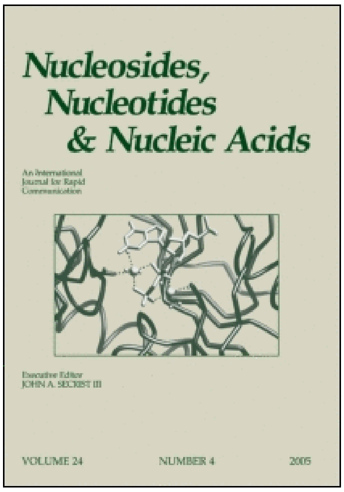

**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# New Purine Derivatives as Efficient Preparation of Nucleoside Analogs via Alkylation

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**To cite this Article** Lukin, Kirill A. , Yang, Chengxi , Bellettini, John R. and Narayanan, B. A.(2000) 'New Purine Derivatives as Efficient Preparation of Nucleoside Analogs via Alkylation', Nucleosides, Nucleotides and Nucleic Acids, 19: 4, 815 — 825

**To link to this Article: DOI:** 10.1080/15257770008035027
**URL:** http://dx.doi.org/10.1080/15257770008035027

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(4), 815–825 (2000)

# NEW PURINE DERIVATIVES FOR EFFICIENT PREPARATION OF NUCLEOSIDE ANALOGS VIA ALKYLATION.

Kirill A. Lukin,* ChengXi Yang, John R. Bellettini, B. A. Narayanan

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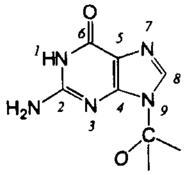
ABSTRACT. New diazabicycloundecenium and phosphazenium derivatives of purines are introduced for mild and efficient preparation of nucleoside analogs via *in situ* alkylation. Diazabicycloundecenium salts of purines were obtained directly as a result of an unusual reaction between two corresponding amino compounds.

The design and synthesis of novel nucleoside analogs with antiviral properties represents an important area of drug discovery.[1] A number of these compounds have already entered drug markets and more are being evaluated as drug candidates.[2]



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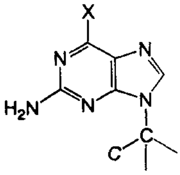

2: X=H, OH

Structurally, in many of the new generation nucleoside analogs the glycoside linkage at the 9-position of a purine molecule (*e.g.* in **1**) is replaced by a carbochain (**2**).[2] Most convergent synthesis of such compounds involves alkylation of a suitable purine derivative (**3**) with the corresponding alkyl bromide, tosylate *etc.* in the presence of a base (commonly potassium carbonate) as outlined in Eq. 1.

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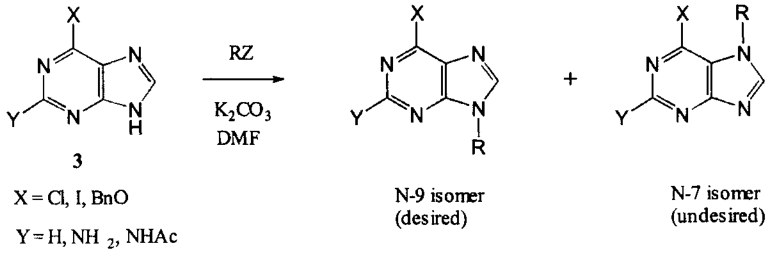


(1)

This synthetic route is usually complicated by two side reactions: a) alkylation of nitrogen at 7-position with the formation of a regioisomer (Eq. 1) and b) base induced decomposition of the alkylating agent and/or of certain purine derivatives themselves. While the improvement of the regioselectivity of these alkylations was targeted by many chemists,[3] the later side reactions were generally neglected as relatively stable or inexpensive substrates were involved. However, base induced decomposition does present a major problem when sensitive, functionally diverse alkylating agents are required for the synthesis of new complex drug candidates (*e.g.* ref. [4]), and it is desirable to develop reagents which allow alkylations to be conducted under *neutral* conditions.

