concentration of the dose that was still effective in protecting the mouse is shown. The units are in milligrams of antibiotic per kilogram weight of a mouse. What we are able to discern from these data is that the ester function is responsible for conferring a great deal of the potency to the compounds, as alpha is considerably less potent than any of the esterified components. In addition, the position of the ester group on the terminal mannose unit also has a significant effect on potency with the epsilon component having the ester at the 4-position being the most potent. These data provide key insight for the design of semisynthetic and biosynthetically derived analogs in a lead optimization program. In the case of mannopeptimycin, this initial natural SAR led to the semisynthesis of numerous lipophilic derivatives on the terminal di-mannose moiety. One of the most potent is shown as compound 708 in Figure 7.14. This compound is one of a series of cyclic acetals that showed remarkably enhanced potency as well as presented excellent chemical and metabolic stability.

7.6 CONCLUDING REMARKS

One of the most exciting developments in the study of secondary metabolites, not touched on in this chapter, is the sequencing and annotation of bacterial genomes. Genome mining has revealed a plethora of potential chemistry waiting to be revealed. Challenges also await as scientists endeavor to elucidate the mechanisms that regulate the expression of these cryptic pathways. Issues of supply of these precious materials have frequently plagued the efforts of drug discovery from higher organisms, such as marine sponges or plants. But there is hope. Jay Keasling's work on engineering of a high-producing terpene cyclase pathway in bacteria promises to enable large-scale economical production of the antimalarial drug artemisinin and thereby unlock the supply chain for these life-saving chemicals.

Natural products remain a fascinating and incredibly rich source of leads for drug discovery. Owing to developments in chemical and biosynthetic technologies, the moment is right for the exploration for new chemistry and further exploitation of known secondary metabolites. Advances in molecular biology will enable experiments aimed at a more fundamental understanding of the intrinsic biological roles for secondary metabolites and this knowledge can be expected to illuminate future applications in drug research.

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