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Synthesis of 2-Alkyl-substituted-N^6-methyladenine Derivatives as Potential Adenosine Receptor Ligand

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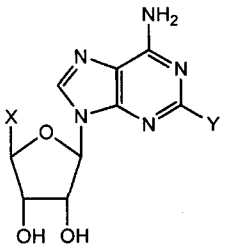
2-(1-Hexynyl), 2-((E)-1-hexenyl) and 2-(n-hexyl)-N^6-methyladenines were synthesized, starting from 2-amino-6-chloropurine using palladium-catalyzed coupling as a key step as potential adenosine receptor ligand.

Key words: Adenosine receptor, Palladium-catalyzed coupling

INTRODUCTION

Adenosine is related to many physiological functions through membrane bound receptors. (Daly and Jacobson, 1995) Adenosine receptors are expressed on the surface of nearly all cells and their activation produces cell-specific physiological responses that are related to various kinds of diseases. Therefore, adenosine receptors have been promising targets for the treatment of hypertension, Parkinsons disease, myocardial and cerebral ischemia, seizure, pain, diabetes, thrombosis, inflammation and etc. (Jacobson *et al.*, 1992) However, despite these kinds of therapeutic potential of adenosine receptors, only adenosine itself has been approved for the clinical use for the treatment of supraventricular tachycardia and for the prevention of postoperative thromboembolic events because adenosine receptors exist so ubiquitously in the body that selective ligand to be activated only at the target tissue can not be obtained. (Erion, 1993) Furthermore, since many types of adenosine receptors are present in the body, it is very difficult to get the selective ligand acting only at particular type of adenosine receptor.

So far, three major types of adenosine receptors (A_1, A_2, and A_3) have been characterized pharmacologically (Poulsen and Quinn, 1988; Stiles, 1992) and through cloning (Zhou *et al.* 1992; Meyerhof *et al*, 1991; Ramkumar *et al.*, 1993). A_1 receptors are coupled to the inhibition of adenylate cyclase through G_i proteins and are also coupled to inhibition or stimulation of phosphoinositol turnover and to activation of ion channels (Poulsen and Quinn, 1988; Stiles, 1992). A_2 receptors are divided into two subtypes, A_{2a} and A_{2b} which are also related to adenylate cyclase (Sebastiao and Riberio, 1996). A_3 receptors are the most recent identified and are coupled to both the inhibition of adenylate cyclase and the stimulation of inositol phosphate metabolism (Kim *et al.* 1994)



1 (X = CH_2OH, Y = $C{\equiv}C{-}(CH_2)_3CH_3$)

2 X = CONHEt, Y = $C{\equiv}C{-}(CH_2)_3CH_3$

Fig. 1. Structures of compounds with high affinities for adenosine receptors

A number of compounds have been synthesized and tested for affinities for adenosine receptors. Among these compounds, 2-hexynyladenosine (**1**) and its 5-*N*-ethyluronamide analogue (**2**) have been shown to have high affinity for A_1 and A_{2a} receptors (Fig. 1) (Cristalli *et al.*, 1922; Matsuda *et al.*, 1992). 2-Hexynyl-adenosine 5-*N*-ethyluronamide, 2-alkynyladenosine, and 2-alkynyl-N^6-alkyladenosine were found to exhibit high affinity for A_3 receptor (Siddiqi *et al.*, 1995; klotz *et al.*, 1999; Volpini *et al.*, 2000) From the molecular modeling study (Poulsen and Quinn, 1988), it has been known that C6 and C2 positions of adenine are participated in hydrophobic

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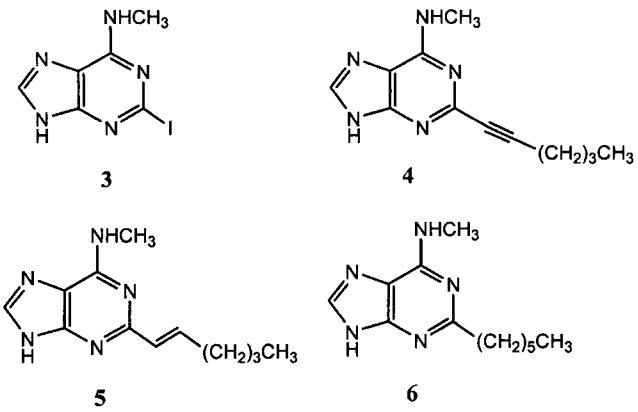


Fig. 2. Structures of 2-substituted-N^6-methyladenines

interaction to show high affinity for A_3 receptor.

