

Long-acting GLP-1 analogue #1

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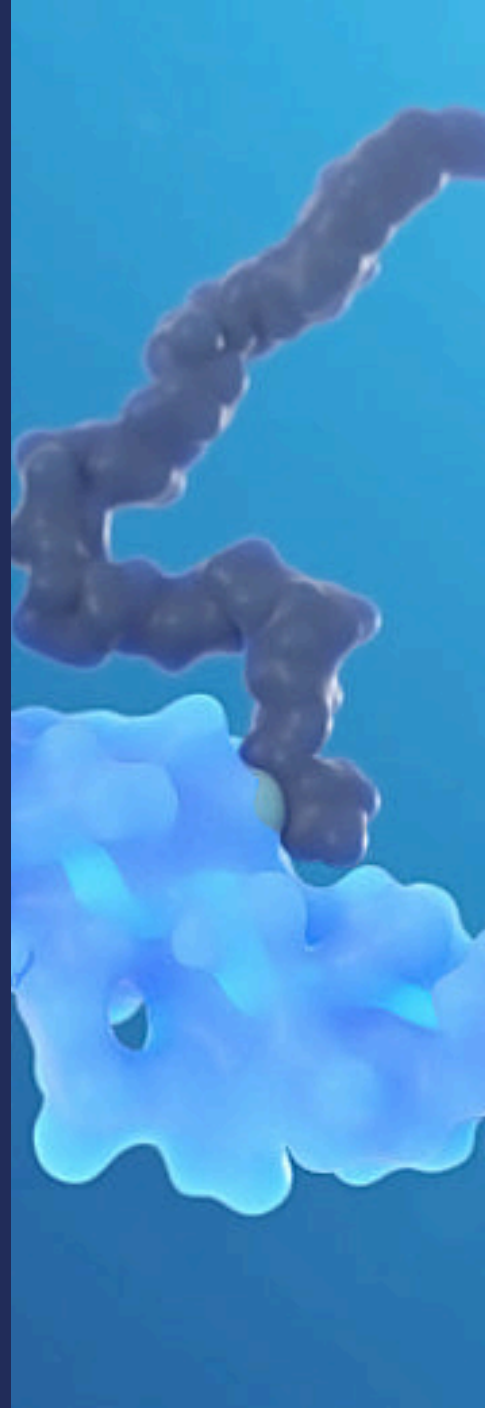
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Long-acting GLP-1 analogue #1

NNC0090-1170 (also known as liraglutide) is a GLP-1 analogue with 97% sequence homology to human GLP-1 that binds to and activates the GLP-1 receptor. Compared to native GLP-1, NNC0090-1170 have been designed to be long-acting *in vivo*. The main mechanism for the extended half-life is albumin binding. Furthermore, the NNC0090-1170 has a delayed uptake from the subcutis.

GLP-1 action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). GLP-1 stimulates insulin secretion in a glucose-dependent manner. Simultaneously, GLP-1 lowers inappropriately high glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, during hypoglycaemia GLP-1 diminishes insulin secretion and does not impair glucagon secretion. GLP-1 is a physiological regulator of appetite and food intake and the GLP-1 receptor is widely expressed in the brain.

Category	GLP-1
ID	NNC0090-1170
Amount pr. vial	1000 nmol (research grade purity)

Calculated properties

Property	NNC0090-1170;	GLP-1 (7-37)-OH
MW (Da)	3751.2	3355.7
pI (calculated)	4.5	5.5
Sequence substitutions (compared to reference)	26K(C16-gGlu), 34R	
Extinction coefficient (calculated, 280 nm)	6990	6990

Selected calculated properties for NNC0090-1170 and GLP-1 (7-37)-OH are listed in the table.

Structural information

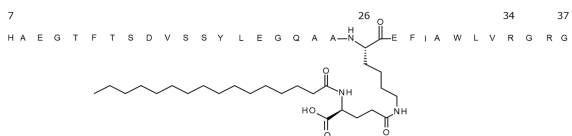


Figure 1

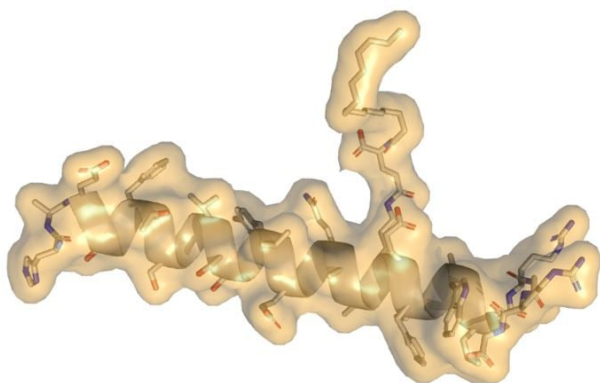


Figure 2

Figure 1

2D sketch of NNC0090-1170. NNC0090-1170 has a C16 fatty acid chain which is attached via a gamma glutamic acid linker to lysine at position 26. In addition, lysine is replaced with arginine at position 34. The fatty acid side chain enables reversible binding to serum albumin in the blood stream, which increases the half-life of the molecule.

