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PATENT HIGHLIGHT

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Endothelial Lipase Inhibitors for the Treatment of Atherosclerosis and Cardiovascular Disorders

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Title:	Tricyclic Indole Derivatives Useful Endothelial Lipase Inhibitors		
Patent Application Number:	WO 2013/123277 A1	**Publication date:**	22 August 2013
Priority Application:	US 61/599,066	**Priority date:**	15 February 2012
Inventors:	Greco, M.; Ye, H.		
Assignee Company:	Janssen Pharmaceutica NV; Tumhoutseweg 30, B-2340 Beerse, Belgium		
Disease Area:	Atherosclerosis and cardiovascular disorders	**Biological Target:**	Endothelial Lipase (EL)

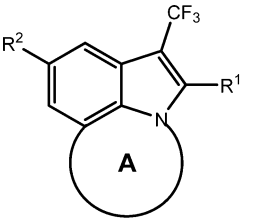
Summary: The invention in this patent application introduces tricyclic indole derivatives, represented generally by formula (I), which possess activity as endothelial lipase (EL) inhibitors and may potentially be used for the treatment of cardiovascular disorders.

Studies have proved an inverse relationship between plasma levels of high-density lipoprotein cholesterol (HDL-C) and the risk for atherosclerosis (a condition in which an artery wall thickens because of the accumulation of fatty materials such as cholesterol and triglyceride) and coronary heart disease (CHD).

Endothelial lipase (EL) is a serine-phospholipase that is synthesized in endothelial cells. It is a recently discovered member of the triglyceride lipase family that was first characterized and cloned in 1999. Earlier studies indicated that endothelial lipase catalyzes the hydrolysis of HDL phospholipids and causes the lowering of HDL levels. Studies in mice have established the role for EL in HDL cholesterol regulation. EL knockout mice have shown an elevation in HDL cholesterol levels relative to wild-type mice. Overexpression of the human endothelial lipase gene in the livers of mice markedly reduces plasma concentrations of HDL cholesterol and its major protein apolipoprotein A-1 (apoA-1). Other recent studies suggest that EL may have a pro-inflammatory effect and may be involved in atherogenesis.

These findings suggest that inhibition of endothelial lipase is an attractive clinical target for the treatment of cardiovascular disorders. EL inhibitors such as the compounds described in this patent application may potentially be beneficial in elevation of HDL-C plasma levels and consequently the treatment of atherosclerosis and cardiovascular disease.

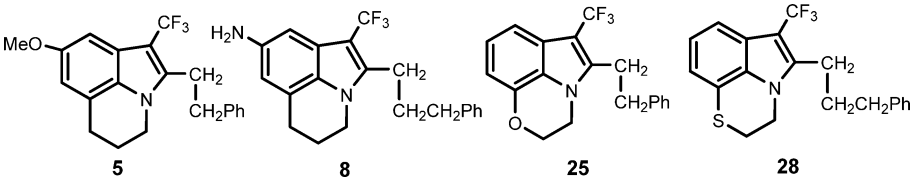
Important Compound Classes:



Formula (I)

Definitions: **A** represents a 5- to 7-membered saturated ring structure

Key Structures: The inventors described and listed 28 structures as examples of the compounds of formula (I) including the four representative structures below:



5 8 25 28

Biological Assay: Endothelial Lipase Assay (Human/Mouse)

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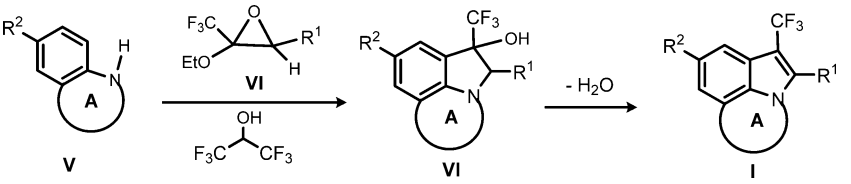
Biological Data: The inventors reported the IC_{50} values (in μM) for the 28 examples. The lowest IC_{50} values were obtained from compounds **5**, **8**, and **25** and the highest from compound **28** as listed in the following table:

Compound	Human IC_{50} (μM)	Mouse IC_{50} (μM
5	0.014	0.017
8	0.004	0.004
25	0.039	0.031
28	33.335	33.335

Synthesis: The compounds of formula (**I**) were generally prepared by the reaction of the intermediates **V** with oxiranes **VI** in hexafluoro-2-propanol followed by dehydration with SO_2Cl or $POCl_3$ as illustrated in the following scheme:



Claims: Claims 1−9: Composition of matter, variations of formula (I)

Claims 10−12: Composition of matter, 27 specific examples of the compounds of formula (I)

Claims 13−15: Pharmaceutical composition

Claims 15−17: Use of compounds in treatments of atherosclerosis, dyslipidemia, low HDL, or high LDL

Recent Review Articles:

1. de Goma, E. M.; Rader, D. J. *Nat. Rev. Cardiol.* **2011**, *8* (5), 266−277.

2. Badellino, K. O.; Rader, D. J. *Curr. Opin. Cardiol.* **2004**, *19* (4), 392−395.

3. Jin, W.; Millar, J. S.; Broedl, U.; Glick, J. M.; Rader, D. J. *J. Clin. Invest.* **2003**, *111* (3), 357−362.

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Notes

The authors declare no competing financial interest.