From these findings, it was interesting to find out the affinity of 2,6-disubstituted adenines with hydrophobic substituents (Fig. 2) for adenosine receptors, especially for A_3 receptors to know if sugar moiety is essential for serving as agonist or antagonist. We also wanted to know if the geometry of C2-alkyl substituent is affecting hydrophobic interaction with adenosine receptors. Here, we wish to report the synthesis of 2-iodo-, alkyl, alkenyl- and alkynyl-N^6-methyladenine, starting from 2-amino-6-chloropurine using palladium-catalyzed coupling as a key step.

MATERIALS AND METHODS

Reactions were checked by TLC on Merck precoated $60F_{254}$ plates and monitored by UV lamp and charring with sulfuric acid. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck). ^{1}H NMR was recorded on Varian-400 spectrometer, using $CDCl_3$ and DMSO-d_6 and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane(TMS) as internal standard. Ultra Violet (UV) spectra were recorded on a Beckman DU-68 spectrophotometer. Mass spectrum was obtained from National Center For Inter-University Research Facilities, Seoul National University, Seoul, 151-742, Korea using HP5890 Series II, JMS-AX 505WA, JEOL and Korea Basic Science Institute, Korea University, Seoul, 136-701, Korea using JMS-700 Mstation, JEOL.

2-Amino-6-chloro-9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)purine (7)

A mixture of 2-amino-6-chloropurine (2.362 g, 13.9 mmol), ammonium sulfate (catalytic amount), hexamethyl-disilazane (90 mL) was refluxed under nitrogen atmosphere until it became a clear solution (for about 24 h). After the reaction mixture was concentrated to dryness, the residue was dissolved in anhydrous 1,2-dichloroethane (60 mL). To the solution were added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (Aldrich Chemical Co. 7.03 g, 13.9 mmol) and trimethylsilyl trifluoromethanesulfonate (2.70 mL, 14.9 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 68 h. Saturated $NaHCO_3$ solution (100 mL) was added and the reaction mixture was stirred at room temperature for 30 min. Two layers were separated, and aqueous layer was extracted with methylene chloride (50 mL × 3). Combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by a silica gel column chromatography (hexanes-ethyl acetate, 2:1 → 1:1 → 1:2) to give **7** [R_f = 0.325 (Hx-EtOAc, 1:1), 7.75 g, 91%] as a colorless foam which was crystallized from ether: UV(MeOH) λ_{max} 310.0 nm; ^{1}H NMR (DMSO-d_6) δ 4.68 (dd, 1 H, J = 11.6 and 5.2 Hz, H_a-5), 4.83 (m, 2 H, H_b-5′ and H-4′), 6.18 (t, 1 H, J = 5.6 Hz, H-3′), 6.35 (m, 1 H, H-4′), 6.45 (d, 1 H, J = 4.4 Hz, H-1′), 7.06 (br s, 2 H, NH_2, exchangeable with D_2O), 7.43-7.51 (m, 6 H, OBz), 7.63-7.69 (m, 3 H, OBz), 7.87-7.89 (m, 2 H, OBz), 7.93-7.98 (m, 4 H, OBz), 8.39 (s, 1 H, H-8).

6-Chloro-2-iodo-9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)purine (8)

A mixture of **7** (3.62 g, 5.89 mmol), isoamyl nitrite (23 mL, 171.20 mmol), and diiodomethane (44 mL, 546.22 mmol) was stirred at 90°C under nitrogen atmosphere for 2 h. After the reaction mixture was concentrated to dryness, the residue was purified on a silica gel (hexanes-ethyl acetate, 5:1 → 3:1 →2:1) to give **8** [R_f = 0.471 (Hx-EtOAc, 1:1), 2.09 g, 49%] as a colorless foam: UV (MeOH) λ_{max} 281nm; ^{1}H NMR ($CDCl_3$) δ 4.74 (dd, 1 H, J = 12.9 and 4.0, H_a-5′), 4.87 (m, 1 H, H-4′), 4.94 (dd, 1 H, J = 12.0 and 3.2 Hz, H_b-5′), 6.13 (m, 2 H, H-2′ and H-3′), 6.47 (m, 1 H, H-1′), 7.38-7.48 (m, 6 H, OBz), 7.55-7.61 (m, 3 H, OBz), 7.94-7.96 (m, 2 H, OBz), 8.02-8.06 (m, 4 H, OBz), 8.20 (s, 1 H, H-8).

