SYNTHESES OF NOVEL ACYCLIC NUCLEOSIDES, 9-(4'-HYDROXY-2'-METHYLBUT-1'-ENYL)ADENINE AND RELATED COMPOUNDS

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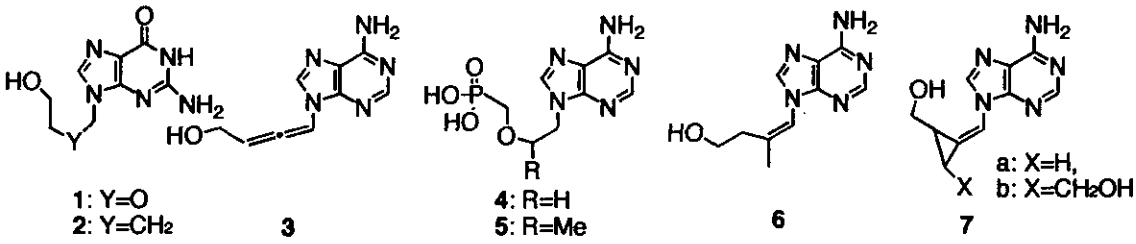
Abstract - An exploratory coupling reaction between adenine and a protected vicinal dibromo-intermediate was carried out to give the β,γ-unsaturated nucleoside analogues and a vinyl bromide derivative. Then a novel CuI catalytic coupling reaction between adenine and the vinyl bromide was successfully developed to afford an α,β-unsaturated acyclic nucleoside, 9-(4'-hydroxy-2'-methylbut-1'-enyl)adenine. All the above nucleosides were subjected to an anti-HIV-1 test.

Nucleoside analogues are the focus of current interest as antiviral chemotherapeutic agents. Modifications of both the nucleobases and sugar moieties have led to many discoveries of bioactive nucleosides,[1] and, in particular, acyclic analogues are a highlighted species.[2] Thus, acyclovir (**1**) in Scheme 1 is well known as a clinically useful antiherpetic drug[3] and the simple analogue (**2**) is also an antiviral agent.[4] It is highly significant that, as a reverse transcriptase inhibitor, adenallene (**3**) shows anti-HIV activity[5] comparable to AZT. Recently, several acyclic nucleoside phosphonate analogues such as PMEA (**4**) and PMPA (**5**) which exhibit high activity against retroviruses have been developed.[6,7] It is notable that **5** can prevent simian immunodeficiency virus (SIV) infection in all macaques without toxicity.[2]

In inspection of the features of the bioactive acyclic nucleosides, it is noted that, besides the hydroxymethyl group at the 3'-position (or a phosphinic acid group at the 4'-position for phosphinic acid-type nucleosides) in an open-chain moiety, the atom at the 2'-position (or the 3'-position for phosphinic acid-type nucleosides) may play an important role in inhibition activities.[2,5] We believe that an oxygen atom which possesses p-orbital lone-pair electrons (similar to the corresponding atom of ribofuranose) or a double-bond carbon atom which possesses *p*-orbital π-electrons are more effective as the atom. This feature perhaps indicates that this position is also a recognition site when an inhibitor is bound to a receptor. Many papers have focused discussion on the relationship of 2'-oxygen (or 3'-oxygen in PMEA analogues) with antiviral activities both in alcohol-type and phosphinic acid-type nucleosides and elucidated its importance.[8,9] The acyclic nucleosides containing a 2'-double-bond carbon atom include the following three types: (i) α,β-

