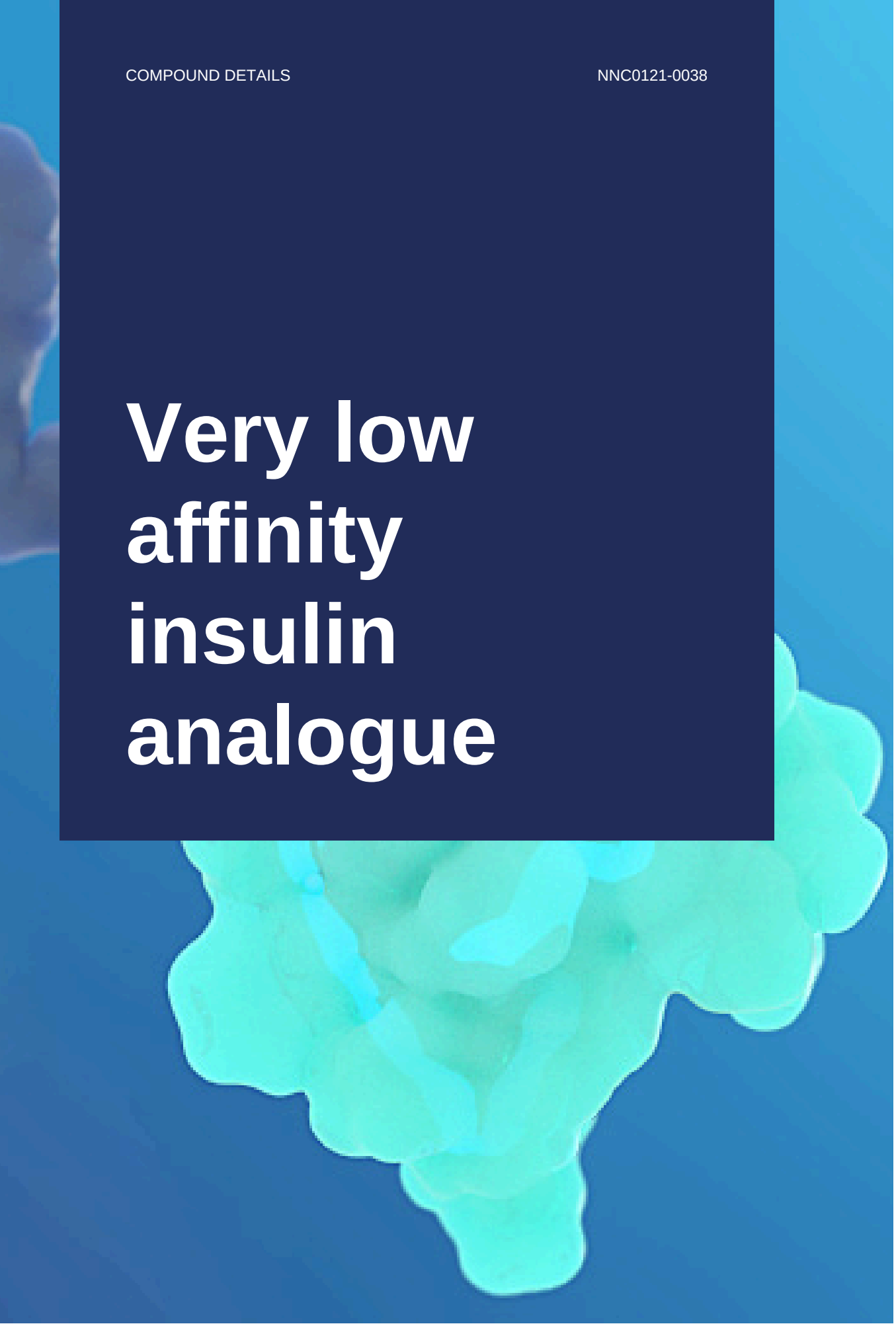
COMPOUND DETAILS NNC0121-0038

Very low affinity insulin analogue



