Tuberculosis

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Natural Calanolides and Their Chemical Biology and Pharmacology on Human Immunodeficiency Virus-1 and *Mycobacterium Tuberculosis*

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1. Description and Topical Outline

This review aims to be a comprehensive, authoritative, critical, and accessible review of general interest to the chemistry community because a natural (+)-calanolide A and it's both natural and synthetic analogues were continuously investigated. (+)-calanolide a was identified in 1992 as a distinguished class of NNRTI for HIV-1 with its unique biological and pharmaceutical properties and subsequently was reported on its anti drug-susceptible and drug-resistant strains of *Mtb* in 2004. Due to its structural diversity and pharmacological potentials, readers may not only realizes the importance of natural product and relative organic and medicinal chemistries for drug development, but may be also interesting in insight of the efforts on biological target identifications, druggable profile investigation (i.e. structure-activity relationship, structure-metabolism relationship and structure-toxicity relationship), pharmaceutical sciences and the translation into clinical application, i.e. as a novel diagnostic agent for TB.

2. Outline of Planed Sections

2.1. Where are calanolides from and their structure diversity?

2.2. The total synthesis of natural (+)-Calanolide A and its derivatives

2.3. Natural 1 was active against HIV-1 as NNRT inhibitor, and its clinical investigation

2.3.1. Anti-HIV-1 activity of calanolides

2.3.1.1. Anti-HIV-1 activity of calanolides in cell culture

2.3.1.2. Anti-HIV-1 activity of calanolides in hollow fiber mouse

2.3.2. Anti-HIV-1 activity of inophyllums

2.3.3. Anti-HIV-1 activity of cordatolides

2.3.4. Investigation of **1** in Clinical Trails

2.4. Improved calanolides as anti-HIV-1 NNRT inhibitor

2.5. (+)-Calanolide A and its derivatives inhibit replicating and non-replicating *M. Tuberculosis (Mtb)*

2.5.1. Identification of **1** as a naturally occurring anti-tubercular compound

2.5.2. Preliminary studies of structural modification based on 1

2.5.3. Identification and optimization of synthetic calanolides with nitrofuran moiety active against replicating and non-replicating *Mtb*.

2.5.4. Other modifications of the calanolides aimed for assay of anti-tuberculosis

2.6. Calanolide nitrofuran derivatives (NFCs) target at a nitro reductase Rv2466c requiring mycothiol as a cofactor

2.7. Development of an Rv2466c-dependent fluorescent probe for *Mtb* diagnosis and drug susceptibility testing

2.8. Investigation of the interaction with Rv2466c and NFCs compound in the presence of MSH

2.8.1. Reduction of NFCs by Rv2466c requires an active conformation induced by mycothiolation

2.8.2. The role of MSH

2.8.2.1. Synthesis of MSH and its derivatives

2.8.2.2. The contribution of different MSH's motifs in activation of Rv2466c

2.8.2.3. Reduction of NFCs requires an active conformation of Rv2466c via mycothiolation

2.9. NFCs developed as a novel fluorescent probe for rapid and high throughput diagnosis of TB

2.9.1. The dilemma of treatment and diagnosis of TB and current diagnostic and DST methods in hospitals and research labs

2.9.2. NFCs developed as a novel fluorescent probe to detect *Mtb*

2.9.2.1. The specificity and sensitivity of NFCs-based *Mtb* detected method

2.9.2.2. Detection of clinical sputum specimens from out-patients by the NFC method

2.9.2.3. Evaluation of pDST by the NFC method in a high-throughput manner

2.10. Summary

chloromethyl-11-demethyl-12-oxo calanolide A with druggable profile. ***J. Med. Chem.***, **2010**, 53: 1397-1401.

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3. List of Previous Reviews of the Subject

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4. List of Five of the Authors' Papers that are Most Closely Related to the Review Topic

1. Ma T, Liu L, Xue H, Li L, Han CY, Wang L, et al. Chemical library and structure-activity relationships of 11-demethyl-12-oxo calanolide A analogues as anti-HIV-1 agents. J. Med. Chem., 2008, 51: 1432-1446.

2. Xue H, Lu XF, Zheng PR, Liu L, Han CY, Hu JP, et al. Highly suppressing wild-type HIV-1 and Y181C mutant HIV-1 strains by 10-chloromethyl-11-demethyl-12-oxo calanolide A with druggable profile. J Med Chem. 2010; 53: 1397-1401.

3. Lu XF, Liu L, Zhang X, Lau TCK, Tsui SKW, Kang YX, Zheng PR, Zheng BJ, Liu G, Chen Z. F18, a novel small-molecule NNRTI, inhibits HIV-1 replication using distinct binding motifs as demonstrated by resistance selection and docking analysis. Antimicrob. Agents Chemother. 2011; 56(1): 341-351.

4. Zheng PR, Somersan-Karakaya S, Lu SC, Roberts J, Pingle M, Warrier T, et al. Synthetic calanolides with bactericidal activity against replicating and non-replicating Mycobacterium tuberculosis. J Med Chem. 2014; 57: 3755-3772.

5. Ran Mu, Chengcheng Kong, Wenjun Yu, Hongyao Wang, Jie Wu, Xueyuan Li, et al. Nitrooxidoreductase Rv2466c-Dependent Fluorescent Probe for Mycobacterium tuberculosis Diagnosis and Drug Susceptibility Testing. ACS Infect. Dis. 2019; 5(6): 949-961.