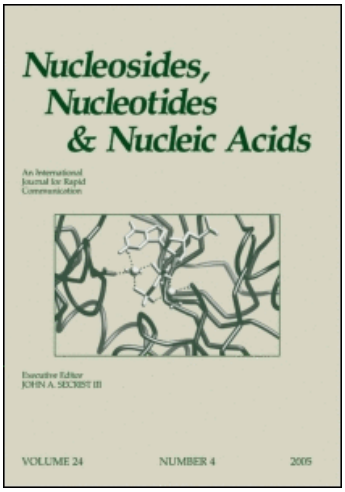

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Steric Effect of a Bulky Substituent At 5'-Position on the Regioselectivity of 2' vs. 3'-O-Methylation of N^6- Cyclohexyladenosine

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STERIC EFFECT OF A BULKY SUBSTITUENT AT 5'-POSITION ON THE REGIOSELECTIVITY OF 2' VS. 3'-O-METHYLATION OF N^6-CYCLOHEXYLADENOSINE

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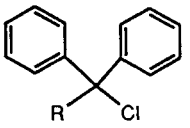
ABSTRACT: Steric effect of a trityl or substituted trityl group at 5'-OH of N^6-cyclohexyladenosine on the regioselective 2' vs. 3'-O-methylation under phase transfer catalysis conditions was investigated. Compound **4** showed only a modest increase in the selectivity of 2' over 3'-O-methylation compared to compound **1**.

Selective 2'-O-methylation of ribonucleosides has been a topic of great interest due to the presence of 2'-O-methylribonucleosides in t-RNA.[1] Selective alkylation of adenosine at the 2'-OH group has been reported.[2] Methylation of 5'-O-trityladenosine under classical conditions was reported to be unsatisfactory yielding 2'-O-methyl-5'-O-trityladenosine in only 4% yield.[3] Our interest in this area was to study the proximity effect of a bulky substituent e.g., a trityl group, at 5'-OH of N^6-cyclohexyladenosine on the regioselectivity of 2' vs. 3'-O-methylation under phase transfer catalysis conditions. Steric hindrance due to a bulky substituent at 5'-OH group might suppress the alkylation at 3'-OH thus leading to a selective methylation at 2'-OH group. In this paper we describe our results on this approach. Such a comparative study has not been previously reported to our knowledge.

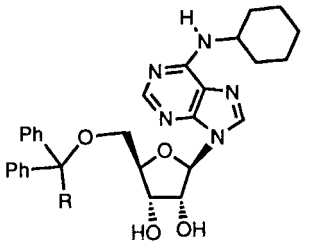
An examination of the Dreiding models of **1** suggested that a trityl group at 5'-OH could sterically hinder the methylation at 3'-OH. Steric crowding could be further increased by the presence of a substituent in the ortho or meta position of one of the phenyl rings of the trityl group. Thus, compounds **2–4**, containing a substituted trityl group at 5'-OH, were chosen to study this effect on selectivity. In compound **4** the additional bulk of a t-butyldiphenylsilyloxymethyl group could make 3'-OH even more crowded thus exposing the 2'-OH group for a more selective methylation compared to compound **1**.

Compounds **1–4** were prepared by tritylation of N^6-cyclohexyladenosine with an appropriate trityl chloride (**5–8**; FIG. 1) in methylene chloride using pyridine as a base. Methylation of **1–4** with methyl iodide in the presence of tetra-n-butylammonium hydrogen sulfate at 55 °C (Method A) or with dimethyl sulfate in the presence of benzyltriethylammonium chloride

