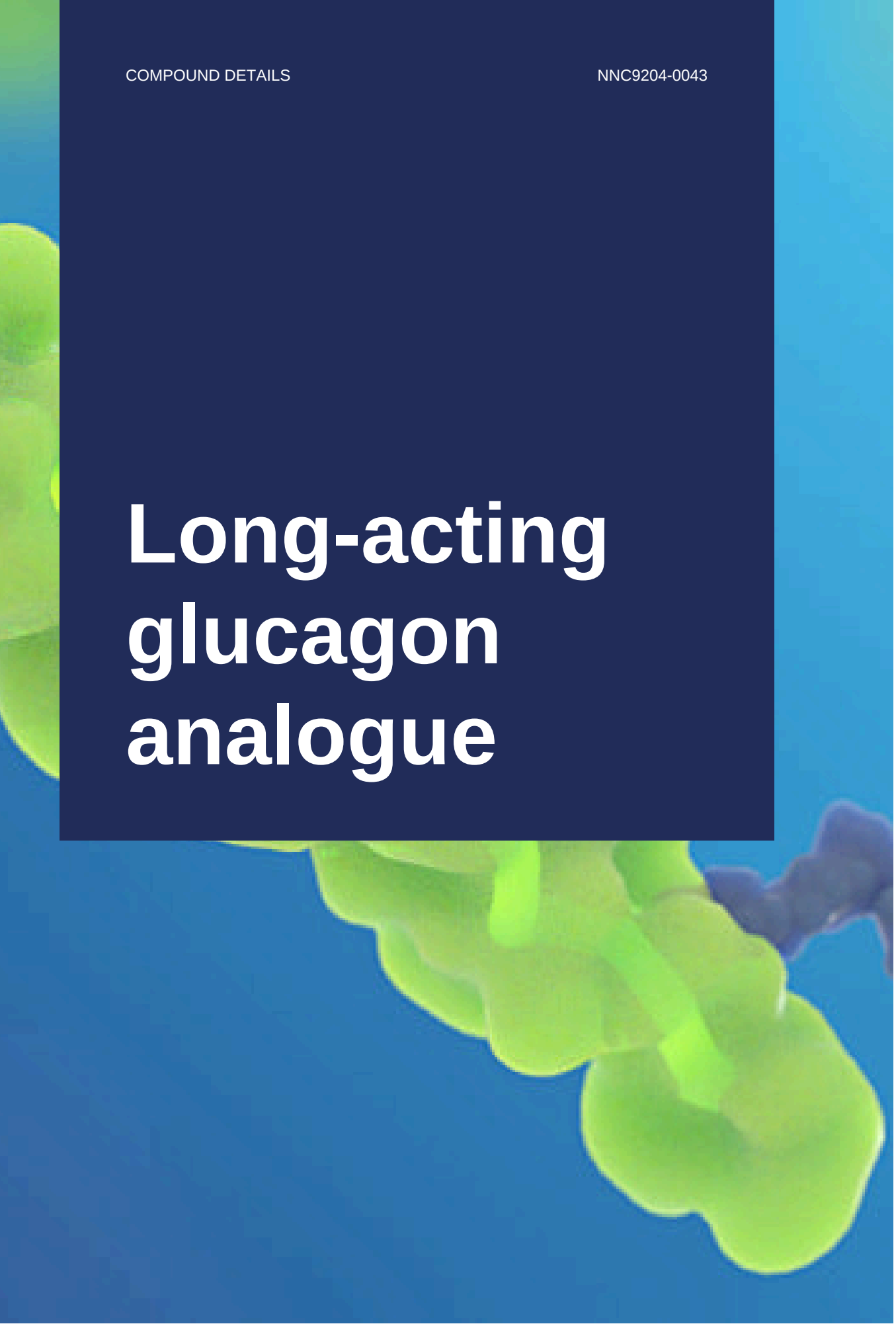
COMPOUND DETAILS NNC9204-0043

Long-acting glucagon analogue



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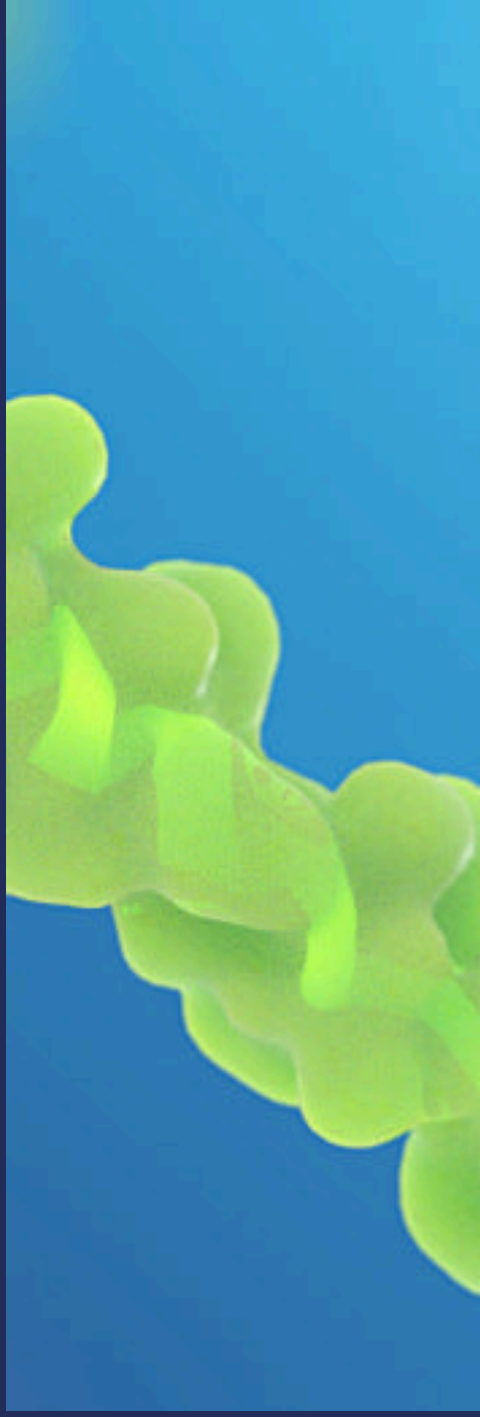
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Long-acting glucagon analogue



