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Discovery of BMS-955176, a Second Generation HIV-1 Maturation Inhibitor with Broad Spectrum Antiviral Activity

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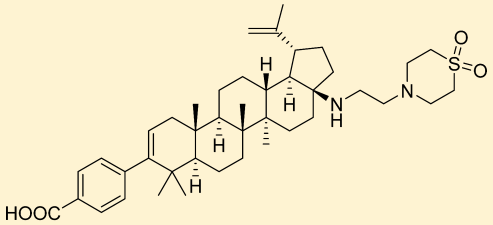
Supporting Information

ABSTRACT: HIV-1 maturation inhibition (MI) has been clinically validated as an approach to the control of HIV-1 infection. However, identifying an MI with both broad polymorphic spectrum coverage and good oral exposure has been challenging. Herein, we describe the design, synthesis, and preclinical characterization of a potent, orally active, second generation HIV-1 MI, BMS-955176 (**2**), which is currently in Phase IIb clinical trials as part of a combination antiretroviral regimen.



BMS-955176 (**2**)
HIV-1 WT EC_{50} = 1.9 nM
HIV-1 WT (HS) EC_{50} =10.2 nM
V370A EC_{50} = 2.7 nM
ΔV370 EC_{50} =13 nM

KEYWORDS: *HIV-1, maturation inhibitors, BMS-955176, betulinic acid, triterpene, antiviral*

HIV-1 infection can be effectively managed with current treatments that rely on long-term administration of multiple antiviral inhibitors designated as combination antiretroviral therapy (cART).[1] Nevertheless, the development of novel agents with improved safety profiles and different mechanisms of action (MOA) is still highly desirable due to long-term toxicity and resistance development with current therapies. New ARTs would preferentially exhibit minimal drug−drug interactions with a relatively low once-daily dose to facilitate combinations with other agents as part of a fixed dose regimen.[2]

In the latter stages of the virus life cycle, the HIV-1 matrix (MA), capsid (CA), nucleocapsid (NC), and p6 proteins are released from the Gag polyprotein via multiple cleavages made by the viral protease. The final and rate-limiting step in this maturation process is cleavage at the CA-SP1 junction, which induces a major structural change within the virion, leading to the formation of the conical core that is characteristic of an infectious virion. Maturation inhibitors (MIs) prevent replication by binding near the CA-SP1 segment of the Gag polyprotein, specifically blocking only this final rate-limiting cleavage event, leading to the production of immature, noninfectious particles.[3,4]

Proof-of-concept for this MOA was demonstrated in a 10 day Phase I/II monotherapy trial with bevirimat,(**1**, Chart 1), an MI derived from betulinic acid (BA, **10**).[5,6] At the highest doses (150 and 250 mg), a maximal viral load reduction (VLR) of 0.72 log_{10} was observed. However, in the Phase IIa trial with highly experienced patients, only 45% of individuals responded to treatment with an HIV-1 RNA change from baseline of >0.5 log_{10}, and only 34% with >1 log_{10} VLR.[7] The restricted response to **1** was subsequently determined to be a consequence of naturally occurring polymorphic variation at Gag amino acid residues 369−371.[8−10] The lack of polymorphic coverage in combination with difficulties in formulation ultimately led to a halt in the development of **1**.[11,12] Three other modified triterpenoid MIs have been evaluated in humans, but none of these compounds have advanced beyond Phase I clinical studies.[13−15]

In order to drive the discovery of a second generation MI with broad polymorphic coverage, it was important to maintain activity against the key polymorphic variation at V370.[16] Therefore, we chose the V370A- and ΔV370-containing viruses as the primary screening viruses due to their high prevalence in B and non-B subtypes, respectively, and their high level resistance to BVM.[17] Additional improvements in a second

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Chart 1. Selected HIV-1 Maturation Inhibitors

