Secondary metabolites are biologically active compounds produced mainly by microorganisms. They are not essential for survival of producing strains, however, they significantly affect their physiology and ecology. They are frequently used in pharmacology, biology and chemistry. The present work describes the current state of knowledge concerning origin and evolution of secondary metabolites. The secondary metabolites biosynthetic genes are usually organised in clusters. The basic mechanisms of secondary metabolite gene clusters modification are gene mutations or intragenic rearrangements. These mechanisms are typically involved in natural evolution of gene clusters coding for secondary metabolites with modular type of biosynthesis. The subclusters of different origin can also fuse to form a new hybrid compound biosynthetic gene cluster. Similar evolutionary event probably occurred also in case of biosynthesis of two model groups of natural compounds – lincosamides and pyrrolobenzodiazepines. Analogous approaches are used in genetic engineering to construct producers of new more efficient bioactive compounds. Examples of such genetic modifications of gene clusters involved in the biosynthesis of compounds from nonribosomal peptides, polyketides and lincosamides groups are described. Possible future modifications of compounds from these groups are also discussed.