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# *N*-Alkyldeoxynojirimycin derivatives with novel terminal tertiary amide substitution for treatment of bovine viral diarrhea virus (BVDV), Dengue, and Tacaribe virus infections

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ABSTRACT

Novel *N*-alkyldeoxynojirimycins (NADNJs) with two hydrophobic groups attached to a nitrogen linker on the alkyl chain were designed. A novel NADNJ containing a terminal tertiary carboxamide moiety was discovered that was a potent inhibitor against BVDV. Further optimization resulted in a structurally more stable lead compound **24** with a submicromolar $EC_{50}$ against BVDV, Dengue, and Tacaribe; and low cytotoxicity.



Viral hemorrhagic fevers (VHFs) are a group of disease syndromes characterized by fever, shock, hemorrhage (bleeding), and multiple organ dysfunction.[1] VHFs can be caused by RNA viruses from five distinct families, including arenaviruses, bunyaviruses, filoviruses, flaviviruses and togaviruses.[2] Some types of hemorrhagic fever viruses (HFVs), such as Dengue and Ebola, can cause severe, life-threatening disease, so these viruses are considered significant public health threats and potential biological weapons. Currently, there are about 55,000 HFV sequences available to the public,[2b] but there are no vaccines or approved therapeutic treatments designed especially to counteract these HFV infections. Ribavirin, an antiviral drug, has achieved some success in patients with Lassa fever or hemorrhagic fever with renal syndrome,[3] nevertheless, there is a still unmet need for an effective broad-spectrum antiviral therapy.

Two strategies have been developed in designing antiviral drugs by targeting at either viral proteins or host factors.[4] In the host-directed approach, a molecule is designed that targets a host factor essential for the virus life cycle, thereby providing antiviral effect.[5] When the viruses are more dependent upon the host pathway than the host does, selectivity and a useful therapeutic benefit is possible. If the targeted host pathways are commonly used by multiple viruses, it is possible to discover broad spectrum antiviral agents.

Hemorrhagic fever viruses contain different RNA genomes, but they are all enveloped viruses with glycosylated envelope proteins[6] and share a similar morphogenesis strategy of budding, which requires processing by endoplasmic reticulum (ER) α-glucosidases I and II and thus are sensitive to glucosidase inhibitors.[7] This is presumably because ER glucosidase is required for the proper trimming and folding of N-linked glycoproteins by calnexin.[8] Most cellular functions can compensate for a reduction in glucosidase function,[8a] however, the maturation of calnexin dependent viral envelope proteins apparently cannot use alternative processing pathways. Thus, glucosidase inhibitors would be selective antiviral agents against multiple enveloped viruses.[7,9]

We[10] and others[11] have reported imino sugars, such as deoxynojirimycin (**1**, DNJ) and its derivatives **2**–**4**, as glucosidase inhibitors and broad spectrum antiviral agents (Fig. 1). The potency of DNJ could be improved by incorporation of a hydrophobic group on the nitrogen atom of DNJ using a carbon chain spacer and a heteroatom linker.[10] This structural modification pattern has also been seen in the design of DNJ derivatives as D-galactosidase inhibitors[12] or for the reduction of visceral glycosphingolipids and buffering of carbohydrate assimilation.[13] In our more recent investigation of ether linkages,[14] we observed that increasing the size of the hydrophobic group may increase the antiviral potency,

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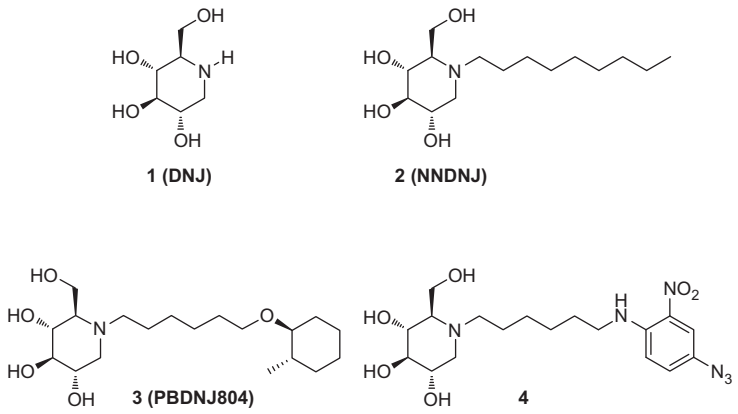