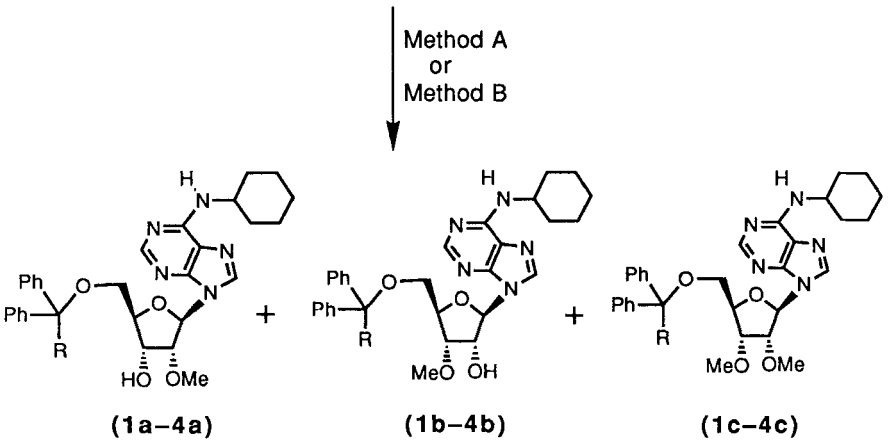


5: R = Phenyl
6: R = 2-Methylphenyl
7: R = 3-(Methoxymethyl)phenyl
8: R = 2-(t-Butyldiphenylsilyloxymethyl)phenyl

FIG. 1



1: R = Phenyl
2: R = 2-Methylphenyl
3: R = 3-(Methoxymethyl)phenyl
4: R = 2-(t-Butyldiphenylsilyloxymethyl)phenyl



SCHEME 1

TABLE 1

Starting Material	Method	Characteristic δ of H-1' in ^{1}H NMR of products			Relative Ratio Of Products		
		2'-OMe	3'-OMe	2',3'-Di-OMe	2'-OMe	3'-OMe	2',3'-Di-OMe
1	A	6.13	5.92	6.06	3.7*	1*	0.4*
1	B	6.13	5.92	6.06	4	1	0.6
2	A	6.16	5.96	6.12	3.3*	1*	0.5*
3	A	6.13	5.92	6.06	3	1	0.4
4	B	5.95	5.79	5.91	5.3	1	0.3

* Ratios based on isolated yields.

at room temperature (Method B) in 7% aqueous sodium hydroxide and methylene chloride yielded a mixture of corresponding 2'-OMe (**1a–4a**), 3'-OMe (**1b–4b**) and 2',3'-di-OMe (**1c–4c**) ethers (SCHEME 1). The mixtures obtained from methylation of **1** and **2** using Method A were separated by a silica gel chromatography to furnish pure **1a–2a**, **1b–2b** and **1c–2c** and their structures were assigned based on ^{1}H NMR data. Their relative ratios based on isolated yields are listed in TABLE 1. The chemical shift of H-1' is characteristic in these ethers and is downfield in 2',3'-di-OMe ethers compared to the corresponding 3'-OMe derivatives, and it is most downfield in 2'-OMe ethers. This characteristic behavior of H-1' chemical shifts was used to determine the ratios of ethers in the crude mixture obtained from methylation of **3** by Method A and of **1** and **4** by Method B and are listed in TABLE 1. Analytical data of **1a–1c**, obtained by Method B, were identical in all respects to those obtained by Method A.

An examination of the results listed in TABLE 1 suggested that introduction of a moderately bulky substituent into one of the phenyl rings of the trityl group does not lead to a significant change in the selectivity of 2'-OH over 3'-OH methylation. In compound **4**, where the bulk was tremendously increased compared to **1**, a modest enhancement in the selectivity was observed. We postulate that this higher selectivity towards 2'-OH methylation might not be due to its intramolecular H-bonding with 3'-OH alone, but other factors may also play some role, such as the relative diffferences in the C–O bond distances.[4]

In summary, the presence of a bulky substituent e.g., a trityl or substituted trityl group at 5'-OH showed a selectivity of 2'-OH over 3'-OH methylation. Introduction of a significantly bulky substituent in one of the phenyl rings of the trityl group lead to a modest increase in the selectivity. Methylation conditions in Method B were preferred.

