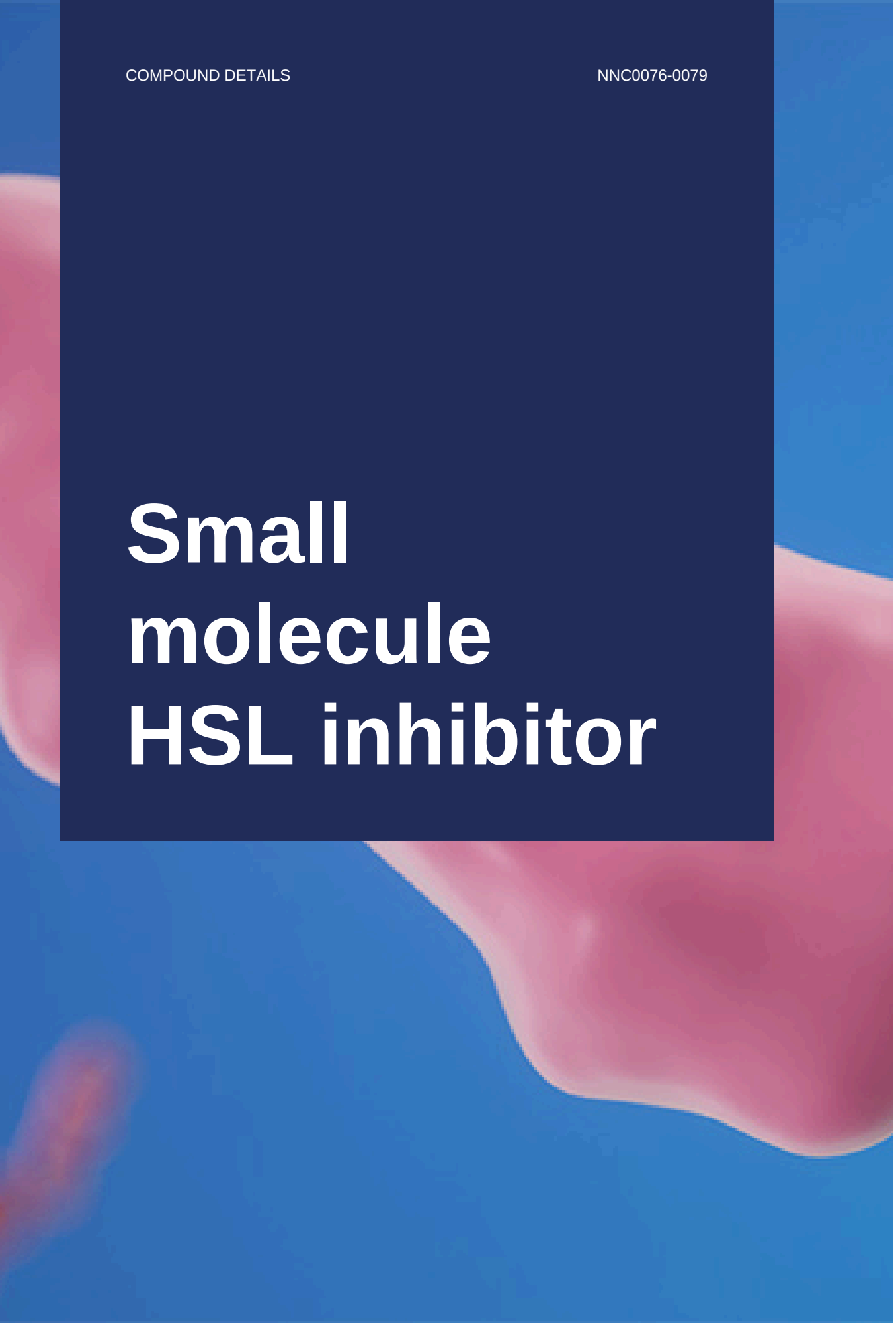
COMPOUND DETAILS NNC0076-0079

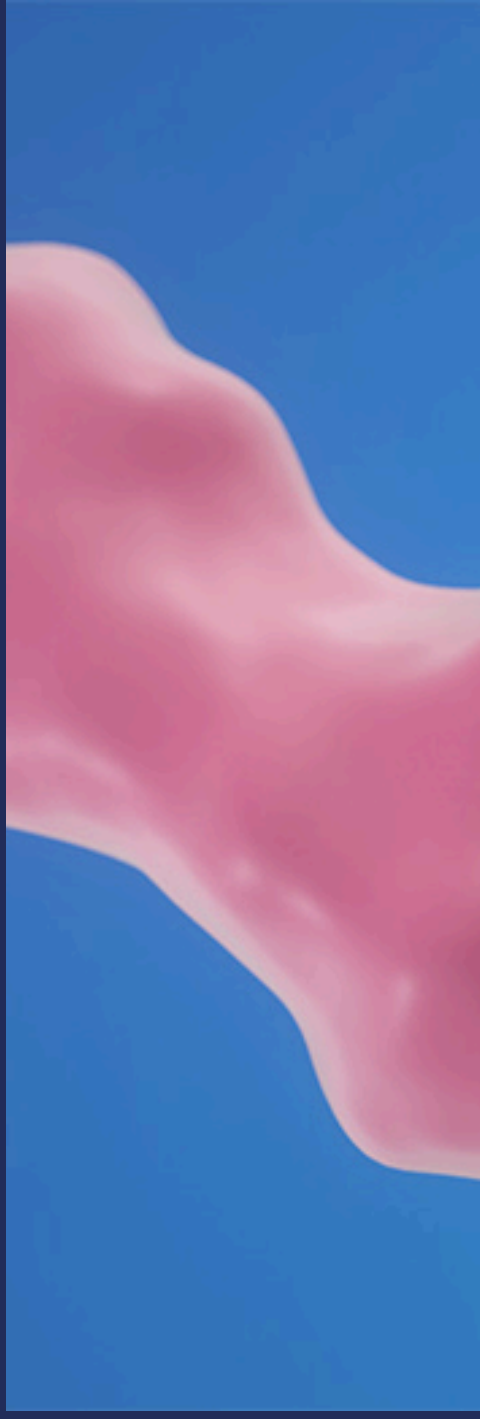
Small molecule HSL inhibitor



NOVO NORDISK COMPOUND SHARING

novo nordisk®

Content



Small molecule HSL inhibitor

Hormone sensitive lipase (HSL) is an intracellular lipase found in most tissues. The lipase, that exists in a long and a short form, is capable of hydrolysing a variety of esters. The long form of HSL is expressed in steroidogenic tissues like testis, where it converts cholesteryl esters to free cholesterol for steroid hormone production. The short form is expressed in adipose tissue where it in concert with two other lipase, adipose triglyceride lipase (ATGL) and monoacylglycerol lipase (MGL), is involved in the hydrolysis triacylglycerols to free fatty acids and (FFAs) and glycerol. The main substrate for HSL in adipose tissue is diacylglycerol. The activity of HSL is regulated by insulin – it is high when circulating insulin levels are low and vice versa.

NNC0076-0079 is classified as a so-called substrate inhibitor. The HSL inhibitor NNC0076-0079 blocks the activity of HSL by interfering with its active site in a non-covalently fashion – the activation of HSL is regained as the enzyme hydrolyses the ester bond of the inhibitor.

Category	HSL inhibitor
ID	NNC0076-0079
Amount pr. vial	20 mg

Calculated properties

Property	NNC0076-0079
MW [Da]	256,69
Sum formula	C11 H13 Cl N2 O3

Structural information

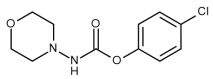


Figure 1

Figure 1

Chemical structure of NNC0076-0079. Morpholin-4-yl-carbamic acid 4-chloro-phenyl ester.

In vitro data

Enzyme	Inhibition (IC50, uM)
Hormone sensitive lipase (h-HSL)	0,11
Lipoprotein lipase (LPL)	>50
Hepatic lipase (HL)	>50
Bile-salt stimulated lipase (BSSL)	>50
Pancreatic lipase (PL)	>50

NNC0076-0079 selectively inhibits hormone sensitive lipase in vitro. The enzyme was preincubated with NNC0076-0079 (up to 50uM) for 30-70 min. at room temperature prior to addition of an emulsified fluorescent labeled triglyceride analogue substrate. Substrate and enzyme were allowed to incubate for 2 hours (37 degrees celcius). Hydrolysis was determined by fluorimetry.

