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# Synthesis of novel analogues of zanamivir as neuraminidase inhibitors

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**Abstract**

A versatile synthesis of novel zanamivir analogues modified at C-4 and C-8 positions was described. The formation of amides from the acid with corresponding amines, followed by click chemistry generated the triazole substituted compounds as novel analogues of neuraminidase inhibitors in good yields.


*Keywords:* Zanamivir; Triazole; Click chemistry

Neuraminidase (NA) located on the surface of the influenza virus particle plays an important role in the spread of virus from cell to cell and within the respiratory tract [1]. The genetic stability of the NA enzymatic active center among all influenza viruses [2] makes it a promising target for therapy of influenza A and B [3]. Reports of structures of NA complexed with a variety of inhibitors [4–8] provided a detailed understanding involved molecular interactions, so a lot of compounds were designed and optimized based on structure-based drug design (SBDD) [9]. Consequently, zanamivir (**1**) (Fig. 1) was approved by FDA as first NA inhibitor for treatment of influenza A and B in 1999 [10].

However, due to poor oral bioavailability [11] of zanamivir, there is still a need to identify more effective NA inhibitors against influenza virus. Research on the structure–activity relationships (SAR) of zanamivir analogues [12–16] have revealed that the glycerol group of 2-deoxy-2,3-didehydro-*N*-acetyl-D-neuraminic acid (**2**) lied in the region of mixed polarity, therefore, the glycerol side chain would be considered to possible structural modifications. In addition, previous research showed some of C-4 modified compounds, such as etherated compound **3** [17] and triazole substituted compound **4** [13], whose inhibitory activities to NA were comparable with zanamivir. Therefore, those results have indicated the structural modification of zanamivir is viable.

As our continuing studies on zanamivir analogues [18], in this communication we would describe the synthesis of zanamivir analogues modified on C-4 and C-8 positions as shown in Scheme 1.

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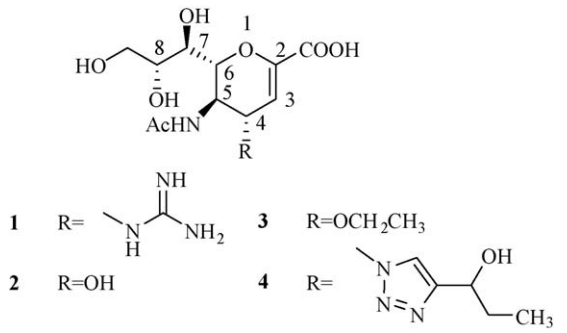
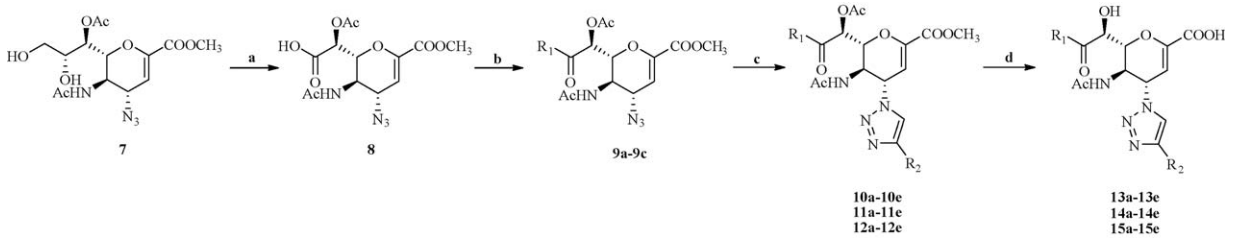



Fig. 1. Zanamivir and its derivatives.




Scheme 1. Reagents and conditions: (a) $NaIO_4$, $H_2O$, $CH_3OH$, then $NaClO_2$, cyclohexene, $KH_2PO_4$, *t*-BuOH, $H_2O$; (b) EDCI, HOBt, THF/$CH_2Cl_2$ (v/v, 1:2), methylamine (**9a**), dimethylamine (**9b**) or pyrrolidine (**9c**); (c) alkynes, $CuSO_4{\cdot}5H_2O$, sodium ascorbate, ethanol, $H_2O$, r.t.; (d) NaOH, $CH_3OH$, then $H^+$-resin, rt.

Modification was firstly implemented on C-8 position. Oxidation of glycerol side chain of mono-protected *O*-acetyl compound **7** [18] by $NaIO_4$, followed by $NaClO_2$ [19] in aqueous solution of cyclohexene, *t*-BuOH and sodium dihydrogen phosphate afforded carboxylic acid **8** almost quantitatively. Then reaction of compound **8** with methylamine, dimethylamine or pyrrolidine in the presence of 1-ethyl-3-(3-dimethyllaminopropyl)-carbodiimide hydrochloride (EDCI) and 1-hydroxybenzo triazole (HOBt) [20] afforded **9a–c** in different yields respectively (Table 1).

After completing the structural modification of C-8 position, we next pay our attention to the preparation of the 1,4-disubstituted-1,2,3-triazole at the C-4 position by the click chemistry, pioneered by Sharpless group, that has been explored as new approach for the synthesis of drug-like molecules and accelerate the drug discovery process [21]. The cycloaddition between terminal alkyne and azide now is an attractive tool in construction of libraries of the structure diversified compounds for studying SAR [22–24]. Using Huisgen cycloaddition catalyzed by Cu(I), triazole **10a–e**, **11a–e** and **12a–e** were obtained by reaction of **9a–c** with different alkynes in 60–80% yield. All alkynes with different substituent groups including aliphatic, cyclic, ester or phenyl groups could give satisfactory yield. Hydrolysis of **10a–e**, **11a–e** and **12a–e** with NaOH/methanol, then neutralize with $H^+$-resin afforded zanamivir analogues **13a–e**, **14a–e** and **15a–e** in over 86% yield individually (Table 2). $^1$H NMR and HRMS spectra of the representative target compounds were performed [25].

In summary, based on the C-8 modified intermediates **9a–c**, the analogues **13a–e**, **14a–e** and **15a–e** were prepared by using the well-documented Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition. A series of novel zanamivir

Table 1
Synthetic conditions and yields of **9a–c** from **8**.

| Entry | Product | $R_1$ | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| **1** | **9a** | $CH_3NH$– | 10 | 86 |
| **2** | **9b** | $(CH_3)_2N$– | 16 | 55 |
| **3** | **9c** |  | 24 | 18 |

[a] Isolated yield.