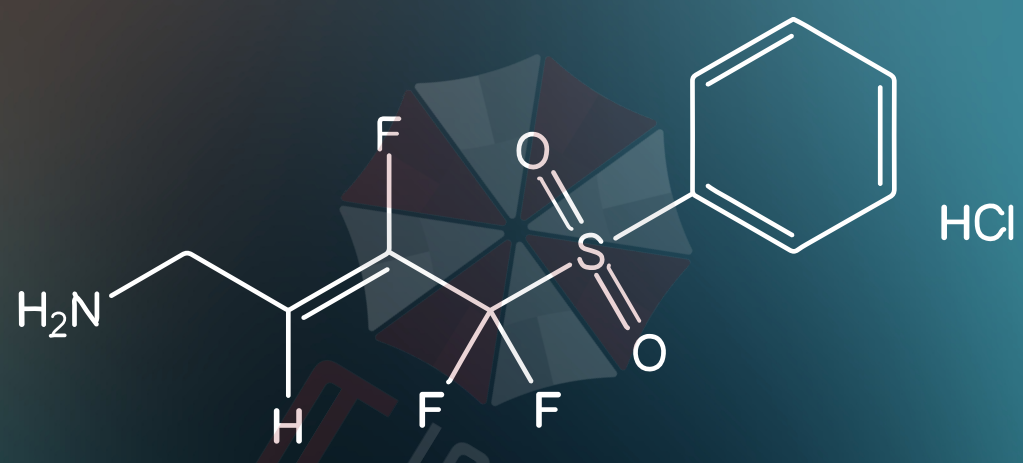

PXS-6302: A Topical Lysyl Oxidase Inhibitor for the Research of Skin Scarring and Fibrosis

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Molecularly, PXS-6302 and PXS-5505 are very similar with 2 differences. PXS-6302 has two additional fluorines at the a-position to the sulfone group (where PXS-5505 simply bears hydrogens). PXS-5505 aromatic moiety is a quinoline, while it's a simply phenyl group in the case of PXS-6302, making PXS-6302 the overall smaller and lighter molecule. Compared to PXS-5505, PXS-6302 shows stronger inhibition of LOXL2, but weaker inhibition of the other oxidase:

C50

3.7 μM (Bovine LOX)

3.4 μM (rh LOXL1)

0.4 μM (rh LOXL2)

1.5 μM (rh LOXL3)

0.3 μM (rh LOXL4)

In contrast to PXS-5505, PXS-6302 was originally environed as a topical anti-scar medication. Injury is known to cause an upregulation of lysyl oxidases. LOX and LOXL1 are significantly increased in scar fibroblasts compared to normal skin. Hence, Lysyl oxidase inhibition was theorized to reduce scar formation.

Originally, development started from a different compound called PXS-4787 which shares both structural elements of of PXS-5505 and PXS-6302.8 Stability data of PXS- 4787 in cream formulations indicated that some unwanted degradation occurred which stopped further preclinical development. PXS-6302 did not show such degradation and also is optimally designed for topical application. It is a small (molecular weight < 300), hydrophilic molecule with high permeability across artificial membranes, a pre-requisite for good skin penetration, as determined by in vitro and ex vivo measurements. In the parallel artificial membrane permeability assay, PXS-6302 demonstrated high permeability. After application of 3% cream to the epidermis of human skin ex vivo, the concentration of PXS-6302 in the opposite reservoir chamber increased 10-fold between 2 and 6 h, with a further 10-fold increase over the next 14 h, demonstrating good skin penetration similar to that observed for PXS-4787. PXS-6302 was formulated as an oil in water cream of different concentrations (0, 0.3, 1, 10%) and applied to a shaved area on the back of a rat (500mg cream applied to 16 cm2). In mice, PXS-6302 reduced skin fibrosis successfully after artificial initiation with bleomycin.

A clinical study assessed the safety and tolerability of PXS-6302, in treating mature scars. Results showed treatment with PXS-6302 significantly inhibited

lysyl oxidase activity (66%). Fifty participants with scars were enrolled and PXS-6302 or placebo cream applied to a 10 cm2area for three months. No significant differences between placebo and PXS-6302 treatment groups were observed in Patient Observer Scar Assessment Scale scores at study conclusion. No severe adverse events were reported. All treatment-related adverse events were localized skin reactions.[9]

Currently, there is another phase I study in progress studying the effects of PXS-6302 in healthy subjects with acute or established scar. (SOLARIA I ACTRN12621000322831) The study uses doses of 0.6–8 mg for 7 days topical in creams ranging from 0,3 to 4 weight %. Results have yet to be posted.

A study with a different lysyl oxidase inhibitor BAPN (β-aminopropionitrile) in rats has shown that intake of the compound can lead to increased penis length increase when combined with a vacuum device. This is likely due to the reason that the integrity of the penis is partially due to the so called tunica albuginea, a fibrous sheath of connective tissue, which consists of collagen fibers which are crosslinked using lysyl oxidases. If the oxidases are inhibited, the collagen crosslinking is reduced and the mechanical stability diminishes, leading to a greater volume increase of the corpora cavernosa and the corpus spongiosum, which fill with blood.[7] It is likely that similar results can be achieved in rats using PXS-6302, due to its similar pharmacological actions. No reports on topical applications exist to this day, but a topical application might reduce systemic side effects of lysyl oxidase inhibitors.

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