**Figure 1.** Deoxynojirimycin (DNJ) and its N-alkylated derivatives.

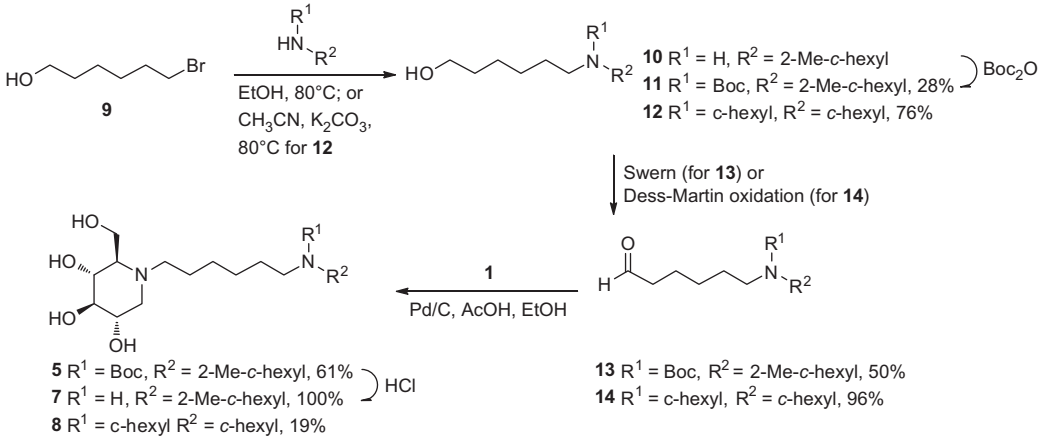
but it also causes increased cellular toxicity. The shape of the terminal hydrophobic group was also found to be critical, as some regioisomers or stereoisomers may deliver better cellular potencies and lower cellular toxicities than others, suggesting that the terminal hydrophobic group could only be modified within a narrow range. In this Letter we report our design, optimization, and biological testing of a terminal tertiary amide series, against viruses from two distinct virus families, including bovine viral diarrhea virus (BVDV), Dengue virus of flaviviridae family, and Tacaribe virus of arenaviridae family.

Introducing a nitrogen linker into the side chain not only allows different polarity from oxygen atom, but also allows introduction of additional functional groups. Although the nitrogen atom has been used as the linker in several reports,[11b,12b,15] only secondary amine, sulfonamide, and amides were synthesized. We envisioned that a tertiary amine derivative would introduce one more lipophilic group than secondary amine derivatives, which may build up additional interaction with the target and thus gain more potency. A previous lead compound, **PBDNJ804**,[10c] in our research was selected as the starting point for making N-analogs. In an initial SAR effort, four compounds **5**–**8** were prepared as described in Schemes 1 and 2.

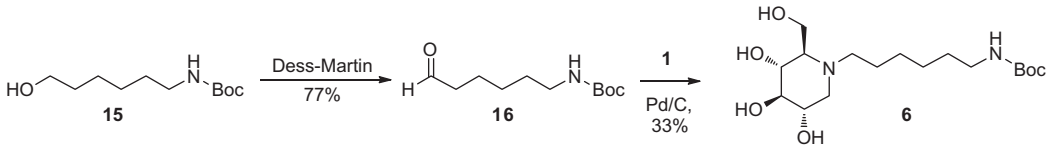
Synthesis began with the alkylation of 2-methylcyclohexylamine or dicyclohexylamine. The secondary amine **10** was converted to Boc-protected carbamate **11** through reaction with $Boc_2O$. Oxidation of alcohol **11** and **12** afforded corresponding aldehydes **13** and **14**, which underwent reductive amination with DNJ to provide compounds **5** and **8**. Treatment of compound **5** with HCl yielded compound **7**. Product **6** was prepared from commercially available aminoalcohol **15**, following the similar sequence via oxidation of alcohol to aldehyde **16** and reductive amination with DNJ **1** (Scheme 2).

