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Review

Recent developments in the chemistry of ferrocenyl secondary natural product conjugates

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ABSTRACT

Secondary natural products are a source of an endless inspiration in medicinal chemistry. They are characterized by a complex structure and potent biological activity. Ferrocene is an organometallic compound which is characterized by simple sandwich-like molecular structure. Ferrocene and its derivatives have not been found in nature so far. Substitution of respected secondary natural product molecule with the ferrocenyl moiety affords a new semi-natural derivative (or conjugate). The review summarizes recent developments in the field of ferrocenyl secondary natural product conjugates. This class of compounds is structurally diverse and was classified into two major groups. First comprise ferrocenyl conjugates derived from microbial (bacterial and fungal) natural products and the second comprise ferrocenyl conjugates derived from plants natural products. The review delineating potential of ferrocenyl secondary natural product conjugates in medicinal chemistry *e.g.*, as antimicrobial, antiparasite and anticancer agents.

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Abbreviations: A549, lung cancer cells; 7-ACA, 7-aminocephalosporanic acid; 7-ADCA, 7-aminodesacetoksycephalosporanic acid; 6-APA, 6-aminopenicillanic acid; Asn, asparagine; Asp, aspartic acid; 4B16, murine melanoma cells; BE7404, liver cancer cells; BJAB, Burkitt's lymphoma cells; DSCG, disodium cromoglycate; ER+, estrogen receptor positive; ER−, estrogen receptor negative; EA.hy 926, vascular endothelial cells; Fc^+, ferrocenium radical cation; FcH, ferrocene; Fc, ferrocenyl group; Gly, glycine; HCC38, triple negative breast cancer cells; HepG2, hepatocellular carcinoma; HF, human foreskin fibroblast cells; HMG CoA, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; Hsp90, heat shock protein 90; HT29, colon carcinoma cells; IC_{50}, half maximal inhibitory concentration; MCF-7, estrogen-positive breast adenocarcinoma; MDA-MB-231, estrogen-negative breast adenocarcinoma; MIC, minimal inhibitory concentration; MRC-5, lung fibroblast cells; MRSA, methicillin-resistant *Staphylococcus aureus*; NCEs, new chemical entities; Ph, phenyl group; Pro, proline; Rc, ruthenocenyl group; RC124, epithelial kidney cells; SAR, structureactivity studies; Ser, serine; SMVT, sodium-dependent multivitamin transporter; SW620, colon-carcinoma; SW620D, doxorubicin-resistant colon-carcinoma; SW620E, etoposide-resistant colon-carcinoma; SW620M, methotrexate-resistant colon carcinoma; SW620V, vincristine-resistant colon-carcinoma; Tca, tongue cancer; Thr, threonine; TI, chemotherapeutic index; Tyr, tyrosine; WHO, World Health Organization; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*.

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1. Introduction

The overall number of living species on planet Earth is greater than 8 million [1]. All of them produce chemical substances commonly termed as natural products. Natural products are divided into two groups, primary and secondary natural products (secondary metabolites). Primary natural products are key building blocks of the cell and they are directly involved in essential molecular processes including growth, development, or reproduction, which make these products essential for life. In contrast, secondary natural products are characterized by complex molecular structure and are usually not essential for the basic survival. Nevertheless, they play important functions. They are produced by organisms to defend against predation and to combat competitor organisms. Furthermore, natural products act as pollinator attractors in plants and they are responsible for plant colors, flavors, and odors. Extracts obtained from plant sources as well as pure phytochemicals have found applications as dyes, perfumes, poisons, psychoactive compounds, and, foremost, as medicines. Great progress in biological screening and chemical purification methods has delivered new bioactive compounds from bacteria, fungi, plants, and invertebrates including difficult to investigate rare species of extremophiles, microbial symbionts, cyanophytes, and plant endophytes [2–6]. However, not all bioactive secondary natural products can be safely use in therapy. Often, structural modifications of the given natural product are required to preserve or potentiate the beneficial activity of these compounds and simultaneously to diminish undesired biological effects. Chemists have developed many approaches toward natural products modifications and syntheses, with the most challenging being multi-step total syntheses [7–8]. Several review articles have covered the topic of the transformation of secondary natural products into drugs or into core structures for natural product-derived drugs. Therefore, these topics will not be considered in detail herein [2–5]. Nevertheless, selected examples of natural product drugs will be provided here in order to illustrate their role in modern medicine. According to analysis published by Newman and Cragg of the 1355 New Chemical Entities (NCEs) discovered from 1981 to 2010, 540 (40%) NCEs were either natural products or derived from natural products [5]. Concerning the field of anticancer drugs, from the 1940 s to 2010, of the 175 small molecules, 85 have been either natural products or their derivatives [5]. With respect to antimicrobial drugs developed from 1981 to 2010, of the 104 new molecules, 78 (75%) have been antibiotics derived from natural products [5]. Doxorubicin and paclitaxel are among the most important anticancer drugs (Fig. 1) isolated from the bacterium