EXPERIMENTAL:

Melting points were measured on a Büchi 535 melting point apparatus. ^{1}H-NMR spectra were recorded on a Bruker 300 instrument. Mass spectra were obtained using a Finnigan 4600 spectrometer. N^6-Cyclohexyladenosine is commercially available from Sigma chemical company. Trityl chloride (**5**) was purchased from Fluka chemicals. 1-(2-Methylphenyl)-1,1-diphenylmethyl chloride (**6**) was prepared following the literature procedure[5].

1-(3-Methoxymethylphenyl)-1,1-diphenylmethyl chloride (7):

To a stirred suspension of magnesium (0.48 g, 20.0 mmol) in dry THF (5 mL) were added 3–4 crystals of iodine followed by a solution of 3-(methoxymethyl)bromobenzene (4.02 g, 20 mmol) in dry THF (7 mL). The resulting mixture was refluxed for 30 minutes and then cooled to room temperature. A solution of benzophenone (3.45 g, 19.0 mmol) in dry THF (10 mL) was added, and the mixture was refluxed for 1.25 hr. After cooling in an ice bath the mixture was quenched with 10% HCl and extracted with ether (150 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated to furnish an oil. The oil was triturated with hexane (60 mL), and the solid so separated was filtered. This crude solid was purified by silica gel chromatography using a mixture of 10% ethyl acetate in hexane followed by a 20% mixture as the eluent to yield 2.8 g (46% yield) of 1-(3-methoxymethylphenyl)-1,1-diphenylmethanol as a solid: mp 94-96 °C; ^{1}H NMR ($CDCl_3$) δ 2.81 (s, 1H, OH), 3.33 (s, 3H, CH_3), 4.4 (s, 2H, CH_2), 7.1-7.33 (m, 14H, Ar-H); Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.76; H, 6.63.

To a solution of 1-(3-methoxymethylphenyl)-1,1-diphenylmethanol (0.6 g, 2.0 mmol) in dry benzene (10 mL) was added acetyl chloride (1.42 mL, 20.0 mmol) and the mixture was refluxed for 22 hr. The solvents were evaporated in vacuo and the traces of acetyl chloride were azeotropically removed with dry toluene to furnish 1-(3-methoxymethylphenyl)-1,1-diphenylmethyl chloride (**7**) as a moisture-sensitive thick oil in quantitative yield. The crude **7** was used for the tritylation step.

1-[2-(t-Butyldiphenylsilyloxymethyl)phenyl]-1,1-diphenylmethyl chloride (8):

To a solution of 1,1-diphenyl-1-(2-hydroxymethylphenyl)methanol[6] (0.72 g, 2.5 mmol) in dry THF (5 mL) was added imidazole (0.24 g, 3.5 mmol) and t-butyldiphenylchlorosilane (0.75 g, 2.75 mmol), and the mixture was stirred at room temperature for 16 hr. After adding water (20 mL) the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and concentrated in vacuo after drying over anhydrous magnesium sulfate. The residue was triturated with hexane and the resulting solid was collected by filtration to furnish pure 1-[2-(t-butyldiphenylsilyloxy)methylphenyl]-1,1-diphenylmethanol (1.22 g, 92% yield); mp 170-171 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 9H, 3xCH_3), 4.31 (s, 2H, CH_2), 6.22 (s, 1H,OH), 6.7 (dd, 1H, J= 3.7 & 7.5 Hz, Ar-H), 6.96 (dd, 1H, J= 3.7 & 7.5 Hz, Ar-H), 7.05-7.45 (m, 19H, Ar-H), 7.56 (d, 3H, J= 7.0 Hz, Ar-H); Anal. Calcd for $C_{36}H_{36}SiO_2$: C, 81.77; H, 6.86. Found: C, 81.55; H, 6.86.

