Development of an Effective Scalable Enantioselective Synthesis of the HIV-1 Entry Inhibitor BNM-III-170 as the Bis-Trifluoroacetate Salt

Penn Master of Chemical Sciences

J. Chen, J. Park, S. M. Kirk, H-C. Chen, X. Li, D. J. Lippincott, B. Melillo, and A. B. Smith, III. *Org. Process Res. Dev.* **2019**, 23, 2464-2469

Name: Hung-Ching Chen
Location: Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States
Advisor: Amos B. Smith, III, Ana-Rita, Mayol
Committee: David Chenoweth, Marisa Kozlowski, Patrick Walsh
Graudation year: May, 2020

Introduction
FACT SHEET – WORLD AIDS DAY 2019[1]

HIV/AIDS (Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome)

- 75 million people have become infected with HIV since the start of the epidemic.
- 2 million people became newly infected with HIV annually. (About 5000 new HIV infections a day)
- Without proper treatment, people with AIDS could only survive three years.
- 1 million people have died from AIDS-related illnesses in 2018
- Although people have access to HAART, the cure has yet to be found

Introduction
HIV Entry Mechanism[2]

Envelope Trimer
- Make up of $gp120_3$ and $gp41_3$
- On the virus and infected cells
- Only virus specific protein

The Smith Group
- CD4mc – binds to gp120 and achieve HIV deactivation
- Sensitze HIV-1 virions to those otherwise non-neutralizing antibodies

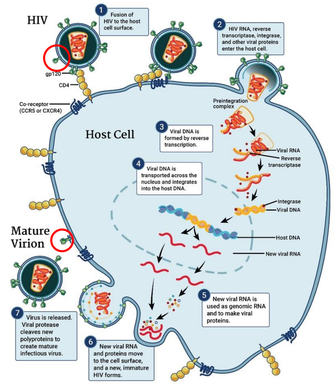
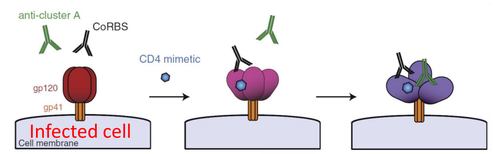


Fig 1. HIV Replication Cycle[2]

Introduction
Antibody Dependent Cellular Cytotoxicity[3, 4]



- CD4mc could sensitize HIV-1 infected cell to ADCC
- CD4mc Protects non-infected cell from ADCC

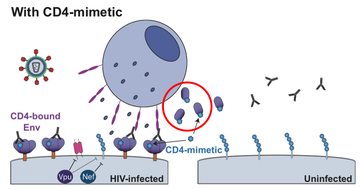


Fig 2. ADCC mechanism[3, 4]

Experimental Design
Small Molecule CD4 Mimetics

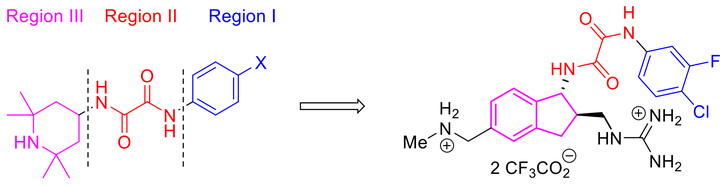
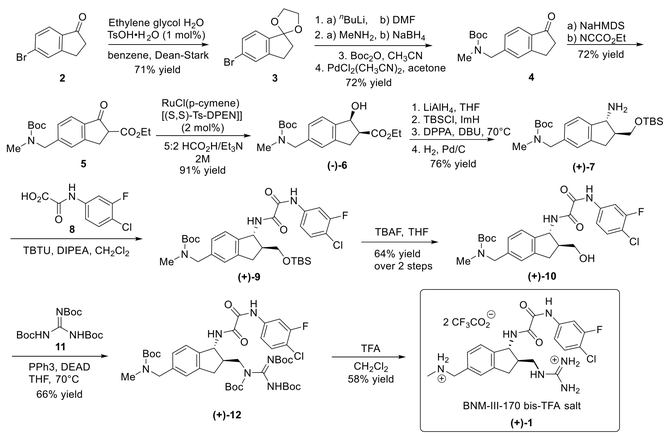


Fig 3. CD4mc design based on the HTS results by Debnath group[5]

