Synthesis of novel 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides under microwave irradiation in neat water†

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Novel 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides were prepared in one step by nucleophilic substitution reaction of 6-choloropurine nucleosides with diethanolamine. Shorter reaction times and higher yields were achieved under microwave irradiation conditions in neat water.

Nucleosides play important roles in many biological processes. Many nucleoside analogues with modifications on the heterocyclic bases have been investigated for their antiviral and anticancer activities.[1] There are extensive interests in the study of purine derivatives with various substituents at C6 due to their broad spectrum of biological activities.[2] N6-(2-hydroxyethyl)adenosine (HEA) (**1**), which behaves as a Ca^{2+} antagonist and an inotropic agent, was isolated from cordyceps and isaria species.[3] 6-[*N*,*N*-Bis (2-hydroxyethyl)amino]-9-(2-β-*C*-methyl-β-D-ribofuranosyl)-purine (**2**)[4] and 6-[*N*,*N*-bis-(2-hydroxyethyl)aminomethyl]-9-(β-D-ribofuranosyl)purine (**3**)[5] showed potency in inhibiting HCV RNA replication (Fig. 1).

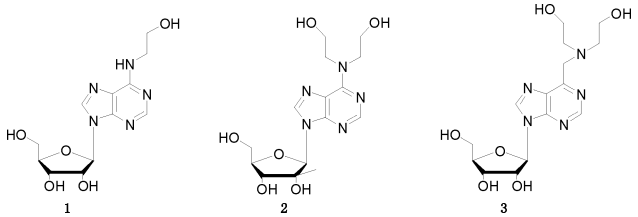
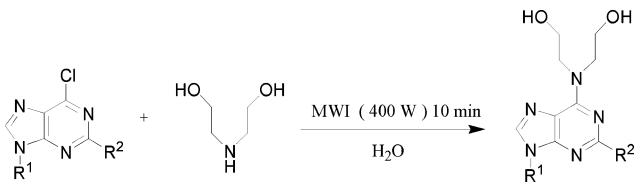


Fig. 1 Structures of some 6-hydroxyethylpurine nucleosides.

However, there are few reports on the synthesis of such 6-hydroxyethylpurine nucleosides[6a,6b] and no detailed study on such compounds. Recently, we have reported the synthesis of C6-modified purine nucleosides such as C6-cyclo secondary amine substituted purine analogues, C6-phosphonated purine nucleosides and 6-*N*-(2-hydroxyethyl)aminopurine nucleosides under microwave irradiation.[7] The results showed that the microwave-promoted method was very successful for various modifications of nucleoside analogues. Based on our preliminary study, we carried out a rapid and convenient method for the preparation of novel 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides in good to excellent isolated yields under microwave irradiation in neat water, aiming at providing an efficient route to the synthesis of new nucleoside analogues which are important candidates for biologically active compounds.

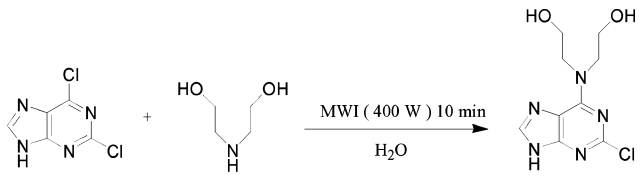
6-[*N*,*N*-Bis(2-hydroxyethyl)amino]purine nucleosides were prepared from commercially available 6-chloropurine nucleosides and various N9-substituted 6-chloropurine nucleosides that can be synthesized by alkylation of 6-chloropurine with nonsugar carbon chain, and then reacted with diethanolamine under microwave irradiation (Scheme 1). The procedures for synthesis of nucleosides analogues under microwave irradiation were well developed in our laboratories. Products (**3a–3m**) were purified by column chromatography in yields of 57–91%. Their structures were confirmed by NMR spectra and high-resolution mass spectrometry.



Scheme 1 Microwave-promoted synthesis of 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides.