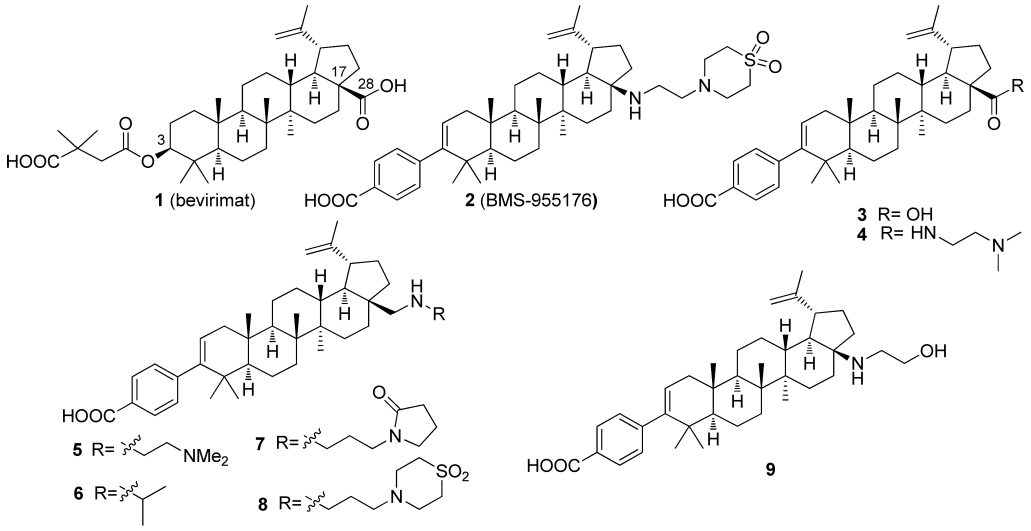

Table 1. HIV-1 Inhibition and Rat $AUC_{0\text{-}6h}$ of Compounds 1−9

	WT EC_{50} (nM)[a]					
	WT	WT + HS[b]	V370A	ΔV370	CC_{50} (μM)	Rat AUC_{0-6h} (nM*h)[c]
1	10 ± 11	1,291 ± 1,011	552 ± 633	>10,000	16.8 ± 14.5	6,390
2	1.9 ± 1.8	10.2 ± 6	2.7 ± 1.5	13 ± 11	9.2 ± 4	4,132 ± 685[d]
3	16 ± 13	105 ± 40	233 ± 305	>6,000	27.2 ± 38.5	5,724
4	2.3 ± 1.3	43 ± 29	7.8 ± 8.8	31 ± 19	2.61 ± 1.78	1, 623 ± 240[d]
5	2.2 ± 0.7	8.7	2.5 ± 2.2	20.6 ± 14	1.24 ± 0.16	153
6	2.2	-	12	61	2.36	-
7	0.7 ± 0.2	-	1.7 ± 0.7	9.9 ± 8.3	5.8 ± 0.8	1,044
8	1.0 ± 0.4	5.7 ± 3.1	2.5 ± 1.4	14.566 ± 8.4	3.5 ± 1.6	1,708
9	1.9 ± 1.2	-	9.9 ± 2.8	66 ± 53	8.48 ± 5.34	4,983

[a]The antiviral activity of the compounds was assessed in a multiple cycle assay in MT-2 cells in 10% fetal bovine serum (FBS). [b]Compounds evaluated for serum effects in 10% FBS + 40% human serum except for **2** (10% FBS + 40% human serum + 27 mg/mL human serum albumin); values are means from experiments performed a minimum of three times ($n \geq 3$). [c]Dose 5 mg/kg po, $n = 2$; see SI for vehicle information. [d]$n = 3$.

generation MI would be lower binding to human serum components that decreased the effective potency of **1** (human serum (HS) binding >99%)[17] and an improvement in physical properties that would allow for an appropriate formulation that could deliver targeted concentrations in vivo. Herein, we describe the discovery of BMS-955176 (**2**), an orally efficacious, second generation HIV-1 maturation inhibitor that is currently in Phase IIb clinical trials.[18] The complete virology profile of BMS-955176 (**2**) is described in a companion manuscript, and resistance studies have been completed and will be published elsewhere.[17]