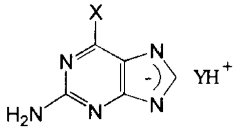
An obvious solution to this problem would be a utilization of preformed purine salts which themselves are not very basic. Initially such salts were prepared by lithiation of various purine derivatives with lithium hydride (Eq. 2). With hydrogen being a single byproduct this procedure allowed preparation of lithiated purines *in situ* - a great benefit for synthetic purposes. Unfortunately, these salts turned out to be very insoluble in organic solvents and required too harsh conditions for alkylations.

More recently quite soluble tetrabutylammonium salts of purines were introduced.[4,5] It was demonstrated that such salts could be efficiently alkylated under milder conditions in a variety of organic solvents.[4] However, the formation of tetrabutylammonium salts of purines requires the use of tetrabutylammonium hydroxide and produces one equivalent of water as a byproduct necessitating their isolation and drying prior to alkylation (Eq. 3).[4]

$$\text{H-PURINE} + \text{LiH} \longrightarrow \text{Li}^{+}(\text{PURINE})^{-} + \text{H}_2\uparrow \qquad (2)$$

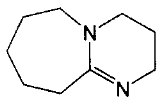
$$\text{H-PURINE} + \text{Bu}_4\text{NOH} \longrightarrow \text{Bu}_4\text{N}^{+}(\text{PURINE})^{-} + \text{H}_2\text{O} \qquad (3)$$

We thought if we could find strong and *neutral organic* bases that are capable of *complete* deprotonation of purines we might achieve *in situ* preparation of reasonably soluble purine salts which would be very beneficial for synthetic purposes. In this paper we report new types of these salts namely: diazabicycloundecenium **4a** – **6a** and phosphazenium **4b** – **6b**, and discuss their advantages for the synthesis of new nucleoside derivatives via alkylation.



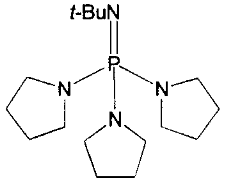
**4**: X = Cl
**5**: X = BnO
**6**: X = I

**a**: Y=



**7**

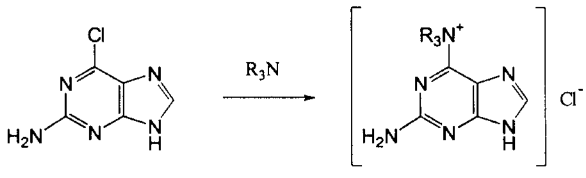
**b**: Y=



**8**

## Diazabicycloundecenium Salts of Purines.

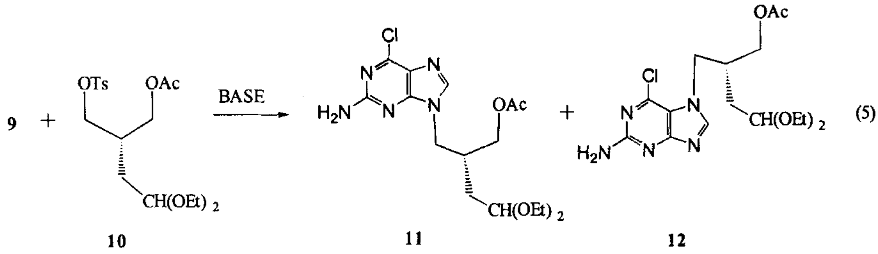
Amines provide a broad range of widely available organic bases. Although electronic and steric effects could substantially alter their basicities[6] amino compounds typically do not react with each other irreversibly with the formation of stable ammonium amides. We hoped that exceptions to this rule could be found in the chemistry of relatively acidic purine derivatives like chloropurine **9**. However, the literature was mostly unsupportive on this idea: it had been demonstrated that primary, secondary, and even some tertiary amines (*e.g.* trimethylamine and diazabicyclooctane) did not deprotonate chloropurine **9** but substituted halogen instead (Eq. 4).[7,8] We could find only one example of successful alkylation of N-acetylguanines using diisopropylethylamine (Hünig's base) .[9]



**9**

(4)

Our attempts to use Hünig's base for the preparation of compound **11** – an intermediate in the synthesis of antiviral ABT-606[10]- *via* alkylation of 2-amino-6-chloropurine (**9**) with tosylate **10** were not rewarding. No purine salt formation was observed and only traces of products were formed when the alkylating agent was added. Similar results were obtained using other tertiary amines (*e.g.* *N*-methylpiperidine).



