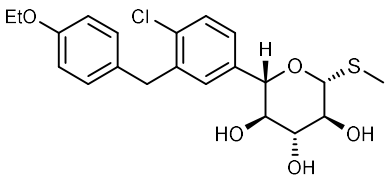
Sotagliflozin (LX4211)

Introduction:



sotagliflozin

- Sotagliflozin, developed by Lexicon and Sanofi, is a dual-inhibitor of sodium glucose cotransporter 1/2 (SGLT-1/2) approved in the EU for the treatment of type 1 diabetes.
- Diabetes mellitus, diabetes characterized by abnormally high blood glucose, can be regulated by inhibition of glucose reuptake in the body.
- Sodium Glucose cotransporters (SGLTs) facilitate the transport of glucose across cell membranes, providing a druggable target.

	Substrate	Apparent affinity for glucose ($K_{0.5}$ mM)	Distribution
SGLT1 (SLC5A1)	Glucose, galactose	0·4	Intestine, trachea, kidney, heart, brain, testes, prostate
SGLT2 (SLC5A2)	Glucose	2	Kidney, brain, liver, thyroid, muscle, heart
SGLT4 (SLC5A9)	Glucose, mannose	2	Intestine, kidney, liver, brain, lung, trachea, uterus, pancreas
SGLT5 (SLC5A10)	Glucose	ND	Kidney cortex
SGLT6 (SLC5A11)	Myo-inositol, glucose	35	Brain, kidney, intestine
SMIT1 (SLC5A3)	Myo-inositol, glucose	>30	Brain, heart, kidney, lung

Apparent affinity values ($K_{0.5}$) are approximate as determined by inhibition of the transport of α-methyl-D-glucoside in various cell types, and tissue distribution of transporters is mostly based on mRNA expression. Human *SGLT3* (*SLC5A4*) is a glucosensor expressed in the enteric nervous system and muscle where it has a high affinity for myo-inositol (*SGLT6* and *SMIT1* also have a high affinity for myo-inositol). Based on data reviewed by Wright and colleagues.[5]
ND=not determined.

	Dose (mg)	IC_{50} SGLT1 vs 2	T_{max} (h)	C_{max}	$t_{1/2}$ (h)	Population and administration regimen
Selective SGLT2 inhibitors						
Dapagliflozin	10	1390 vs 11 nmol/L Ratio ~1200:1	15–20	~160 ng/mL	~13	Healthy individuals steady state
Canagliflozin	100	910 vs 2·2 nmol/L Ratio 160:1	~1·5	~1·0 ug/mL	10·6	Type 2 diabetes single dose
	300	910 vs 2·2 nmol/L Ratio 160:1	~1·9	2·7 ug/mL	13·1	Type 2 diabetes single dose
Empagliflozin	10	8300 vs 3·1 nmol/L	1·5	259 nmol/L	13·2	Type 2 diabetes steady state
	25	8300 vs 3·1 nmol/L	1·5	687 nmol/L	13·3	Type 2 diabetes steady state
Ipragliflozin	150	254 fold selectivity for SGLT2 vs SGLT1	~1	2493 ng/mL	17·8	Healthy individuals
Combined SGLT1 and SGLT2 inhibitor						
LX4221	150	36 vs 1·8 nmol/L	0·5–2·0	82–115 ng/mL	20·7	Type 2 diabetes steady state
	300	36 vs 1·8 nmol/L	0·5–2·0	230–307 ng/mL	13·5	Type 2 diabetes steady state

IC_{50}=half maximum inhibitory concentration. T_{max}=time to maximum circulating concentration. C_{max}=maximum circulating concentration. $t_{1/2}$=terminal half-life.

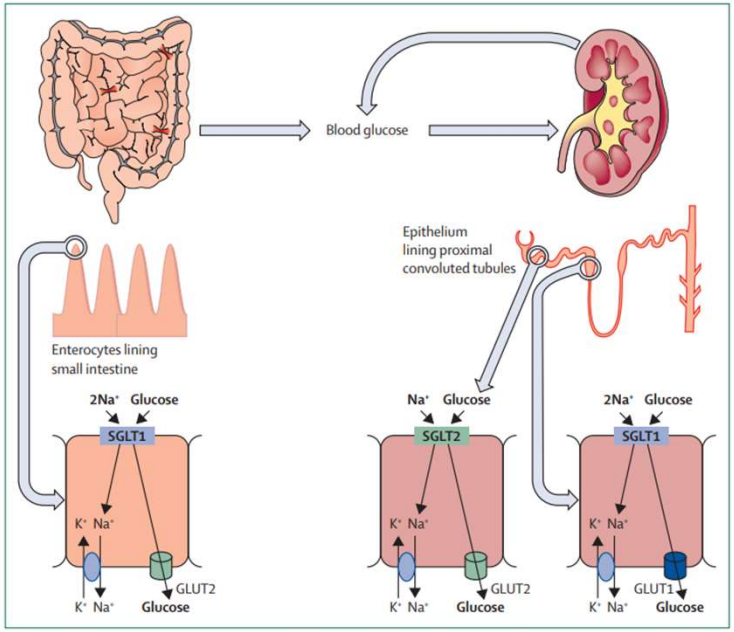
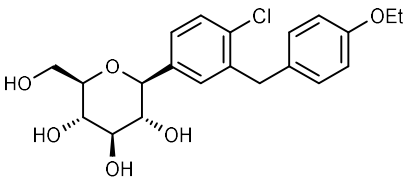
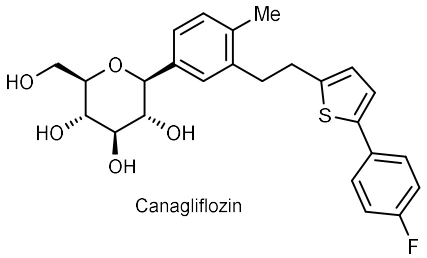