The description of the effect of Gag polymorphisms on the antiviral response to bevirimat (**1**) stimulated our interest in maturation inhibition as a target, since this identified a screening paradigm, but there was no evidence in the literature that structural modification of **1** could address the fundamental problem. As the first step in our study of this chemotype, we explored changes to the succinic acid-based side chain at C-3, a moiety that appeared to have largely been accepted as a pharmacophoric element, with a view to revealing key aspects of the topography of the carboxylic acid while providing new opportunities for structural modification.[19,20] The benzoic acid derivative **3** emerged very quickly from that effort, exhibiting good antiviral activity against wild-type (WT) virus, a modest 7-fold shift in the presence of HS, and good oral exposure in rats (Table 1). The *para*-substitution pattern in **3** was critical for antiviral activity. However, potency against Gag V370A, the most prevalent polymorphism in the region of Gag associated with MI activity, was lacking.[19]

Attention was then directed toward derivatization of the C-28 position of **3**, where an extensive series of analogues were prepared that incorporated a wide range of functionality. Amides such as **4**, incorporating a basic side chain, provided excellent potency against both WT and V370A viruses, while maintaining a low human serum shift (~4-fold). In addition, **4** exhibited an EC_{50} of 31 nM against the ΔV370 Gag polymorphism. However, **4** exhibited low oral exposure, attributed to a combination of poor solubility and low membrane permeability, precluding its further advancement.[20] With further probing of this region, the dibasic C-28 amine **5** was found to retain good polymorphic coverage, but displayed even lower oral exposure than **4**, while the more lipophilic monobasic isopropyl amine **6** exhibited 3- to 5-fold reduced activity toward the polymorphic viruses, demonstrating that a single amine installed close to the core was acceptable.[21]

Based on this discovery, the introduction of a nonbasic polar group in the side chain was probed with **7**, which improved the antiviral profile of **6**, with EC_{50} values of <10 nM against the 3 screening viruses (Table 1).[22] However, while this combination of basicity and polarity afforded good polymorphic coverage,

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Table 2. Antiviral Activity of Bevirimat (1) and BMS-955176 (2) toward HIV-1 Viruses Containing Naturally-Occurring Polymorphisms in the Gag Protein[17,a]

	EC_{50}					
	V362I	Q369H	V370M	V370A/ΔT371	ΔV371A	ΔT371
bevirimat (1)	74 ± 59	7.0 ± 2.0	1,810 ± 190	1,114 ± 119	40 ± 48	77 ± 97
BMS-955176 (2)	4.5 ± 2.2	1.9 ± 0.9	2.8 ± 0.3	3.6 ± 3.9	2.0 ± 0.1	7.3 ± 3.9

[a]Values are means from experiments performed a minimum of three times ($n \geq 3$).

poor oral exposure in rats (AUC_{0-6h} of 7 in rats =1,044 nM·h) remained an issue. The introduction of a moderately basic amine, 1,1-dioxidothiomorpholine heterocycle, pK_a = 4.5,[23] provided **8**, which demonstrated targeted antiviral activity and improved oral exposure in rats, although still 2- to 3-fold less than for **1** and **3**. We hypothesized that installing the more basic amine closer to the lipophilic core would have the effect of shielding the NH and may have a positive impact on the permeability properties of the molecule and, ultimately, on oral exposure. This concept was initially probed with the alcohol **9**, which exhibited improved oral exposure (AUC_{0-6h} in rats = 4,983 nM·h), although at the expense of reduced activity toward the polymorphic viruses, particularly ΔV370.[24] With further experimentation, merging the C-17 amine with the 1,1-dioxidothiomorpholine heterocycle of **8** provided BMS-955176 (**2**), a compound with an optimal combination of antiviral potency and oral exposure. This compound exhibits excellent potency toward the key Gag mutations, with EC_{50} values of 1.9, 2.7, and 13 nM against WT, V370A, and ΔV370 viruses, respectively. Furthermore, following oral dosing of 5 mg/kg of BMS-955176 to rats, the AUC_{0-6h} was 4,132 nM·h, demonstrating exposure comparable to **1** (Table 1). In the presence of HS, BMS-955176 exhibited a ∼5-fold reduction in antiviral activity, reflecting moderate serum binding (determined to be 84% using an ultracentrifugation method).[17] The potent antiviral activity of **2** extended to a library of clinically relevant isolates (N = 87), representing sequence variability in the 362−370 Gag region of subtype B viruses, with a mean EC_{50} value of 3.9 ± 3.4 nM.[17] In addition, other site directed Gag polymorphisms known to be resistant to **1** were introduced into a laboratory strain, with the results for a select group compiled in Table 2, illustrating that **2** retains activity toward all of these viruses.[17] BMS-955176 was shown to be an MI by a series of mechanistic experiments which ruled out entry, reverse transcription, and protease as targets, while demonstrating that **2** acts late in the viral life cycle. The compound binds saturably and reversibly to HIV-1 Gag pseudoparticles and this binding is specifically displaced by **1**. In addition, **2** specifically inhibits cleavage of CA/SP1 p25, resulting in inhibition of the production of capsid p24.[17]