2-Iodo-6-methylamino-9-β-D-ribofuranosylpurine (9) and 2,6-dimethylamino-9-β-D-ribofuranosylpurine (10)

A mixture of **8** (2.064 g, 2.85 mmol) and 40% methylamine in water (4 mL) in 1,4-dioxane (10 mL) was stirred at room temperature for 27 h. After the reaction mixture was concentrated to dryness, the residue was purified by a silica gel column chromatography (CH_2Cl_2-MeOH, 20:1 →10:1) to give **9** [R_f = 0.40 (CH_2Cl_2-MeOH, 10:1), 0.907 g, 78 %] as a colorless solid and **10** [R_f = 0.329 (CH_2Cl_2-MeOH, 10:1), 0.05 g, 6%] as a colorless solid.

Compound 9: ^{1}H NMR(DMSO-d_6) δ 2.90 (br d, 3 H, J = 4.0 Hz, NHC<u>H</u>$_3$), 3.53 (dd, 1 H, J = 12.0 and 4.0 Hz, H_a-5′), 3.63 (dd, 1 H, J = 12.0 and 4.4 Hz, H_b-5′),

3.93 (q, 1 H, J = 3.6 Hz, H-3′), 4.11 (m, 1 H, H-4′), 4.51 (m, 1 H, H-2′), 5.03 (pseudo t, 1 H, J = 6.0 and 5.2 Hz, exchangeable with D_2O, 5′-OH), 5.20 (d, 1 H, J = 4.4 Hz, exchangeable with D_2O, OH), 5.45 (d, 1 H, J = 6.0 Hz, exchangeable with D_2O, OH), 5.81 (d, 1 H, J = 6.4 Hz, H-1′), 8.13 (br d, 1H, J = 4.4 Hz, NH), 8.29 (s, 1 H, H-8).

Compound 10: ^{1}H NMR (DMSO-d_6) δ 2.77 (br d, 3 H, J = 4.8 Hz, NHC$\underline{H}_3$), 2.90 (br s, 3 H, NHC$\underline{H}_3$), 3.52 (dd, 1 H, J = 12.0 and 4.0 Hz, H_a-5′), 3.63 (dd, 1 H, J = 12.0 and 4.0 Hz, H_b-5′), 3.89 (q, 1 H, J = 4.0 Hz, H-3′), 4.12 (m, 1 H, H-4′), 4.60 (m, 1 H, H-2′), 4.78 (br s, 1 H, exchangeable with D_2O, OH), 5.11 (d, 1 H, J = 4.4 Hz, exchangeable with D_2O, OH), 5.34 (d, 1 H, J = 6.0 Hz, exchangeable with D_2O, OH), 5.73(d, 1 H, J = 6.4 Hz, H-1′), 7.87 (s, 1 H, H-8).

2-Iodo-N^6-methyladenine (**3**). A mixture of **9** (114 mg, 0.21 mmol)) and 0.1% sulfuric acid in methanol (4 mL) was stirred at 60°C for 6 days. After more 0.1% sulfuric acid in methanol (4 mL) added, the reaction mixture was stirred at 60°C for another 2 days. Solvent was removed to half volume by rotary evaporation and the resulting slightly yellow solid was collected by filtration to give **3** (45 mg, 76%): ^{1}H NMR(DMSO-d_6) δ 2.89 (s, 3 H, NHC$\underline{H}_3$), 7.91 (br s, 1 H, NH), 8.03 (s, 1 H, H-8), 13.0 (br s, 1 H, exchangeable with D_2O, H-9). MS (EI) m/z 275.0000 (M^+).

2-Hexynyl-N6-methyl-9-β-D-ribofuranosyladenine (11a) and 2-hexynyl-N6-methyl-9-(2,3,5-tri-O-acetyl-β-D-ribofura-nosyl)adenine (11b).

