[S2-3] [10/19/2001(Fri) 11:30-12:00 / Hall B]

Angiogenesis inhibitors acting on methionine aminopeptidase-2

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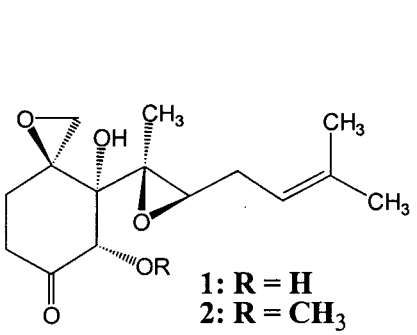
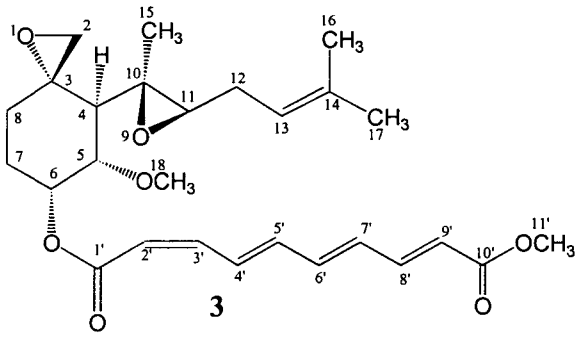
Tumor growth relies on angiogenesis, the formation of new blood vessel. Since angiogenesis inhibitors introduced as cancer drugs working in new way, a lot of materials have been proposed to regulate angiogenesis and tumorigenesis. Most promising targets to control angiogenesis may be VEGF and VEGF-related entities, because the VEGF is major angiogenic factor. Nevertheless endostatin, one of the star candidates for the angiogenesis drug, still in debate to elucidate its mechanism although integrin proposed as a key factor recently. As a result of the ambiguous mechanism of angiogenesis and anti-angiogenesis, much more information for angiogenesis and for molecular networking in tumor cell was collected. Now, more than 20 companies are developing anti-angiogenic therapy with more than 40 drugs in clinical stage.

Methionine aminopetidase type 2(MetAP2) was suggested as a common molecular target for the most potent anti-angiogenesis reagent TNP-470 and ovalicin in 1997. Biotinylated probes bound covalently to MetAP2 specifically. Human MetAP, having two isomers type 1 and type 2, was established in recombinant yeast as a screening tool by the co-work with Professor Chang in St. Louis University. The abundant sources for the MetAP2 inhibitors were mycotoxins those are major secondary metabolites of fungi. Fumagillin and ovalicin analogues were isolated from fungal metabolite.

Microbial natural products have been good sources for the new drugs for over 30 years although some big pharmaceutical companies recently terminated their natural product activities. The problems for the microbial natural products may originate from its redundancy and repetitive re-discover of known compounds. To find out trace compounds from crude microbial metabolites and to increase the possibility of molecular diversity acting on MetAP2, statistical approach was adapted into the fermentation of producing microbes. Molecular diversity could be elicited from metabolic diversity by regulate its physicochemical culture conditions, and trace compounds could be amplified up to detectable amounts. As a result of the optimization two new analogues, demethylovalicin(**1**) and *cis*-fumagillin(**3**) were discovered from

Penicillium and *Chrysoporium* as well as three known compounds.





