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 CHCl3/MeOH (50:1). G5Alk12 was obtained as a white solid (2.6 g, 74%). 1H NMR (300 MHz, CDCl3): δ = 7.70 (bs, 1H, H2), 6.43 (s, 2H, Ar-2,6), 5.34 (bs, 2H, CH2N=), 5.10 (s, 2H, N9CH3), 3.90 (q, J = 7.0 Hz, 6H, OCH3), 1.72 (m, 6H, OCH2CH2), 1.55-1.05 (m, 60H, OCH2CH2CH2CH3), 0.88 (t, J = 6.9 Hz, 6H, O(CH2CH2)2) ppm. 13C NMR (75 MHz, DMSO-d6): δ = 159.7, 153.9, 149.3, 142.9, 123.4, 38.2, 14.9 ppm. HRMS (ESI+): For C20H21N3O5S: 399.1380 [M+H]+. Found: 399.1367 [M+H]+.

2-amino-9-(3,4,5-tris(dodecyloxy)benzyl)-6-chloro-purine (G5Alk23): A suspension of 2-amino-6-chloropurine (2.0 g, 11.79 mmol) and K2CO3 (1.9 g, 14.15 mmol) in dry DMF (130 mL) was stirred at 40 ºC for 30 min. After solvent evaporation, the crude solid was purified by column chromatography on silica gel eluted with CHCl3/MeOH (50:1). G5Alk23 was obtained as a white solid (2.6 g, 74%). 1H NMR (300 MHz, CDCl3): δ = 7.70, 6.43, 5.34, 5.10, 3.90, 1.72, 1.55-1.05, 0.88 ppm. 13C NMR (75 MHz, DMSO-d6): δ = 159.7, 153.9, 149.3, 142.9, 123.4, 38.2, 14.9 ppm. HRMS (ESI+): For C33H55N3O5S: 594.3846 [M+H]+. Found: 594.3849 [M+H]+.
1.6 (m, 2H, N=C(CH2)3CH2H3), 1.3-1.1 (m, 2H, N=C(CH2)3CH2H3), 1.1-1.0 (m, 2H, OCH2CH2TMS). 0.84 (t, J = 7.1 Hz, 3H, CH3), 0.06 (s, 9H, Si(CH3)3) ppm. 13C NMR (75 MHz, C6D6): δ = 161.4, 159.2, 153.9, 139.1, 116.5, 64.8, 43.5, 31.8, 29.8, 29.4, 29.0, 29.0, 26.9, 22.6, 17.6, 14.0, 1.41 ppm. HRMS (ESI+): Calculated for C39H28N6O8Si: 690.1945 [M+H]+. Found: 690.1944 [M+H]+.

2-amino-6-(2-(trimethylsilyl)ethoxy)-9-ethyl-purine (G4Alk2): 1.6 (m, 2H, Ar-CH2), 1.26 (t, J = 7.2 Hz, 3H, CH2), 1.14 (m, 2H, OCH2CH2TMS), 1.1-1.0 (m, 2H, OCH2CH2TMS). 0.84 (t, J = 6.7 Hz, 3H, N=CH2CH2H3), 0.06 (s, 9H, Si(CH3)3) ppm. 13C NMR (75 MHz, C6D6): δ = 160.1, 159.0, 154.7, 135.2, 116.0, 65.0, 44.1, 31.9, 29.7, 29.5, 29.3, 29.1, 26.5, 22.7, 17.6, 14.1, 1.42 ppm. HRMS (ESI+): Calculated for C37H27N6SiO3Br: 670.1945 [M+H]+. Found: 670.1941 [M+H]+.