To a solution of 1-[2-(t-butyldiphenylsilyloxymethyl)phenyl]-1,1-diphenylmethanol (0.79 g, 1.5 mmol) in dry toluene (8 mL) was added acetyl chloride (1.18 g, 15.0 mmol), and the mixture was refluxed for 46 hr. The solvents were evaporated in vacuo and the traces of acetyl chloride were removed azeotropically with toluene to yield 1-[2-(t-butyldiphenylsilyloxymethyl)phenyl]-1,1-diphenylmethyl chloride (**8**) as a moisture-sensitive syrup in quantitative yield. The crude **8** was used for the tritylation step.

General method of 5'-O-tritylation of N^6-cyclohexyladenosine:

To a suspension of N^6-cyclohexyladenosine (1.5 mmol) in methylene chloride (8 mL) and pyridine (2 mL) was added an appropriate trityl chloride (**5-8**; 1.65 mmol), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was washed with aqueous $NaHCO_3$ and water. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residual pyridine was removed azeotropically with toluene in vacuo. The crude product was either purified by crystallization with methylene chloride and hexane (**1** and **2**) or by silica gel chromatography using a mixture of 5% methanol in methylene chloride as the eluent (**3** and **4**).

N^6-Cyclohexyl-5'-O-triphenylmethyladenosine (**1**):

Yield 84%; mp 167-169 °C; ^1H NMR ($CDCl_3$) δ 1.15-1.57 (m, 5H, cyclohexyl-H), 1.62-1.87 (m, 3H, cyclohexyl-H), 2.03-2.2 (m, 2H, cyclohexyl-H), 3.22 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.45 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.6 (s, 1H, OH), 4.1-4.27 (m, 1H, cyclohexyl-H), 4.4 (d, 1H, J= 6 Hz, H-3'), 4.45 (bs, 1H, H-4'), 4.77 (dd, 1H, J=7.5 & 8.5 Hz, H-2'), 5.84 (d, 1H, J= 7.5 Hz, NH), 5.95 (d, 1H, J= 7.5 Hz, H-1'), 6.68 (s, 1H, OH), 7.02-7.47 (m, 15H, Ar-H), 8.02 (s, 1H, H-8), 8.3 (s, 1H, H-2); Anal. Calcd for $C_{35}H_{37}N_5O_4$: C, 71.05; H, 6.3; N, 11.84. Found: C, 70.96; H, 6.55; N, 11.59.

N^6-Cyclohexyl-5'-O-[(2-methylphenyl)diphenylmethyl]adenosine (**2**):

Yield 73%; mp 129-134 °C; ^1H NMR ($CDCl_3$) δ 1.16-1.57 (m, 5H, cyclohexyl-H), 1.61-1.85 (m, 3H, cyclohexyl-H), 1.87 (s, 3H, CH_3), 2.03-2.17 (m, 2H, cyclohexyl-H), 3.17 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.25 (s, 1H, OH), 3.45 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 4.08-4.27 (m, 1H, cyclohexyl-H), 4.43 (d, 1H, J= 6 Hz, H-3'), 4.5 (bs, 1H, H-4'), 4.75 (t, 1H, J= 7.5 Hz, H-2'), 5.75 (bs, 1H, NH), 5.92 (d, 1H, J= 7.5 Hz, H-1'), 6.96 (s, 1H, OH), 7.05-7.42 (m, 14H, Ar-H), 8.07 (s, 1H, H-8), 8.32 (s, 1H, H-2); Anal. Calcd for $C_{36}H_{39}N_5O_4$: C, 71.38; H, 6.49; N, 11.56. Found: C, 71.16; H, 6.59; N, 11.47.