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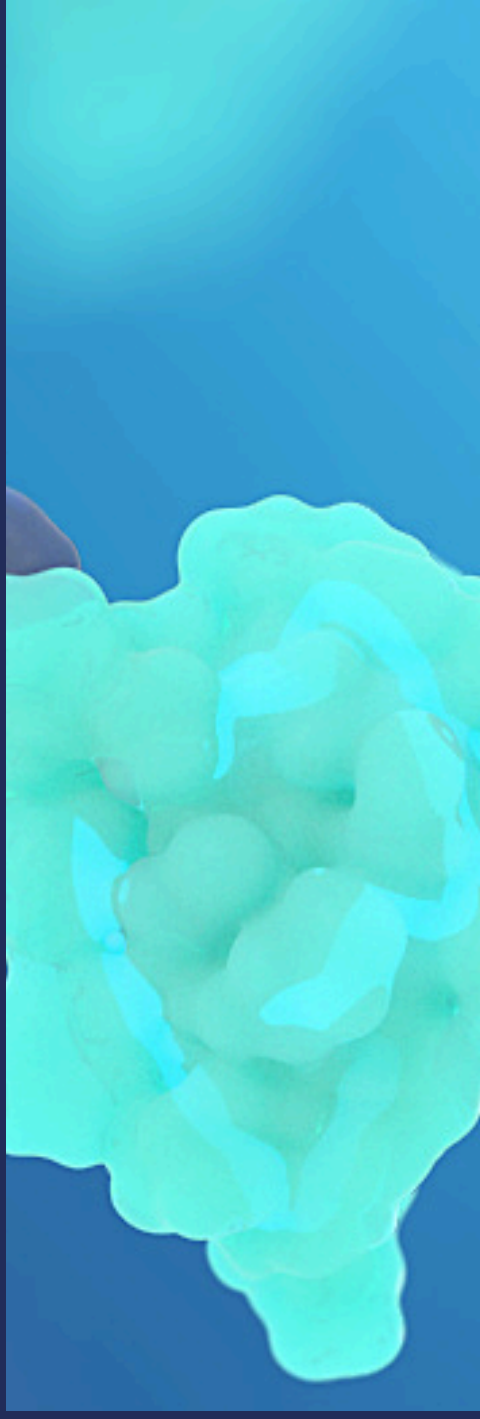
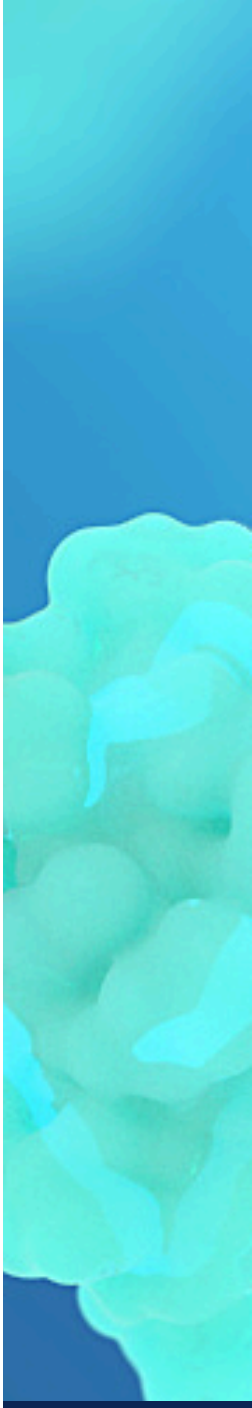
Content



