COMPOUND DETAILS NNC0368-0056

Long-acting CCK analogue

NOVO NORDISK COMPOUND SHARING

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Content

Long-acting CCK analogue

PLEASE NOTE THAT THIS COMPOUND CAN ONLY BE USED FOR *IN VITRO* STUDIES (NOT *IN VIVO*)

Cholecystokinin (CCK) is a gut and brain peptide hormone that plays an important role in the regulation of energy balance. CCK binds to two G-protein-coupled receptors, the CCK 1 receptor (CCK-1R) and the CCK 2 receptor (CCK-2R). Both receptors are found in the gastrointestinal tract and in the central nervous system. Activation of CCK-1R has effects on appetite regulation and a number of other effects (gallbladder contraction, pancreatic enzyme secretion, delay of gastric emptying). The CCK-2R has effects on anxiety, pain, attention, memory and the stimulation of gastric acid by gastrin is mediated by the activation of the CCK-2R.

NN0368-0056 is a long-acting and highly selective CCK-1R analogue. In the Senfuss *et al.* 2019 reference listed in the reference section, NNC0368-0056 is compound **10**.

Due to unexpected finding *in vivo* (see the Nyborg et al. 2020 reference listed in the reference section), NNC0368-0056 can only be used for *in vitro* studies.

Category	CCK (only for in vitro studies)
ID	NNC0368-0056
Amount pr. vial	1000 nmol

Calculated properties

In the Senfuss*;et al.*;2019 reference listed in the reference section, NNC0368-0056 is compound 10 and CCK-8 is compound 1.

Property	NNC0368-0056	CCK-8
MW (Da)	1849.1	1107.2
pI (calculated)	0.75	1.90
Sequence	C18 diacid-gGlu-2xOEG-Asp-Phe(4sm)-Nle-Gly-Trp-Nle-DMeAsp-MePhe-NH2	Asp-sTyr-Met-Gly-Trp-Met-Asp-Phe-NH2
Extinction coefficient (calculated, 280 nm)	5500	6990

Structural information

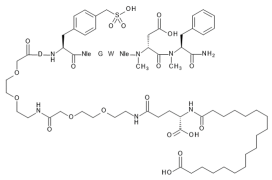

Figure 1

Figure 1

2D sketch of NNC0368-0056. The compound has several substitutions and an N-terminal 2xOEG-gGlu-C18 diacid for protraction compared to the native reference.

In vitro data

The binding affinity to human CCK-1R and CCK-2R was measured by the ability of the compounds to displace 125-iodine-labelled CCK-8 from the receptors in a plasma membrane-based scintillation proximity assay (SPA). The *in vitro* potencies were determined by measuring the accumulation of inositol 1 phosphate (IP1) in cells expressing human CCK-1R or CCK-2R. Since albumin binding is a key mechanism for the design of NNC0368-0056, be aware that the apparent affinity and potency will be very dependent on whether the *in vitro* assays contain albumin or not. The assays below are performed in the absence of human serum albumin. Please see the Sensfuss *et al*., 2019 reference listed in the reference section for further data and details regarding the experimental setup of the *in vitro* assays.

	Affinity (pIC50, M) **Mean (95% confidence interval)**	
Compound	**CCK-1R**	**CCK-2R**
CCK-8	9.95 (9.90 to 10.01)	9.54 (9.49 to 9.59)
NNC0368-0056	10.28 (10.17 to 10.38)	<5
	Potency (pEC50, M) Mean (95% confidence interval)	
	CCK-1R	**CCK-2R**
CCK-8	10.36 (10.24 ro 10.48)	9.30 (9.22 ro 9.37)
NNC0368-0056	9.60 (9.48 to 9.73)	<6

CCK-1R: cholecystokinin 1 receptor; CCK-2R: cholecystokinin 2 receptor

Reference Compound

At present no reference compound is available.

Compound handling instructions

NNC0368-0056 can be dissolved in MilliQ water, neutral buffer or DMSO. 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.

References

1. Sensfuss U et al.
Structure-Activity Relationships and Characterization of Highly Selective, Long-Acting, Peptide-Based Cholecystokinin 1 Receptor Agonists

J Med Chem 2019; 62; 1407-1419

2. Nyborg et al
Cholecystokinin-1 receptor agonist induced pathological findings in the exocrine pancreas of non-human primates

Toxicol Appl Pharmacol. 2020 Jul 15;399: 115035

3. Christoffersen et al
Long-acting CCK analogue NN9056 lowers food intake and body weight in obese Göttingen Minipigs

Int J Obes (Lond). 2020 Feb;44(2):447-456