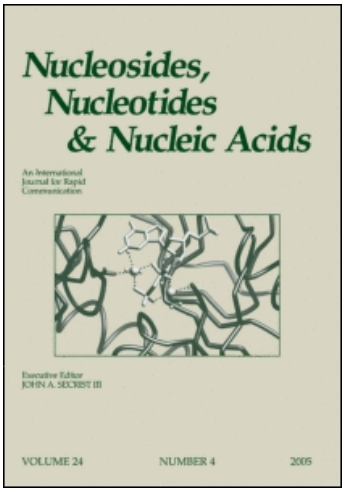


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Selective Metalation of 6-Methylpurines: Synthesis of 6-Fluoromethylpurines and Related Nucleosides

Abdalla E. A. Hassan[a]; William B. Parker[a]; Paula W. Allan[a]; John A. Montgomery[a]; John A. Secrist III[a]
[a] Drug Discovery Division, Southern Research Institute, Birmingham, Alabama, USA

Online publication date: 09 August 2003

To cite this Article Hassan, Abdalla E. A. , Parker, William B. , Allan, Paula W. , Montgomery, John A. and Secrist III, John A.(2003) 'Selective Metalation of 6-Methylpurines: Synthesis of 6-Fluoromethylpurines and Related Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 747 — 749
To link to this Article: DOI: 10.1081/NCN-120022625
URL: http://dx.doi.org/10.1081/NCN-120022625

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 747–749, 2003

Selective Metalation of 6-Methylpurines: Synthesis of 6-Fluoromethylpurines and Related Nucleosides

Abdalla E. A. Hassan,* William B. Parker, Paula W. Allan, John A. Montgomery, and John A. Secrist III

Drug Discovery Division, Southern Research Institute, Birmingham, Alabama, USA

ABSTRACT

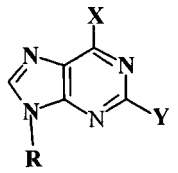
A selective metalation at the 6-CH3 over C-8 of 6-methylpurine derivative **6** was observed with softer counter cation (Na^+ or K^+) of the base, while the harder Li^+ showed no selectivity. In the presence of *N*-fluorobenzenesulfonamide (NFSI), this property was utilized for the synthesis of 6-fluoromethylpurine derivatives **4** and **5** as potential toxins for suicide gene therapy.

We have developed a cancer gene therapy strategy that is based on the activation of a non-toxic purine nucleoside (prodrug) to a highly toxic purine analog by a non-human gene, *E. coli* purine nucleoside phosphorylase (*E. coli* PNP), which is selectively expressed in tumor cells.[1] *E. coli* PNP differs from human PNP in its ability to accept not only 6-oxopurine nucleosides, but also 6-aminopurine and certain adenine nucleoside analogs as substrates. This property has been used to cleave non-toxic adenine nucleoside analogs to very toxic adenine analogs, which would readily diffuse across cell membranes and have high bystander activity.[1c] The toxic

*Correspondence: Abdalla E. A. Hassan, Pharmasset Inc., 1860 Montreal Road, Tucker, GA 30084, USA; Fax: +1 678 395 0039; E-mail: ahassan@services.pharmasset.com.

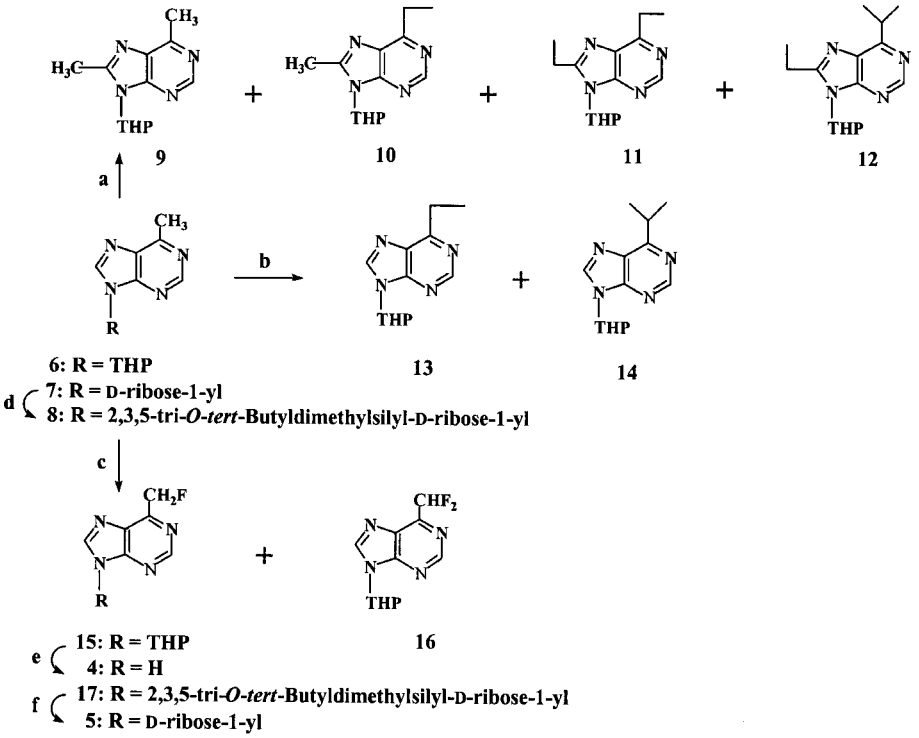
DOI: 10.1081/NCN-120022625
1525-7770 (Print); 1532-2335 (Online)