N^6-Cyclohexyl-5'-O-[(3-methoxymethylphenyl)diphenylmethyl]adenosine (**3**):

Yield 75%; mp 83-87 °C; ^1H NMR ($CDCl_3$) δ 1.2-1.57 (m, 5H, cyclohexyl-H), 1.63-1.87 (m, 3H, cyclohexyl-H), 2.04-2.18 (m, 2H, cyclohexyl-H), 3.21 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.3 (s, 3H, OCH_3), 3.33 (s, 1H, OH), 3.46 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 4.12-4.3 (m, 1H, cyclohexyl-H), 4.33 (s, 2H, CH_2), 4.36 (d, 1H, J= 6 Hz, H-3'), 4.42 (bs, 1H, H-4'), 4.75 (t, 1H, J= 7.5 Hz, H-2'), 5.76 (bs, 1H, NH), 5.91 (d, 1H, J= 7.5 Hz, H-1'), 6.67 (s, 1H, OH), 7.15-7.33 (m, 14H, Ar-H), 8.03 (s, 1H, H-8), 8.32 (s, 1H, H-2); Anal. Calcd for $C_{37}H_{41}N_5O_5$: C, 69.9; H, 6.5; N, 11.02. Found: C, 69.87; H, 6.56; N, 10.75.

N^6-Cyclohexyl-5'-O-[(2-(t-butyldiphenylsilyloxymethylphenyl)diphenylmethyl]adenosine (4):

Yield 30%; mp 106-110 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 9H, 3xCH_3), 1.3 (m, 3H, cyclohexyl-H), 1.47 (m, 2H, cyclohexyl-H), 1.67 (m, 1H, cyclohexyl-H), 1.8 (m, 2H, cyclohexyl-H), 2.1 (m, 2H, cyclohexyl-H), 2.7 (s, 1H, OH), 3.05 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.32 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 4.0 (d, 1H, J= 5 Hz, H-3'), 4.2 (m, 1H, cyclohexyl-H), 4.27 (bs, 1H, H-4'), 4.3 (q, 2H, J= 15.6 & 56.0 Hz, CH_2), 4.43 (t, 1H, J= 6.0 Hz, H-2'), 5.7 (bs, 1H, NH), 5.78 (d, 1H, J= 7.0 Hz, H-1'), 6.27 (s, 1H, OH), 6.96-7.5 (m, 23H, Ar-H), 7.93 (s, 1H, H-8), 8.0 (d, 1H, J= 7.0 Hz, Ar-H), 8.31 (s, 1H, H-2); Anal. Calcd for $C_{52}H_{57}N_5O_5Si$: C, 72.61; H, 6.68; N, 8.14. Found: C, 72.35; H, 6.81; N, 7.83.

General methods of O-methylation under phase transfer catalysis conditions:

Method A:

A mixture of an appropriate 5'-O-substituted-N^6-cyclohexyladenosine (**1-3**; 1.0 mmol), methylene chloride (4 mL), 7% aqueous sodium hydroxide (2 mL), tetra-n-butylammonium hydrogen sulfate (0.2 mmol) and methyl iodide (0.1 mL, 1.6 mmol) was refluxed at 55 °C for 16 to 24 hr. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated. The crude mixture was either analyzed by ^{1}H NMR to determine the ratios of the products (in case **3**; TABLE 1) or purified by silica gel chromatography (in case **1** and **2**) using a mixture of 20% hexane in ethyl acetate followed by pure ethyl acetate as the eluent.

Method B:

A mixture of an appropriate 5'-O-substituted-N^6-cyclohexyladenosine (**1** and **4**; 1.0 mmol), methylene chloride (4 mL), 7% aqueous sodium hydroxide (2 mL), benzyltriethylammonium chloride (0.1 mmol) and dimethyl sulfate (1.4 mmol) was stirred at room temperature for 24 hr. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated. The crude mixture was analyzed by ^{1}H NMR to determine the ratios of the products (TABLE 1).