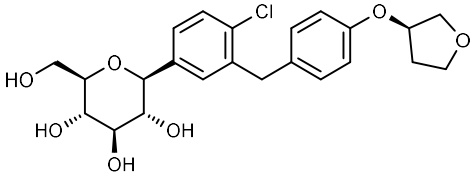
***Figure 1*: Sodium glucose cotransporters (SGLT1 and SGLT2) and facilitative glucose transporters (GLUT1 and GLUT2) in the intestine and renal proximal tubules**
SGLT1 is a high-affinity low-capacity transporter and SGLT2 is a low-affinity high-capacity cotransporter. SGLT1 and SGLT2 are secondary active cotransporters, driven by the Na^+/K^+-ATPase pump, which actively extrudes sodium across the basolateral membrane.[4,13,31]



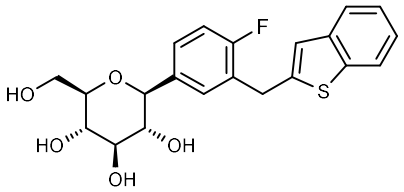
Dapaglifozin



Canagliflozin



Empagliflozin



Ipragliflozin

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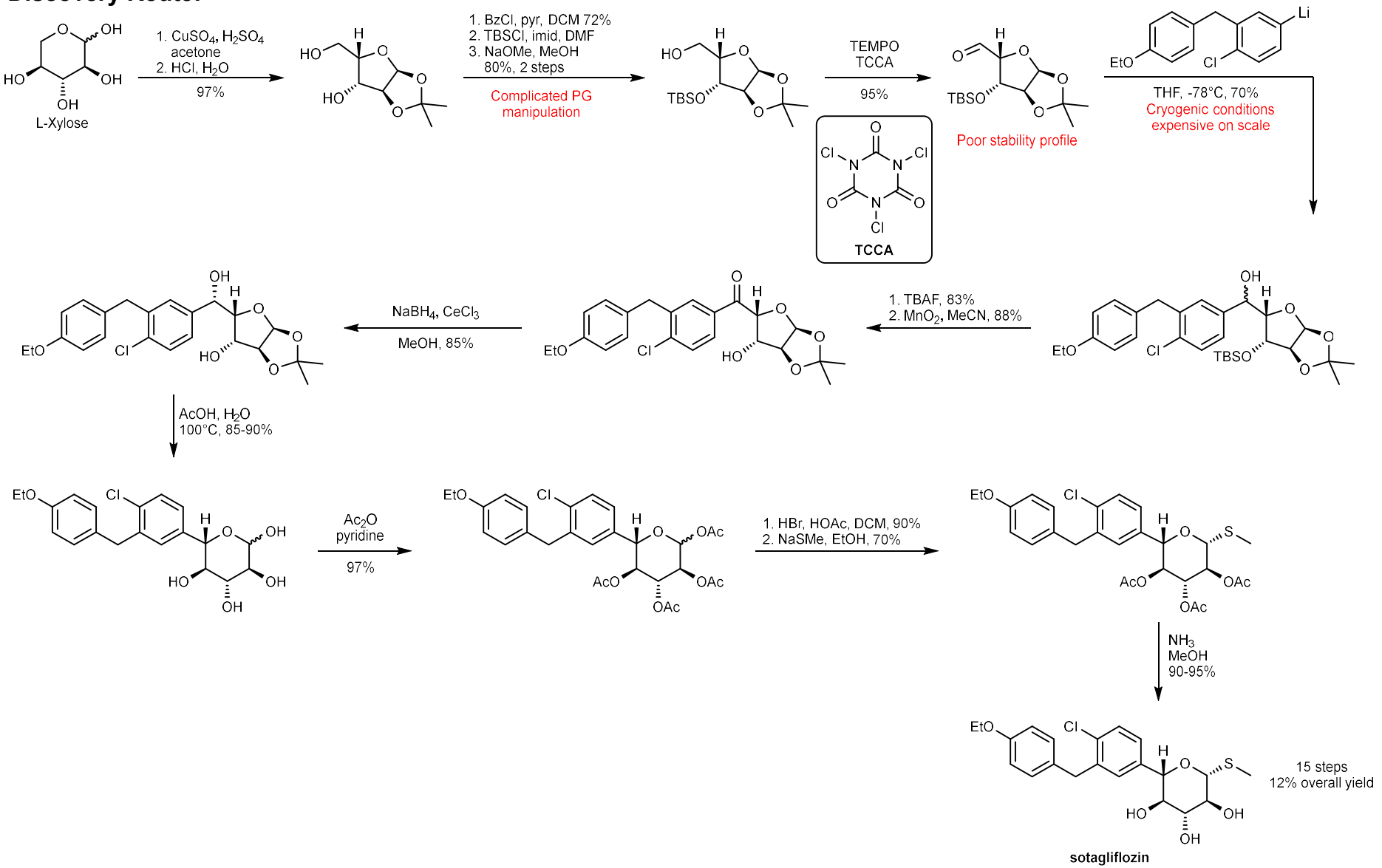
Discovery Route:



