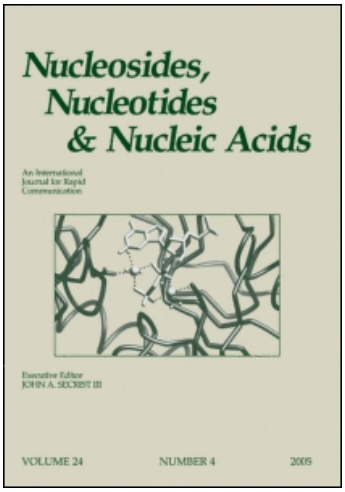


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

SYNTHESIS OF 8-AMINO AND 8-SUBSTITUTED AMINO DERIVATIVES OF ACYCLIC PURINE NUCLEOSIDE AND NUCLEOTIDE ANALOGS. ALKYLATION OF 8-SUBSTITUTED PURINE BASES

Z. Janeba[a]; A. Holý[a]
[a] Academy of Sciences of the Czech Republic, Institute of Organic Chemistry and Biochemistry, Prague, Czech Republic

Online publication date: 31 March 2001

To cite this Article Janeba, Z. and Holý, A.(2001) 'SYNTHESIS OF 8-AMINO AND 8-SUBSTITUTED AMINO DERIVATIVES OF ACYCLIC PURINE NUCLEOSIDE AND NUCLEOTIDE ANALOGS. ALKYLATION OF 8-SUBSTITUTED PURINE BASES', Nucleosides, Nucleotides and Nucleic Acids, 20: 4, 1103 — 1106
To link to this Article: DOI: 10.1081/NCN-100002498
URL: http://dx.doi.org/10.1081/NCN-100002498

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4–7), 1103–1106 (2001)

SYNTHESIS OF 8-AMINO AND 8-SUBSTITUTED AMINO DERIVATIVES OF ACYCLIC PURINE NUCLEOSIDE AND NUCLEOTIDE ANALOGS. ALKYLATION OF 8-SUBSTITUTED PURINE BASES

Z. Janeba* **and A. Holý**

Institute of Organic Chemistry and Biochemistry,
Academy of Sciences of the Czech Republic,
Prague, Czech Republic

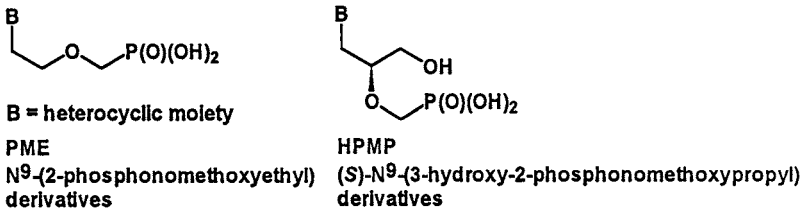
ABSTRACT

Two synthetic approaches were used for preparation of 8-amino-, 8-methylamino-, and 8-dimethylaminoadenine and -guanine analogs of PME and HPMP series: (a) direct modification of 8-bromopurine acyclic nucleotide analogs at the 8-position of the base, (b) alkylation of 8-modified purine bases with alkylation agents.

8-Substituted purine derivatives occupy significant position in N&N chemistry. The importance of these compounds as potential antiviral and anticancer agents is obvious. Among them, 8-hydroxy derivatives (e.g. 8-hydroxyguanine (1)), 8-mercapto derivatives (8-mercaptoguanosine (2)), and 8-amino derivatives (e.g. 8-aminoguanine (1) or 8-amino-9-benzylguanine (3,4)) should be particularly mentioned.

This work is a continuation of the structure-activity relationship study in the series of N-(2-phosphonomethoxyethyl) (PME) and (*S*)-N-(3-hydroxy-2-phosphonomethoxy-propyl) (HPMP) derivatives (5–7) of purine bases which concerns the effect of the substitution at the 8-position on the antiviral and/or cytostatic activity in these series.

*Corresponding author.