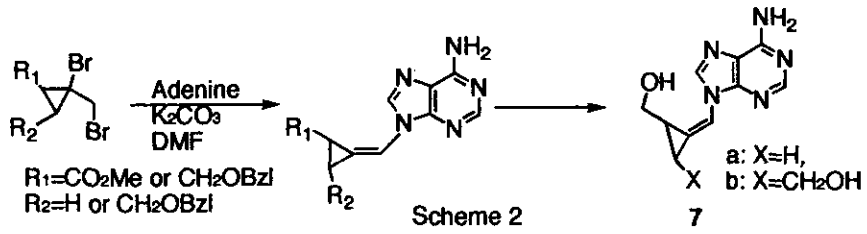
unsaturated; (ii) β,γ-unsaturated, and (iii) α,β,γ-cumulated unsaturated compounds. Compound (**3**), a third-type compound, shows high anti-HIV activity and some second-type compounds also show anti-HSV activities.[10] Similarly, carbovir has also a β,γ-double bond.[11] So, it is interesting to investigate whether the novel first-type compounds possess such activities. Thus, we designed a such α,β-unsaturated acyclic nucleoside (**6**) which is similar to adenallene (**3**) in the 4'-hydroxyl group and in the 1'-double bond, and also similar to PMPA (**5**) in the 2'-methyl group.



Scheme 1

There are many methods to synthesize nucleoside analogues,[12] but no reaction for formation of α,β-unsaturated nucleosides has been reported yet.

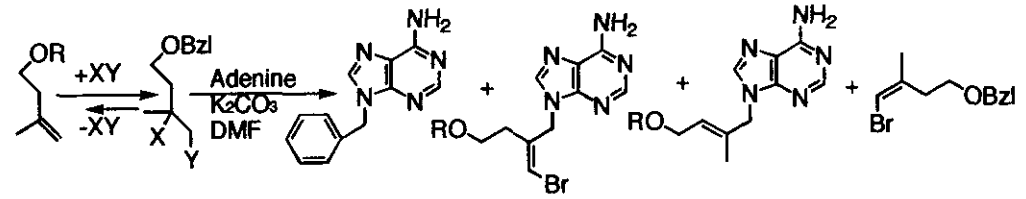
Recently, we successfully coupled a vicinal dibromo-intermediate with adenine in a one-pot reaction to afford α,β-unsaturated three-membered carbocyclic nucleosides, 9-cyclopropylidenemethylenyladenines (**7**) as shown in Scheme 2, one of which (**7**a) has been proved to have anti-HIV-1 activity.[13] So, we first tried to utilize this procedure to synthesize such α,β-unsaturated acyclic nucleosides.



Scheme 2

Thus, as postulated in Scheme 3, ether (**9**) was smoothly prepared from alcohol (**8**), NaH, and benzyl chloride in the presence of benzyltriethylammonium chloride (0.02 equiv.), and **9** was quantitatively converted to benzyl (1,2-dibromo-2-methyl)butyl ether (**10**) with bromine at 0 ℃ in chloroform. **10** reacted with 4 equiv. adenine and 4 equiv. K_2CO_3 in DMF at 85 ℃ to give 4-benzyloxy-1-bromo-2-methyl-1-butene (**11**) (15%, *trans/cis*=2:1), 9-(4'-benzyloxy-2'-methylbut-2'-enyl)adenine (**12**) (12%, *trans/cis*=1.2:1), 9-[2'-(2-benzyloxyethyl)-3'-bromoprop-2'-enyl]adenine (**13**) (20%, *trans/cis*=10:1) and 9-benzyladenine (**14**) (45%), but gave no target molecule (**18**) (in Scheme 5). These results indicated that this reaction is different from the previous one in which a substitution-elimination mechanism was proposed[13] and it is reasonably inferred that the elimination reaction preferentially took place to give **9**, **11**,

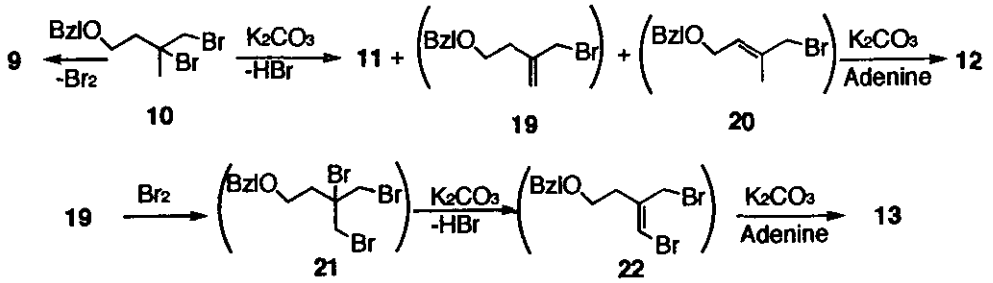
19, **20**, respectively, as shown in Scheme 4. Then **20** reacted with the adenine anion by substitution to form **12**. **19** reacted with bromine which was formed *in situ* from the procedure of debromination of **10** to give **21**, and **21** was converted to **22** by dehydrobromination. **22** successively reacted with the adenine anion by substitution to form **13**. In addition, it is easily understood that the adenine anion cleaved a protective benzyl group to give **14**.



