

MoGAT-2 Inhibitors May Provide Effective Treatment for Hypertriglyceridemia

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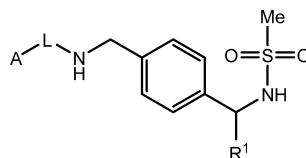
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Title: Novel Benzyl Sulfonamide Compounds Useful as MoGAT-2 Inhibitors
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Assignee Company: Eli Lilly and Company [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285, USA
Disease Area: Hypertriglyceridemia and diet induced obesity
Biological Target: Monoacylglycerol acyltransferase 2 (MoGAT-2)
Summary: The invention in this patent application relates to *N*-(substituted benzyl)-methanesulfonamide derivatives, which are MoGAT-2 inhibitors and may be useful in the treatment of hypertriglyceridemia.

Monoacylglycerol acyltransferase 2 (MoGAT-2) is an enzyme that is believed to facilitate the absorption of dietary fat in the small intestines. The main form of the human dietary fat is triacylglycerol (triglyceride) that is almost all absorbed in the small intestine. Studies using MoGAT-2 deficient mice have demonstrated their resistance to developing obesity, glucose intolerance, hypercholesterolemia, or fatty liver when fed a high fat diet. The MoGAT-2 deficient mice have also exhibited lower plasma triacylglycerol levels after a dietary olive oil challenge.

There is a need for the discovery and development of new effective drugs that can treat diet induced obesity and hypertriglyceridemia. Inhibition of the MoGAT-2 receptor with compounds such as those described in this invention is a promising and viable approach that may potentially provide an effective treatment of hypertriglyceridemia.

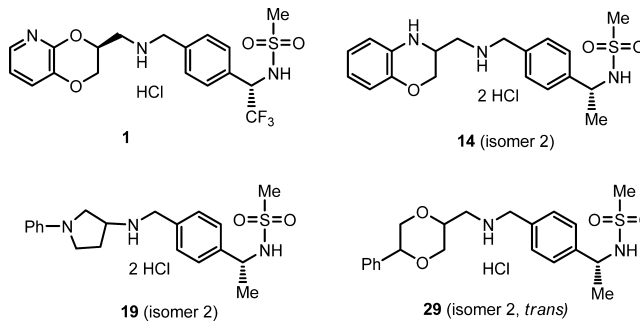
Important Compound Classes:



Formula (I)

Key Structures:

The inventors reported the synthesis and structures of 32 examples of formula (I), all isolated in pure enantiomeric forms using chiral chromatography.



Biological Assay:

The compounds of the invention were evaluated using the following biological assays:

- MOGAT-2 Inhibitory Assay
- Inhibitory Activity in MOGAT-2 Cell Assay
- Pharmacological Effects in a Dog Oil Bolus Model

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Biological Data: The results for the MOGAT-2 cell based assay are listed in the following table for examples **1**, **14**, **19**, and **29** (structures above):

Example	IC ₅₀ nM (Std. Dev.; n*)
1	3.8 (2.7; 2)
14	479 (N/A; 1)
19	105 (N/A; 1)
29	294 (N/A; 1)

n* = number of experiments

Claims:

Claims 1–20:	Composition of matter; variations of formula (I)
Claim 21:	Composition of matter; example 1 structure
Claim 22:	A pharmaceutical composition
Claim 23:	A method of treating hypertriglyceridemia
Claims 24–26:	Use of compounds

Recent Review Articles:

- Zhang, J.; Xu, D.; Nie, J.; Cao, J.; Zhai, Y.; Tong, D.; Shi, Y. *J. Biol. Chem.* **2014**, *289* (15), 10909–10918.
- Tsuchida, T.; Fukuda, S.; Aoyama, H.; Taniuchi, N.; Ishihara, T.; Ohashi, N.; Sato, H.; Wakimoto, K.; Shiotani, M.; Oku, A. *Lipids Health Dis.* **2012**, *11*, 75.
- Nelson, D. W.; Gao, Y.; Spencer, N. M.; Banh, T.; Yen, C.-L. *E. J. Lipid Res.* **2011**, *52* (9), 1723–1732.

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Notes

The authors declare no competing financial interest.