A mixture of **9** (351 mg, 0.86 mmol), tetrakis (triphenylphosphine)palladium(0) (100 mg, 0.09 mmol), copper(I) iodide (100 mg, 0.5 mmol), triethylamine (3.6 mL, 25. 8mmol), and 1-hexyne (1 mL, 8.7 mmol) in anhydrous DMF (5 mL) was stirred at 80°C for 48 h under nitrogen atmosphere. After the reaction mixture was concentrated to dryness, the residue was purified by a silica gel column chromatography (CH_2Cl_2-MeOH, 20:1 →10:1) to give crude **11a**. For further purification, crude **11a** was dissolved in acetonitrile (5 mL) and treated with pyridine (1.4 mL, 17.3 mmol) and acetic anhydride (1.61 mL, 17.2 mmol). After the reaction mixture was stirred at room temperature for 20 h, it was concentrated to dryness and purified on a silica gel (hexanes-ethyl acetate, 1:1 →1:3) to give **11b** (319 mg, 61% from **9**) as a colorless foam.

Compound 11a : UV(MeOH) λ_{max} 295.0 nm; ^{1}H NMR (DMSO-d_6) δ 0.92 (m, 3 H, CH_3), 1.44 (m, 2 H, CH_2), 1.54 (m, 2 H, CH_2), 2.42 (t, 2 H, J = 7.2 Hz, CC-CH_2), 2.92 (br s, 3 H, NHC$\underline{H}_3$), 3.54 (dd, 1 H, J = 12.0 and 3.2 Hz, H_a-5′), 3.65 (dd, 1 H, J = 12.0 and 3.6 Hz, H_b-5′), 3.93 (q, 1 H, J = 3.2 Hz, H-4′), 4.11 (dd, 1 H, J = 5.2 and 4.8 Hz, H-3′), 4.51 (t, 1 H, J = 5.6 Hz, H-2′), 5.18 (d, 1 H, J = 4.8 Hz, exchangeable with D_2O, OH), 5.22 (m, 1H, exchangeable with D_2O, 5′-OH), 5.45 (d, 1H, J = 6.4 Hz, exchangeable with D_2O, OH), 5.86 (d, 1 H, J = 6.0 Hz, H-1′), 7.84 (br s, 1H, exchangeable with D_2O, NH), 8.37 (s, 1 H, H-8).

Compound 11b : UV(MeOH) λ_{max} 271.0 nm, 295.0 nm (sh); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7.2 Hz, CH_3), 1.49 (m, 2 H, CH_2), 1.65 (m, 2 H, CH_2), 2.06 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 2.16 (s, 3 H, OAc), 2.46 (t, 2 H, J = 7.2 Hz, CC-CH_2), 3.23 (br s, 3 H, NHC$\underline{H}_3$), 4.39 (m, 2 H, H-5′), 4.41 (m, 1 H, H-4′), 5.56 (dd, 1 H, J = 5.2 and 3.2 Hz, H-3′), 5.71 (br s, 1 H, NH), 5.75 (pseudo t, 1 H, H-2′), 6.32 (d, 1 H, J = 5.6 Hz, H-1′), 7.92 (s, 1 H, H-8); IR (KBr) 2239.17 cm^{-1} (CC). MS (FAB) m/z 488.2 (M^++1).

2-Hexynyl-N^6-methyladenine (**4**). A mixture of **11b** (72 mg, 0.15 mmol) and 4% H_2SO_4 in methanol (1 mL) was stirred at 65°C for 24 h. After the reaction mixture was neutralized with saturated $NaHCO_3$ to pH 9, solid was filtered off and the solid was washed with methanol thoroughly. The filtrate was concentrated to dryness and the residue was purified by a silica gel column chromatography (CH_2Cl_2-MeOH, 20:1) to give **4** (25 mg, 71%) as a colorless solid: UV (MeOH) λ_{max} 271.0 nm, 295.0 nm (sh); ^{1}H NMR (DMSO-d_6) δ 0.91 (pseudo t, 3 H, J = 7.6 and 7.2 Hz, CH_3), 1.44 (m, 2 H, CH_2), 1.53 (m, 2 H, CH_2), 2.41 (t, 2 H, J = 6.8 Hz, CC-CH_2), 2.92 (br s, 3 H, NHC$\underline{H}_3$), 8.06 (s, 1H, H-8); MS (EI) m/z 229.13 (M^+).