Glucagon is s a 29 amino acid residue peptide hormone produced by the alpha-cells in the pancreas. Together with insulin it regulates blood glucose levels. It stimulates release of glucose from the liver at low blood glucose levels by increasing gluconeogenesis and glycogenolysis, and by suppressing glycolysis. Glucagon is used to treat insulin-induced severe hypoglycemia.

NNC9204-0043 is a long-acting glucagon analogue.

Category	Glucagon
ID	NNC9204-0043
Amount pr. vial	1000 nmol

Calculated properties

Property	NNC9204-0043	Native glucagon
MW (Da)	4138.6	3482.7
pI (calculated)	4.9	6.4
Sequence substitutions (compared to reference)	17K, 18K, 21E, 24K(2xOEG-gGlu-C18 diacid), 27L	-
Extinction coefficient (calculated, 280 nm)	8480	8480



Structural information

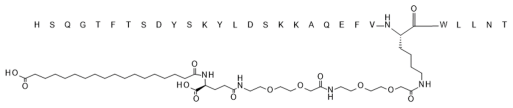


Figure 1

HSQGTFTSDYSKYLDSRRAQDFVQWLMNT

Figure 2

Figure 1

2D sketch of the structure of NNC9204-0043. The compound has the following sequence substitutions compared to native glucagon: 17K, 18K, 21E, 24K(2xOEG-gGlu-C18 diacid), 27L.

Figure 2

The sequence of native glucagon.

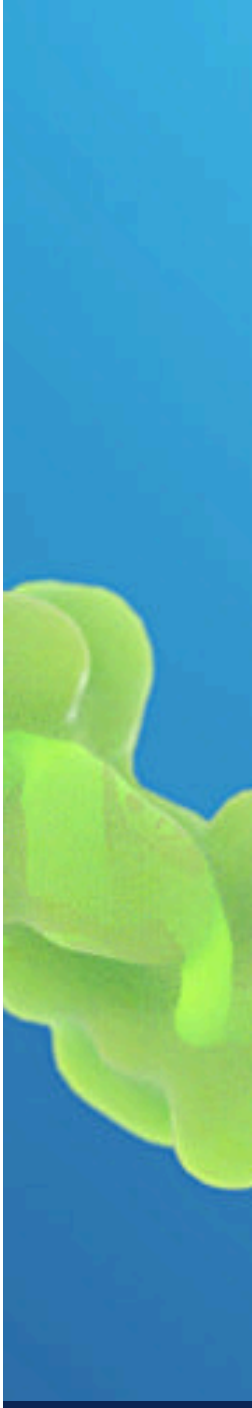
In vitro data

The binding affinity to human GCGR was measured by the ability of the compounds to displace 125-iodine-labelled glucagon from baby hamster kidney (BHK) cell plasma membranes stably expressing the human GCGR in a scintillation proximity assay (SPA) setup. The *in vitro* potencies were determined by luciferase assays using BHK cells stably transfected with the human GCGR and CRE luciferase. Since albumin binding is a key mechanism for the design of NNC09204-0043, be aware that the apparent affinity and potency will be very dependent on whether the *in vitro* assays contain albumin or not.

Compound	**Potency No HSA; (EC50, pM ± SEM)**	**Potency 1% HSA; (EC50, pM ± SEM)**
Native glucagon	9.8 ± 0.7 (n=194)	8.4 ± 0.7 (n=94)
NNC9204-0043	7.1 ± 0.6 (n=52)	440 ± 57 (n=32)

	Receptor affinity No BSA (IC50, nM ± SEM)	**Receptor affinity 0.2% BSA** (IC50, nM ± SEM)
Native glucagon	0.63 ± 0.02 (n=142)	0.33 ± 0.01 (n=138)
NNC9204-0043	0.45 ± 0.04 (n=42)	31 ± 2.7 (n=40)

BSA: bovine serum albumin; HSA: human serum albumin



In vitro potency and receptor binding data for NNC9204-0043 and native glucagon (unpublished data).

In vivo data

The terminal half-life of NNC9204-0043 is 5-6 h following s.c. administration of a single 3 nmol /kg dose in mice.



Reference Compound

The reference compound to NNC9204-0043 is native glucagon (NNC0025-8000). Please indicate (with a check mark at 'Please add the reference compound if available) during your compound request if you would like to have native glucagon (NNC0025-8000) included in your shipment.

Compound handling instructions

Peptides and proteins have a tendency 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. The freeze-dried material should be stored at -18C. NNC9204-0043 can be dosed in vivo in a formulation vehicle containing 50mM sodium phosphate, 145mM propylene glycol, (0.007% polysorbate 20 if concentrations are so low that adsorption to vials may affect the concentration), pH 7.4. Stability in aqueous media is poor thus formulations should be used fresh. For in vitro it is recommended to dissolve human glucagon in 100% DMSO (e.g at a concentration of 300 uM) and keep at max 5C.

References

1. Elmelund E et al.
Opposing effects of chronic glucagon receptor agonism and antagonism on amino acids, hepatic gene expression, and alpha cells

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