The compounds were evaluated for their activity against BVDV in MDBK cells as an in vitro cell-based antiviral screening assay and a surrogate assay for other viruses.[10] The antiviral activity was measured by a yield reduction assay and expressed as $EC_{50}$ values; cytotoxicity was measured by a MTT assay and expressed as $CC_{50}$ values. Compound **8** with dicyclohexyl terminal group showed weak activity (6.3 μM), while compound **5** with a carbamate and 2-methylcyclohexyl side chain was 10-fold more potent ($EC_{50}$ = 0.4 μM). However, compound **7** displayed no cellular activity after the carbamate group was removed, which was surprising when compared with its oxygen analog **3** ($EC_{50}$ = 3.3 μM against BVDV).[10c] Interestingly, compound **6**, which contained Boc group on the nitrogen but without cyclohexyl group, only displayed moderate activity. These results indicated the preference for a less polar non-basic terminal group and a requirement for two substituents on the nitrogen. The next question was to what degree that these two steric bulky groups enhance hydrophobic interactions. Although compound **5** exhibited good potency, it was also fairly toxic ($CC_{50}$ = 250 μM). In addition, the Boc-group is considered labile under acidic conditions, making it unsuitable for a lead candidate. Therefore, our focus shifted towards finding a replacement for the Boc-group and reducing the cellular toxicity, while maintaining antiviral activity.

First, we chose the amide group to replace the carbamate functionality due to its stability and ready variability. The compounds were synthesized in a general procedure, which allowed us to




**Scheme 1.** Synthesis of NADNJs with nitrogen derived terminals.




**Scheme 2.** Preparation of compound **6**.

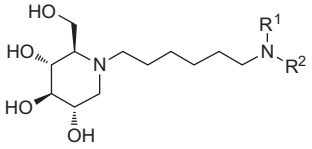
diversify the acyl $R^3$ substituent (Scheme 3). Alkylation of commercially available ((6-bromohexyl)oxy)(*tert*-butyl)dimethylsilane with a primary amine, followed by acylation with an acid chloride gave a protected tertiary amide **19**. Subsequent deprotection with TBAF and oxidation of the resulting alcohol **20** generated the corresponding aldehyde **21**. Reductive amination with DNJ provided a final DNJ derivative **22**.

The effect of the carbamate to amide conversion is illustrated by comparing compound **5** and **23**, whose structures differ only in the acyl groups (Tables 1 and 2). The amide analog **23** demonstrated twice the potency ($EC_{50}$ = 0.22 μM) as compared to the carbamate DNJ derivative **5** ($EC_{50}$ = 0.4 μM). Notably, **23** showed significant improvement on cellular toxicity ($CC_{50}$ >500 μM), indicating a clear advantage of this alteration. Compound **24**, without the 2-methyl substituent, exhibited comparable efficacy ($EC_{50}$ = 0.20 μM) and safety ($CC_{50}$ >500 μM) to compound **23**, suggesting the 2-methyl substituent contributed insignificantly to activity. Thus, in order to simplify our lead structure, a cyclohexyl ring was used as a substitution of choice for variation of other acyl groups. Changing the size of the acyl group, from *t*-butylcarbonyl to a smaller acetyl or a larger *t*-butylacetyl, retained the submicromolar potency (Table 2, compounds **25**, and **26**) with no significant improvements amongst these structural changes.