Figure 2

3D model of NNC0090-1170 based on a crystal structure and modelling of the fatty acid side chain.

Structural information

H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R G

Figure 3

Figure 3

2D sketch of human GLP-1 (7-37)-OH (NNC0113-0007).

In vitro data

All *in vitro* data are based on *in vitro* assays using cloned human GLP-1 receptors expressed in baby hamster kidney cells. Since albumin binding is a key mechanism for the design of NNC0090-1170, the apparent affinity and potency will be very dependent on whether the assays contain albumin or not. See the Lau *et al.* 2015 reference listed in the reference section for further details on the experimental setup of the *in vitro* assays that have been used to generate the data in the table.

hGLP-1R binding (IC50, nM +/- SEM)		
Compound	0% HSA	2% HSA
GLP-1 (7-37)-OH	0.19 +/- 0.03	0.10 +/- 0.02
NNC0090-1170	0.11 +/- 0.02	4.78 +/- 1.01

hGLP-1R potency (EC50 pM, +/- SEM)	
GLP-1 (7-37)-OH	16.2 +/- 0.9
NNC0090-1170	8.5 +/- 0.7

hGLP-1R: human GLP-1 receptor; *HSA*: human serum albumin

In vivo data

The terminal half-life of NNC0090-1170 is around 14 h in pigs while shorter in mice, rats, rabbits and monkeys (4-8 h).

NNC0090-1170 has been evaluated in several diabetic and obese animal models. NNC0090-1170 shows a dose-dependent and long-lasting anti-hyperglycaemic effect in *ob/ob* and *db/db* mice. The mean area under the curve (AUC) for blood glucose is dose-dependently reduced after a single subcutaneous injection of NNC0090-1170 (30, 100, 300 or 1000 ug/kg). In *db/db* mice, the ED50 for lowering of blood glucose (6 hours post dosing) is estimated to be approximately 24 ug/kg following an acute dose. With twice daily administration of 100 ug/kg NNC0090-1170 for two weeks, blood glucose AUCs were significantly reduced in *ob/ob* mice. These anti-hyperglycaemic effects are also observed in *db/db* mice treated for 15 days with NNC0090-1170 (200 ug/kg twice daily s.c.).

In young ZDF rats, 6 week treatment with NNC0090-1170 (30 and 150 ug/kg twice daily s.c.) reduces blood glucose levels and insulin levels following a glucose tolerance test. In candy-fed rats, NNC0090-1170 (0.2 mg/kg, twice daily, s.c.) reduces food intake and subsequently weight gain, especially fat mass.;

When administering NNC0090-1170 to animals it is necessary to do dose titrations. A good dose for pharmacological experiments could be 1 mg/kg once daily titrated up from 0.1 mg/kg to 0.3 mg/kg to 1.0 mg/kg.

If using ELISA to detect NNC0090-1170 in your samples, ensure to use a kit that is able to detect this analogue of GLP-1.

Reference Compound

Human GLP-1(7-37)-OH (NNC0113-0007) is available as a reference compound to NNC0090-1170. Please indicate (with a check mark at 'Please add the reference compound if available) during your compound request if you would like to have NNC0113-0007 included in your shipment.

Compound handling instructions

Peptides and proteins tend to adhere to glass and plastic surfaces. This may at low concentration impact the actual amount in solution. To minimize this unspecific adherence, adding detergents or inert proteins like e.g., ovalbumin or other serum albumins to the solution can minimize this phenomenon. In case albumins are added to peptide/protein solutions, ensure that the albumins are free of any proteases, but be aware that it will affect the apparent potency and affinity in in vitro assays in case a fatty acid is attached to the compound. For in vitro studies, NNC0090-1170 can be dissolved in 80/20% DMSO/MilliQ water (e.g. at a concentration of 300 μ M). NNC0090-1170 can be dosed in vivo in a formulation vehicle containing 50mM sodium phosphate, 70mM sodium chloride, pH 8.0. If concentrations of the intended dosing formulations are very low (low μ M to sub μ M concentrations), adsorption to vials may affect the measurable concentration. In this case, consider adding 0.007% polysorbate 20. Formulations should be used fresh, but can be stored for up to one week refrigerated. The compound is research /laboratory grade purity.

References

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