2-amino-8-bromo-6-(2-(trimethylsilyl)ethoxy)-9-ethyl-purine (G3Alk2): G3Alk2 was obtained following Standard Procedure D using G4Alk2 (0.63 g, 2.3 mmol) in CCl4 (10 mL) and NBS (0.04 g, 2.5 mmol), added over a period of 30 min. The reaction mixture was completed in 4 h. The crude solid 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 CHCl3/hexane (100:1), affording 0.60 g of G3Alk2 as a white solid (72% yield). 1H NMR (300 MHz, DMSO-d6): δ = 6.48 (bs, 2H, NH), 4.48 (m, 2H, OCH2CH2TMS), 4.02 (q, J = 7.1 Hz, 2H, N=CH2CH2H3), 1.26 (t, J = 7.2 Hz, 3H, CH2), 1.11 (m, 2H, OCH2CH2TMS), 0.06 (s, 9H, Si(CH3)3) ppm. 13C NMR (75 MHz, C6D6): 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 C37H27N6O3SiBr: 658.0693 [M+H]+. Found: 658.0693 [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 disopropylamine (7.5 eq) and nBuLi (2.5 M, 5.0 eq) in THF (volume indicated in each case) at -78 ºC. After 4 h, a solution of I2 (3.0 eq) in THF (volume indicated in each case) was added and the mixture was stirred at -78 ºC until the reaction was completed, which was monitored by TLC. The mixture was left to warm up to 0 ºC, followed by hydrolysis with NaHCl 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 Na2SO4 (sat). NaHCO3 (sat) and brine. The organic layer was then dried over MgSO4 and concentrated in vacuo. Purification methods are indicated in each case.

2-amino-8-iodo-6-(2-(trimethylsilyl)ethoxy)-9-ethyl-purine (G2a): Following Standard Procedure E, LDA was prepared from disopropyl amine (1.6 mL, 11.82 mmol) and a 2.5 M nBuLi 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 G4Alk2 (1.41 g, 1.58 mmol) in THF (21 mL) was added via cannula. The resulting mixture was stirred at -78 °C for 5 h. A solution of I2 (1.19 g, 4.7 mmol) in THF (10 mL) was added. Once the reaction was completed, saturated NaHCl (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 CH2Cl2 (3 x 15 mL). The combined organic layer was washed with Na2SO4 (sat) (1 x 30mL), NaHCO3 (sat) (1 x 30 mL) and brine (1 x 30 mL). The organic layer was dried over MgSO4 and the solvent was evaporated. The resulting solid was purified by column chromatography eluted with cyclohexane/AcOEt (5:1) to afford G2a as a white solid; m. p. 77-79 °C (977 mg, 60%). 1H NMR (300 MHz, CDCl3): δ = 6.46 (s, 2H, Ar-2,6), 5.07 (s, 2H, N=C(H3)2), 4.59-4.43 (m, 2H, O=C(CH3)2), 4.01-3.72 (m, 6H, OCH2CH2TMS), 3.97 (t, J = 7.2 Hz, 2H, N=CH2CH2H3), 2.58-2.45 (m, 2H, OCH2CH2TMS), 1.70 (s, 9H, Si(CH3)3) ppm. 13C NMR (75 MHz, CDCl3): δ = 161.0, 159.3, 155.0, 153.2, 137.9, 130.5, 118.5, 106.2, 79.7, 73.0, 69.1, 65.0, 48.5, 31.9, 30.3, 29.68, 29.59, 29.59, 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 C37H27N6O3Si: 620.1692 [M+H]+. Found: 620.1621 [M+H]+.

9-decy1-8-ethylguanine (G1Anne): G1Anne was prepared following Standard Procedure B. G3Anne (2.3 g, 4.9 mmol), Pd(PPh3)4Cl2 (68.6 mg, 0.10 mmol) and Cul (9.3 mg, 0.05 mmol) were dissolved in the THF/NES 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-3H2O (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 CHC13/MeOH (1:10). G1iso2 was obtained as a light yellow solid; m. p. > 250 ºC (1.1 g, 70%). 1H NMR (300 MHz, CDCl3): δ = 11.90 (bs, 1H, NHi), 6.57-6.24 (m, 3H, Ar-2,4,6), 5.16 (s, 2H, NPhC6H5), 3.86 (t, J = 6.5 Hz, 5H, OCH3), 3.35 (s, 1H, CSCH3), 1.88-1.58 (m, 6H, OCH2CH2CH2), 1.26 (m, 3OH, OCH2CH2(CH2)CH3, OCH2CH2), 0.98-0.72 (m, 6H, O(CH2)2CH2) ppm. 13C NMR (75 MHz, DMSO-d6): 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, 29.5, 29.48, 29.15, 29.62, 22.8, 14.2 ppm. HRMS (ESI+): Calculated for C22H24N3O7: 624.1673 [M+H]+. Found: 624.1671 [M+H]+.