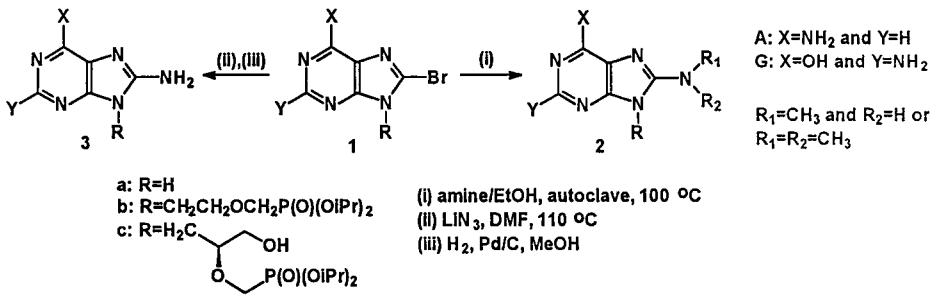


There are two principal approaches for preparation of 8-substituted purine acyclic nucleoside and nucleotide analogs, either modification of the corresponding derivative at the 8-position of purine moiety or, preparation of the appropriate 8-substituted purine base and its subsequent alkylation.

In our previous work (8–10), syntheses of 8-hydroxy-, 8-mercapto-, and 8-methylthio-purine derivatives of PME and HPMP type were performed by these two approaches.

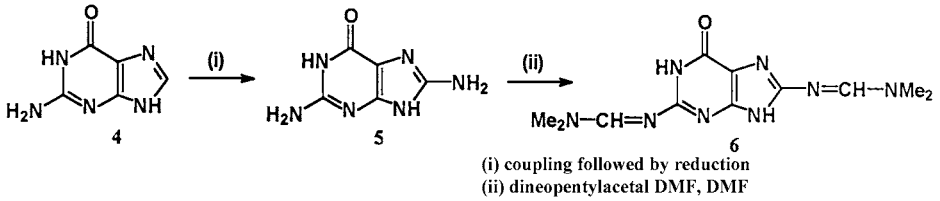
Acyclic nucleotide analogs **2** containing methylamino and dimethylamino group at the 8-position of purine moiety were prepared by the reaction of the appropriate 8-bromo derivatives **1** with the solution of methylamine or dimethylamine in ethanol (33%) in an autoclave at 100°C for 15 h (Scheme 1). The reaction of 8-bromo derivatives **1** with LiN_3 in DMF at 110°C followed by catalytic hydrogenation on Pd/C in methanol afforded the corresponding 8-amino derivatives **3** only in adenine series. Conversion of 8-bromo-guanine analogs to the 8-aminoguanine derivatives was unsuccessful. The phosphonate diesters were cleaved by the standard procedure using TMSBr in acetonitrile followed by hydrolysis and standard isolation of the free phosphonates.

8-Aminoadenine (**3a A**) and 8-dimethyladenine (**2a A**) as starting compounds for subsequent alkylations were prepared by the same procedure as in the case of acyclic nucleotide analogs (Scheme 1). Synthesis of 8-aminoguanine (**5**) was performed by the coupling of diazotized 4-chloroaniline with guanine, followed by reduction with sodium hydrosulfite (11). To improve its solubility and reactivity, 8-aminoguanine (**5**) was converted to the bis(N-dimethylaminomethylene) derivative **6** (Scheme 2).



Scheme 1.

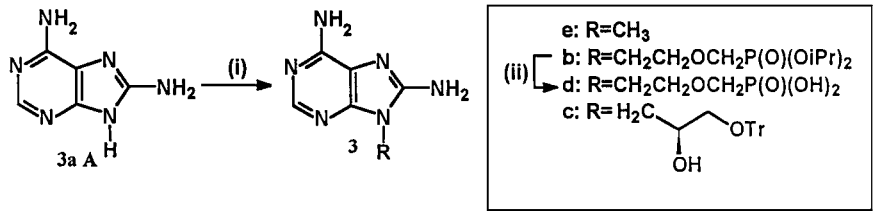
MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



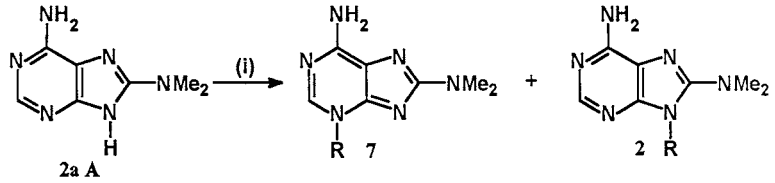
Scheme 2.