However, when diazabicycloundecene (DBU, 7) was used as a base a surprisingly clean reaction was observed. This result was quite unexpected as DBU was believed to be less basic then Hünig's base.[11] In addition, DBU is known to be an excellent eliminating agent (in particular in aprotic solvents and at elevated temperatures) so primarily decomposition of the alkylating agent was expected in reaction 5 under these conditions.[12] To account for the clean alkylation we suggested that DBU is capable of deprotonating purine **9**.

Indeed, the typically very poorly soluble compound **9** went into solution in a couple of minutes when treated with one equivalent of DBU in DMF. Later this solution precipitated salt **4a** which was obtained in 90 % yield. The same salt could be prepared in THF.

The structure of **4a** was supported by its $^1H$ and $^{13}C$ NMR spectra. Comparisons of $^1H$ NMR spectra of compound **4a** with those of neutral chloropurine **9** and its tetrabutylammonium salt (**4c**, $Y = Bu_4N$) supported ionic character of **4a**. Thus chemical shifts from protons at $C^8$ recorded in DMSO-$d_6$ were 8.1 for **9** and 7.7 and 7.6 ppm for **4a** and **4c** respectively.

Similar salts were obtained from other synthetically important purine derivatives namely, 2-amino-6-benzyloxypurine and 2-amino-6-iodopurine (compounds **5a** and **6a** respectively). At this point we cannot conclude whether the underestimation of the basicity of DBU or an additional interaction between DBU and purine system should account for the unusual formation of these salts. We hope to comment on this matter in due course.

We have found that diazabicyloundecenium salts of purines (**4a** – **6a**) could be used in alkylation reactions with similar efficiency as their corresponding tetrabutylammonium salts. However, for synthetic purposes the former could be prepared and used *in situ* – a valuable benefit over tetrabutylammonium salts which need to be isolated. The details will be discussed in a later section of this paper.

## Phosphazenium Salts of Purines.

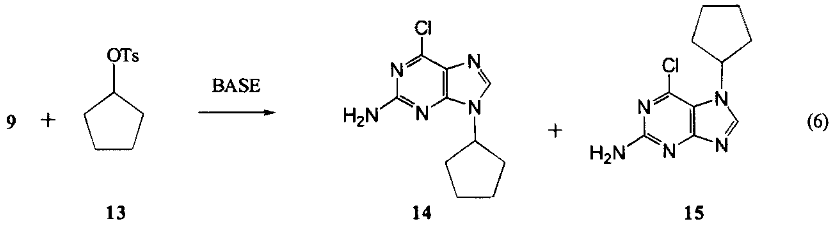
A few years ago Schwesinger introduced phosphazenes (*e.g.* **8**) as powerful organic bases.[13] With basicities about a thousand times higher than those of amines there were no doubts that these compounds would deprotonate purines irreversably.[13] Indeed when the above purines were treated with one equivalent of the most available phospazene base **8** in DMF or THF homogeneous solutions were formed shortly. We have found that phosphazenium salts **4b** – **6b** could be alkylated under very mild conditions such as in THF at 35 - 40 °C with the yields of the products approaching quantitative. These salts would be reagents of choice when sensitive alkylation agents have to be used.

## Comparison of the Efficiency of Alkylations of Various Purine Derivatives.

In order to compare alkylations of new purine salts with literature procedures we have performed a series of side by side experiments in which the yields of the products were obtained from HPLC potency determinations measured relative to the corresponding pure isolated materials as described in the Experimental section. The results are summarized in Table 1 and some general comments are provided below.

