MICRO LABS LIMITED AND MICRO LABS USA INC., Petitioner, v. SANTEN PHARMACEUTICAL CO., LTD. AND ASAHI GLASS CO., LTD., Patent Owner.

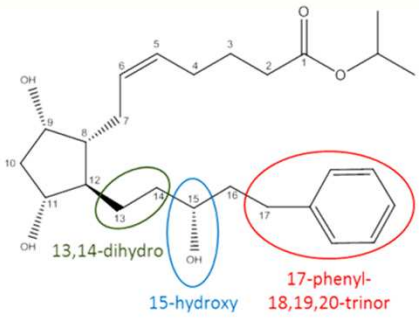
Patent Owner's Demonstratives

September 6, 2018

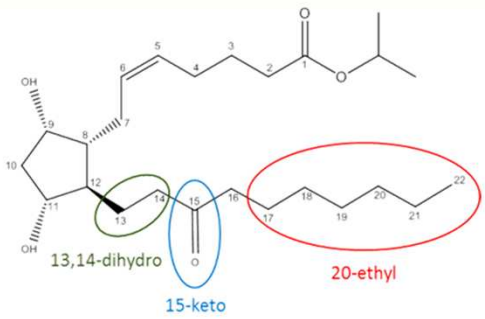
Case IPR2017-01434

Patent No. 5,886,035

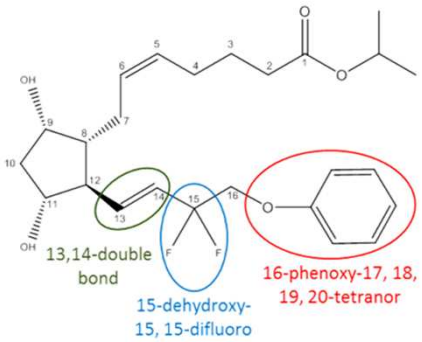
Tafluprost Differs from 2 Commercially Avail PG Analogs in 3 Ways



latanoprost



isopropyl unoprostone



tafluprost

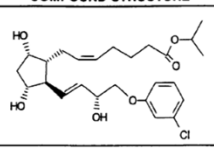
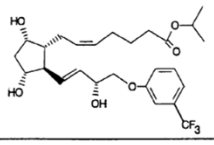
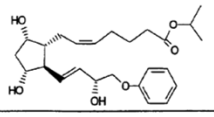
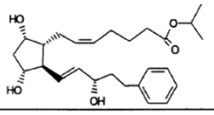
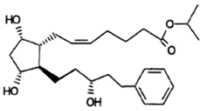
- Only tafluprost has 2 Fs at 15 position (v. OH)
- Only tafluprost has phenoxy at 16 position

Medicinal Chemistry of Prostaglandins Highly Unp

- Medicinal chemistry of prostaglandins highly unpredictable as
  December 1996 (and remains so today)

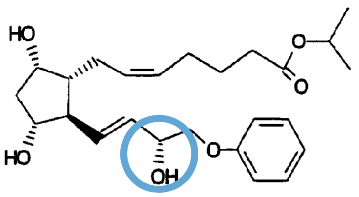
> As is apparent in Table 2, the five compounds differ only slightly in structure; however, as Examples
> and 6 will show, such seemingly slight structural differences produce greatly different IOP-lowering effec
> and levels of hyperemia.

Ex. 1003 (Klimko), 15:54

	COMPOUND NAME	COMPOUND STRUCTURE
A	Cloprostenol, isopropyl ester	
B	Fluprostenol, isopropyl ester	
C	16-Phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$, isopropyl ester	
D	17-Phenyl-18,19,20-trinor $PGF_{2\alpha}$, isopropyl ester	
E	13,14-Dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$, isopropyl ester	

Ex. 1003 (Klimko), 15:1-50 (Tab

Petitioner's Proposed Trajectory from Compou
Tafluprost Made in Hindsight

Proposed Scheme	Asserted Prior Art	
Compound C as lead compound C | 16-Phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$, isopropyl ester  Ex. 1003 (Klimko), 15:1-50 (Table 2)	• Klimko (Ex. 1003)	• Not a Com • Othe Supe • Intol (Hyp • Unfa (Initi • No " Effica
Replace 15-OH with 15-H to diminish side effects	• Kishi (Ex. 1004)	• Char Redu Activ
Replace 15-H with 15-F to mimic (removed) 15-OH	• Bezuglov 1982 (Ex. 1007) • Bezuglov 1986 (Ex. 1008) • Ueno Japan (Ex. 1006)	• Char Hope IOP-I But N Side
Inserting 2Fs at C15	• Ueno Japan (Ex. 1006)	• 2Fs ≠

Petitioner Picked Compound C as Lead Based on I

- The standard:

> Importantly, "[a]bsent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection." *Id.* "Were it otherwise, the analysis would impermissibly rely upon *ex post* reasoning. *Id.*

Paper 22 (POR), 27-28 (citing *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012))

- But Petitioner's expert, Dr. deLong, worked backwards f tafluprost to get to Compound C:

> A. Okay. In the issue at hand with tafluprost, one of the three compounds in one of the claims is a chloride in there. So had the -- had the company taken the chloro one as one of those three instead of the nonchloro one, we would say, "Well, it's more appropriate to have the chloro one be the lead compound because that's the closest one to the chloro tafluprost in -- in that claim in -- in their patent.

Ex.2025 (
79:13-22

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