Very low affinity insulin analogue



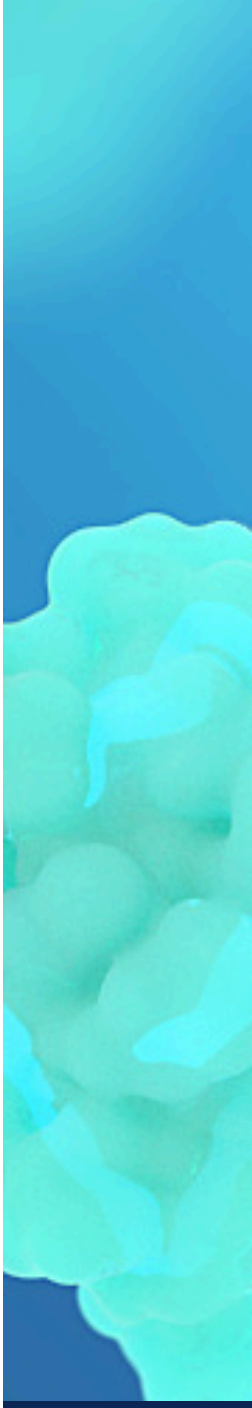
Insulin is a peptide hormone acting as a key regulator of glucose homeostasis. Insulin binds to the insulin receptor (InsR), which exists in two alternatively spliced isoforms, InsR-A and InsR-B. The insulin receptor belongs to the same family of receptor tyrosine kinases as the IGF1 receptor (IGF1R) and insulin is therefore also able to bind to the IGF1R albeit with considerably lower affinity as compared to the insulin receptor.

NNC0121-0038 is a very low affinity insulin analogue in which the phenylalanine in position 25 of the B-chain is mutated to aspartic acid causing NNC0121-0038 to bind the insulin receptor with ~2000-fold lower affinity than human insulin.

Category	Insulin
ID	NNC0121-0038
Amount pr. vial	2000 nmol

Calculated properties

Property	NNC0121-0038	Human insulin
MW (Da)	5775	5808
pI	5.0	5.7
Sequence substitutions	B25D	-
Sum formula	C252 H379 N65 O79 S6	C257 H383 N65 O77 S6



Structural information

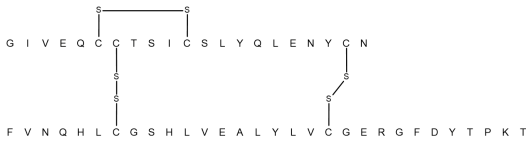


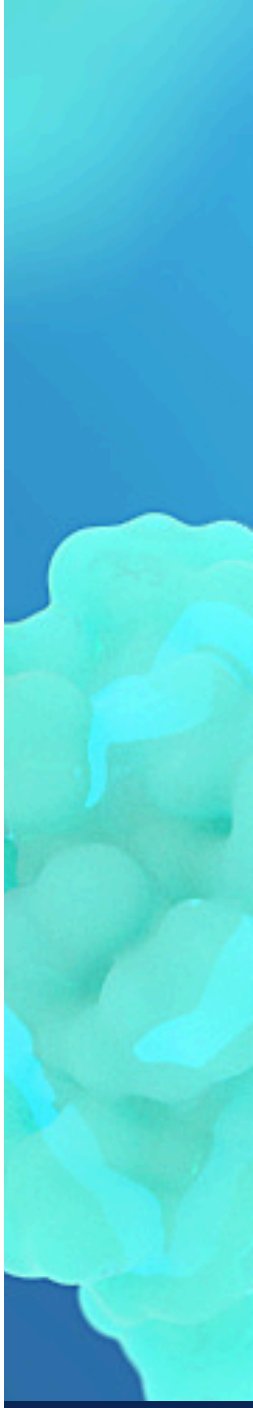
Figure 1

Figure 1

2D sketch of NNC0121-0038. Compared to human insulin, the amino acid at position 25 of the B-chain has been changed from phenylalanine to aspartic acid.