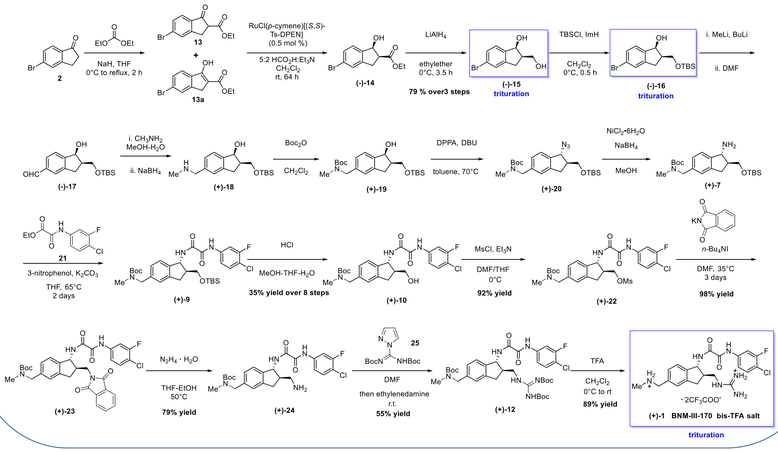
Strain	Clade	BNM-III-170 (IC50 μM)
JR-FL	B	11.6
YU2	C	1.8
AD8	A	7.1
C5	C	2.1
AMLV		>300

Chart 1. Bioactivity of BNM-III-170

First Generation Synthesis of BNM-III-170[6]
(15 steps, 6.2% yield, 12 column chromatagraphy)

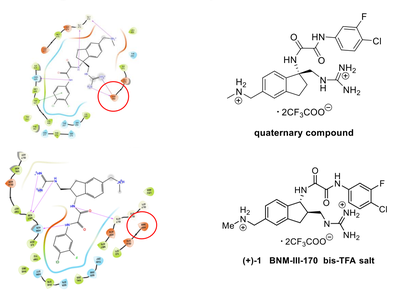


Scaled up Synthesis of BNM-III-170[7]
(16 steps, 9.64% yield, 1 column chromatagraphy)



Discussion/Conclusion

- Scale up synthesis which required only 1 column chomatagraphy in overall 16 steps and 9.64% yield has been achieved
- 45g of BNM-III-170 has been synthesized
- New analogs should be synthesized to increase the bioactivity



G-Score: -9.743

G-Score:-9.513

Fig 3. Computational analysis of BNM-III-170 and new analog[8]

FUNDING AND SUPPORT

HIV Entry Antagonists
P01-GM 56550

NIGMS

Synthetic Chemistry
Althea E. Gaffney
Cheyenne Chaplain
Christopher Fritschi
Daniel Lippincott
Junhua Chen
Jun Park
Melissa C. Grenier
Ta-Jung Chiu
Tyler Higgins

Joseph Sodroski (Harvard)
Immunology and Biology Team

Irwin Chaiken (Drexel)
Biochemistry Team

Wayne Hendrickson (Columbia)
Crystallography Team

Walther Mothes (Yale)
smFRET Team

Navid Madani

Cameron Abrams (Drexel)
Computational Team

Andrés Finzi (CRCHUM)
ADCC Team

Reference

1. UNAID, *Global AIDS Update 2019 Fact Sheet, UNAIDS*
2. https://www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle
3. N. Madani, A. B. Smith, III, J. Sodroski, et al. *J. Virol.* **2014**, 6542; J. Richard, A. B. Smith, III, A. Finzi et al. *PNAS* **2015**, *112*, E2687;
4. J. Richard, A. B. Smith, III, A. Finzi et al. E. BioMed, **2016**, 122; W. S. Lee, A. B. Smith, III, J. Sodroski, , A. Finzi, S. Kent , et al. *J. Virol.* **2014**, 6542. A. Finzi. *TEDxMontreal*. **2015**.
5. Q. Zhao, N. Strick, N. Neamati. A.K. Debnath, *J. Virol*. **2005**, *339*, 213.
6. Melillo, B.; Liang, S.; Park, J.; Schön, A.; Courter, J. R.; LaLonde, J. M.; Wendler, D. J.; Princiotto, A. M.; Seaman, M. S.; Freire, E.; Sodroski, J.; Madani, N.; Hendrickson, W. A.; Smith, III, A. B. *ACS. Med. Chem. Lett.* **2016**, *7,* 330–334.
7. J. Chen, J. Park, S. M. Kirk, **H-C. Chen**, X. Li, D. J. Lippincott, B. Melillo, and A. B. Smith, III. *Org. Process Res. Dev.* **2019**, 23, 2464-2469
8. Work with Prof. Cameron Abrams, Mohammadjavad Mohammadi