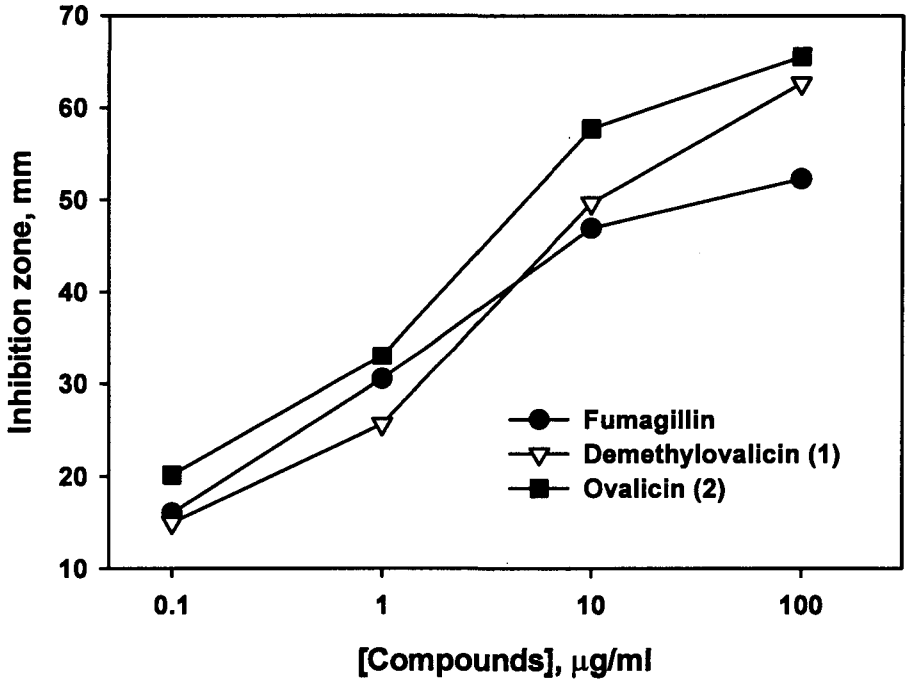


Figure 1. Determination of MetAP2 inhibitory activities of the compounds using agar diffusion assay on the recombinant yeast *Saccharomyces cerevisiae* (map1::HIS3).

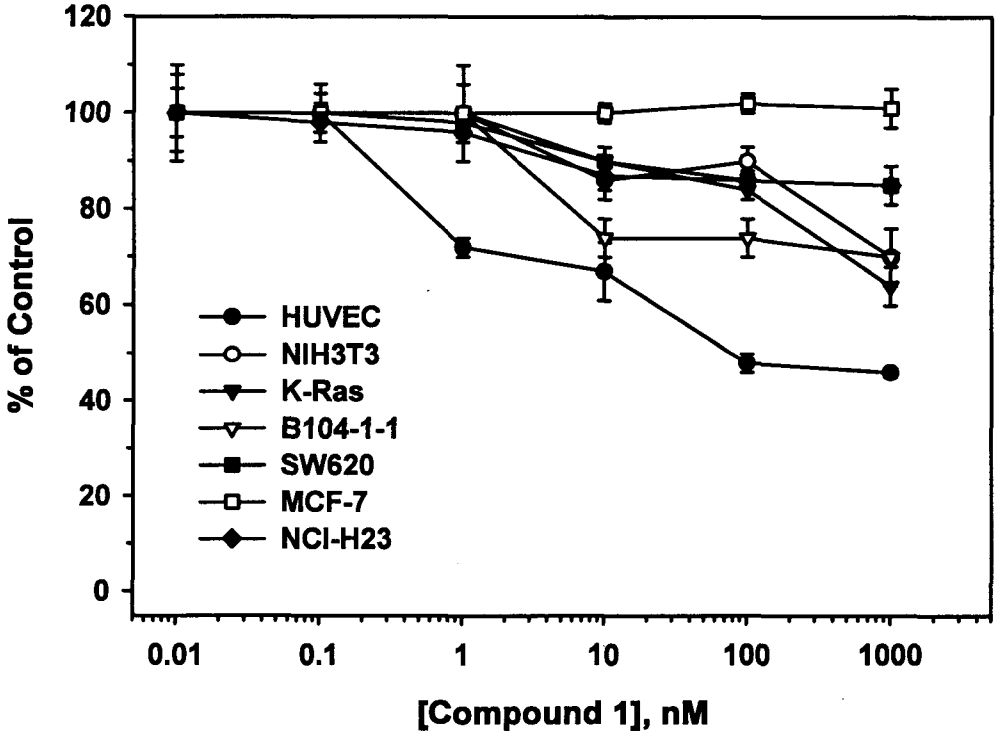


Figure 2. Growth-inhibition assay using the colorimetric method with WST-1.