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



1: X = CH_3, Y = H, R = H
2: X = NH_2, Y = F, R = H
3: X = CH_3, Y = H, R = D-ribose-1-yl
4: X = CH_2F, Y = H, R = H
5: X = CH_2F, Y = H, R = D-ribose-1-yl

Chart 1.



Scheme 1. [a]Reagents and conditions: a) Base (*n*-BuLi, or LDA, or LTMP, or LiHMDS), THF, −78°C, excess CH_3I; b) Base (NaHMDS or KHMDS), THF, −78°C, excess CH_3I; c) NaHMDS, THF, −78°C, 30 min, then NFSI, 48–56%; d) *tert*-Butyldimethylsilyl chloride, Im, DMF, r. t., 84%; e) 1N HCl, THF, r.t., 94%; f) Et4NF, CH_3CN, r.t., 95%.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

adenine analogs of most interest to date are 6-methylpurine (6-MeP, **1**) and 2-fluoroadenine (**2**) (Chart 1); however, we still continue to search for the optimal toxin/prodrug combination that would have the desired biological properties. Herein, we report on the selective metalation at the 6-CH_3 moiety of 6-methylpurine derivatives and the utilization of this property for the synthesis of 6-fluoromethylpurine (6-FMeP, **4**) and related nucleosides of potential use for this project.

Lithiation[5] of **6**[1d] with *n*-BuLi in THF at −78°C, in the presence of MeI resulted in the formation of a mixture of 6,8-dimethylpurine derivative, **9** as a major product along with a mixture of compounds **10**, **11**, and **12**, respectively. A non-selective lithiation was also observed with LDA, LiHMDS, or LTMP in THF at −78°C, irrespective of the molar equivalence of the base. On the other hand, when the base was changed to NaH, or $(CH_3)_3COK$ at 0°C in the presence of MeI, a mixture of 6-ethylpurine derivative **13** (major) and 6-isopropyl derivative **13** (minor) was obtained in good yield. A similar selectivity at the 6-CH_3 position was also observed with NaHMDS or KHMDS at −78°C in THF (Sch. 1). Quenching the sodium salt of **6** (generated by NaHMDS at −78°C in THF) with NFSI gave the 6-FMeP derivative **15** in good yield along with traces of **16** (Sch. 1). The 6-FMe-P riboside derivative **17** was also synthesized by applying the same chemistry on compound **8** (Sch. 1). Deprotection of **15** and **17** under conventional conditions gave **4** and **5** in good yields, respectively.

The newly synthesized compounds were evaluated for their cytotoxic activity as well as their substrate activity to *E.coli* PNP. 6-FMe-P (**4**) showed potent cytotoxic activity against CCRF-CEM cells (2 μM) and moderate activity against our solid tumor panel. Furthermore, the riboside derivative **5** showed potent cytotoxic activity against CCRF-CEM cells (0.03 μM) and was also as good a substrate as the parent compound **2** in terms of substrate activity to *E. coli* PNP.

REFERENCES

1. a) Sorscher, E.J.; Peng, S.; Bebok, Z.; Allan, P.W.; Bennett, L.L., Jr.; Parker, W.B. Gene Therapy **1994**, *1*, 233–238; b) Parker, W.B.; King, S.A.; Allan, P.W.; Bennett, L.L., Jr.; Secrist III, J.A.; Montgomery, J.A.; Gilbert, K.S.; Waud, W.R.; Wells, A.H.; Gillespie, G.Y.; Sorscher, E.J. Human Gene Therapy, **1997**, *8*, 1637–1644; c) Hughes, B.W.; King, S.A.; Allan, P.W.; Parker, W.B.; Sorscher, E.J. J. Biol. Chem. **1998**, *273*, 2322–2328; d) Hassan, A.E.A.; Abou-Elkhair, R.A.I.; Montgomery, J.A.; Secrist III, J.A. Nucleosides, Nucleotides & Nucleic Acids **2000**, *19* (7), 1123–1134.
2. Komamoto, H.; Tanaka, H.; Takioka, R.; Ishida, Y.; Nakamura, A.; Kimura, S.; Hayakawa, H.; Kato, K.; Miyasaka, T. J. Org. Chem. **1999**, *64*, 7773–7780.

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

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