To initiate our study, the influence of reaction conditions was examined. As shown in Table 1, when CH_2Cl_2 was used as the solvent, no reaction was observed (entry 1), when CH_3CH_2OH

Table 1 Effect of solvent and the optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Solvent	*T*/°C	Time/min	Yield[b] (%)
1	CH_2Cl_2	40	10	No reaction
2	CH_3CH_2OH	80	10	40
3	DMF	60	10	89
4	H_2O	80	15	88
5	H_2O	100	10	91
6	H_2O	120	8	90

[a] Reaction conditions: 2,6-dichloropurine (1 mmol), diethanolamine (1.5 mmol), H_2O (5 mL), MWI 400 W (100 °C). [b] Isolated yields based on nucleobases.

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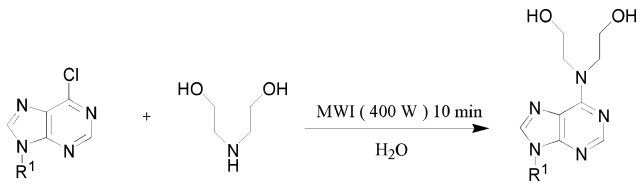
was used as the solvent, low yield was obtained (entry 2) (40%). With increasing solvent polarity, the yields were improved. When DMF was used as the solvent, the yields could reach to 89% (entry 3), but many side products were produced in this reaction medium. To overcome the disadvantages of these organic solvent, we used neat water as the solvent, and product **3a** was still formed in good yield (entry 5) (91%). It is noteworthy that no side products were obtained in water and the product **3a** could crystallize from the reaction system and could be separated easily by direct filtration. At room temperature, the yield was low. By increasing the temperature to 80 °C, the reaction completed within 15 min with a yield of 88% (entry 4). By increasing the temperature to 100 °C, the reaction completed within 10 min with a yield of 91% (entry 5). By increasing the temperature to 120 °C, no significant change in yield was observed (entry 6) (90%). Therefore, 100 °C and 10 min were the optimized reaction conditions. Further screening of irradiation power confirmed that 400 W was the best condition.

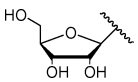
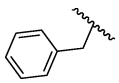
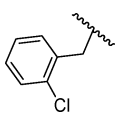
The substrate scope of 6-chloropurine nucleosides is summarized in Table 2, a group of different substituents at N9 were subjected to the optimized reaction conditions, including ribofuranosyl, *n*-butyl, allyl, benzyl, *etc.* The kinds of substituents had some impact on the yields. When R^1 was H, the yield was much higher (entry 1) (90%), ribofuranosyl-substituted substrates also give high yield (entry 2) (82%), and allyl-substituted substrates gave product **3f** with 78% (entry 3). With all these substrates, the products were prepared in good to excellent yields by using this one-step reaction.

Intrigued by the above-described results, more electron-rich 2-amino-6-chloropurine nucleosides were chosen as the substrates to probe whether the nucleophilic substitution could be easily accessed. As shown in Table 3, under microwave irradiation, 2-amino-6-chloropurine **1k** reacted with diethanolamine to afford **3k** with 83% yield (entry 3) and 2-amino-6-chloropurine nucleoside **1l** gave the corresponding product **3l** with 80% yield (entry 6), which indicated that 2-amino-6-chloropurine nucleosides can also react with this nucleophile smoothly in good yields. Our synthetic method using microwave irradiation is definitely valuable for the rapid access of these bioactive heterocyclic bases. The results in Table 3 also show that the relative activity of heterocyclic substrates for the nucleophilic substitution is in the order: 2,6-dichloropurine > 6-chloropurine > 2-amino-6-chloropurine, which indicated that

Table 2 Reaction of diethanolamine with various 6-chloropurines[a]

