穿心蓮內酯的微生物與化學轉換

Microbial and Chemical Transformations of Andrographolide

中文摘要

穿心蓮內酯 (1) (andrographolide, ent-(14R)-3β,14,15,19-tetrahydroxy-labda-8(20),12E-dien-16-oic acid-15-lactone)取自於爵床科 (Acanthaceae)草本植物穿心蓮 Andrographis paniculata Nees，屬 labdane 結構的二萜類 (diterpenes)，是中國傳統草藥用來治療感冒、發炎等疾病。文獻中指出具有多種活性，包含解熱、抗菌、抗病毒、抗發炎、免疫調節、抗腫瘤、抗心血管疾病、抗生育、保肝利膽及降血糖作用，因此有“中藥抗生素”之稱。目前鮮少人針對其代謝物作研究，促使我們以此爲受質進行微生物轉換之實驗。
經過 24 株菌種篩選，發現利用 Nocardia sp.進行轉換實驗可得到不同於受質的代謝物，經抽取、分離、純化取得 andrographolide 19-O-acetate (2)、andrographolide 3-O-acetate (3)、andrographolide 3,19-O-diacetate (4)，另取得一新的化合物 ent-(14R)-3α,14,15,19- tetrahydroxy-labda-8(20),12E-dien-16-oic acid-15-lactone (5)。
此外，利用受質透過合成的方式得到代謝物 2 和 4，另外將 4 做部分的修飾得到以下化合物：andrographolide 3,14,19-O-triacetate (6)、andrographolide 3,19-O-diacetyl-14-O-propionate (7)、andrographolide 3,19-O-diacetyl-14-O-butyrate (8)、andrographolide 3,19-O-diacetyl-14-O-valerate (9)、andrographolide 3,19-O-diacetyl-14-O-isovalerate (10)、andrographolide 3,19-O-diacetyl-14-O-trans-cinnamate (11)以及 14-deoxy-11,12-didehydroandrographolide 3,19-O-diacetate (12)。
經過 DPPH 自由基清除實驗和 superoxide anion 清除實驗，目前僅發現化合物 12 具有這方面的活性，其他類似物則沒有明顯的活性。這些 andrographolide 類似物將繼續進行其他生物活性試驗及作爲代謝相關研究之標準品。

英文摘要

Andrographolide (1) (ent-(14R)-3β,14,15,19-tetrahydroxy-labda-8(20),12E-dien-16-oic acid-15-lactone) is structurally designated as a labdane diterpenoid, and is one of main active constituent of Andrographis paniculata Nees (Acanthaceae), a famous Chinese herb. It called “Chinese herbal antibiotic” has many bioactivities such as analgesic, antimicrobial, antiinflammatory, anti-virus, hepatoprotective, antioxidant and antihyperglycemic activities.
By screening twenty-four microorganisms, Nocardia sp. was selected for the preparative-scale microbial transformation of andrographolide. Microbial transformation of andrographolide produced andrographolide 19-O-acetate (2),

andrographolide 3-O-acetate (3), andrographolide 3,19-O-diacetate (4), and a new compound, ent-(14R)-3α,14,15,19-tetrahydroxy-labda-8(20),12E-dien-16-oic acid-15-lactone (5). The structures of metabolites are established on the basis of MS, 1D and 2D NMR.
In addition, we also semi-synthesized metabolites 2 and 4, and used compound 4 as starting material to modify 14-hydroxyl group to obtain andrographolide 3,14,19-O-triacetate (6), andrographolide 3,19-O-diacetyl-14-O-propionate (7), andrographolide 3,19-O-diacetyl-14-O-butyrate (8), andrographolide 3,19-O-diacetyl-14-O-valerate (9), andrographolide 3,19-O-diacetyl-14-O-isovalerate (10), andrographolide 3,19-O-diacetyl-14-O-trans-cinnamate (11) and 14-deoxy-11,12-didehydroandrographolide 3,19-O-diacetate (12).
This is the first report that Nocardia sp. could process acetylation. The reactivity of hydroxyl group of andrographolide decreases in the order of C-19 > C-3 > C-14. Through the screening of DPPH and superoxide anion scavenging testings, the results indicate that only compound 12, 14-deoxy-11,12- didehydroandrographolide 3,19-O-diacetate, presents the antioxidation activity. These analogues will be processed for other biological activity testings and used as reference standards for monitoring our continuing studies on the microbial models of mammalian metabolism of andrographolide.