8: R=H **9**: R=Bzl **10**: X=Y=Br **17**: X=Cl, Y=I **14** **13**: R=Bzl **16**: R=H **12**: R=Bzl **15**: R=H **11**

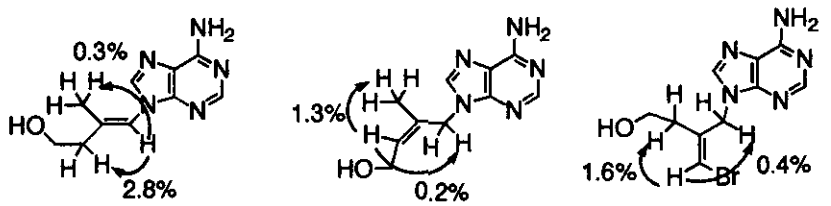
Scheme 3

To prevent cleavage of the protective group, this reaction was carried out at room temperature for a week. It afforded vinyl bromide (**11**) in 61% isolated yield with the *trans/cis* ratio 2:1, the same as above. According to the general synthetic method of vinyl halide, **11** may be obtained in higher yield by dehydrobromination of **10** using K_2CO_3 as a base without the adenine.



Scheme 4

Compounds (**12**) and (**13**) were deprotected by 6 equiv. BCl_3 at -20 ℃ to afford 9-(4'-hydroxy-2'-methylbut-2'-enyl)adenine (**15**) and 9-[2'-(2-hydroxyethyl)-3'-bromoprop-2'-enyl]adenine (**16**) in 90% yield with the same *trans/cis* ratio as to **12** and **13**, respectively. The *trans/cis* isomers of **15** and **16** were separated by a reverse phase HPLC and were determined by NOE measurements (Figure 1).

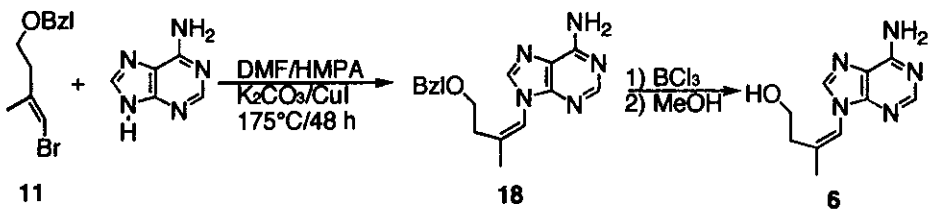


trans-**6** *cis*-**15** *cis*-**16**

Figure 1

An attempt at coupling adenine with an intermediate 2-chloro-1-iodo analogue (**17**) which was synthesized by adding ICl to olefin (**9**) led to formation of the starting olefin (**9**) in almost quantitative yield by elimination of ICl. This procedure probably took place as a reverse reaction of halogenation, similar to the debromimation of **10** in Scheme 4.

Ogawa *et al.* reported a catalytic coupling reaction between amide and vinyl halide to synthesize *N*-vinylamide derivatives.[14] We examined a similar coupling reaction of adenine with a vinyl bromide (**11**), and successfully obtained the α,β-unsaturated acyclic nucleoside, 9-(4'-benzyloxy-2'-methylbut-1'-enyl)adenine (**18**) in 53% yield, although high temperature (175 ℃) was required as shown in Scheme 5. The by-product 9-benzyladenine (**14**) in Scheme 3 was also isolated in 15% yield. The *trans/cis* ratio of **18** is 2:1, the same as the ratio of vinyl bromide (**11**), so this may be a configuration-maintaining reaction as described in the literature.[14] Then the *trans/cis* mixture of **18** was deprotected by 6 equiv. BCl_3 at low temperature (-20 ℃) to afford the final target molecule, 9-(4'-hydroxy-2'-methylbut-1'-enyl)adenine (**6**) in 90% yield. The *trans/cis* isomers of **6** were separated by a reverse phase HPLC and were assigned by NOE measurements as shown in Figure 1.