As might be expected the use of preformed neutral salts of purines had minimum advantage over classic reaction conditions involving potassium carbonate as a base when alkylating reagents were not base sensitive. Such chemical behavior was observed in alkylations of chloropurine **9** and its salts with tosylate **10** (Eq. 5; Table 1, entries 1 - 6).

Utilization of purine salts was clearly beneficial in combination with base sensitive alkylating agents. For example reaction of chloropurine **9** with tosylate **13** (Eq. 6; Table 1, entries 7 - 12) gave a complex mixture of products in the presence of potassium carbonate. The problem was circumvented by using either tetrabutylammonium or DBU salts of the purine. The highest yield was obtained from phosphazenium salt **4b** in THF as the solvent (Entry 11) indicating that tosylate **13** had limited stability in more polar solvents such as DMF and DMSO commonly used in these type of rections.



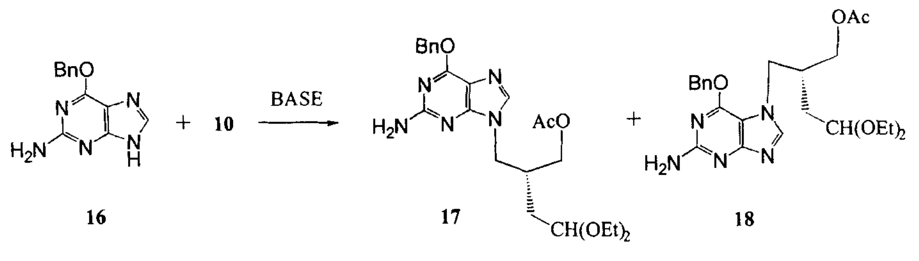
(6)

**TABLE 1.** Comparative Alkylations of Various Purines.[a)]

| Entry | Purine | Tosylate | Solvent | Yield (%)<br>9 + 7-isomers | Ratio<br>9 to 7-isomer |
|---|---|---|---|---|---|
| 1 | **9**[b)] | **10** | DMF | 86 | 4.2 |
| 2 | **4a** | **10** | DMF | 79 | 4.1 |
| 3 | **4a** | **10** | DMSO | 85 | 4.0 |
| 4 | **4b** | **10** | DMF | 91 | 4.7 |
| 5 | **4b** | **10** | THF | 91 | 5.9 |
| 6 | **4c**[c)] | **10** | DMF | 86 | 5 |
| 7 | **9**[b)] | **13** | DMF | 59 | 3.3 |
| 8 | **4a** | **13** | DMF | 75 | 3.0 |
| 9 | **4a** | **13** | DMSO | 66 | 3.4 |
| 10 | **4b** | **13** | DMF | 80 | 3.8 |
| 11 | **4b** | **13** | THF | 83 | 4.8 |
| 12 | **4c**[c)] | **13** | DMF | 75 | 3.7 |
| 13 | **16**[b)] | **10** | DMF | 57 | 1.1 |
| 14 | **5a** | **10** | DMF | 85 | 1.6 |
| 15 | **5a** | **10** | DMSO | 81 | 1.7 |
| 16 | **5b** | **10** | DMF | 89 | 1.9 |
| 17 | **5b** | **10** | THF | 91 | 1.5 |
| 18 | **5c**[c)] | **10** | DMF | 87 | 1.9 |

a) reaction conditions: 15 h, 45 °C; b) in the presence of 1.85 equivalents of $K_2CO_3$; c) tetrabutylammonium salt.

Salts **5a-c** also gave distinctly better results in alkylations of 2-amino-6-benzyloxy-purine - another purine derivative extensively used in synthesis (Eq. 7, Table 1, entries 13 - 18). This reaction was sluggish in the presence of potassium carbonate and left a lot of unreacted starting material (probably as a result of lower acidity of benzyloxypurine).