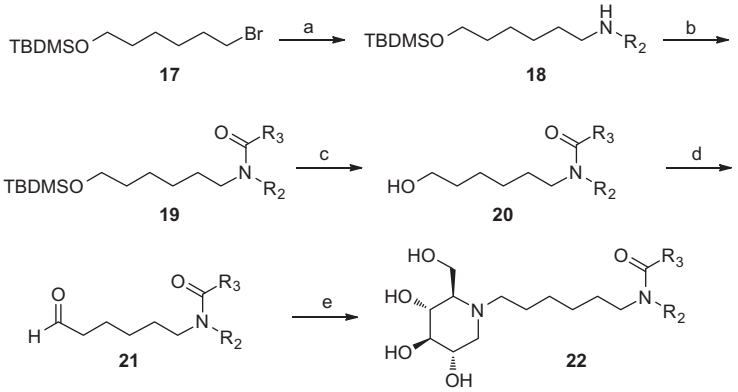
Second, we carried out optimization of the cycloalkyl ring at the terminus. Our past study[14] revealed that a fluorinated phenyl group provided better overall cellular activity and lower toxicity. Thus, two difluorinated phenyl groups were used to replace the cyclohexyl ring, and two acyl groups, acetyl and pivaloyl, were selected to explore the influence of lipophilicity on antiviral activity (Table 3). Pivaloyl derivatives **27** and **29** maintained submicromolar $EC_{50}$ and high $CC_{50}$ values, and presented 12.5- and 24-fold higher potencies than the corresponding acetylated derivatives **28** and **30**, demonstrating that hydrophobic and steric bulky amides are favored for antiviral activity in this series.

With this information in hand, we continued to optimize the cycloalkyl rings based on their hydrophobicity and steric size. Therefore, the cyclohexyl group in compound **24** was replaced with other monocycloalkyl rings ranging from three- to eight-membered, or with the bulkier tricycloadamantanyl groups (Table 4). A greater influence of ring size on the $EC_{50}$'s was observed. Compared with the six-membered compound **24**, the three-membered compound **31** resulted in about 19-fold loss of potency to a low micromolar $EC_{50}$ value; four-membered compound **32** and five-membered compound **33** both gained similar moderate improvement ($EC_{50}$ ~0.8 μM), but were still four-fold less potent than the six-membered derivative (**24**); when the ring size reached seven, however, a slight potency loss (2-fold) was obtained while retaining low cellular toxicity. Increasing the ring size to eight provided comparable $EC_{50}$ compared to compound **24**, however toxicity increased ($CC_{50}$ = 270 μM). The two tricycloadamantanyl derivatives also displayed low submicromolar $EC_{50}$'s and increased toxicity. Between them, 1-adamantyl substitution (compound **37**) showed a better safety profile. In summary, the optimal antiviral activity and cellular safety is provided by a six- or seven-membered cycloalkyl ring.

**Table 1**
Nitrogen-derived terminal NADNJ compound evaluation ($n$ = 2)

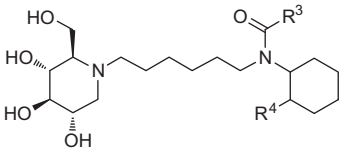



| Compound | $R^1$ | $R^2$ | $EC_{50}$ (μM) | $CC_{50}$ (μM) |
|---|---|---|---|---|
| **5** | Boc |  | 0.4 | 250 |
| **6** | Boc | H | 2.5 | >500 |
| **7** | H |  | >100 | >500 |
| **8** |  |  | 6.3 | >500 |



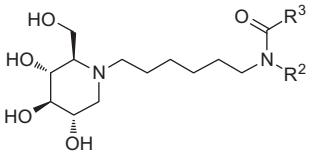

**Scheme 3.** Reagents and conditions: (a) $NH_2R^2$, $K_2CO_3$, $CH_3CN$, 80 °C, 60–90%; (b) $Et_3N$, $R^3COCl$, $Et_3N$, $CH_2Cl_2$; (c) TBAF, THF, 47–80% for combined steps b and c; (d) PCC or Dess–Matin periodane, 52–100%; (e) DNJ, AcOH, EtOH, Pd/C, 20–47%.

