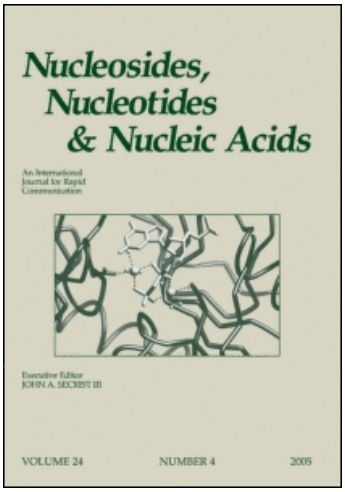

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Synthesis of 3′-Deoxy-3′-[4-(pyrimidin-1-yl)methyl-1,2,3-triazol-1-yl]thymidine via 1,3-Dipolar Cycloaddition

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ABSTRACT

The synthesis of new 3′-deoxy-3′-[4-(pyrimidin-1-yl)methyl-1,2,3-triazol-1-yl]-thymidine **6a–f**, from 3′-azido-3′-deoxy-5′-*O*-monomethoxytrityl-thymidine is described. The key step is the 1,3-dipolar cycloaddition between the azido group of the protected AZT **3** and *N*-1-propargylpyrimidine derivatives **2a–f**. All new derivatives **6a–f** were evaluated for their inhibitory effects against the replication of HIV-1 (IIIB), HIV-2 (ROD). No marked activity was found.

Key Words: Propargylpyrimidine; 1,2,3-Triazole; 1,3-Dipolar cycloaddition.

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INTRODUCTION

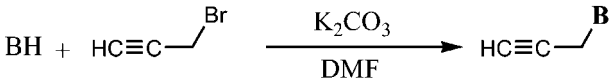
Azole nucleosides are a large class of antimetabolites. Important drugs of this class are bredenin, pyrazofurin and ribavirin and their analogs,[1] which are endowed with immuno-suppressive, antitumor and antiviral activity, respectively. On the other hand, several small heterocyclic groups were introduced in the 3′-position of 2′-deoxyribose nucleosides in which the three nitrogen system of AZT was replaced by a series of 1,2,3 or 1,2,4-triazoles substituted with different functional group (such as amide and ester) at positions 4 or 5.[2–5]

Following our research program on the chemistry of 1,2,3-triazole derivatives [6,7] and in connection with a project on the synthesis of bioisosters of AZT and related deoxynucleosides, we tried to convert 3′-azidothymidine into 3′-(1,2,3-triazolyl) derivatives through 1,3-dipolar cycloaddition reactions. Our purpose is a better understanding of the structure-activity relationship, especially with regards to the size and structure of the substituent in the positions 4 or 5 of the triazole ring. Introduction of the additional methylene unit between triazole and nucleobase should facilitate the conformational flexibility. Furthermore the 5-halopyrimidines derivatives display significant antiviral and anticancer activities.[8]

RESULTS AND DISCUSSION

1,3-dipolar cycloaddition reactions are known to be one of the useful methods for the synthesis of five-membered heterocycles.[9] Indeed, numerous glycosylated – 1,2,3-triazole compounds were prepared using this method and have been reported in the literature.[10] For the synthesis of 3′-(1,2,3-triazol-1-yl)-3′-deoxy thymidine nucleoside analogues, we employed the methodology of aglycon construction on the sugar moiety using 1,3-dipolar cycloaddition. The dipolarophilic *N*-1-propargyl-pyrimidine **4a–f** (Sch. 1) was prepared regioselectively by a modification of a known method.[11]

The synthesis involved the use of propargyl bromide (alkylating agent), in DMF solution in the presence of potassium carbonate at room temperature. Reaction times were in the range 4–24 h. The desired products *N*-1-propargylpyrimidines **2a–f** were obtained in good yields.[12]



1a:	B=Thymin-1-yl	**2a**
1b:	BH=Uracil-1-yl	**2b**
1c:	BH=5-Fluorouracil-1-yl	**2c**
1d:	BH=5-Chlorouracil-1-yl	**2d**
1e:	BH=5-Bromouracil-1-yl	**2e**
1f:	BH=5-Iodouracil-1-yl	**2f**

Scheme 1.