(7)

Noteworthy, in all alkylations described above we did not observe significant differences in the ratios of isomeric products. These findings are in line with earlier literature data that the subtituents on purine rather than solvent or cationic component of the salt affect these ratios.[3]

In conclusion, we have introduced new diazabicycloundecenium and phosphazenium salts of purines (**4a,b** – **6a,b**) for the preparation of their alkylated derivatives. Similar to the previously reported tetrabutylammonium salts, these neutral reagents are designed to eliminate the use of a base in reactions of purines with alkylating agents which decompose under basic conditions. However, unlike tetrabutylammonium salts, the new purine derivatives (**4a,b** – **6a,b**) can be simply prepared *in situ* by mixing equimolar amounts of the corresponding components as no side products are formed and no purification is required. Phosphazenium salts gave the highest yields of alkylated products under very mild conditions and should be the reagents of choice when sensitive or expensive nucleoside analogs need to be prepared.

## EXPERIMENTAL

**Typical Procedure for Comparative Alkylation of Various Purine Derivatives.** Purine (3.6 mmol), a base (3.6 mmol)[14] and a solvent [THF (4.5 mL), DMF (3 mL),or DMSO (2.5 mL)] were stirred at 40 – 41 °C for 15 h under nitrogen atmosphere. The reaction mixture was transferred into a 25 mL volumetric flask and diluted with THF to the volume. An aliquot of this solution (2 ± 0.02 mL) was transferred into another 25 ml flask and diluted with water (0.5 mL) and THF to the volume. Resulting solution was analyzed by HPLC for the peak area of the desired product. The yield was obtained by adjusting to the corresponding peak area of a known amount of the isolated pure material. Each reaction was repeated at least twice. Each HPLC analysis – three times. The accuracy of analyses was within 3 % range. The ratios of isomeric alkylation products were determined from $^1$H NMR spectra (300 or 400 MHz, DMSO-$d_6$) of crude reaction mixtures (after solvent removal or from reactions ran in DMSO-$d_6$ directly) by integration of sharp singlets from protons at *C*.$^8$ The results are summarized in Table 1.

**Alkylation of 2-Amino-6-chloropurine with Tosylate (10). Synthesis Chloropurine Acetates 11 and 12.** *tert*-Butyliminotri(pyrrolidino)phosphorane (1.1 g, 3.6 mmol) was added to a slurry of 2-amino-6-chloropurine (**9**) in THF (4 mL). The mixture was heated to 40 °C stirred for 10 min and tosylate **10** ( g, 3.3 mmol) was added via syringe. The mixture was stirred at 40 – 43 °C overnight. The solvent was evaporated and the residue was diluted with methyl *tert*-butyl ether (10 mL), water (5 mL) and brine (5 mL). Organic layer was separated and aqueous layer was extracted with toluene (2 x 10 mL). The combined organic layer was washed with water (25 mL) and concentrated under vacuum. The residue was slurried in methyl *tert*-butyl ether (12 mL) and water (0.1 mL) then filtered. The filtercake was washed with methyl *tert*-butyl ether (mL) and dried to provide 7-isomer **12** (0.1 g, 10 %).The filtrate was concentrated in vacuo and slurried with hexane (10 mL) and methyl *tert*-butyl ether (1 mL). The resulting solid was filtered and dried to provide isomer **11** (0.73 g, 71%).

For **(R)-2-amino-6-chloro-9-(2-acetoxymethyl-4,4,-diethoxybutyl)purine (11)** $^1$H NMR (DMSO-$d_6$, δ): 1.1 (m, 6 H), 1.55 (m, 2 H), 1.98 (s, 3 H), 2.45 (m, 1 H), 3.3 – 3.6 (m, 6 H), 3.95 (d, 2 H), 4.1 (d, 2 H), 4.5 (t, 1 H), 6.9 (s, 2 H), 8.15 (s, 1 H). $^{13}$C NMR (DMSO-$d_6$, δ): 15.1 (2 C, $CH_3$), 20.5 (CH), 32.7 ($CH_2$), 33.9 ($CH_3$), 44.8 ($CH_2$), 60.6 ($CH_2$), 61.0 ($CH_2$), 64.2 ($CH_2$), 100.4 (CH), 123.2 (C), 143.5 (CH), 149.3 (C), 154.4 (C), 159.7 (C), 170.2 (C). Anal. Calcd. for $C_{16}H_{24}ClN_5O_4$: C, 49.81; H, 6.27; N, 18.15. Found: C, 50.24; H, 6.41; N, 17.94.

