



Identification of a diverse synthetic abietane diterpenoid library and insight into the structure-activity relationships for antibacterial activity

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ABSTRACT

A diverse natural product-like (NPL) synthetic abietane diterpenoid library containing 86 compounds were obtained and the SARs were studied based on their antibacterial potential. Further *in vitro* cytotoxic and *in silico* drug-like properties evaluation showed that the potent antibacterial compound **84** had good drug-like properties and displayed low cytotoxicity toward noncancerous mammalian cells, indicating the study of AA and DHAA might be a good starting point for the search of novel antimicrobial molecules. Future work should be focused on the optimization of their potency and selectivity.

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Despite our growing knowledge about infectious diseases and the availability of various antibiotics and chemotherapeutics, the rapid development of resistance in pathogenic bacteria towards available antibiotics remains a global public health threat. In particular, a rapidly increasing number of multidrug-resistant strains have emerged.¹ As reported by the American Center for Disease Control and Prevention (CDC), more than 1.2% out of 2 million people die from infections with multidrug-resistant bacteria (MDRB) in the United States each year.² Therefore, the discovery and development of new effective antimicrobial agents with novel chemical structures and mechanisms to address the drug resistance and improve the antimicrobial potency is of prime interest.

Natural products (NPs) are structural-complex and biologically validated molecules that have a profound impact upon drug discovery efforts for the treatment of human diseases.³ Their diverse three-dimensional shapes, functionalities, stereochemistries as well as various interesting biological activities have always provided medicinal chemists with a reliable source in their search

for new drug-like molecules. For example, terpenoids, as the largest class of NPs, are the most abundant and widely distributed naturally occurring interesting metabolites containing approximately 25,000 chemical structures. Therefore, extensive pharmaceutical activities were exhibited.⁴ Among them, abietic acid (AA, **1**) and dehydroabietic acid (DHAA, **5**) are naturally occurring resin acids that can be readily obtained from pinus rosin or disproportionated rosin (Fig. 1). It is reported that AA, DHAA and their semisynthetic derivatives possess a broad spectrum of biological properties such as anti-inflammatory, antiviral, antitumor, BK channel-opening, anticonvulsant, antiprotozoal, antifungal, antileishmanial and especially antimicrobial activities.⁵ Moreover, due to their abundance and commercial availability, AA and DHAA have been widely used as starting materials for the construction of several NPs and structurally diverse natural product-like (NPL) molecules library.^{5f,g}

In light of these findings and in our continuing efforts on the structural modification of bioactive natural products and construction of natural product-like (NPL) library from resources-rich NPs^{5f,7}, herein, we report the identification of a diverse synthetic abietane diterpenoid library with antibacterial activity. The novel small NPL library contains 86 compounds, which were obtained during our total synthesis and structure-activity relationships

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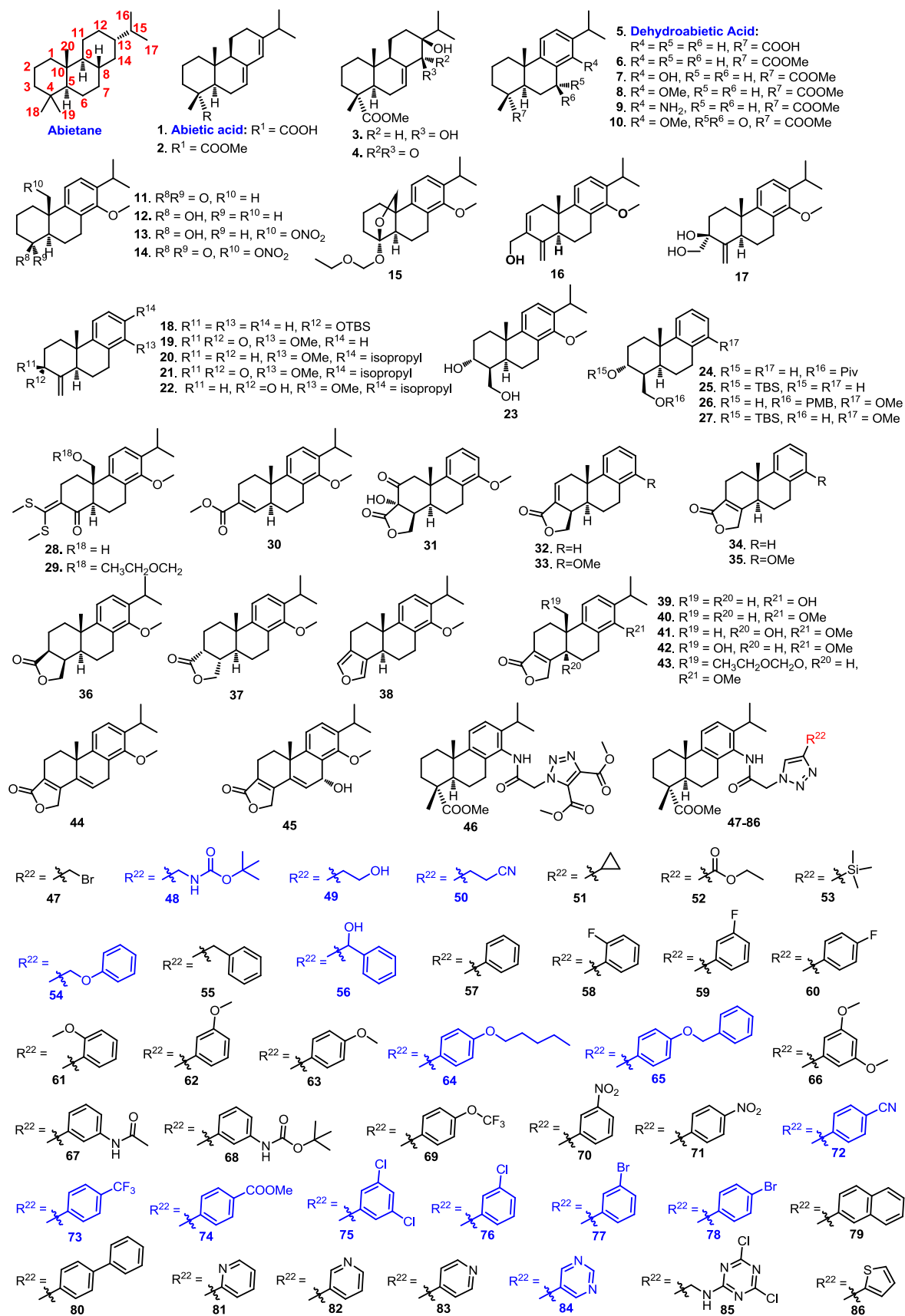


Fig. 1. Compounds 1–86. (The newly synthesized compounds were marked in blue (Supporting information section)).

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