9-ethyl-8-ethylguanine (G1Alk2): Following Standard Procedure A, a solution of the crude in DMSO (75 mL) was stirred for 30 min. Then, tert-butyl-bromocacetate (839 µL, 5.68 mmol) was added and the resulting mixture was stirred at 40 ºC overnight. The solvent was evaporated after completion and the residue was dissolved in CHCl3 (15 mL). The resulting mixture was stirred at reflux overnight. Then, the mixture was filtered and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography eluted with CHCl3/MeOH (1:10) obtaining G1Alk2 as a white solid; m. p. 104-139 ºC (8.17 g, 78%). 1H RNM (300 MHz, DMSO-d6): δ = 12.16 (bs, 1H, NHi), 11.89 (s, 1H, NHi), 7.51-7.26 (m, 10H, Ph), 2.77 (sept, J = 6.9 Hz, 1H, CHPr) ppm. 13C RNM (75 MHz, DMSO-d6): δ = 180.0, 154.3, 150.7, 147.2, 39.7, 34.7, 19.0 ppm. HRMS (FAB+): Calculated for CH3Cl+Br+N3O6: 300.0096 [M+H]+. Found: 300.0092 [M+H]+.

9-bromo-6-diphenylcarbamoyl-8-isobutyrylguanine (G12): To a suspensión of G1-9-bromo-8-isobutyrylguanine (G12) (2.67 g, 21.22 mmol), DMAP (51.53 mg, 0.42 mmol) and diphenylcarbamoyl chloride (5.89 g, 42.44 mmol) in CHCl3 (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 evaporated under reduced pressure. The crude was purified by column chromatography eluted with CHCl3/MeOH (1:10) obtaining G11 as a white solid; m. p. 140-141 ºC (8.17 g, 78%). 1H RNM (300 MHz, DMSO-d6): δ = 12.16 (bs, 1H, NHi), 11.89 (s, 1H, NHi), 7.51-7.26 (m, 10H, Ph), 2.77 (sept, J = 6.9 Hz, 1H, CHPr) ppm. 13C RNM (75 MHz, DMSO-d6): δ = 180.0, 154.3, 150.7, 147.2, 39.7, 34.7, 19.0 ppm. HRMS (FAB+): Calculated for C24H20N3O7: 604.1555 [M+H]+. Found: 604.1553 [M+H]+.

9-bromo-6-(2-tertbutylacetyl)-8-diphenylcarbamoyl-8-isobutyrylguanine (G10lo): Following Standard Procedure A, a solution of G11 (2.35 g, 4.74 mmol) and K2CO3 (0.8 g, 5.8 mmol) in dry DMF (60 mL) was stirred for 30 min. Then, tert-butyl-bromocacetate (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 CHCl3 (15 mL). The organic layer was washed with water (2 x 15 mL) and brine (20 mL) and dried over MgSO4. The solvent was removed under reduced pressure, affording G10lo as a white solid; m. p. 102-104 ºC (0.81 g, 28%). 1H RNM (300 MHz, CDCl3): δ = 7.75 (s, 1H, NHCOPr), 7.49-7.08 (m, 10H, Ph), 4.88 (s, 2H, CH2), 3.24 (sep, J = 6.8 Hz, 1H, CHPPr), 1.40 (s, 9H, CH3Bu), 1.27 (d, J = 6.8 Hz, 6H, CH2Pr) ppm. 13C RNM (75 MHz, DMSO-d6): δ = 176.1, 166.2, 158.3, 153.4, 151.8, 147.0, 129.1, 127.6, 126.9, 126.5, 124.1, 116.8, 82.3, 63.6, 34.9, 27.7, 19.0 ppm. HRMS (ESI+): Calculated for C23H19N3O7Br: 609.1455 [M+H]+. Found: 609.1459 [M+H]+.

Synthesis of the adenine derivatives.

2,6-diamino-9-decyl-purine (A42iso2): A42iso2 was obtained following Standard Procedure A using 2,6-diamino-purin (5.0 g, 33 mmol), K2CO3 (5.5 g, 40 mmol), 1-iododecane (8.6 mL, 40 mmol) and DMF (100 mL).