For **(R)-2-amino-6-chloro-7-(2-acetoxymethyl-4,4,-diethoxybutyl)purine (12)**. $^1$H NMR (DMSO-$d_6$, δ): 1.01 (t, 7 Hz, 3 H), 1.04 (t, 7 Hz, 3 H) 1.42 – 1.67 (m, 2 H), 1.91 (s, 3 H), 2.40 (m, 1 H), 3.2 – 3.6 (m, 6 H), 3.95 (d, 5.1 Hz, 2 H), 4.3 (m, 2 H), 4.44 (t, 5.2 Hz, 1 H), 6.75 (s, 2 H), 8.35 (s, 1 H). $^{13}$C NMR (DMSO-$d_6$, δ): 15.1 (2 C, $CH_3$), 20.5 (CH), 32.6 ($CH_2$), 35.0 ($CH_3$), 48.28 ($CH_2$), 60.6 ($CH_2$), 61.0 ($CH_2$), 64.2 ($CH_2$), 100.2 (CH), 114.9 (C), 142.2 (C), 149.9 (CH), 159.9 (C), 164.3 (C), 170.1 (C). Anal. Calcd. for $C_{16}H_{24}ClN_5O_4$: C, 49.81; H, 6.27; N, 18.15. Found: C, 50.15; H, 6.19; N, 17.84.

Alkylations of chloropurine **9** with tosylate **13**, and of benzyloxypurine **16** with tosylate **10** were performed in the described above manner, however, in those cases the regioisomers were separated by column chromatography.

For **2-amino-6-chloro-9-cyclopentylpurine (14)** $^1$H NMR (DMSO-$d_6$, δ): 1.65 - 1.80 (m, 2 H), 1.82 - 2.09 (m, 4 H), 2.16 (m, 2 H), 4.76 (m, 1 H), 6.96 (s, 2 H), 8.27 (s, 1 H); $^{13}$C NMR (DMSO$d_6$, δ): 23.4 (2 C, $CH_2$), 31.6 (2 C, $CH_2$), 55.3 (CH), 123.7 (C), 141.5 (CH), 149.3 (CH), 153.9 (C), 159.5 (C), 159.5 (C).[15]

For **2-amino-6-chloro-7-cyclopentylpurine (15)** $^1$H NMR (DMSO-$d_6$, δ): 1.70 - 1.95 (m, 4 H), 1.95 - 2.1 (m, 2 H), 2.15 – 2.30 (m, 2 H), 5.11 (m, 1 H), 6.67 (s, 2 H), 8.53 (s, 1 H); $^{13}$C NMR (DMSO-$d_6$, δ): 23.1 (2 C, $CH_2$), 32.6 (2 C, $CH_2$), 58.0 (CH), 115.1 (C), 142.2 (C), 146.5 (CH), 153.9 (C), 159.5 (C), 159.5 (C), 164.3 (C).[15]