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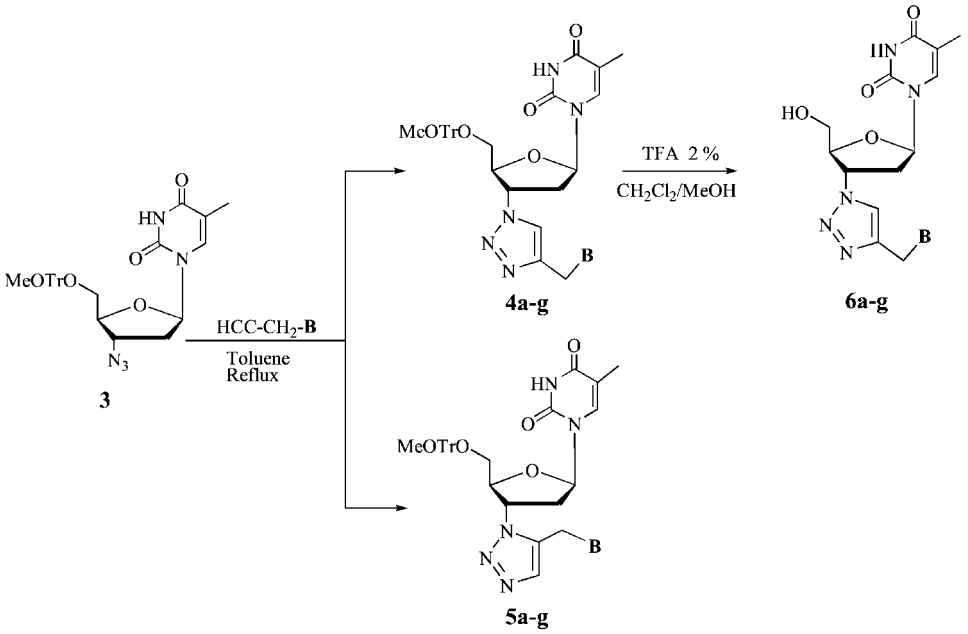
The second step of the synthesis was the preparation of 3′-azido-3′-deoxy-5′-*O*-monomethoxytritylthymidine **3**.[13] The cycloaddition reaction of the azidothymidine derivative **3** with *N*-1-propargylpyrimidine **2a–f** in dry toluene under reflux, afforded a mixture of two regioisomers, **4a–f** (major component) and **5a–f** (traces) (Sch. 2), without the formation of other side products or any noticeable decomposition.

The ratio **4**:**5** was 9:1 as estimated from ^{1}H NMR spectra. After separation by silica gel column chromatography, only the isomers **4a–f** were obtained as pure products (Table 1).

It is known from the literature that the outcome of the addition of azides to unsymmetrical acetylenes is determined by steric and electronic factors. In general, such an addition tends to give mainly the isomers with electron withdrawing groups at the 4-position.[14–16] On the other hand, the sterically less hindered isomers tend to be the major isomer.[17,18] The structures of new compounds were assigned on the basis of the corresponding analytical and spectroscopic data. The distinction between 4- or 5-location of substitutent in triazolic regioisomers **4a–f** was achieved on the basis of the chemical shifts of the triazole proton (H-5).[18–22] Due to the effect of the adjacent sugar the triazole proton in the 1,4-substituted 1,2,3-triazole isomers **4a–f** appeared at lower field (8.07–8.30 ppm) than in the isomeric 1,5-substituted 1,2,3-triazole derivatives **5a–f** (7.50–7.75 ppm) (Table 2).

The deprotection of the 5′-methoxytrityl group was smoothly performed by treatment with 2% TFA in CH_2Cl_2/MeOH (4/1) to give **6a–f** (Sch. 2) in high yields.



a: B = Thymin-1-yl; **b**: B = Uracil-1-yl, **c**: B = 5-Fluorouracil-1-yl,
d : B = 5 Chlorouracil-1-yl, **e** : B = 5-Bromouracil-1-yl, **f** : B = 5-Iodouracil-1-yl.

Scheme 2.

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Table 1. Reaction conditions of 1,3-dipolar cyloaddition of *N*-propargylpyrimidine derivatives **4a–f** with azidonucleoside **3**.