[Standard Procedure A]

9-(3,5-bis(dodecyl)oxy)-benzyl-8-ethylguanine (G1iso2): Following Standard Procedure A, 288 mg (8.87 mmol), K2CO3 (144 mg, 1.04 mmol) and 1-(chloromethyl)-3,5-bis(dodecyl)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 CHC13/MeOH (100:1). The residue was dissolved in the THF/MeOH mixture with Pd(PPh3)2Cl2 (12.3 mg, 0.0175 mmol) and CuI (17 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 reaction crude was dissolved in THF (10 mL) and TBAF-3H2O (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 CHCl3/MeOH (100:1). G1iso2 was obtained as a light yellow solid; m. p. 88-90 ºC (219.3 mg, 77%). 1H NMR (300 MHz, CDCl3): δ = 11.90 (bs, 1H, NHi), 6.57-6.24 (m, 3H, Ar-2,4,6), 5.16 (s, 2H, NPhC6H5), 3.86 (t, J = 6.5 Hz, 5H, OCH3), 3.35 (s, 1H, CSCH3), 1.88-1.58 (m, 6H, OCH2CH2), 1.26 (m, 3OH, OCH2CH2(CH2)CH3, OCH2CH2), 0.98-0.72 (m, 6H, O(CH2)2CH2) ppm. 13C NMR (75 MHz, DMSO-d6): 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, 29.5, 29.48, 29.15, 29.62, 22.8, 14.2 ppm. HRMS (ESI+): Calculated for C22H24N3O7: 624.1673 [M+H]+. Found: 624.1671 [M+H]+.
The reaction was completed overnight. After solvent evaporation, the crude was dissolved in CHCl₃ (200 mL) and washed with water (3 x 100 mL) and brine (100 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude solid was purified by column chromatography on silica gel eluted with CHCl₃/MeOH (50:1). A₄Alk₁₀ was obtained as a white solid (6.7 g, 69%). H NMR (300 MHz, DMSO-d₆): δ = 7.69 (s, 1H, N₉CH₂), 6.61 (bs, 2H, C₂NH₃), 5.75 (bs, 2H, C₂NH₃), 3.92 (t, J = 6.7 Hz, 2H, N₉CH₂CH₂CH₃), 1.8-1.6 (m, 2H, N₉CH₂CH₂CH₃), 1.3-1.1 (m, 14H, N₉(CH₂CH₂CH₂)₂CH₃), 0.84 (t, J = 6.5 Hz, 3H, CH₃) ppm. ¹³C NMR (75 MHz, DMSO-d₆): 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 C₁₅H₂₆IN₆: 417.1258 [M+H]+. Found: 417.1275 [M+H]+.

2.6-diamino-9-ethyl-8-iodo-purine (A₂Alk₁₀): A₂Alk₁₀ was obtained following Standard Procedure D using 2,6-diaminopurine (3.0 g, 20 mmol), K₂CO₃ (0.91 g, 6.5 mmol), 1-bodoethane (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 CHCl₃/MeOH (10:1), affording 0.8 g of A₂Alk₁₀ (67% yield). H NMR (300 MHz, DMSO-d₆): δ = 7.71 (s, 1H, N₉H), 6.64 (bs, 2H, C₂NH₃), 5.77 (bs, 2H, C₂NH₃), 3.97 (q, J = 7.3 Hz, 2H, N₉CH₂CH₃), 1.32 (t, J = 7.3 Hz, 3H, CH₃) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ = 160.2, 156.0, 151.3, 137.0, 37.3, 15.3. HRMS (ES⁺): Calculated for C₁₅H₂₆IN₆: 417.1258 [M⁺H]+. Found: 417.1230 [M⁺H]+.

2.6-diamino-8-bromo-9-decyl-purine (A₃Alk₁₀): A₃Alk₁₀ was obtained following Standard Procedure D using A₄Alk₁₀ (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 CHCl₃/MeOH (30:1), affording 0.9 g of A₃Alk₁₀ (38%) as an oil; m. p. 140-145 ºC (130 mg, 82%). H NMR (300 MHz, DMSO-d₆): δ = 6.67 (bs, 2H, C₂NH₃), 5.87 (bs, 2H, C₂NH₃), 3.90 (t, J = 7.1 Hz, 2H, N₉CH₂CH₂CH₃), 1.68 (m, 2H, N₉CH₂CH₂CH₃), 1.3-1.1 (m, 14H, N₉(CH₂CH₂CH₂)₂CH₃), 0.82 (t, J = 7.1 Hz, 3H, CH₃) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ = 160.3, 150.5, 152.7, 121.0, 113.5, 43.0, 31.2, 28.8, 28.7, 28.6, 25.9, 22.0, 13.9 ppm. HRMS (ES⁺): Calculated for C₁₅H₂₆IN₆Br: 369.1396 [M⁺H]+. Found: 369.1411 [M⁺H]+.

