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(54) **SYNTHESIS OF
2-ARALKYLOXYADENOSINES,
2-ALKOXYADENOSINES, AND THEIR
ANALOGS**

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patent is extended or adjusted under 35
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This patent is subject to a terminal dis-
claimer.

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536/27.7; 536/27.11

(58) **Field of Classification Search** 536/27.11,
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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,140,015 A 8/1992 Olsson et al. 514/46
5,430,027 A 7/1995 Knutsen et al. 514/46
5,432,164 A 7/1995 Knutsen et al. 514/46
5,484,774 A 1/1996 Lau et al. 514/46
5,578,582 A 11/1996 Knutsen et al. 514/46
5,654,285 A 8/1997 Ingall et al. 514/47
5,683,989 A 11/1997 Lau et al. 514/46
6,951,932 B2 10/2005 Moorman 536/27.6

FOREIGN PATENT DOCUMENTS

DE 2258378 6/1973
DE 2324130 11/1973

OTHER PUBLICATIONS

[R] Victor-Vega et al., "Adenosine 14 A2A Receptor Agonists
Promote More Rapid Wound Healing than Recombinant Human
Platelet-Derived Growth Factor (Becaplermin Gel)," *Inflammation*,
26(1), 19-24 (Feb. 2002).*

R. Olsson et al., "Synthesis and Cardiac Pharmacology of
2-(AR)Alkoxyadenosines," *Nucleosides & Nucleotides*, vol. 10,
No. 5, 1991, pp. 1049-1055.

H. Schaeffer et al., "Synthesis of Potential Anticancer Agents. XIV.
Ribosides of 2,6-Disubstituted Purines," *J. Am. Chem. Soc.* vol. 80,
1958, pp. 3738-3742. Jul. 20, 1958.

M. Ueeda et al., "2-Alkoxyadenosines: Potent and Selective
Agonists at the Coronary Artery A₂ Adenosine Receptor," *J. Med.
Chem.*, 1991, vol. 34, No. 4, pp. 1334-1339.

M. Ueeda et al., "2-Aralkoxyadenosines: Potent and Selective
Agonists at the Coronary Artery A₂ Adenosine Receptor," *J. Med.
Chem.*, 1991, vol. 34, No. 4, pp. 1340-1344.

R. Barlett et al., "Synthesis and Pharmacological Evaluation of a
Series of Analogues of 1-Methylisoguanosine," *J. Med. Chem.*,
1981, vol. 24, No. 8, pp. 947-954.

K. Miyai et al., "Synthesis and Anti-Deoxyribonucleic Acid Virus
Activity of certain 9-β-D-Arabinofuranosyl-2-substituted
Adenosine Derivatives," *J. Med. Chem.*, 1974, vol. 17, No. 2, pp.
242-244.

Halbfinger et al., "Molecular Recognition of Modified Adenine
Nucleotides by the P2y1 -Receptor. I.A Synthetic, Biochemical, and
NMR Approach," *J. of Med. Chem.*, 1999, vol. 42, No. 26, pp.
5325-5337 (WEB Dec. 4, 1999).

Wanner et al., "2-Nitro Analogues of Adenosine and
1-Deazaadenosine: Synthesis and Binding Studies at the Adenosine
A1, A2A, A3 Receptor Subtypes," *Bioorganic & Medicinal Chem-
istry Letters*, Sep. 18, 2000, vol. 10, No. 18, pp. 2141-2144.

Robins et al., "Nucleic Acid Related Compounds. 114. Synthesis of
2,6-(Disubstituted)purine 2',3'-Dinucleosides and Selected
Cytotoxic, Anti-Hepatitis B, and Adenosine Deaminase Substrate
Activities," *J. of Heterocyclic Chemistry*, Nov.-Dec. 2001, vol. 38,
No. 6, pp. 1297-1306.

Marumoto et al., "Synthesis and Enzymatic Activity of Adenosine
3', 5'-Cyclic Phosphate Analogs," *Chem. & Pharm. Bulletin*, Apr.
1979, vol. 27, No. 4, pp. 990-1003.

Marumoto et al., "Synthesis and Coronary Vasodilating Activity of
2-Substituted Adenosines," *Chem & Pharm. Bulletin (Japan)*, 1975,
vol. 23, No. 4, pp. 759-774.

(Continued)

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(57) **ABSTRACT**

Provided is a method for the synthesis of an aralkyloxyad-
enosine or an alkoxyadenosine. The method includes pro-
tecting the hydroxyl sugar groups with a protecting group to
produce a protected halogenated adenosine. The protected
halogenated adenosine is alkoxyated, and the hydroxyl
sugar groups of the protected halogenated adenosine are
deprotected to provide the aralkyloxyadenosine or alkoxy-
adenosine.