In vivo data

Species	Glycerol	FFA
ob/ob mouse;	73%	52%
Sprague Dawley rat	59%	36%
High fat fed hamster	63%	14%
Isoproterenol stimulated hamster	51%	41%

NNC0076-0079 inhibits lipolysis in vivo. Study protocol for the data shown in the table: overnight fasted ob /ob mice, Sprague Dawley rats, high fat fed hamsters, and isoproterenol stimulated hamsters were treated orally with either vehicle or NNC0076-0079. The antilipolytic effects of NNC0076-0079 were evaluated in plasma samples collected 15 min – 5 hours after treatment using the biochemical markers glycerol and FFA. Compared to vehicle dosing, oral dosing of NNC0076-0079 in doses 30 mg/kg lowers circulating glycerol levels 30-75% relative to pre-dosing levels in the overnight fasted rat without access to food during the experiment. In this model, the glycerol lowering effect of NNC0076-0079 lasts for 3 hours. A similar effect pattern is seen in overnight-fasted mice.

Reference Compound

no reference compound is available

Compound handling instructions

For in vitro experiments on cell supernatants and tissue cultures Stock solution: NNC0076-0079 is dissolved in DMSO and stored at 4 °C prior to use Test solution: 0.4% DMSO For in vivo experiments NNC0076-0079 can be formulated in the form of a suspension in 0,4 % Tween 80 (4 g/l) (BAKER 7394 batch 1931801868); 0,2 % carboxymethylcellulose sodium salt (2 g/l) (SIGMA C4888-500G batch SLCB7664). Make suspension vehicle as follows: 0.4 g Tween 80 and 0.2 g carboxymethylcellulose is dissolved in 100 ml MQ-H2O. An oral dose of 25 mg/kg and above gives rise to solid inhibition of HSL (drop in plasma glycerol) in the fasted rat.

References

1. de Jong JC et al.
Carbazates as potent inhibitors of hormone-sensitive lipase

Bioorg. Med. Chem. Lett., 14, 2004, 1741–1744

2. Alsted TJ et al.
Adipose triglyceride lipase in human skeletal muscle is upregulated by exercise training

Am J Physiol Endocrinol Metab 296: E445–E453, 2009