2-(E)-Hexenyl-N6-methyl-9-(β-D-ribofuranosyl)adenine (12)

A mixture of **9** (250 mg, 0.61 mmol), tetrakis(triphenylphosphine) palladium(0) (71 mg, 0.06 mmol), potassium carbonate (373 mg, 2.70 mmol), and (*E*)-1-catecholboranylhexene (Vittori *et al.*, 1996) (372 mg, 1.84 mmol) in acetonitrile-DMF (1:1, 10 mL) was stirred at 80°C for 3 days. After the solid was filtered off, the residue was concentrated and purified by a silica gel column chromatography (CH_2Cl_2-MeOH, 20: 1) to give **12** (80 mg, 36%) as a colorless foam: ^{1}H NMR (DMSO-d_6) δ 0.90 (pseudo t, 3 H, J = 7.2 and 6.8 Hz, CH_3), 1.35 (quintet, 2 H, J = 7.2 Hz, CH_2), 1.45 (quintet, 2 H, J = 7.6 Hz, CH_2), 2.23 (q, 2 H, J = 7.2 Hz, CH= CH-C$\underline{H}_2$), 2.97 (br s, 3 H, NHC$\underline{H}_3$), 3.55 (dd, 1 H, J = 12.0 and 3.2 Hz, H_a-5′), 3.66 (dd, 1 H, J = 12.0 and 3.2 Hz, H_b-5′), 3.97 (q, 1 H, J = 2.8 Hz, H-4′), 4.13 (dd, 1 H, J = 5.2 and 2.8 Hz, H-3′), 4.63 (pseudo t, 1 H, J = 6.0 and 5.6 Hz, H-2′), 5.20 (br s, 1H, exchangeable with D_2O, OH), 5.22 (m, 1 H, exchangeable with D_2O, 5′-OH), 5.45 (br s, 1 H, exchangeable with D_2O, OH), 5.86 (d, 1 H, J = 6.0 Hz, H-1′), 6.29(d, 1 H, J = 15.6 Hz, C$\underline{H}$=CH-CH_2), 6.98 (m,

1 H, CH=C<u>H</u>-CH_2), 8.25 (s, 1 H, H-8), 8.80 (br s, 1 H, exchangeable with D_2O, NH).

2-(*E*)-Hexenyl-N^6-methyladenine (**5**). A mixture of **12** (71 mg, 0.19 mmol) and 4% H_2SO_4 in methanol (2 mL) was stirred at 60°C for 3 h. After the reaction mixture was neutralized by saturated $NaHCO_3$ solution, it was concentrated to dryness and purified by a silica gel column chromatography (CH_2Cl_2-MeOH, 20:1) to give **5** (42 mg, 93%) as a colorless solid: ^{1}H NMR(DMSO-d_6) δ 0.90 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.35 (m, 2 H, CH_2), 1.44 (m, 2 H, CH_2), 2.22 (q, 2 H, *J* = 6.4 Hz, CH=CH-C<u>H</u>$_2$), 2.98 (br s, 3 H, NHC<u>H</u>$_3$), 6.29 (d, 1 H, *J* = 15.6 Hz, C<u>H</u>=CH-CH_2), 6.90 (m, 1 H, CH=C<u>H</u>-CH_2), 8.00 (s, 1 H, H-8); MS (EI) *m/z* 231(M^+).

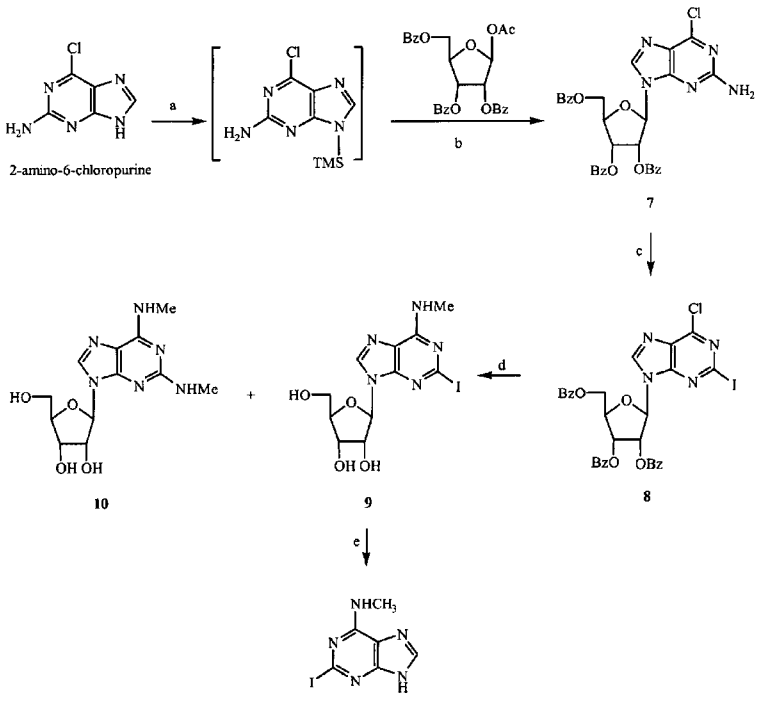
2-Hexyl-N6-methyl-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)adenine (13)