11 **18** **6**

Scheme 5

The anti-HIV-1 activities of **14**, **15**-*trans*, **15**-*cis*, **16** (10:1 *trans/cis* mixture), **6**-*trans* and **6**-*cis* were tested using MT-4 cell *in vitro*. None of them showed significant activity and toxicity. They will also be tested for other viruses, and the work on syntheses of the non-2'-methyl analogues of **6** and other derivatives is in progress.

EXPERIMENTAL SECTION

General method. NMR spectra were measured with a JEOL-JNM-GSX-400; HPLC was run on a Shimatsu CL 64 with the UV detector. High-resolution MS spectra were determined by a Hitachi M-2000AM. All chemical reagents are commercially available. The compounds subjected to an anti-HIV-1 test were purified by reverse phase HPLC and their purities were checked by the ^{1}H NMR.

Halogenation (synthesis of **10**, **17**): To a stirred solution of 4-benzyloxy-2-methyl-1-butene (**9**) (3.53 g, 20 mmol in 50 mL of chloroform), a solution of bromine [3.20 g, (or iodine monochloride, 3.25 g), 20 mmol in 50 mL of chloroform] was added dropwise at 0 ℃ for 5 h. After being stirred at 0 ℃ overnight (or reflux 30 h for ICl), the colorless solution was evaporated by a rotary pump to give a light yellow liquid **10** or **17** in quantitative yield. The products were used in the following reactions without further

purification. **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 4.53 (s, 2H), 3.92 (d, 1H, J=10 Hz), 3.83 (d, 1H, J=10 Hz), 3.75 (m, 2H), 2.30 (m, 2H), 1.96 (s, 3H); HRMS calcd for $C_{12}H_{16}OBr_2$ 317.8315, found 317.8315. **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (m, 5H), 4.36 (s, 2H), 3.53 (m, 4H), 2.10 (m, 2H), 1.59 (s, 3H); HRMS calcd for $C_{12}H_{16}OClI$ 337.9936, found 337.9940.

Reaction of vicinal dihalocompound (**10**, **17**) with adenine (syntheses of mixture of **11**, **12**, **13**, **14**): A mixture of vicinal dihalocompound [(3.36 g of **10**, or 3.39 g of **17**), 10 mmol], adenine (5.41 g, 40 mmol) and potassium carbonate (5.53 g, 40 mmol) was suspended in 50 mL of anhydrous DMF and stirred under nitrogen atmosphere at 85 ℃ for 20 h (or at rt for a week for the formation of only **11**). After the mixture was filtrated, the filter cake was washed with 3×20 mL of DMF, and the combined filtrate was evaporated under vacuum and the residue was chromatographed on a silica gel column in a solvent of 6:1 (v/v) ethyl acetate/methanol. The different Rf fractions were evaporated to give **11** (15%), **12** (12%), **13** (20%), **14** (45%), respectively. **11** (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (m, 5H), 5.97 (s, 1H), 4.52 (s, 2H), 3.59 (t, 2H, J=6.8 Hz), 2.41 (t, 2H, J=6.8 Hz), 1.80 (s, 3H); HRMS calcd for $C_{12}H_{15}OBr$ 237.9053, found 237.9055. **11** (*cis*): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (m, 5H), 5.94 (s, 1H), 4.52 (s, 2H), 3.59 (t, 2H, J=6.8 Hz), 2.56 (t, 2H, J=6.8 Hz), 1.82 (s, 3H); HRMS calcd for $C_{12}H_{15}OBr$ 237.9053, found 237.9055. **12** (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 7.95 (s, 1H), 7.37 (m, 5H), 5.08 (s, 2H), 4.66 (s, 2H), 4.59 (s, 1H), 4.57 (s, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.38, 152.71, 149.63, 140.17, 137.02, 134.15, 128.29 (2C), 127.88 (2C), 127.46, 124.03, 118.55, 72.45, 71.87, 47.92, 16.89; HRMS calcd for $C_{17}H_{19}N_5O$ 309.1591, found 309.1589. **12** (*cis*): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27 (s, 1H), 7.87 (s, 1H), 7.37 (m, 5H), 4.91 (s, 2H), 4.61 (s, 2H), 4.52 (s, 1H), 4.38 (s, 2H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.38, 152.62, 149.63, 140.11, 136.92, 133.99, 128.22 (2C), 127.78 (2C), 126.95, 122.28, 118.55, 71.91, 70.84, 44.57, 21.30; HRMS calcd for $C_{17}H_{19}N_5O$ 309.1591, found 309.1589. **13** (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25(s, 1H), 7.94 (s, 1H), 7.29 (m, 5H), 6.49 (s, 1H), 5.03 (s, 2H), 4.42 (s, 2H), 3.54 (t, 2H, J=6.4 Hz), 2.38 (t, 2H, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.18, 152.21, 149.19, 140.10, 137.18, 136.59, 127.74 (2C), 127.14 (3C), 118.10, 108.15, 72.35, 67.00, 44.23, 33.98; HRMS calcd for $C_{17}H_{17}N_5O$ (M-HBr) 307.1435, found 307.1428 .