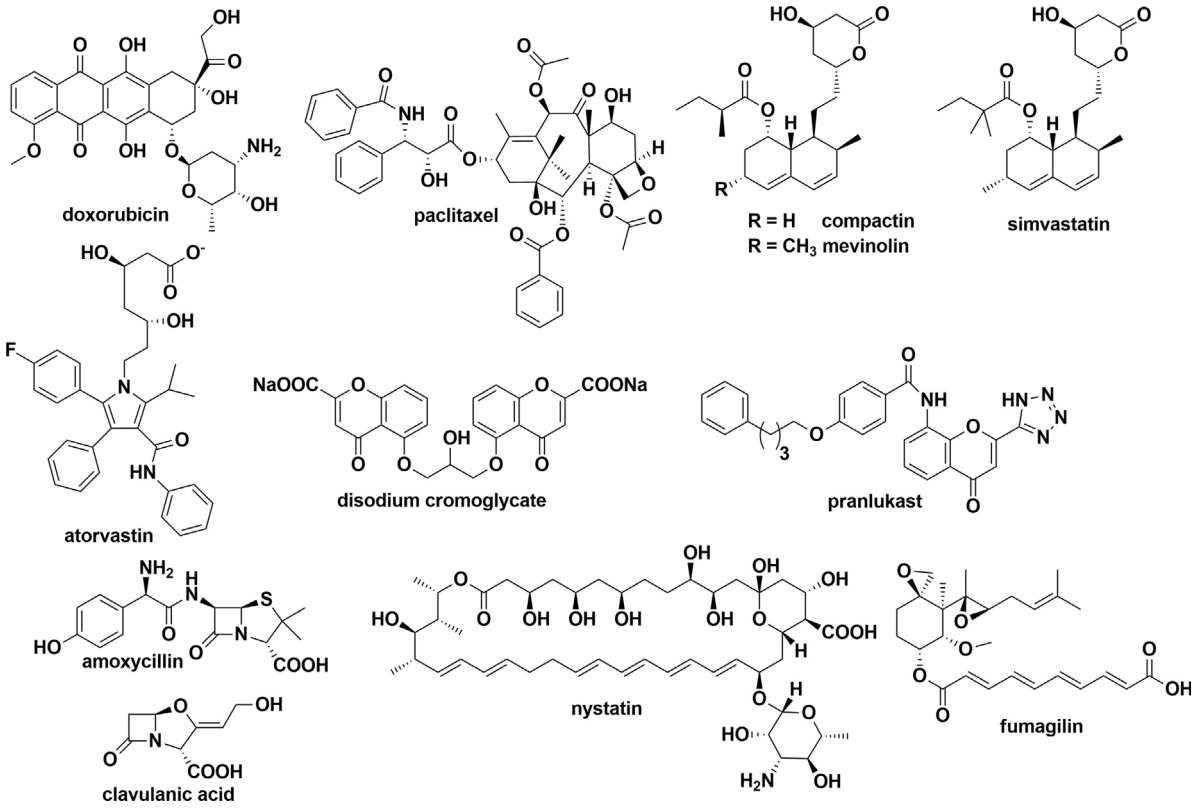

Fig. 1. Examples of medicinally marketed natural products and natural product-derived drugs.