The metabolic stability of **2** in vitro was high, with a $t_{1/2}$ of >120 min when incubated in human, rat, and dog liver microsomes in the presence of NADPH, predicting low clearance in vivo. However, in monkey liver microsomes, **2** exhibited high metabolic turnover, with a $t_{1/2}$ of only 12 min. It was not possible to accurately assess the in vitro permeability of **2** due to limited solubility under the assay conditions, but it is presumed to be satisfactory, since **2** demonstrated good oral exposure in rats, with an AUC_{total} of 14,198 nM·h after a dose of 5 mg/kg (Table 3). In this experiment, the C_{24} of **2** was 128 nM, 21-fold higher than that of **1** under comparable circumstances. The oral bioavailability (%F) of **2** ranged from low in the dog and cynomologus monkey, reflecting the reduced metabolic stability in the latter species, to moderate in mice and rats, with long $t_{1/2}$ values in all species tested. Allometric scaling and mean residence time methodology using data from all four species were used to predict the human PK profile of **2**, which, combined with a targeted C_{trough} value of 281 nM (3-fold the protein binding-adjusted EC_{90} vs the ΔV370 virus), indicated that **2** may be suitable for once-daily administration of reasonable low doses (≤120 mg). Efficacy at these doses has been confirmed in clinical studies.[25] Safety profiling of BMS-955176 showed no evidence of mutagenicity in an Ames reverse mutation assay, and low potential for off-target liabilities based on evaluation in a panel of receptor, ion channel, and enzyme activity assays. There was also a low potential for drug−drug interactions based on CYP450 human microsomal inhibition assays.

Table 3. In Vivo Pharmacokinetic Properties of BMS-955176 in Mice,[a] Rats,[b] Dogs,[c] and Cynomolgus Monkeys[d]

	F (%)	AUC_{total} (nM·h)	C_{24} (nM)	IV $t_{1/2}$ (h)
Mouse	27	28,912	256 ± 78	8.9
Rat	26	14,198 ± 1,083	128 ± 27	6.6
Dog	8.5	29,358 ± 16,436	559 ± 345	31.7
Cyno	3.9	995 ± 318	17.4 ± 10.9	8.6

[a]Oral vehicle (solution): 90% polyethylene glycol 300 (PEG 300), 10% EtOH, n = 3; dose = 5 mg/kg PO. [b]Oral vehicle (solution): 84.5% PEG 300, 10% EtOH, 50.1 N NaOH and 0.5% Tween 80 (TW80), n = 3; dose = 5 mg/kg PO. [c]Oral vehicle (solution): 80% 50 mM citrate buffer; 20% sulfobutylether-beta-cyclodextrin (SBC), pH = 3, n = 3; dose = 1.85 mg/kg. [d]Oral vehicle (solution): 80% 50 mM citrate buffer; 20% SBC, pH = 3, n = 3; dose = 2 mg/kg.