Alkylations of 8-aminoadenine (**3a A**), 8-dimethylaminoadenine (**2a A**), and protected 8-aminoguanine **6** were performed with diverse alkylation agents: methyl tosylate, diisopropyl [(2-chloroethoxy)methyl]phosphonate, (*S*)-tritylglycidol.

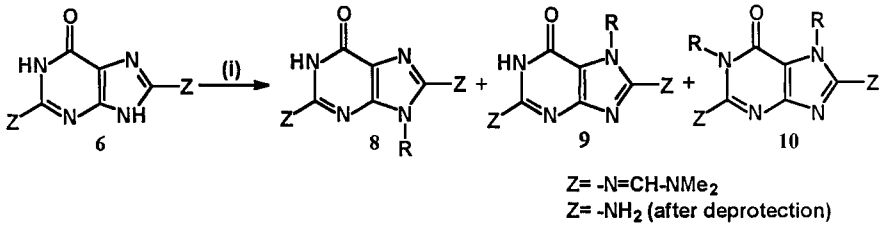
Alkylation of 8-aminoadenine (**3a A**) afforded largely its N^9-substituted derivatives **3** (Scheme 3a), alkylation of 8-dimethylaminoadenine (**2a A**) a mixture of N^3- and N^9-regioisomers **7** and **2** (Scheme 3b), and alkylation of 8-amino-2,



Scheme 3a.



Scheme 3b.



Scheme 3c.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

8-bis(N-dimethylaminomethylene)guanine (**6**) gives a rich mixture of products, from which N^9- and N^7-monosubstituted derivatives **8** and **9** and N (1,7)-disubstituted derivatives **10** were isolated as main components (Scheme 3c).

Different independent methods for preparation of acyclic nucleoside and nucleotide analogs derived from 8-amino and 8-substituted aminopurine bases were used. These are: (a) modification of 8-bromoadenine at 8-position of the base, (b) alkylation of 8-modified bases with diverse alkylation agents. The first method is direct and most convenient one, and good yields of products can be achieved. The second method, the base alkylation, can make accessible other regioisomers.

ACKNOWLEDGMENTS

This study was supported by the Czech State Grant Agency (grant #203/96/K001) and by Gilead Sciences (Foster City, CA, USA).

REFERENCES

1. Doskočil, J.; Holý, A. *Collect. Czech. Chem. Commun.* **1977**, *42*, 370.
2. Reitz, A. B. et al: *J. Med. Chem.* **1994**, *37*, 3561.
3. Daddona, P. E.; Wiecmann, W. P.; Milhouse, W.; Chern, J. W.; Townsend, L. B.; Hersfield, M. S.; Webster, H. K. *J. Biol. Chem.* **1986**, *261*, 11667.
4. Shewach, D. S.; Chern, J. W.; Pillote, K. E.; Townsend, L. B.; Daddona, P. E. *Cancer. Res.* **1986**, *46*, 519.
5. De Clercq, E.; Baba, M.; Pauwels, R.; Balzarini, J.; Rosenberg, I.; Holý, A. *Antiviral Res.* **1987**, *8*, 261.
6. Balzarini, J.; Naesens, L.; Herdewijn, P.; Rosenberg, I.; Holý, A.; Pauwels, R.; Baba, M.; Johns, D. G.; De Clercq, E. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 332.
7. Holý, A. *Collect. Czech. Chem. Commun.* **1993**, *58*, 649.
8. Janeba, Z.; Holý, A.; Masojídková, M. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1126.
9. Janeba, Z.; Holý, A. *Collect. Czech. Chem. Commun.-Symp. Ser.* **1999**, *2*, 260.
10. Janeba, Z.; Holý, A. XXII. Conference of Organic Chemists on Advances in Organic Chemistry, Častá-Papiernička, Slovak Republic, June 11–13, 1997.
11. Beaman, A. G.; Jones, J. W.; Robins, R. K. in Synthetic Procedures in Nucleic Acid Chemistry (Zorbach W. W. and Tipson R.S.; Eds.), Vol. 1, p. 41, 1968.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Request Permission or Order Reprints Instantly!