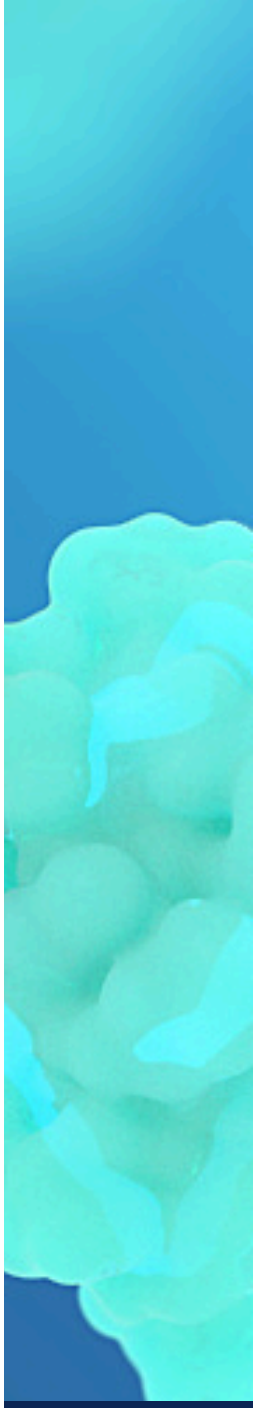
In vitro data

The single amino acid mutation (phenylalanine to aspartic acid) at position 25 of the B-chain causes a major decrease in insulin receptor as well as IGF1 receptor affinity of NNC0121-0038 which is < 0.05% relative to the affinity of human insulin (see the Drejer K et al. reference listed in the reference section below).



In vivo data

NNC0121-0038 has been tested in vivo by subcutaneous injections in prediabetic NOD mice as described by Karounos DG et al. reference listed in the reference section below.

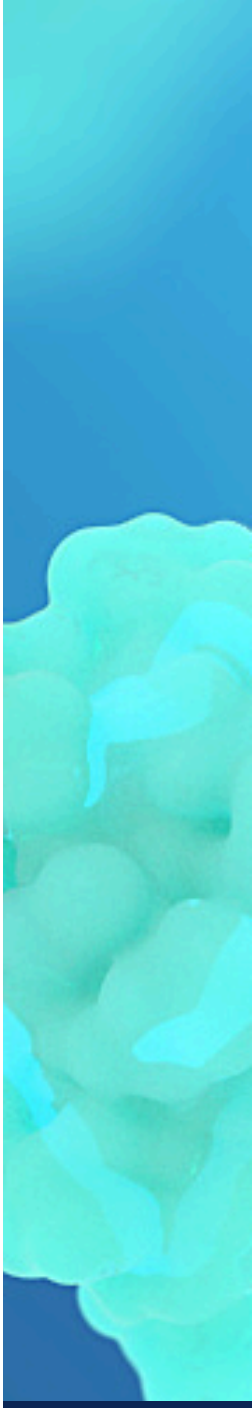


Reference Compound

Human insulin (NNC0121-0308) is available as a reference compound to NNC0121-0038. Please indicate (with a check mark at ‘Please add the reference compound if available) during your compound request if you would like to have human insulin (NNC0121-0308) 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. Recommended procedure for in vitro studies: dissolve the entire content of the vial by adding 4 mL 30 mM HEPES buffer pH 8. Gently rotate the vial until all content is dissolved. Avoid harsh shaking or stirring of the solution. Keep the stock solution at 4C overnight and make the desired number of aliquots (use low protein binding vials) of the stocks. Snap freeze the aliquots in liquid nitrogen and store them at minus 20C. When thawed, the stock solution should be stable for up to three weeks at 4C. Recommended procedure for in vivo studies: NNC0121-0038 (and the human insulin reference) can be dosed in vivo in a zinc-free and phenol/m-cresol-free formulation vehicle. This vehicle may contain 10mM sodium phosphate, 140mM sodium chloride, pH 7.4. If concentrations of the intended dosing formulations are very low (low uM to sub nM concentrations), adsorption to vials may affect the measurable concentration. In this case, consider adding 0.007% polysorbate 20. If insulin oligomeric /multimeric properties are of interest, zinc and phenol/m-cresol can be added. Zinc is typically added as zinc acetate between 0 and 6 moles/mole of insulin analogue.



Compound handling instructions

The resulting tonicity should be recalculated. Formulations should be used fresh but can be stored for up to one week refrigerated.

References

1. Drejer K, et al.
Receptor binding and tyrosine kinase activation by insulin analogues with extreme affinities studied in human hepatoma HepG2 cells

Diabetes. 1991; 40(11): 1488-95

2. Karounos DG et al.
Metabolically inactive insulin analog prevents type I diabetes in prediabetic NOD mice

J Clin Invest. 1997; 100(6): 1344-48