The synthesis of **2** (BMS-955176) is shown in Scheme 1.[22] Commercially available **10** was treated with benzyl bromide in the presence of K_2CO_3, followed by oxidation with PCC to afford ketone **11**, which was converted into the enol triflate **12**. Suzuki coupling of **12** with (4-(methoxycarbonyl)phenyl)-boronic acid afforded **13**. The C-28 carboxylic acid in **13** was selectively deprotected using *tert*-butyldimethylsilane in the presence of $Pd(OAc)_2$ to afford silyl ester **14**, which upon treatment with TBAF generated **15**. Curtius rearrangement of **15** using DPPA afforded the C-17 primary amine **17** in a process that could be carried out either in a single operation or stepwise via isolation of the corresponding C-28 isocyanate **16**. Derivatization of the primary amine in **17** turned out to be a challenge, presumably due to a combination of steric hindrance and decreased nucleophilicity of the *N* atom caused by its proximity to the steroid core. A 3-step procedure was initially developed to install the side chain present in **2** via reductive amination of **17** using *tert*-butyl 2-oxoethylcarbamate in the presence of $NaBH(OAc)_3$ and $Ti(OiPr)_4$, which rendered **18**. The BOC protecting group was removed using HCl to provide the C-17 primary amine **19**. *In situ* trapping of **19** via a double Michael addition to divinylsulfone afforded **20**, with an overall yield of 38% for the 3-step procedure. Ultimately, the reductive amination/hydrolysis/Michael addition sequence was replaced

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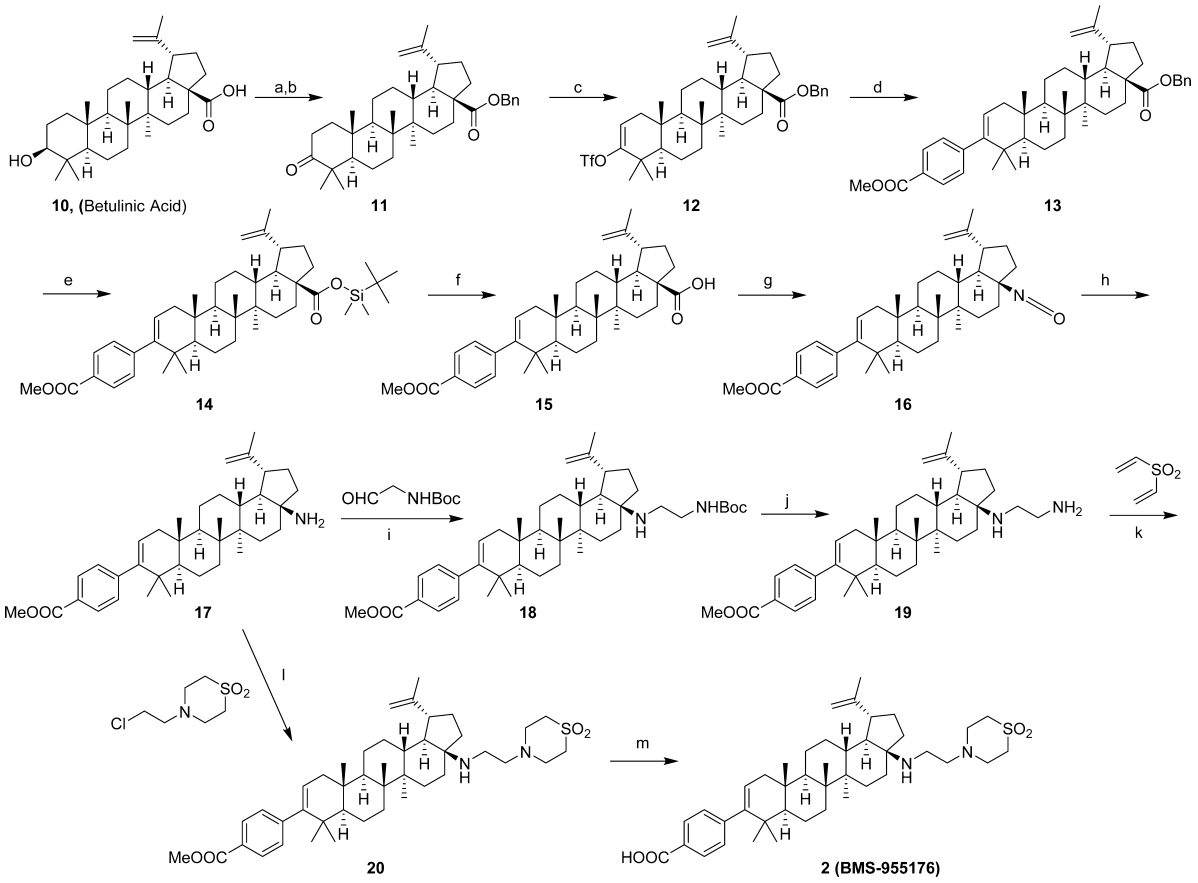
Scheme 1. Synthesis of 2 (BMS-955176)[a]