To a solution of **11b** (192 mg, 0. mmol) in anhydrous MeOH (10 mL) was added 10% Pd/C under hydrogen (replaced at 5 torr) and the mixture was stirred at room temperature overnight. The mixture was filtered through a Celite pad and successively washed with methanol. After evaporation of the solvent, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to give **13** (166 mg, 85%) as a colorless syrup: UV (MeOH)) λ_{max} 268.0 nm; ^{1}H NMR ($CDCl_3$) δ 0.89 (pseudo t, 3 H, *J* = 7.2 and 6.8 Hz, CH_3), 1.33 (m, 4 H, 2x CH_2), 1.38 (m, 2 H, CH_2), 1.82 (m, 2 H, CH_2), 2.08 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 2.14 (s, 3 H, OAc), 2.81 (t, 2 H, *J* = 7.6 Hz, CC-CH_2), 3.21 (br s, 3 H, NHC<u>H</u>$_3$), 4.36 (dd, 1 H, *J* = 11.6 and 4.8 Hz, H_a-5'), 4.42 (m, 1 H, H-4'), 4.47 (dd, 1 H, *J* = 11.6 and 3.2 Hz, H_b-5'), 5.55 (br s, 1 H, NH), 5.81 (pseudo t, 1 H, *J* = 5.6 and 4.8 Hz, H-3'), 5.98 (t, 1 H, *J* = 5.2 Hz, H-2'), 6.11 (d, 1 H, *J* = 4.8 Hz, H-1'), 7.78 (s, 1 H, H-8); MS (FAB) *m/z* 492 (M^++1).

2-Hexyl-N^6-methyladenine (**6**). A mixture of **13** (180 mg, 0.37 mmol) and 4% H_2SO_4 in methanol (1 mL) was stirred at 60°C for 2 days. After the reaction mixture was neutralized by saturated $NaHCO_3$ solution to pH 7, it was concentrated to dryness. The residue was purified on a silica gel to give **6** (80 mg, 94%) as a colorless solid: UV (MeOH) λ_{max} 268.0 nm; ^{1}H NMR(DMSO-d_6) δ 0.85 (pseudo t, 3 H, *J* = 9.2 and 6.0 Hz, CH_3), 1.28 (m, 6 H, 3xCH_2), 1.72 (m, 2 H, CH_2), 2.65 (t, 2 H, *J* = 7.2 Hz, CC-CH_2), 2.95 (br s, 3 H, NHC<u>H</u>$_3$), 7.97 (s, 1 H, H-8); MS (EI) *m/z* 233 (M^+)