Catalytic coupling reaction (synthesis of **18**): A mixture of **11** (0.46 g, 1.8 mmol), CuI (0.34 g, 1.8 mmol), adenine (0.74 g, 5.5 mmol) and K_2CO_3 (0.25 g, 1.8 mmol) was suspended in 45 mL of anhydrous DMF and 20 mL of HMPA and stirred under nitrogen atmosphere at 175 ℃ for 48 h. The mixture was filtrated, the filter cake was washed with 3×20 mL of DMF, and the combined filtrate was evaporated under vacuum of 5 mmHg for DMF and then 0.3 mmHg for HMPA. The solid obtained by evaporation was solved in 30 mL of ethyl acetate and 30 mL of water and filtrated (for removal of adenine), and the organic

phase was separated and washed with 3×10 mL of water to remove inorganic salts and DMF. After evaporation, the viscous residue was chomatographed on a silica gel column in a solvent of 5:1 (v/v) ethyl acetate/methanol. The different Rf fractions were evaporated to give **18** (53%) and **14** (15%), respectively. **18** (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (s, 1H), 7.78 (s, 1H), 7.31 (m, 5H), 6.65 (s, 1H), 5.67 (br, 2H), 4.57 (s, 2H), 3.71 (t, 2H, J=6.8 Hz), 2.58 (t, 2H, J=6.8 Hz), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.72, 153.73, 150.50, 140.82, 138.42, 137.56, 128.76 (2C), 128.04 (2C), 119.50, 117.28, 116.77, 73.37, 68.21, 37.20, 17.07; HRMS calcd for $C_{17}H_{19}N_5O$ 309.1591, found 309.1551. **18** (*cis*): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36 (s, 1H), 8.12 (s, 1H), 7.31 (m, 5H), 6.65 (s, 1H), 5.67 (br, 2H), 4.51 (s, 2H) , 3.62 (t, 2H, J=6.4 Hz), 2.37 (t, 2H, J=6.4 Hz), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.72, 153.60, 150.50, 142.20, 138.30, 137.41, 128.76 (2C), 128.04 (2C), 119.90, 117.28, 116.77, 73.53, 67.04, 32.37, 20.50; HRMS calcd for $C_{17}H_{19}N_5O$ 309.1591, found 309.1551.