Acetylenic product	Equivalent of azidonucleoside	Solvent	Time (h)	Yield (%)
4a	5	Toluene	66	71
4b	5	Toluene	66	75
4c	5	Toluene	48	68
4d	5	Toluene	48	79
4e	5	Toluene	48	77
4f	5	Toluene	48	75

Table 2. Chemical shifts (δ(ppm), 250 MHz, DMSO-d_6) of compounds **4a–f**.

Product	H-3′	H-5′	CH_2-	H-5 (triazole)	H-6 (Nucleobases)
4a	5.65	3.25	4.90	8.30	7.60; 7.65
4b	5.6	3.25	4.94	8.26	7.60; 7.76
4c	5.59	3.33	4.94	8.34	7.68; 8.21
4d	5.54	3.27	4.96	8.31	7.64; 8.27
4e	5.59	3.33	5.02	8.39	7.70; 8.35
4f	5.50	3.26	4.95	8.30	7.63; 8.26

In conclusion, the successful preparation of new 3′-modified 2′,3′-dideoxynucleosides using 1,3-dipolar cycloaddition, containing three heterocyclic bases (thymine, 1,2,3-triazole and nucleobases), has been performed.

ANTIVIRAL ACTIVITY

Compounds **6a–f** were evaluated for their inhibitory effect against the cytopathicity of HIV-1 (III_B) and HIV-2 (ROD) in MT-4 cells.[23] No activity was observed against the replication of these viruses at compound concentrations up to 100 μg/mL (data not shown).

EXPERIMENTAL SECTION

Melting points (mp) were determined on an electro thermal digital melting point apparatus Buchi and were uncorrected. Ultraviolet spectral (UV) were recorded with a Cary 219 spectrometer. The ^{1}H NMR spectra were recorded using a Brucker AC 250 MHz spectrometer. Mass spectra (MS) were obtained with JEOL JMS DX 300 instrument using fast atomic bombardment (FAB pos.). Thin layer chromatography was performed on plates of kieselgel 60 F254 (Merck) and short-wave ultraviolet light (254 nm) was used to detect the UV-absorbing spots. Column chromatography

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separation was carried out on silica gel (0.063–0.2 mm Merck). Elemental analysis was determined by the French Micro analytical Central Service Vernaison.

General Procedure for the Synthesis of Compounds 4a–f. A solution of 2.5 mmol protected AZT **3** and 2.5 mmol of *N*-1/*N*-9-propargylpyrimidine/purine **2** in anhydrous toluene (40 mL) was heated under reflux for 2 to 3 days (see Table 1). Evaporation of the solvent furnished a mixture of **4** and **5**. Ratio of **4**:**5** is 9/1 and was determinate by ^{1}H NMR based on the integration of triazolic protons H-4 (1,5-isomer) and H-5 (1,4-isomer), after purification on silica gel column chromatography using $MeOH/CH_2Cl_2$, 0–10% as eluent.

3′-Deoxy-3′-[4-(thymin-1-yl-methyl)-1,2,3-triazol-1-yl]-5′-*O*-monomethoxytrityl Thymidine 4a. Yield: 71%; ^{1}H NMR (DMSO-d_6) δ: 1.60 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.75 (m, 2H, 2 × H-2′), 3.25 (m, 2H, 2 × H-5′), 3.75 (s, 3H, OCH_3), 4.30 (m, 1H, H-4′), 4.90 (s, 2H, CH_2), 5.65 (m, 1H, H-3′), 6.40 (m, 1H, H-1′), 6.85 and 7.25 (2m, 14H, trityle), 7.60 (s, 1H, H-6), 7.65 (s, 1H, H-6), 8.30 (s, 1H, H-5, triazole), 11.30 (bs, 1H, NH), 11.40 (bs, 1H, NH); U.V. (MeOH) λ_{max} 260 nm; MS (EI) *m*/*z*: 703 (M^+).