2.6-diamino-9-decyl-8-iodo-purine (A₂Alk₁₀): Iodine (2.3 g, 9.3 mmol) was added to a solution of 2,6-diaminopurine (3.0 g, 20 mmol), Na₂S₂O₅ (sat) (10 mL), and MeOH (10 mL) at room temperature. The reaction mixture was stirred at room temperature. After 10 min, a solution of 1H, 5IO₆ (1.3 g, 5.6 mmol) was added. The reaction was completed in 12 h. The mixture was concentrated under reduced pressure, dissolved in THF (15 mL) and TBAF·3H₂O (0.3 g, 0.9 mmol) was added. A₁Alk₁₀ was purified by column chromatography on silica gel eluted with CHCl₃/MeOH: (10:1) affording 0.8 g of A₁Alk₁₀ (51%). A₁Alk₁₀ can also been obtained following Standard Procedure B with A₃Alk₁₀ (0.91 g, 2.5 mmol), Pd(PPh₃)₂Cl₂ (36.1 mg, 0.05 mmol) and Cu (4.9 mg, 0.02 mmol) were dissolved in the THF/NEt₃ 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·3H₂O (0.9 g, 2.8 mmol) was added. A₁Alk₁₀ was purified by column chromatography on silica gel eluted with CHCl₃/MeOH: (20:1) affording A₁Alk₁₀ as a white solid (130 mg, 51%). A₁Alk₁₀ was obtained following Standard Procedure B.

2.6-diamino-9-decyl-8-ethyl-purine (A₁Alk₁₀): A₁Alk₁₀ was prepared following Standard Procedure B using 2,6-diaminopurine (3.0 g, 20 mmol), K₂CO₃ (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 CHCl₃/MeOH (10:1), affording 0.9 g of A₁Alk₁₀ (38%) as an oil; m. p. 140-145 ºC (130 mg, 82%). H NMR (300 MHz, DMSO-d₆): δ = 6.86 (bs, 2H, C₂NH₃), 5.94 (bs, 2H, C₂NH₃), 4.69 (s, 1H, C₂H₃), 3.98 (t, J = 6.9 Hz, 2H, N₉CH₂CH₂CH₃), 1.71 (m, 2H, N₉CH₂CH₂CH₂CH₃), 1.4-1.1 (m, 14H, N₉(CH₂CH₂CH₂)₂CH₃), 0.84 (t, J = 6.9 Hz, 3H, CH₃) ppm. ¹³C NMR (75 MHz, DMSO-d₆): 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 (ES⁺): Calculated for C₉H₁₁N₆: 203.1039 [M+H]+. Found: 203.1040 [M+H]+.

Synthesis of the isoguanine derivative.

9-ethyl-8-ethyl-isoguanine (iG₁Alk₂): iG₁Alk₂ was prepared following the same procedure than A₁Alk₂ but, before TMS-deroprotection, the crude mixture after the Sonogashira coupling was suspended in a 1:1 THF/H₂O mixture (18 mL). Then, a solution of NaN₃O (0.15 g, 2.2 mmol) in H₂O (2 mL) was added. The mixture was heated at 50 ºC and a 1:1 AcOH/H₂O 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 NH₃ was added until pH 8. The reaction mixture was concentrated under reduced pressure. Then, K₂CO₃ (0.15 g, 1.1 mmol) was added over a MeOH (10 mL) solution of the resulting crude salt. The reaction mixture was stirred at room temperature for 1 h. Until completion, after solvent evaporation the crude salt was purified by column chromatography on silica gel eluted with CHCl₃/MeOH (20:1). ⁴¹⁺ gave 1H NMR (300 MHz, DMSO-δ): δ = 11.0 (bs, 1H, N₃), 7.90 (bs, 2H, NH), 4.80 (s, 1H, C=NH), 3.97 (q, J = 7.2 Hz, 2H, N(CH₂CH₃)₂), 1.26 (t, J = 7.2 Hz, 3H, CH₂) ppm. ¹³C NMR (75 MHz, DMSO-δ): δ = 130.0, 85.5, 79.2, 73.2, 56.1, 45.9, 37.5, 14.7, 8.7 ppm. HRMS (ESI+): Calculated for C₉H₁₀N₅O: 204.0879 [M+H]⁺. Found: 204.0879 [M+H]⁺.

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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.

*N-8- Ethynylated Nucleobases