

NEW PROTOESCIGENIN DERIVATIVE FOR THE TREATMENT OF PARKES WEBER SYNDROME

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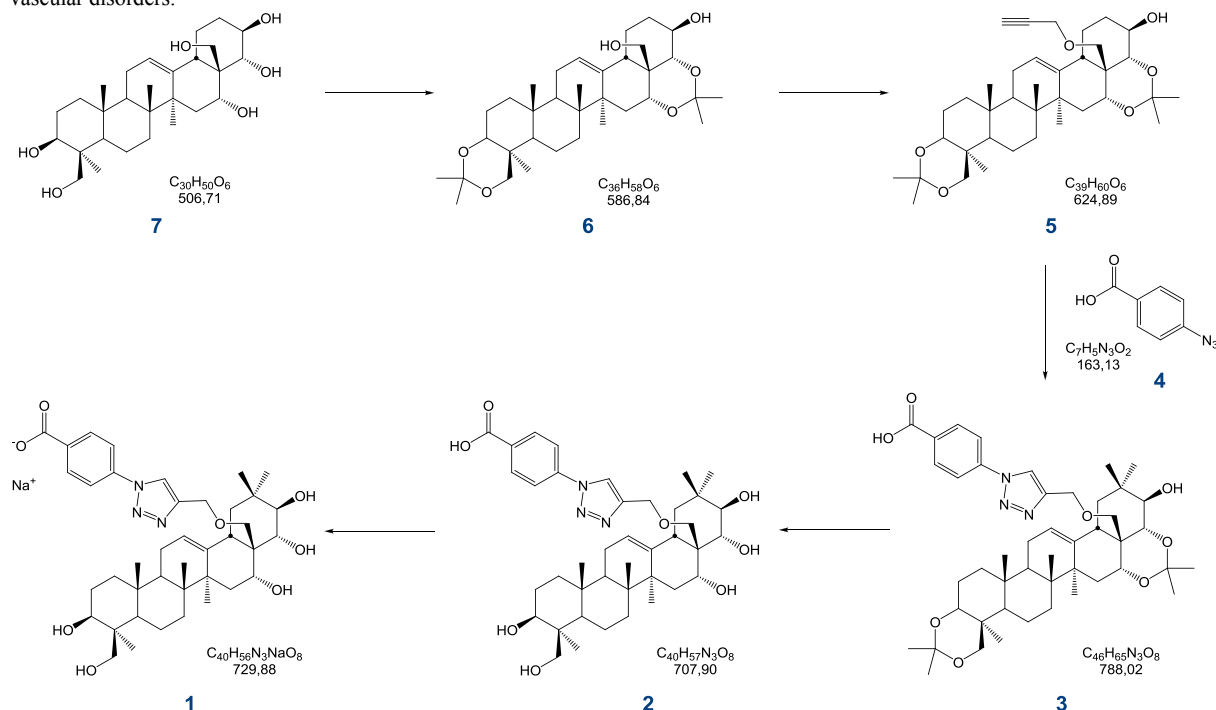
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The Parkes Weber syndrome (PWS), first described in 1907 [1], is characterized by triad of arteriovenous fistulas (AVF), varicose veins and bone and soft tissue hypertrophy leading to limb enlargement. The symptoms of PWS are congenital and present at birth. Vascular anomalies usually affect a limb, most commonly a leg, and less often a trunk. Capillary malformations, forming geographic patterns, are typically located on lateral side of the limb, buttocks or trunk. The appearance of varicose veins and dilated superficial veins in older age is triggered by arteriovenous shunt, venous hypertension and insufficiency of the deep venous system. The enlargement of a limb is present at birth, and the axial overgrowth can enlarge in postnatal period [2, 3]. Cases of shortened lower extremity and pelvis malformations have also been described [4]. Arteriovenous leak may also lead to cardiac system failure or to limb ischemia. Not surprisingly, PWS, similarly to other vascular malformations, significantly reduces the quality of life of the affected patients [5].

The treatment of patients with PWS is mainly symptomatic. Compression therapy is used to reduce symptoms of chronic venous insufficiency and lymphatic edema. In selected cases invasive procedures are performed. Surgical treatment is difficult and may require several intravascular procedures, such as embolization, sclerotherapy or classic open operations involving arteriovenous fistula ligation. In severe cases of ischemic extremities amputation is the only therapy. Therefore, there is an ever-existing need to develop a safe and effective pharmacological therapy for PWS patients.

For the purpose of the study we have established the first animal model reproducing complex manifestations of PWS and applicable for research on etiology, treatment and prevention of the disease. The model mimics major clinical features characteristic for the human PWS: venous hypertension and dilatation, varicose veins formation, and the limb hypertrophy [6] [7].

Cellular biology tools were applied to examine protective effect of ca. 30 new semi-synthetic compounds derived from the main aglycone of escin saponins, on the vascular endothelium under inflammatory conditions. The *in vitro* tests evaluated *i.a.* cell proliferation, migration, endothelial monolayer permeability, and the effect on NFκB signal transduction. One particular molecule (1), obtained in 5 steps as illustrated on the Scheme below, showing promising biological characteristics and favorable physicochemical properties has been selected for *in vivo* studies [8]. The obtained results confirmed valuable pharmacological properties of the tested compound as all the animals treated with the selected compound showed significantly reduced symptoms of PWS as compared to untreated control. Furthermore, we believe that the molecule should be considered as a promising candidate for the prevention and treatment of other, more common vascular disorders.



Acknowledgements

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- [7] Animal model for the Parkes Weber syndrome (EP14001527.2)
- [8] Protoescigenin derivative, process of its preparation, use of said compound and pharmaceutical composition comprising that compound (EP 15000566.8)

The form of presentation proposed by the Author: oral presentation