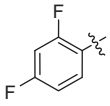
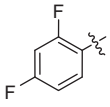
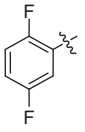
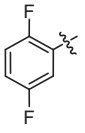
**Table 2**
Influence of acyl groups in tertiary amide series ($n = 2$)



| Compound | $R^3$ | $R^4$ | $EC_{50}$ (μM) | $CC_{50}$ (μM) |
|---|---|---|---|---|
| **23** |  | Me | 0.22 | >500 |
| **24** |  | H | 0.2 | >500 |
| **25** | Me | H | 0.28 | >500 |
| **26** |  | H | 0.18 | >500 |

**Table 3**
*N*-Phenyl amide evaluation ($n = 2$)

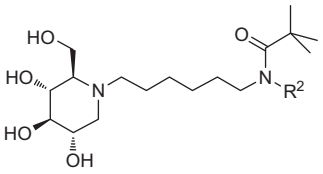


| Compound | $R^3$ | $R^2$ | $EC_{50}$ (μM) | $CC_{50}$ (μM) |
|---|---|---|---|---|
| **27** |  |  | 0.25 | >500 |
| **28** | Me |  | 6 | >500 |
| **29** |  |  | 0.4 | >500 |
| **30** | Me |  | 5 | >500 |

With several terminal tertiary amide DNJ derivatives in hand with potent activity against BVDV, we next studied their inhibition potential against DENV (flavivirus) infection in BHK cells and Tacaribe (arenavirus) in Huh7.5 cells. The antiviral activity was measured by a yield reduction assay and expressed as $EC_{50}$ values; cytotoxicity was measured by a MTT assay and expressed as $CC_{50}$ values (Table 5).

Consistent with the results obtained from BVDV infection, amide analogs **23** and **24** showed comparable inhibitory potencies to the early carbamate lead **5** against both Dengue and Tacaribe viruses with $EC_{50}$'s at 0.32 and 0.28 μM, respectively; moreover, the cellular toxicities were improved in both tests, especially for compound **24** with $CC_{50}$ greater than 500 μM in both cell lines. When cyclohexyl was used, a bulkier acyl (*tert*-butyl acetyl, **26**) group presented more than 9-fold and 2-fold higher potency than acetyl (**25**) against Dengue and Tacaribe viruses, respectively. In the aniline series, both **27** and **29** demonstrated low micromolar

**Table 4**
Effects of ring sizes of cycloalkanes on $EC_{50}$ and $CC_{50}$ ($n = 2$)



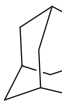
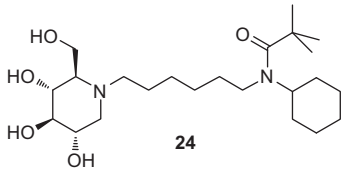
| Compound | $R^2$ | $EC_{50}$ (μM) | $CC_{50}$ (μM) |
|---|---|---|---|
| **31** |  | 3.75 | >500 |
| **32** |  | 0.8 | >500 |
| **33** |  | 0.85 | >500 |
| **34** |  | 0.4 | >500 |
| **35** |  | 0.24 | 270 |
| **36** |  | 0.31 | 180 |
| **37** |  | 0.21 | 420 |

**Table 5**
Potencies and cell toxicities of selected compounds against Dengue and Tacaribe ($n = 2$)

| Compound | Dengue | | Tacaribe | |
|---|---|---|---|---|
| | $EC_{50}$ (μM) | $CC_{50}$ (μM) | $EC_{50}$ (μM) | $CC_{50}$ (μM) |
| **5** | 0.3 | 230 | 0.3 | 240 |
| **23** | 0.32 | >500 | 0.2 | 310 |
| **24** | 0.28 | >500 | 0.2 | 500 |
| **25** | 14 | >500 | 1 | >500 |
| **26** | 1.5 | >500 | 0.4 | >500 |
| **27** | 2.2 | >500 | 2.5 | >500 |
| **29** | 5.4 | >500 | 0.62 | >500 |
| **31** | 8.8 | >500 | ND | ND |
| **32** | 1.9 | >500 | ND | ND |
| **33** | 2 | >500 | 4 | >500 |
| **34** | 0.8 | >500 | 1 | >500 |
| **35** | 0.8 | 207.5 | 0.29 | 150 |
| **36** | 0.125 | 192.5 | 0.5 | 125 |
| **37** | 1.38 | >500 | 0.21 | 170 |