For **(R)-2-amino-6-benzyloxy-9-(2-acetoxymethyl-4,4,-diethoxybutyl)purine (17)** $^1$H NMR (DMSO-$d_6$, δ): 1.04 (t, 7.0 Hz, 3 H), 1.06 (t, 7.0 Hz, 3 H), 1.50 (m, 2 H), 1.98 (s, 3 H), 2.43 (m; 1 H), 3.3 – 3.6 (m, 6 H), 3.85 - 4.15 (m, 4 H), 4.48 (t, 5.6 Hz,1 H), 5.50 (s, 2 H), 6.44 (s, 2 H),7.3 – 7.45 (m, 3 H), 7.5 (m, 2 H), 7.86 (s, 1 H). $^{13}$C NMR (DMSO-$d_6$, δ): 15.2 (2 C, $CH_3$), 20.5 (CH), 32.7 ($CH_2$), 34.0 ($CH_3$), 44.4 ($CH_2$), 60.5 ($CH_2$), 61.0 ($CH_2$), 64.2 ($CH_2$), 66.8 ($CH_2$), 100.4 (CH), 113.6 (C), 128.0 (CH), 128.3 (2 C, CH), 128.4 (2 C, CH), 136.7 (C), 140.2 (CH), 154.7 (C), 159.6 (C), 160.0 (C), 170.3 (C). FAB-MS: 458 ($MH^+$).

For **(R)-2-amino-6-benzyloxy-7-(2-acetoxymethyl-4,4,-diethoxybutyl)purine (18)** $^1$H NMR (DMSO-$d_6$, δ): 0.97 (t, 7.0 Hz, 3 H), 1.00 (t, 7.0 Hz, 3 H), 1.35 – 1.6 (m, 2 H), 1.88 (s, 3 H), 2.40 (m, 1 H), 3.2 – 3.5 (m, 6 H), 3.86 (m, 2 H), 4.14 (m, 2 H), 4.25 (t, 5.6 Hz,1 H), 5.50 (m, 2 H), 6.20 (s, 2 H),7.3 – 7.45 (m, 3 H), 7.5 (m, 2 H), 8.09 (s, 1 H). $^{13}$C NMR (DMSO-$d_6$, δ): 15.1 (2 C, $CH_3$), 20.4 (CH), 32.4 ($CH_2$), 35.0 ($CH_3$), 48.7 ($CH_2$), 60.4 ($CH_2$), 60.9 ($CH_2$), 64.1 ($CH_2$), 67.1 ($CH_2$), 100.3 (CH), 105.7 (C), 128.0 (CH), 128.1 (CH), 128.4 (2 C, CH), 136.3 (C), 145.9 (CH), 156.3 (C), 159.6 (C), 164.2 (C), 170.2 (C). FAB-MS: 458 ($MH^+$).

**Preparation of Diazabicycloundecenium Salts of 2-Aminopurines (4a, 5a, 6a).** 2-Aminopurine (3 mmol), 1,8-diazabicyclo[5.4.0]undecene (0.46 g, 3 mmol), and DMF (2.5 mL) or THF (5 mL) were mixed at room temperature for 0.5 h. The precipitate was filtered off, washed with *t*-butyl methyl ether (10 mL), and dried under vacuum to give salts **4a** –**6a**.

Diazabicycloundecenium salt of 2-amino-6-chloropurine (**4a**) was obtained in 90 % yield. $^1$H NMR (DMSO-$d_6$, δ): 1.5 - 1.7 (m, 6 H), 1.89 (m, 2 H), 2.68 (m, 2 H), 3.27 (m, 2 H), 3.43 (m, 2 H), 3.50 (m, 2 H), 5.69 (s, 2 H), 7.70 (s, 1 H). $^{13}$C NMR (DMSO-$d_6$, δ): 19.1 ($CH_2$), 23.5 ($CH_2$), 26.1 ($CH_2$), 28.3 ($CH_2$), 31.7($CH_2$), 37.8 ($CH_2$), 47.8 ($CH_2$), 53.2 ($CH_2$), 126.2 (C), 145.1 (C), 153.4 (CH), 157.4 (C), 164.5 (C), 165.0 (C).

