

Inhibition of Notch Pathway Signaling: A One Compound Mission To Treat Cancer

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Title:	Notch Pathway Signaling Inhibitor Compound		
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Priority Application:	US 61/512,016	Priority date:	27 July 2011
	US 61/560,486		16 November 2011
Inventors:	Hipskind, P. A.; Stephenson, G. A.		
Assignee Company:	Eli Lilly and Company; Lilly Corporate Center, Indianapolis, IN 46285, United States		
Disease Area:	Cancer	Biological Target:	The Notch pathway signaling receptors

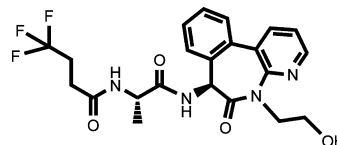
Summary: The invention in this patent application is unique, as it relates to only one specific compound; the claimed compound I is a Notch pathway signaling receptor inhibitor that may potentially be used for the treatment of cancer.

The Notch receptors are cell surface heterodimeric proteins composed of extracellular and intracellular domains that are initially synthesized as a single polypeptide. There are four known Notch receptors found in rodents and humans, named Notch 1 to Notch 4. Notch receptors mediate a central signaling system used by neighboring cells to communicate with each other through direct cell-to-cell contact in order to assume their proper developmental role. The interaction between Notch and its ligands initiates a signaling cascade known as the Notch signaling pathway. Binding with the ligands starts the Notch activation cascade and triggers a series of proteolytic cleavages of the Notch receptor polypeptide in which γ -secretase plays a pivotal role. This releases an intracellular domain of Notch (NICD), which is the active form of the protein, from the membrane tether.

Notch signaling is an evolutionary conserved pathway that governs cell fate decisions such as differentiation, proliferation, apoptosis, angiogenesis, migration, and self-renewal in numerous tissue types. Aberrant Notch receptor signaling activity is associated with different forms of cancer. The oncogenic functions of Notch signaling include the inhibition of apoptosis and the promotion of cell proliferation. Thus, inhibition of the Notch receptor may potentially provide a treatment for some forms of cancer. The patent application refers to earlier investigations of γ -secretase inhibitors as potential Notch inhibitors and the unmet need for discovering compounds with Notch signaling pathway inhibition activity.

Important Compound Classes:

Compound I is the only compound claimed in the patent application with the indicated stereochemistry; none of the other stereoisomers was claimed. The XRD data are reported and claimed for a crystalline hydrate form of compound (I).



Compound I

Biological Assay:

- Notch NIICD Nuclear Accumulation Cellular Imaging Assay
- Inhibition of NIICD cleavage in human tumor cell lines
- In-vivo efficacy and target inhibition studies; animal studies

Biological Data:

- **Notch NIICD Nuclear Accumulation Cellular Imaging Assay:** The average IC_{50} for compound I is 0.41 nM ($n = 7$). The compound does not affect cell number up to 1000 nM concentration.
- The IC_{50} value for compound I in various tumor cell lines:

Inhibition of NIICD cleavage in human tumor cell lines					
Cell Line	IC_{50} (nM)	Cell Line	IC_{50} (nM)	Cell Line	IC_{50} (nM)
A2780	1.03	HCT 116	0.72	SUP-T1	1.24
MIA PaCa-2	0.71	DLD-1	0.98	K-562	0.74
BxPC-3	0.39	MDA-MB-231	0.50	Jurkat	5.95
SW480	0.10	U-87-MG	0.28	MOLT-3	0.61
A-375	0.48	CCRF-CEM	0.76	MOLT-4	0.74
HEL 92.1.7	0.23				

Recent Review Articles:

1. Takebe, N.; Harris, P. J.; Warren, R. Q.; Ivy, S. P. *Nat. Rev. Clin. Oncol.* 2011, 8 (2), 97–106.
2. Al-Hussaini, H.; Subramanyam, D.; Reedijk, M.; Sridhar, S. S. *Mol. Cancer Ther.* 2011, 10 (1), 9–15.
3. Miele, L. *Clin. Cancer Res.* 2006, 12 (4), 1074–1079.

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Notes

The author declares no competing financial interest.