3′-Deoxy-3′-[4-(uracil-1-yl-methyl)-1,2,3-triazol-1-yl]-5′-*O*-monomethoxytrityl Thymidine 4b. Yield: 75%; ^{1}H NMR (DMSO-d_6) δ: 1.60 (s, 3H, CH_3), 2.75 (m, 2H, 2 × H-2′), 3.25 (m, 2H, 2 × H-5′), 3.75 (s, 3H, OCH_3), 4.30 (m, 1H, H-4′), 4.95 (s, 2H, CH_2), 5.60 (m, 2H, H-5 + H-3′), 6.50 (m, 1H, H-1′), 6.90 et 7.30 (2m, 14H, trityle), 7.65 (s, 1H, H-6), 7.75 (d, 1H, H-6, $J = 7.5$ Hz), 8.26 (s, 1H, H-5′, triazole), 11.35 (bs, 1H, NH), 11.40 (bs, 1H, NH); U.V. (MeOH): λ_{max} 260 nm; MS (EI) *m*/*z*: 689 (M^+).

3′-Deoxy-3′-[4-(5-fluorouracil-1-yl-methyl)-1,2,3-triazol-1-yl]-5′-*O*-monomethoxytrityl Thymidine 4c. Yield: 68%; ^{1}H NMR (DMSO-d_6) δ: 1.63 (s, 3H, CH_3), 2.79 (m, 2H, 2 × H-2′), 3.33 (m, 2H, 2 × H-5′), 3.97 (s, 3H, OCH_3), 4.34 (m, 1H, H-4′), 4.94 (s, 2H, CH_2), 5.59 (m, 1H, H-3′), 6.44 (t, 1H, H-1′, $J = 6.35$ Hz), 6.91–7.39 (m, 14H, trityle), 7.68 (s, 1H, H-6), 8.21 (d, 1H, H-6, $J = 6.7$ Hz), 8.34 (s, 1H, H-5, triazole), 11.40 (s, 1H, NH), 11.52 (s, 1H, NH); U.V. (MeOH): λ_{max} 268 nm; MS (FAB) *m*/*z*: 708 $(M + H)^+$.

3′-Deoxy-3′-[4-(5-chlorouracil-1-yl-methyl)-1,2,3-triazol-1-yl]-5′-*O*-monomethoxytrityl Thymidine 4d. Yield: 79%; ^{1}H NMR (DMSO-d_6) δ: 1.58 (s, 3H, CH_3), 2.75 (m, 2H, 2 × H-2′), 3.27 (m, 2H, 2 × H-5′), 3.72 (s, 3H, OCH_3), 4.30 (m, 1H, H-4′), 4.96 (s, 2H, CH_2), 5.54 (m, 1H, H-3′), 6.39 (t, 1H, H-1′, $J = 6.3$ Hz), 6.86–7.34 (m, 14H, trityle), 7.64 (s, 1H, H-6), 8.27 (s, 1H, H-6), 8.31 (s, 1H, H-5, triazole), 11.40 (s, 1H, NH), 11.88 (s, 1H, NH); U.V. (MeOH): λ_{max} 274 nm; MS (FAB) *m*/*z*: 725 $(M + H)^+$.

3′-Deoxy-3′-[4-(5-bromouracil-1-yl-methyl)-1,2,3-triazol-1-yl]-5′-*O*-monomethoxytrityl Thymidine 4e. Yield: 77%; ^{1}H NMR (DMSO-d_6) δ: 1.64 (s, 3H, CH_3), 2.79 (m, 2H, 2 × H-2′), 3.33 (m, 2H, 2 × H-5′), 3.79 (s, 3H, OCH_3), 4.36 (m, 1H, H-4′), 5.02 (s, 2H, CH_2), 5.59 (m, 1H, H-3′), 6.44 (t, 1H, H-1′, $J = 6.3$ Hz), 6.92–7.40 (m, 14H, trityle),

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7.70 (s, 1H, H-6), 8.35 (s, 1H, H-6), 8.39 (s, 1H, H-5, triazole), 11.44 (s, 1H, NH), 11.91 (s, 1H, NH); U.V. (MeOH): λ_{max} 272 nm; MS (FAB) m/z: 769 $(M+H)^+$.

3′-Deoxy-3′-[4-(5-iodouracil-1-yl-methyl)-1,2,3-triazol-1-yl]-5′-*O*-monomethoxytrityl Thymidine 4f. Yield: 75%; ^{1}H NMR (DMSO-d_6) δ: 1.58 (s, 3H, CH_3), 2.73 (m, 2H, 2 × H-2′), 3.26 (m, 2H, 2 × H-5′), 3.71 (s, 3H, OCH_3), 4.29 (m, 1H, H-4′), 4.95 (s, 2H, CH_2), 5.50 (m, 1H, H-3′), 6.37 (t, 1H, H-1′, $J = 6.3$ Hz), 7.15–7.32 (m, 14H, trityle), 7.63 (s, 1H, H-6), 8.26 (s, 1H, H-6), 8.30 (s, 1H, H-5, triazole), 11.38 (s, 1H, NH), 11.70 (s, 1H, NH); U.V. (MeOH): λ_{max} 273 nm; MS (FAB) m/z: 816 $(M+H)^+$.

Deprotection Method. Treatment of 100 mg of compounds **4a–f** with 2 mL of solution (2% of trifluoroacetic acid in CH_2Cl_2/MeOH, 4/1, V/V) and after stirring for 30 mn gave the corresponding deprotected products **6a–f**. These products were recovered after evaporation of solvent then washed with 3 × 10 mL of CH_2Cl_2 and purified by column chromatography. (eluent:gradient 1–10%) of methanol in CH_2Cl_2.

3′-Deoxy-3′-[4-(thymin-1-yl-methyl)-1,2,3-triazol-1-yl]thymidine 6a. Yield: 65%; ^{1}H NMR (DMSO-d_6) δ: 1.75 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.62 (m, 2H, 2 × H-2′), 3.59–3.63 (m, 2H, 2 × H-5'), 4.18 (m, 1H, H-4′), 4.90 (s, 2H, CH_2), 5.24 (t, 1H, OH), 5.34 (m, 1H, H-3′), 6.40 (m, 1H, H-1′), 7.62 (s, 1H, H-6), 7.97 (s, 1H, H-6), 8.25 (s, 1H, H-5, triazole), 11.31 (bs, 1H, NH); U.V. (MeOH): λ_{max} 261 nm; mp: 220–222°C (CH_2Cl_2/CH_3OH) (decomposition); MS (EI) m/z: 430 $(M)^+$; Anal. calcd. for $C_{18}H_{20}N_7O_6$: C, 50.23; H, 4.68; N, 22.18, found, C, 50.13; H, 4.73; N, 22.11.

3′-Deoxy-3′-[4-(uracil-1-yl-methyl)-1,2,3-triazol-1-yl]thymidine 6b. Yield: 75%; ^{1}H NMR (DMSO-d_6) δ: 1.79 (s, 3H, CH_3), 2.62–2.72 (m, 2H, 2 × H-2′), 3.40–3.74 (m, 2H, 2 × H-5′), 4.55 (m, 1H, H-4′), 4.94 (s, 2H, CH_2), 5.26 (t, 1H, OH), 5.33 (m, 2H, H-3′), 5.58 (d, 1H, $J = 7.8$ Hz, H-5), 6.39 (t, 1H, $J = 6.6$ Hz, H-1′), 7.73 (s, 1H, H-6), 7.74 (d, 1H, H-6, J = 7.8 Hz), 8.25 (s, 1H, H-5, triazole), 11.32 (bs, 2H, 2 × NH); U.V. (MeOH): λ_{max} 260 nm; mp: 160–162°C (CH_2Cl_2/CH_3OH) (decomposition.); MS (EI) m/z: 417 $(M)^+$; Anal. calcd. for $C_{17}H_{18}N_7O_6$: C, 49.04; H, 4.36; N, 23.55, found, C, 49.15; H, 4.43; N, 23.39.

3′-Deoxy-3′-[4-(fluorouracil-1-yl-methyl)-1,2,3-triazol-1-yl]thymidine 6c. Yield: 78%; ^{1}H NMR (DMSO-d_6) δ: 1.79 (s, 3H, CH_3), 2.67 (m, 2H, 2 × H-2′), 3.65 (m, 2H, 2 × H-5′), 4.20 (m, 1H, H-4′), 4.92 (s, 2H, CH_2), 5.33 (m, 1H, OH), 5.37 (m, 1H, H-3′), 6.40 (t, 1H, $J = 6.6$ Hz, H-1′), 7.80 (s, 1H, H-6), 8.19 (d, 1H, H-6, $J = 6.7$ Hz), 8.29 (s, 1H, H-5, triazole), 11.35 (s, 1H, NH), 11.86 (s, 1H, NH); U.V. (MeOH): λ_{max} 268 nm; mp: 224–226°C (CH_2Cl_2/CH_3OH) (decomposition.); MS (FAB) m/z: 436 $(M+H)^+$; Anal. calcd. for $C_{17}H_{18}N_7O_6F$: C, 49.90; H, 4.17; N, 22.52, found, C, 49.71; H, 4.23; N, 22.25.

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3′-Deoxy-3′-[4-(chlorouracil-1-yl-methyl)-1,2,3-triazol-1-yl]thymidine 6d. Yield: 72%; ^{1}H NMR (DMSO-d_6) δ: 1.80 (s, 3H, CH_3), 2.71 (m, 2H, 2 × H-2′), 3.70 (m, 2H, 2 × H-5′), 4.24 (dd, 1H, H-4′, $J = 5.1$ Hz), 5.00 (s, 2H, CH_2), 5.31 (t, 1H, OH, $J = 5.1$ Hz), 5,39 (m, 1H, H-3′), 6.44 (t, 1H, $J = 6.6$ Hz, H-1′), 7.84 (s, 1H, H-6), 8.33–8.31 (2s, 2H, H-5, triazole + H-6), 11.35 (s, 1H, NH), 11.92 (s, 1H, NH); U.V. (MeOH): λ_{max} 274 nm; mp: 216–218°C (CH_2Cl_2/CH_3OH) (decomposition); MS (FAB) m/z: 452 $(M + H)^+$; Anal. calcd. for $C_{17}H_{18}N_7O_6Cl$: C, 45.19; H, 4.02; N, 21.70, found, C, 45.27; H, 4.11; N, 21.65.

3′-Deoxy-3′-[4-(bromouracil-1-yl-methyl)-1,2,3-triazol-1-yl]thymidine 6e. Yield: 77%; ^{1}H NMR (DMSO-d_6) δ: 1.80 (s, 3H, CH_3), 2.66 (m, 2H, 2 × H-2′), 3.65 (m, 2H, 2 × H-5′), 4.19 (m, 1H, H-4′), 5.06 (s, 2H, CH_2), 5.32 (m, 1H, OH), 5.36 (m, 1H, H-3′), 6.40 (t, 1H, $J = 6.6$ Hz, H-1′), 7.80 (s, 1H, H-6), 8.30–8.28 (2s, 2H, H-5, triazole + H-6), 11.38 (s, 1H, NH), 11.82 (s, 1H, NH); U.V. (MeOH): λ_{max} 272 nm; mp: 202–204°C (CH_2Cl_2/CH_3OH) (decomposition); MS (FAB) m/z: 497 $(M + H)^+$; Anal. calcd. for $C_{17}H_{18}N_7O_6Br$: C, 41.14; H, 3.66; N, 19.76, found, C, 41.19; H, 3.72; N, 19.82.

3′-Deoxy-3′-[4-(iodouracil-1-yl-methyl)-1,2,3-triazol-1-yl]thymidine 6f. Yield: 82%; ^{1}H NMR (DMSO-d_6) δ: 1.81 (s, 3H, CH_3), 2.67 (m, 2H, 2 × H-2′), 3.65 (m, 2H, 2 × H-5′), 4.19 (m, 1H, H-4′), 4.94 (s, 2H, CH_2), 5.28 (t, 1H, OH, $J = 5.1$ Hz), 5.38 (m, 1H, H-3′), 6.42 (t, 1H, $J = 6.6$ Hz, H-1′), 7.80 (s, 1H, H-6), 8.34–8.29 (2s, 2H, H-5, triazole + H-6), 11.38 (s, 1H, NH), 11.72 (s, 1H, NH); U.V. (MeOH): λ_{max} 272 nm; mp: 245–247°C(CH_2Cl_2/CH_3OH); (decomposition); MS (FAB) m/z: 544 $(M + H)^+$; Anal. calcd. for $C_{17}H_{18}N_7O_6I$: C, 37.58; H, 3.34; N, 18.05, found, C, 37.64; H, 3.28; N, 18.14.

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