Diazabicycloundecenium salt of 2-amino-6-benzyloxypurine (**5a**) was obtained in 80 % yield. $^{1}$H NMR (DMSO-$d_6$, δ): 1.6 (m, 6H), 1.8 (m, 2 H), 2.5 (m, 2 H), 3.18 (m, 2 H), 3.25 – 3.4 , m, 4 H), 5.48 (s, 2 H), 5.93 (s, 2 H), 7.25 – 7.45 (m, 3 H), 7.5 (m, 2 H), 7.71 (s, 1 H). $^{13}$C NMR (DMSO-$d_6$, δ): 19.8 ($CH_2$), 24.1 ($CH_2$), 26.6 ($CH_2$), 28.5 ($CH_2$), 32.5 ($CH_2$), 38.9 ($CH_2$), 47.7 ($CH_2$), 52.8 ($CH_2$), 66.4 ($CH_2$), 113.8 (C), 127.8 (CH), 128.3 (4C, CH), 137.2 (C), 143.5 (CH), 158.5 (C), 159.0 (C), 160.1 (C), 163.9 (C).

Diazabicycloundecenium salt of 2-amino-6-iodopurine (**6a**) was obtained in 92 % yield. $^{1}$H NMR (DMSO-$d_6$, δ): 1.5 – 1.7 (m, 6 H), 1.9 (m, 2 H), 2.62 (m, 2 H), 3.27 (t, 6 Hz, 2 H), 3.44 (t, 6 Hz, 2 H), 3.52 (m, 2 H), 5.67 (s, 2 H), 7.66 (s, 1 H). $^{13}$C NMR (DMSO-$d_6$, δ): 19.1 ($CH_2$), 23.5 ($CH_2$), 26.1 ($CH_2$), 28.3 ($CH_2$), 31.6 ($CH_2$), 37.8 ($CH_2$), 47.8 ($CH_2$), 53.2 ($CH_2$), 118.6 (C), 133.5 (C), 151.6 (CH), 157.6 (C), 159.6 (C), 165.1 (C).

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2) *Lobucavir*, *Drugs of the Future*, **1997**, ***22***, 359–370.

3) See, for example: Green, G. R., Grinter; T. J., Kincey, P. M.; Jarvest, R. L. *Tetrahedron*, **1990**, ***16***, 6903-6914.

4) Bisacchi, G. S.; Singh, J.; Godfrey, J. D.; Kissick, T. P.; Mitt, T.; Malley, M. F.; Di Marco, J. D.; Gougoutas, J. Z.; Mueller, R. H.; Zahler, R. *J. Org. Chem.* **1995**, ***60***, 2902–2905.

5) Hagberg, C.-E.; Johansson, K. N.-G.; Kovacs, Z. M. I.; Stening, G. B. *Eur. Pat. Appl.* 55239, **1981**.

6) Amines basicity increases substantially in aprotic solvents. For the p*K*a values obtained in acetonitrile see: a) Leffek, K. T.; Pruszynski, P.; Thanapaalasinghham, K. *Can. J. Chem.* **1989**, ***67***, 590-595 , b) Footnote 11 in ref. 13.

7) Ashwell, M.; Bleasdale, C.; Golding, B. T.; O'Neill, I. K. *J. Chem. Soc. Chem. Commun.*, **1990**, 955-956.

8) Linn, J. A.; McLean, E. W.; Kelley, J. L. *J. Chem. Soc. Chem. Commun.*, **1994**, 913-914.

9) Breipohl, G.; Will, D. W.; Peyman, A.; Uhlmann, E. *Tetrahedron*, **1997**, *43*, 14671–14686.

10) ABT-606 is an antiviral found to be active against Herpes Zoster.

11) DBU was reported to be ~ 5 times less basic then diisopropylethylamine in acetonitrile. See footnote 11 in ref. 13.

12) Not surprising that DBU was used only for purine alkylations via Michael additions. We could find only one example of *intramolecular* alkylation of a mesylate using DBU: Secrist, J. A. *Carbohydrate Res.*, **1975**, *42*, 379-381.

13) Schwesinger, R. *Chimia*, **1985**, *39*, 269-272.

14) No base was added when preformed tetrabutylammonium salts of purines were used. Potassium carbonate was used in excess (1.85 equivalent)

15) For literature data see: Toyota, A.; Katagiri, N.; Kaneko, C. *Heterocycles*, **1993**, *36*, 1625 – 1629.