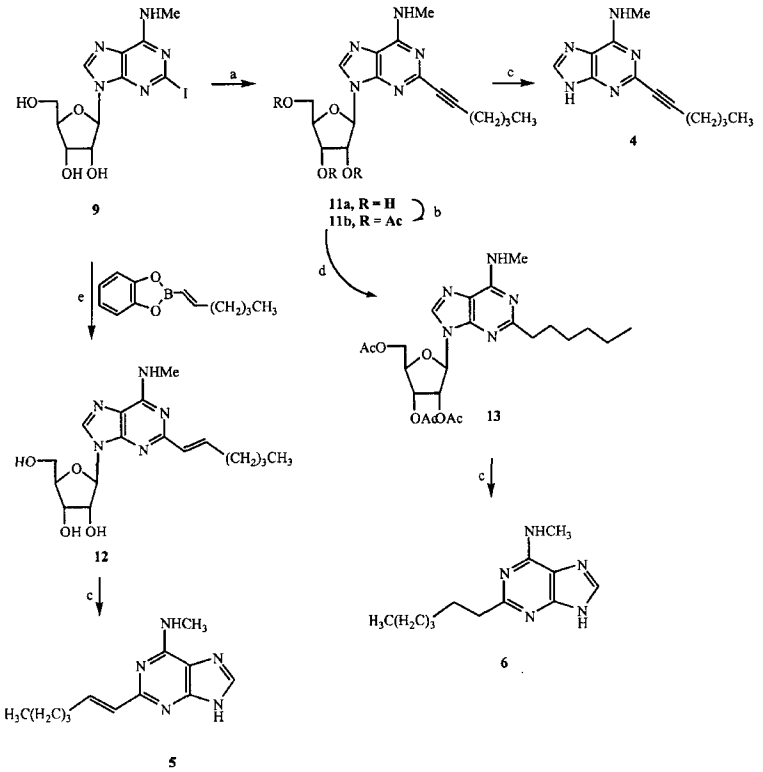
RESULTS AND DISCUSSION

For the synthesis of 2-substituted-N^6-methyladenine deri-



Reagents: a) HMDS, $(NH_4)_2SO_4$, reflux; b) TMSOTf, $ClCH_2CH_2Cl$, rt; c) CH_2I_2, isoamyl nitrite, 85°C; d) 40%CH_3NH_2/H_2O, 1,4-dioxane; e) 4% H_2SO_4, 60°C.

Scheme 1. Syntheses of 2-iodo-N^6-methyladenine (**3**)



Reagents: a) hexyne, $(PPh_3)_4Pd$, CuI, Et_3N, DMF; b) Ac_2O, pyridine; c) 4% H_2SO_4/MeOH, 60 °C; d) H_2, Pd/C, MeOH; e) $(PPh_3)_4Pd$, K_2CO_3, CH_3CN:DMF (1:1).

Scheme 2. Syntheses of 2-(1-hexynyl-, (E)-1-hexenyl-and *n*-hexyl)-N^6-methyladenines

vatives, we first synthesized 2-iodo-N^6-methyladenosine as a key intermediate, starting from 2-amino-6-chloropurine. As shown in Scheme 1, silylated 2-amino-6-chloropurine prepared by refluxing 2-amino-6-chloropurine with hexamethyldisilazane (HMDS) was condensed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-â-D-ribofuranoside in the presence of TMSOTf in 1,2-dichloroethane to give tribenzoate **7** in 91% yield. Modified diazothization (Nair and Richardson, 1982) of **7** with isoamyl nitrite and diiodomethane produced **8** in 49% yield. Treatment of **8** with 40% aqueous methylamine gave 2-N^6-methylamino-6-iodopurine derivative **9** and 2,6-di-N^6-methylaminopurine derivative **10** in 13:1 ratio. It is interesting to note that C6-position of 6-chloro-2-iodopurine derivative **8** is much more reactive than C2-position although iodo group is better leaving group than chloro group. Compound **9** serves as a versatile intermediate for the synthesis of 2-alkyl-substituted N^6-methyladenines.

In order to obtain the desired purine, compound **9** was treated with 4% sulfuric acid to give 2-N^6-methylamino-6-iodopurine **3** in 76% yield. In scheme 1, we used the ribose moiety to synthesize the desired compound **3** without manipulating nucleobase itself because nucleoside is much more convenient than nucleobase in purification.

For the synthesis of C2-alkyl substituted purine derivatives (Scheme 2), the key intermediate **9** was first coupled with 1-hexyne by modified procedure of reference (Cristalli *et al.*, 1992) in the presence of tetrakis (triphenylphosphine)palladium(0), triethylamine and copper(I) iodide in DMF at 85°C to give C-C coupled product **11a** which for further puri-fication, was acetylated to give **11b** (61% yield from **9**). Acid-catalyzed deglycosylation of **11b** afforded the final 2-(1-hexynyl)-N^6-methyladenine **4** in 71% yield. To synthe-size the alkenyl derivative, compound **9** was treated with (*E*)-1-catecholboranyl-hexene (Nair and Richardson, 1982) under the same palladium-catalyzed coupling conditions of the reference to give (*E*)-alkenyl product **12** which was treated with 4% sulfuric acid to yield 2-{(E)-1-hexenyl}-N^6-methyladenine **5** in 93% yield. For the synthesis of saturated compound **6**, 1-hexynyl derivative **11b** was reacted with palladium on carbon under hydrogen (5 atm) to give **13** (85%) which was deglycosylated under the acidic conditions to afford the saturated analogue **6** (94%).

In summary, we synthesized 2-substituted N^6-methyladenines starting from 2-amino-6-chloropurine using palladium-catalyzed C-C coupling as a key reaction. Affinity test for adenosine receptors and molecular modeling study of all synthesized final compounds are in progress and will be reported elsewhere.

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