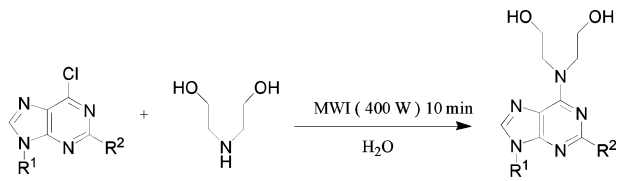


1e-1j **2a** **3e-3j**

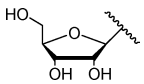
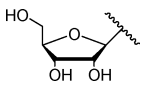
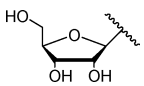
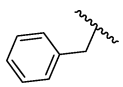
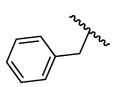
Entry	Product	R^1	Yield[b] (%)
1	**3e**	H	90
2	**3f**		82
3	**3g**		78
4	**3h**		75
5	**3i**		68
6	**3j**		61

[a] Reaction conditions: 6-chloropurine nucleosides (1 mmol), diethanolamine (1.5 mmol), H_2O (5 mL), MWI 400 W (100 °C). [b] Isolated yields based on nucleobases.

Table 3 Reaction of diethanolamine with various 6-chloropurines, 2,6-dichloropurines and 2-amino-6-choloropurines[a]



R^2=Cl, R^2=H, R^2=NH_2 **1a-1d, 1e-1h, 1k-1l** **2a** R^2=Cl, R^2=H, R^2=NH_2 **3a-3d, 3e-3h, 3k-3l**

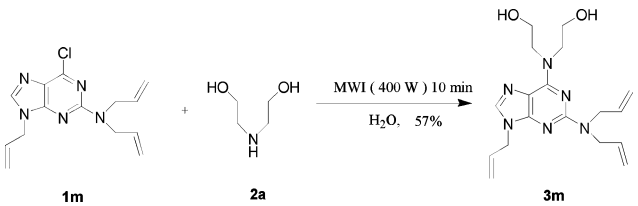
Entry	Product	R^1	R^2	Yield[b] (%)
1	**3e**	H	H	90
2	**3a**	H	Cl	91
3	**3k**	H	NH_2	83
4	**3f**		H	82
5	**3b**		Cl	85
6	**3l**		NH_2	80
7	**3g**		H	78
8	**3c**		Cl	79
9	**3h**		H	68
10	**3d**		Cl	72

[a] Reaction conditions: 6-chloropurines (2,6-dichloropurines or 2-amino-6-chloropurines) nucleosides (1 mmol), diethanolamine (1.5 mmol), H_2O (5 mL), MWI 400 W (100 °C). [b] Isolated yields based on nucleobases.

the electron-donating effects on C2 could lead to decrease of the yields.

In order to compare the efficiency of microwave irradiation with conventional heating, 2-amino-6-chloropurine was heated with 1.5 equiv of diethanolamine at 100 °C in an oil bath for 10 min to give 30% of 2-amino-6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine, far less than the 85% under microwave irradiation. This clearly indicated that the microwave-assisted reaction exhibited significant advantages over the conventional heating by not only reducing the reaction time but also improving the reaction time.

The use of microwave irradiation to generate 6-hydroxyethylpurine nucleosides was also tested on other 6-chloropurine derivatives. For example, 9-allyl-2-(*N*,*N*-diallyl)-6-[*N*,*N*-bis-(2-hydroxyethyl)amino]purine could also be synthesized from the corresponding 9-allyl-2-(*N*,*N*-diallyl)-6-chloropurine with an isolated yield of 57% using the same reaction conditions (Scheme 2).



1m 2a 3m

Scheme 2 Reaction of diethanolamine with 9-allyl-2-(*N*,*N*-diallyl)-6-chloropurine.

It was found that the reaction of 6-chloropurine nucleoside and its analogues with diethanolamine could occur efficiently under microwave irradiation within 10 min. It is very easy to handle because most of the products can crystallize from the solution and the pure samples can be obtained in excellent yields after simple filtration and washing. And using water as solvent makes this method environmentally benign. This will be a highly useful method for the synthesis of 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides.

In conclusion, we have developed a rapid and operationally simple method for the preparation of various 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides which are important candidates for biologically active compounds. The synthetic method using microwave irradiation is definitely valuable for the rapid access of these bioactive heterocyclic bases, and the pharmacological evaluation of these compounds is underway in our laboratories.

Acknowledgements

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Notes and references

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