**Table 6**
Summary of antiviral activities of compound **24**



**24**

| BVDV | | Dengue | | Tacaribe | |
|---|---|---|---|---|---|
| $EC_{50}$ (μM) | $CC_{50}$ (μM) | $EC_{50}$ (μM) | $CC_{50}$ (μM) | $EC_{50}$ (μM) | $CC_{50}$ (μM) |
| 0.2 | >500 | 0.28 | >500 | 0.2 | 500 |

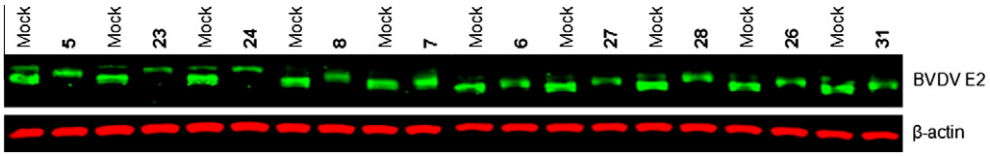



**Figure 2.** Effects of the compounds on the mobility rate of BVDV E2 protein in Western blot assay. MDBK cells were infected with BVDV at an MOI of one for 1 h followed by mock-treatment or treatment with indicated compounds at concentration of 100 μM. Cells were harvested at 22 h post infection and aliquots of cell lysates were analyzed by electrophoresis followed by Western blotting to simultaneously detect BVDV E2 glycoprotein (green), and a loading control, β-actin (red), using reagents and apparatus from LI-COR Biosciences.

or submicromolar $EC_{50}$ against Dengue and Tacaribe. Consistent with BVDV results, when pivaloyl was used as the acyl group, a cyclopropyl ring (**31**) was the least potent in this series. Increased ring size in compounds **32** and **33** demonstrated similar improvement up to 2 μM, but still about 7-fold less potent than compound **24**. Extension of the ring size continued to improve the $EC_{50}$, but the cellular toxicities increased as before in the eight-membered ring compound **35** and admantyl ring containing isomers **36** and **37**. These results also clearly showed that a terminal amide with a six-membered cyclohexyl ring and pivaloyl acyl group (**24**) provided the optimal antiviral activities across these two families of viruses (Table 6).

In order to confirm that all the new DNJ derivatives functioned as inhibitors of glucosidases, we performed a cell-based surrogate assay, in which Western blot approach was used to analyze the BVDV glycosylated envelop protein (BVDV E2 protein). When glucosidases are inhibited, alteration of the glycan structure on the BVDV E2 protein will results in a slower mobility rate of BVDV E2 protein (Fig. 2). And subsequently, the glycoprotein undergoes misfolding and degradation leading to reduced protein density on the blot. We selected 10 compounds with different $EC_{50}$'s ranging from 0.18 to more than 100 μM for analysis. Treatment with compounds **5**, **23**, **24**, **26**, and **27**, which had $EC_{50}$'s lower than 1 μM, resulted in slower mobility rate and reduced intensity in E2 protein compared to the mock reference; while for the treatment with compounds with $EC_{50}$ higher than 1 μM but lower than 10 μM (**6**, **8**, **28**, and **31**), slower mobility of E2 protein was also observed. However, for treatment with compound **7** ($EC_{50}$ >100 μM) with a secondary amine terminal group, neither E2 protein mobility or intensity was changed. These results demonstrated that treatment of the compounds with observed anti-BVDV activity were able to change the mobility of the E2 protein, and reduce the quantity of the protein correspondingly, supporting their inhibitory effect on the target enzymes.

In conclusion, through addition of a new hydrophobic branch to the alkyl terminal of alkyl-DNJs, we identified novel DNJ derivatives with terminal tertiary carboxamide moieties showing potent antiviral activities against BVDV, Dengue, and Tacaribe. Optimization in the acyl and N-substitution groups led to the discovery of a novel series of DNJ derivatives with terminal tertiary amide exhibiting submicromolar $EC_{50}$'s and low cellular toxicities. PK and in vivo efficacy tests are in progress and will be reported in due course.

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