N^6-Cyclohexyl-2'-O-methyl-5'-O-triphenylmethyl adenosine (**1a**):

Yield 56%; mp 86-90 °C; ^{1}H NMR ($CDCl_3$) δ 1.22-1.55 (m, 4H, cyclohexyl-H), 1.61-1.86 (m, 4H, cyclohexyl-H), 2.05-2.17 (m, 2H, cyclohexyl-H), 2.7 (d, 1H, J= 7.5 Hz, OH), 3.42 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.51 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.55 (s, 3H, OCH_3), 4.15 (m, 1H, cyclohexyl-H), 4.2 (m, 1H, H-4'), 4.42 (m, 1H, H-2'), 4.47 (m, 1H, H-3'), 5.61 (d, 1H, J= 7.5 Hz, NH), 6.13 (d, 1H, J= 3.7 Hz, H-1'), 7.27 (m, 9H, Ar-H), 7.46 (m, 6H, Ar-H), 7.93 (s, 1H, H-8), 8.31 (s, 1H, H-2); Anal. Calcd for $C_{36}H_{39}N_5O_4$+0.5 H_2O: C, 70.34; H, 6.56; N, 11.39. Found: C, 70.39; H, 6.71; N, 11.02.

N^6-Cyclohexyl-3'-O-methyl-5'-O-triphenylmethyl adenosine (**1b**):

Yield 15%; mp 93-97 °C; ^{1}H NMR ($CDCl_3$) δ 1.2-1.57 (m, 4H, cyclohexyl-H), 1.62-1.85 (m, 4H, cyclohexyl-H), 2.05-2.17 (m, 2H, cyclohexyl-H), 3.3 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.45 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.48 (s, 3H, OCH_3), 4.06 (m, 1H, H-3'), 4.22 (m, 1H, cyclohexyl-H), 4.33 (m, 1H, H-4'), 4.45 (d, 1H, J= 6.4 Hz, OH), 4.86 (q, 1H, J= 6.4

& 11.2 Hz, H-2'), 5.62 (d, 1H, J= 7.5 Hz, NH), 5.92 (d, 1H, J= 6.4 Hz, H-1'), 7.25 (m, 9H, Ar-H), 7.38 (m, 6H, Ar-H), 7.92 (s, 1H, H-8), 8.3 (s, 1H, H-2); Anal. Calcd for $C_{36}H_{39}N_5O_4$+0.7 H_2O: C, 69.93; H, 6.59; N, 11.32. Found: C, 69.73; H, 6.57; N, 10.9.

N^6-Cyclohexyl-2',3'-di-O-methyl-5'-O-triphenylmethyl adenosine (**1c**):

Yield 6.3%; thick syrup; ^1H NMR ($CDCl_3$) δ 1.2-1.56 (m, 4H, cyclohexyl-H), 1.62-1.87 (m, 4H, cyclohexyl-H), 2.06-2.18 (m, 2H, cyclohexyl-H), 3.4 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.43 (s, 3H, OCH_3), 3.5 (s, 3H, OCH_3), 3.56 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 4.1 (t, 1H, J= 6.4 Hz, H-3'), 4.21 (m, 1H, cyclohexyl-H), 4.31 (q, 1H, J= 6.4 & 11.2 Hz, H-4'), 4.63 (t, 1H, J= 6.4 Hz, H-2'), 5.58 (d, 1H, J= 7.5 Hz, NH), 6.06 (d, 1H, J= 6.4 Hz, H-1'), 7.3 (m, 9H, Ar-H), 7.45 (m, 6H, Ar-H), 7.91 (s, 1H, H-8), 8.27 (s, 1H, H-2); Anal. Calcd for $C_{37}H_{41}N_5O_4$: C, 71.7; H, 6.66; N, 11.3. Found: C, 71.43; H, 6.51; N, 11.1.