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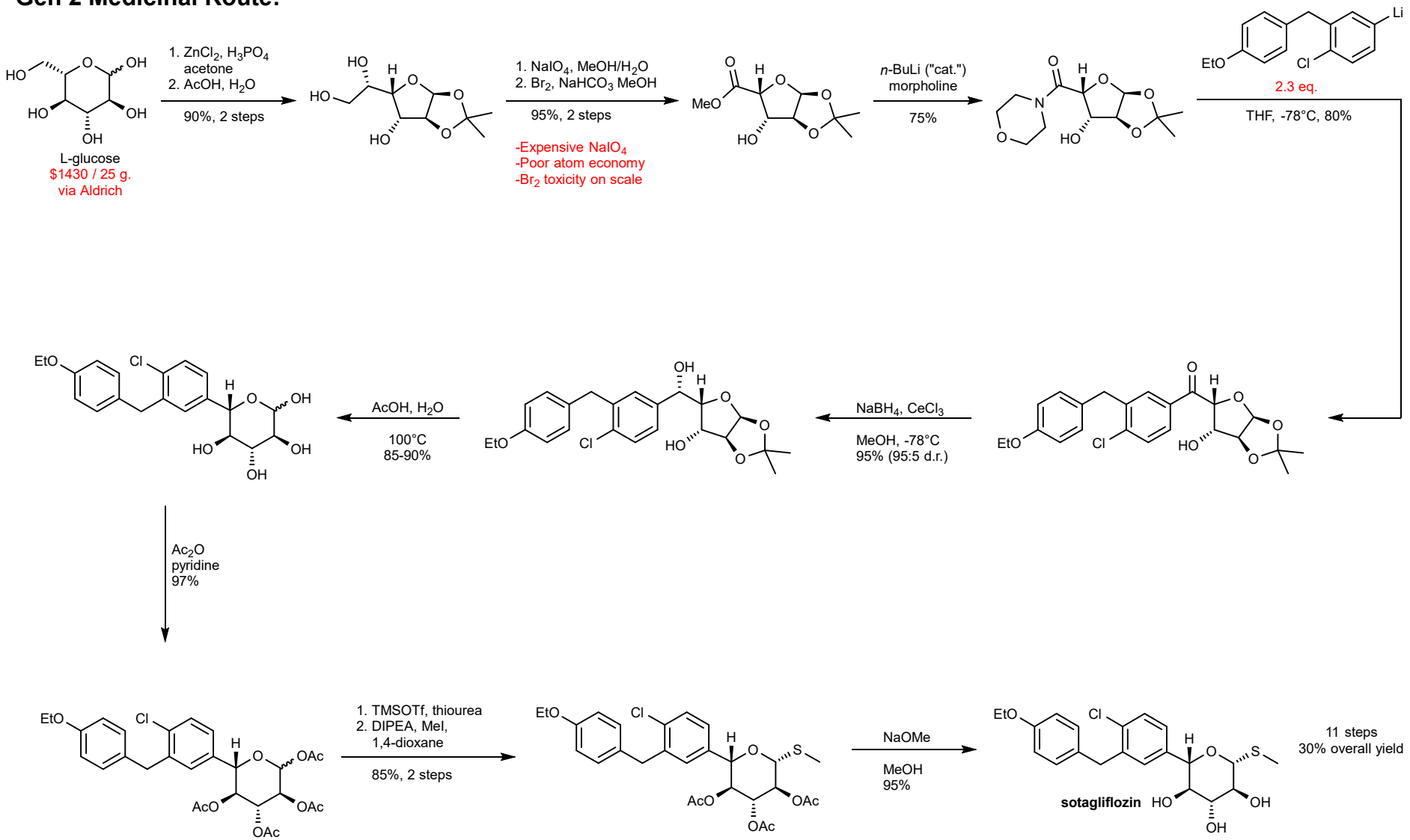
Gen 2 Medicinal Route:



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Process Route: