生物活性クアシノイド化合物に関する研究
── 単離、合成、及び構造活性相関 ──*

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Studies on Bioactive Quassinoids
— Isolation, Synthesis, and Structure-Activity Relationships —

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Quassinoids, isolated from the Simaroubaceous plants, demonstrates various biological activities, such as antitumor, anti-inflammatory, antimalarial. amoebicidal, antifeedant, insecticidal, and herbicidal effects. As a result, the bitter principles have been extensively investigated from a structural viewpoint, their versatile biological activity, and interesting structure-activity relationships.

The discovery of the potent antineoplastic activity of bruceantin, a quassinoid from *Brucea antidysenterica*, which was in phase II crinical trial as an anticancer drug by the National Cancer Institute of USA, has generated much synthetic and biological interest in this class of natural products from the Simaroubaceae. Later detailed investigation on the same species led to the isolation of many antileukemic quassinoids.

The fruits of *Brucea javanica* (L.) Merr. are well known as "Ya-Tan-Tzu" in Chinese folklore as herbal remedies for human cancer, malaria, as well as for amoebiasis. The quassinoid bruceoside C isolated from this plant demonstrated potent cytotoxicity against human epidermoid carcinoma of the nasopharynx and CNS carcinoma, as well as murine lymphocytic leukemia. The novel quassinoids bruceosides D, E, and F from the same species showed selective cytotoxicity in leukemia, non-small cell lung cancer, prostate cancer, and breast cancer cell lines.

The inhibitory activities of forty-five natural quassinoids on 12-O-tetradecanoyl phorbol-13-acetate (TPA)-induced Epstein-Barr virus early antigen (EBV-EA) activation and their potential as anti-tumor-promoting agents have been reported, of which fifteen quassinoids were isolated from *Brucea javanica.*

As a result of our profound interest in the bioactive constituents of Ya-Tan-Tzu as well as the structure-activity relationship corelation, we carried out a detailed investigation on the components of the 1-butanol extract. Recently, we isolated a new quassinoid, desmethyl-brusatol,

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and two new quassinoid glucosides, bruceoside G and bruceoside H. Their structures were elucidated by spectral evidence such as UV, IR, NMR (^{1}H, ^{13}C, DEPT, ^{1}H-^{1}H, and ^{13}C-^{1}H COSY), and MS (HRSIMS) and chemical transformation to or from the known compopunds. During the process of isolation of new quassinoids, known quassinoids were also isolated.

Since in structure-activity relationship studies of antitumor and anti-inflammatory quassinoids, we found that the lipophilicity of the ester side chain is very important for the activity. However, bruceantin has not yet progressed to drug development. Enzymatic oxidation of the side chain might cause deactivation of the quassinoid and limit its efficacy.

Accordingly, substituting the side chain with a moiety more stable to oxidation might prove beneficial. Introducing fluorine into the quassinoid side chain might increase both lipophilicity and bond strength. The modified quassinoid then could be transported easily into the cell, but might not be decomposed by enzymatic oxidation. So, quassinoid derivatives with fluorine were decided to synthesize.

Isobrucein B, a major quassinoid was isolated from *Brucea antidysenterica*. The acetyl group of isobrucein B was removed by alkaline hydrolysis to desacetyl-isobrucein B. Then, five quassinoid derivatives were prepared by esterification of desacetyl-isobrucein B with the following acid chlorides: isovaleryl chloride, 3,3-dimethylacryloyl chloride, 4,4,4-trifluoromethylbutanoyl chloride, 3-fluorobenzoyl chloride, and 3-trifluoromethylbenzoyl chloride. The structures of the semisynthetic quassinoids were confirmed by spectral evidence.

We are very intersted in determining various biological activities of the quassinoids, especially antitumor, anti-tumor-promoting, and anti-HIV effects. Recently, seventy-two quassinoids which were isolated from the four plants of Simaroubaceae or derived from natural quassinoids were assayed as inhibitors against Epstein-Barr virus early antigen (EBV-EA) activation and over all structure-activity relationships were discussed: (a) a methylenoxy bridge, an ester side chain, and fluorination of the side chain (especially aliphatic one) enhance the activity, but (b) a sugar moiety reduces the activity.

The three new quassinoids and related five other compounds were more active than the reference compounds, curcumin, β-carotene, and glycyrrhizin. Desmethyl-brusatol and bruceoside G (which is desmethyl-bruceantinoside A) were less active than brusatol and bruceantinoside A, respectively. Similarly, bruceoside H (the butyl ester of bruceoside D) was more active than bruceoside D.

All the ester derivatives showed higher anti-tumor-promoting activity than that of the potent stirting material, desacetyl-isobrucein B. The derivative containing fluorinated aliphatic ester side chain showed the highest potency.

Isobrucein B was assayed further for *in vivo* inhibitory effect against mouse skin tumor promotion and the result was very promising.

TAACF (the tuberculosis antimicrobial acquisition and coordinating facility) has set up a new drug screening program to discover novel agents for the treatment of tuberculosis. We were interested in this program and sent fifty-six quassinoids isolated in our laboratory from the Simaroubaceous plants, *Brucea javanica*, *Brucea antidysenterica*, *Picrasma ailanthoides*, and *Ailanthus altissima* for screening as anti-tuberculosis agent. As a result, eighteen quassinoids showed anti-tuberculosis activity. Although the activities were very low, the resulting data

provided a picture of structure-activity relationships which may provide clues for the development of more active compounds, and structural diversity is very important for the drug discovery effort.

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