N^6-Cyclohexyl-2'-O-methyl-5'-O-[(2-methylphenyl)diphenylmethyl]adenosine (**2a**):

Yield 64%; mp 93-97 °C; ^1H NMR ($CDCl_3$) δ 1.15-1.53 (m, 5H, cyclohexyl-H), 1.6-1.85 (m, 3H, cyclohexyl-H), 2.02 (s, 3H, CH_3), 2.02-2.17 (m, 2H, cyclohexyl-H), 2.77 (d, 1H, J= 7.5 Hz, OH), 3.39 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.52 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.58 (s, 3H, OCH_3), 4.15 (m, 1H, cyclohexyl-H), 4.21 (m, 1H, H-4'), 4.38 (m, 1H, H-2'), 4.55 (q, 1H, J= 7.5 & 11.2 Hz, H-3'), 5.68 (d, 1H, J= 7.5 Hz, NH), 6.16 (d, 1H, J= 3.7 Hz, H-1'), 7.2 (m, 9H, Ar-H), 7.42 (m, 5H, Ar-H), 7.98 (s, 1H, H-8), 8.3 (s, 1H, H-2); Anal. Calcd for $C_{37}H_{41}N_5O_4$+1.0 H_2O: C, 69.68; H, 6.8; N, 10.98. Found: C, 70.03; H, 6.73; N, 10.6.

N^6-Cyclohexyl-3'-O-methyl-5'-O-[(2-methylphenyl)diphenylmethyl]adenosine (**2b**):

Yield 19.3%; mp 89-93 °C; ^1H NMR ($CDCl_3$) δ 1.15-1.53 (m, 5H, cyclohexyl-H), 1.6-1.83 (m, 3H, cyclohexyl-H), 1.91 (s, 3H, CH_3), 2.0-2.15 (m, 2H, cyclohexyl-H), 3.25 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.45 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.5 (s, 3H, OCH_3), 4.17 (m, 1H, H-3'), 4.2 (m, 1H, cyclohexyl-H), 4.4 (m, 1H, H-4'), 4.53 (d, 1H, J= 6.4 Hz, OH), 4.88 (q, 1H, J= 6.4 & 11.2 Hz, H-2'), 5.7 (d, 1H, J= 7.5 Hz, NH), 5.96 (d, 1H, J= 6.4 Hz, H-1'), 7.07-7.42 (m, 14H, Ar-H), 8.0 (s, 1H, H-8), 8.31 (s, 1H, H-2); Anal. Calcd for $C_{37}H_{41}N_5O_4$+0.9 H_2O: C, 69.88; H, 6.78; N, 11.01. Found: C, 69.94; H, 6.72; N, 10.7.

N^6-Cyclohexyl-2',3'-di-O-methyl-5'-O-[(2-methylphenyl)diphenylmethyl]adenosine (**2c**):

Yield 9.65%; mp 79-84 °C; ^1H NMR ($CDCl_3$) δ 1.15-1.55 (m, 5H, cyclohexyl-H), 1.62-1.83 (m, 3H, cyclohexyl-H), 1.96 (s, 3H, CH_3), 2.03-2.15 (m, 2H, cyclohexyl-H), 3.37 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.46 (s, 3H, OCH_3), 3.53 (dd, 1H, J= 3.7 & 11.2 Hz, H-5'), 3.57 (s, 3H, OCH_3), 4.17 (m, 1H, cyclohexyl-H), 4.21 (t, 1H, J= 6.4 Hz, H-3'), 4.38 (q, 1H, J= 6.4 & 11.2 Hz, H-4'), 4.6 (t, 1H, J= 6.4 Hz, H-2'), 5.62 (d, 1H, J= 7.5 Hz, NH), 6.12 (d, 1H, J= 6.4 Hz, H-1'), 7.2 (m, 9H, Ar-H), 7.41 (m, 5H, Ar-H), 8.0 (s, 1H, H-8), 8.28 (s, 1H, H-2); Anal. Calcd for $C_{38}H_{43}N_5O_4$: C, 72.01; H, 6.84; N, 11.05. Found: C, 71.89; H, 7.1; N, 10.72.

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