A071 Sophoflavescenol: a potent and selective inhibitor of cGMP phosphodiesterase 5 from *Sophora flavescens*

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Phosphodiesterase type 5 (PDE5) is very abundant in vascular smooth muscle cells and appears to play a significant role in modulating penile corpus cavernosal smooth muscle tone (1). The inhibitors of guanosine 3¢,5¢-cyclic monophosphate (cGMP)-specific PDE5 act in sexual organs to produce enhanced blood flow and an erectile response of sexual organs by increasing the level of cGMP (2). Although sildenafil citrate is a selective inhibitor of cGMP-PDE5, its effects on other body organs may produce side effects such as nausea, headache, and cutaneous flushing. Accordingly, the second generation of PDE5 inhibitors would be needed that possesses potentially fewer PDE-associated side effects and greater efficacy for the treatment of erectile dysfunction.

During the search program for biologically active compounds from traditional herbal medicine, a methanol extract of the roots of *Sophora flavescens* was found to show strong inhibitory activity against cGMP-PDE5 prepared from the rat diaphragm. Therefore, the inhibitory activities of five flavonoids, kushenol H, kushenol K, kurarinol, sophoflavescenol, kuraridine, isolated from *S. flavescens* were measured against cGMP-PDE5 to identify potent cGMP-PDE5 inhibitory constituents. Among tested compounds, sophoflavescenol, a C-8 prenylated flavonol, showed the most potent inhibitory activity (IC_{50} = 13 nM) against cGMP-PDE5 with 32- and 196-fold selectivity over PDE3 and PDE4, respectively. Kinetic analysis revealed that sophoflavescenol was a mixed inhibitor of PDE5 with a K*i* value of 5 nM. Sophoflavescenol is not structurally related to the classical cGMP-PDE5 inhibitors that have been synthesized through the modification of the sildenafil structure. In conclusion, sophoflavescenol can be considered as a lead structure for the synthesis of selective and potent cGMP-PDE5 inhibitors with more desirable pharmacological profiles.

References: 1. Beavo, J. A. (1995) Physiol. Rev. 75: 725. **2.** Terret, N. K. et al. (1996) Bioorg. Med. Chem. Lett. 6: 1819.

A072 LFA-1\ICAM-1 dependent cell adhesion inhibitors isolated from *Verbascum* species

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The flowers of *Verbascum pterocalycinum* var. mutense Hub.-Mor. (VPM) and *V. lasianthum* Boiss ex Bentham (VL) were extracted with methanol, separately. Chromatographic studies on the methanolic extracts resulted in the isolation of two saponins as, 3-O-{[α-L-rhamnosyl-(1→4)-(β-D-glucopyranosyl-(1→3)]-β-D-glucopyranosyl]-(1→2)-β-fucopyranosyl}-11-metoxy-olean-12-ene-3β, 23, 28-triol (**1**), and 3-O-{[α-L-rhamnosyl-(1→4)-(β-D-glucopyranosyl-(1→3)]-β-D-glucopyranosyl]-(1→2)-β-fucopyranosyl}-13β, 28-epoxyolean-11-ene-3β, 23-diol (**2**) from VPM and verbascoside (**3**) from VL. Their structures were determined by spectroscopic methods (NMR, MS).

Many studies have so far represented that *Verbascum* species show various kinds of biological activities (1, 2). Cell adhesion process play roles in pathological conditions such as chronic inflammation and cancer metastases (3). There is no report concerning the cell adhesion inhibitory effects. In this study, the screening programme for inhibitors of cell adhesion by using CytoFluor 2350, Fluorescence Measurement system with exciation wavelenght of 496 nm and emission at 519 nm was investigated (3, 4). Compounds **1** (IC_{50} 33.0 µg/ml), **2** (IC_{50} 4.0 µg/ml) and **3** (IC_{50} 62.5 µg/ml) showed moderate cell adhesion inhibitory activity. Positive control was Cytochalasin B: IC_{50} 43.0 µg/ml.

References: 1. Baytop, T. (1984) Therapy with Medicinal Plants in Turkey (Past and Present) Publications of the Istanbul University, No:3255, Istanbul. **2.** Bisset, N. G. (1994) Herbal Drugs and Phytopharmaceuticals, Stuttgart, Germany. **3.** Musza; L.L. et al. (1994) Tetrahedron, 50, 1369-1378. **4.** Bronner-Fraser, M. (1985) J. Cell. Biol., 101, 610-617.