Deprotection (syntheses of **6**, **15**, **16**): To a solution of protected nucleoside [(0.15 g of **12** or **18**, or 0.19 g of **13**), 0.5 mmol, in 20 mL of methylene dichloride], BCl_3 solution (1.0 M in methylene dichloride, 3.0 mL) was added dropwise at -20 ℃ and stirred for 6 h. After warming the mixture to 0 ℃, 20 mL of methanol was added and stirred until the mixture was allowed to warm to rt. The mixture was then evaporated at atmosphere pressure (for methylene dichloride), 15 mmHg (for methnaol) and 0.5 mmHg (for benzyl chloride). The solid residue obtained above was chomatographed on a silica gel column in a solvent of 5:1 (v/v) methylene dichloride/methanol to give **6** (90%) or **15** (90%) or **16** (90%), respectively. The *trans/cis* isomers were further separated by a reverse phase HPLC (μ Bondasphere column) with an eluate of methanol/water [35:65 (v/v), for **15**, **16** and 10:90 (v/v), for **6**]. **6** (*trans*): ^{1}H NMR (400 MHz, CD_3OD) δ: 8.20 (s, 1H), 8.07 (s, 1H), 6.62 (s, 1H), 3.79 (t, 2H, J=6.0 Hz), 2.50 (t, 2H, J=6.0 Hz), 1.70 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 162.18, 154.80, 149.84, 142.70, 140.93, 120.25, 118.45, 61.35, 31.47, 17.25; HRMS calcd for $C_{10}H_{13}N_5O$ 219.1122, found 219.1084. Anal. Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.70; H, 6.06; N, 31.85. **6** (*cis*): ^{1}H NMR (400 MHz, CD_3OD) δ: 8.19 (s, 1H), 8.15 (s, 1H), 6.64 (s, 1H), 3.68 (t, 2H J=6.4 Hz), 2.24 (t, 2H, J=6.4 Hz), 2.00 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 162.18, 154.80, 149.84, 143.43, 140.60, 120.25, 118.59, 61.01, 36.10, 21.30; HRMS calcd for $C_{10}H_{13}N_5O$ 219.1122, found 219.1084. Anal. Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.73; H, 6.04; N, 31.86. **15** (*trans*): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.16 (s, 1H), 8.15 (s, 1H), 7.29 (br, 2H), 5.66 (t, 1H, J=5.2 Hz), 4.98 (s, 2H), 4.55 (d, 2H, J=5.2 Hz), 1.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 156.07, 152.50, 150.04, 140.88, 131.95, 128.73, 118.57, 63.74, 44.13, 21.26; HRMS calcd for $C_{10}H_{12}N_5O$ (M-H) 218.1043, found 218.1018. Anal. Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.73; H, 5.92; N, 32.02. **15** (*cis*): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.15 (s, 1H), 8.09 (s, 1H), 7.24 (br, 2H), 5.30 (t,

1H J=6.4 Hz), 4.94 (s, 2H), 4.25 (d, 2H, J=6.4 Hz), 1.63(s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ: 155.98, 152.72, 149.72, 140.75, 131.57, 124.07, 118.41, 63.36, 49.00, 16.43; HRMS calcd for $C_{10}H_{13}N_5O$ 219.1122, found 219.1085. Anal. Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.70; H, 6.01; N, 31.85. **16** (*trans*): ^{1}H NMR (400 MHz, CD_3OD) δ: 8.22 (s, 1H), 8.09 (s, 1H), 6.51 (s, 1H), 5.06 (s, 2H), 3.60 (t, 2H, J=6.8 Hz), 2.27 (t, 2H, J=6.8 Hz), the peaks of NH_2 and OH were included in the broad peak of water; ^{13}C NMR (100 MHz, DMSO-d6) δ: 155.97, 152.68, 149.69, 140.68, 137.92, 118.41, 106.55, 58.68, 44.48, 36.79; HRMS calcd for $C_{10}H_{12}N_5OBr$ 297.0226, found 297.0177. Anal. Calcd for $C_{10}H_{12}N_5OBr$: C, 42.57; H, 4.29; N, 24.82. Found: C, 42.64; H, 4.37; N, 24.73. **16** (*cis*): ^{1}H NMR (400 MHz, CD_3OD) δ: 8.21 (s, 1H), 8.12 (s, 1H), 6.34 (s, 1H), 4.94 (s, 2H), 3.63 (t, 2H, J=6.8 Hz), 2.45 (t, 2H, J=6.8 Hz), the peaks of NH_2 and OH were included in the broad peak of water; HRMS calcd for $C_{10}H_{12}N_5OBr$ 297.0226, found 297.0182.

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