[a]Reagents and conditions: (a) K_2CO_3, BnBr, DMF, 60 °C, 3.5 h, 99%; (b) PCC, CH_2Cl_2, 6 h, 96%; (c) KHMDS, $PhNTf_2$, THF, −78 °C, 4 h, 90%; (d) (4-(methoxycarbonyl)phenyl)boronic acid, Na_2CO_3, $Pd(Ph_3P)_4$, 1,4-dioxane/*i*-PrOH/H_2O, reflux, 14.5 h, 68.1%; (e) TBDMSH, $Pd(OAc)_2$, TEA, DCE, 60 °C, 2 h, 97%; (f) TBAF, H_2O/1,4-dioxane, rt, 4 h, 99%; (g) DPPA, TEA, 1,4-dioxane, 100 °C, 5 h, 93%; (h) conc. HCl, THF, rt, 72 h, quant.; (i) $Na(OAc)_3BH$, $Ti(OiPr)_4$, DCE, rt, 19 h 79%; (j) HCl, 1,4-dioxane, rt, 4 h, 95%; (k) TEA, 1,4-dioxane/EtOH, 85 °C, 3 h, 91%; (l) K_3PO_4, KI, MeCN, 115−125 °C, 48 h, 73%; (m) NaOH, 1,4-dioxane, 78 °C, 3 h, 77%.

by a one-step procedure in which **17** was alkylated with 4-(2-chloroethyl)thiomorpholine 1,1-dioxide to afford **20** in 73% yield. This combination of base and solvent appeared to be optimal in order to achieve the complete conversion of **17** to **20**. Final hydrolysis of **20** to unmask the carboxylic acid was performed with aqueous NaOH to afford **2** (BMS-955176). Overall, **2** was prepared in 10 steps from **10** with a total yield of 20%.

In conclusion, BMS-955176 is a potent HIV-1 inhibitor in cell culture that, unlike **1**, exhibits broad spectrum antiviral effects that encompass the V370A- and ΔV370-containing polymorphic viruses. In addition, BMS-955176 exhibits low serum binding, which translates into a modest 5-fold effect on potency in vitro, and preclinical PK predictive of once-daily dosing in humans. In a Phase IIa clinical trial, 10-days of monotherapy with **2** administered daily to treatment-naive and treatment-experienced subjects infected with HIV-1 subtypes B or C was generally safe and well-tolerated and demonstrated >1 $\log_{10}$ reduction in viral RNA.[18,25] BMS-955176 is currently being evaluated in a Phase IIb clinical study as a part of a treatment regimen with mechanistically different antiretroviral agents.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00010.

Characterization data for key compounds and experimental procedures for the preparation of **2**, as well as descriptions of biologic and pharmacokinetic assays (PDF)

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Notes

[#]Deceased April eighth, 2016.

The authors declare the following competing financial interest: The authors were employees of Bristol-Myers Squibb at the time this work was completed.

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DEDICATION

This article is dedicated to the memory of Beata Nowicka-Sans, who passed away on April 8th, 2016.

ABBREVIATIONS

AUC, area under the curve; BA, betulinic acid; CA, capsid; cART, combination antiretroviral therapy; Cyno, cynomologous monkey; DCE, dichloroethane; DCM, methylene chloride; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; F, oral bioavailability; FBS, fetal bovine serum; HS, human serum; KHMDS, potassium bis(trimethylsilyl)amide; LANL, Los Alamos National Laboratory; MA, matrix; MI, maturation inhibitor; MeOH, methanol; MOA, mechanism of action; NC, nucleocapsid; NFV, nelfinavir; PCC, pyridinium chlorochromate; PEG, polyethylene glycol; PK, pharmacokinetic; PO, *per os*; rt, room temperature; SP, spacer peptide; TBDMSH, *tert*-butyldimethylsilylhydride; TEA, trimethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TW, tween; VLR, viral load reduction; WT, wild-type

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