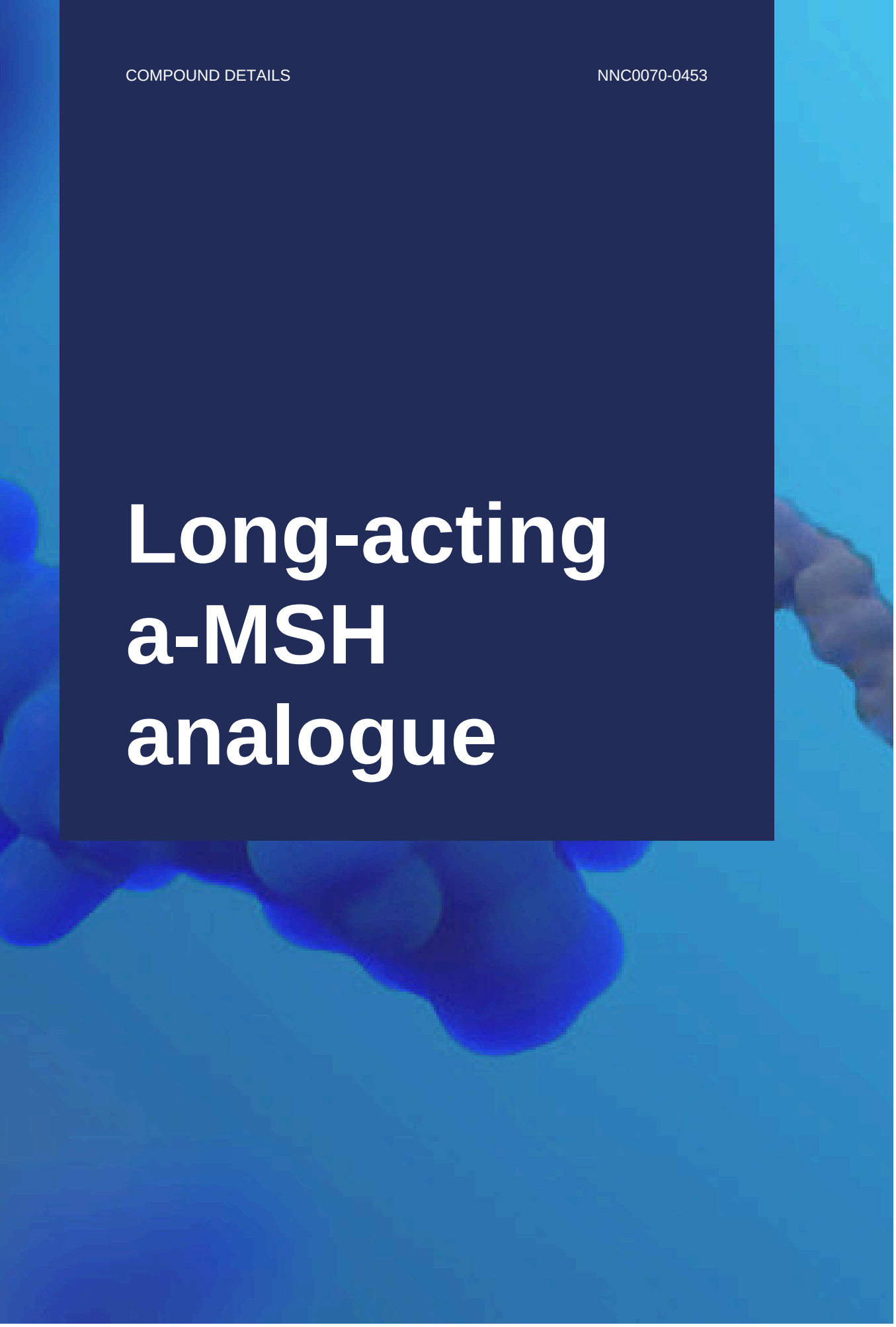
COMPOUND DETAILS NNC0070-0453

Long-acting a-MSH analogue



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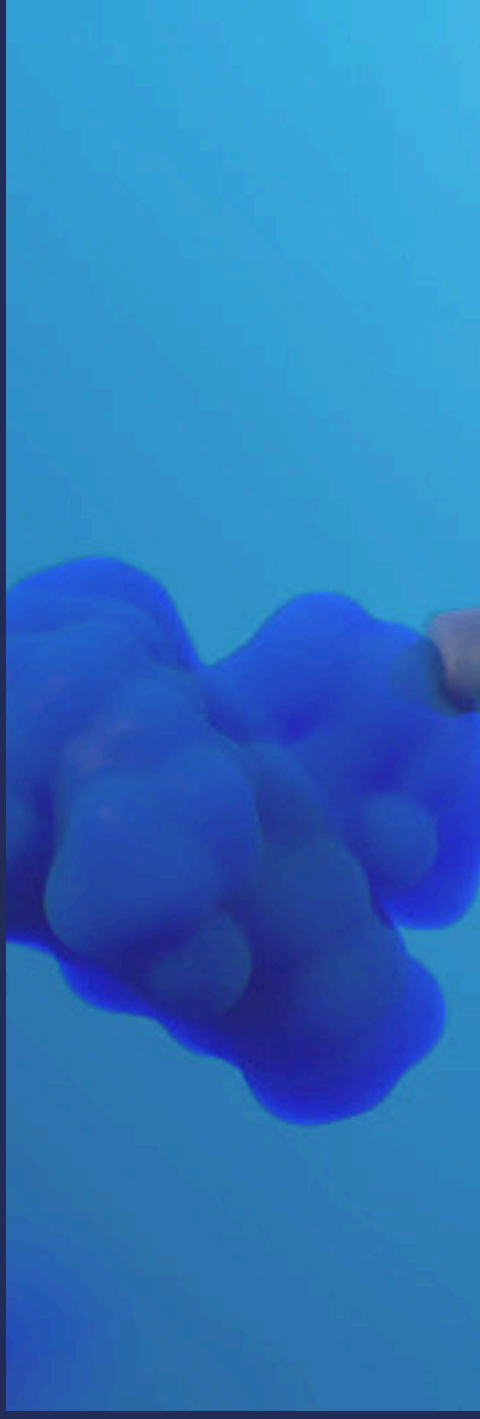
Content



Long-acting a-MSH analogue

Alpha-melanocyte-stimulating hormone (a-MSH) is one of the native ligands for the melanocortin receptors 1-5. The melanocortin 4 receptor (MC4-R) is involved in the regulation of food intake and body weight.

NNC0070-0453 is a long-acting MC4-R selective a-MSH analogue which is N-terminally modified with a long chain fatty acid derivative.

Category	a-MSH
ID	NNC0070-0453
Amount pr. vial	1000 nmol

Calculated properties

Property	NNC0070-0453	MT-II (NNC0090-1735)
MW (Da)	2092	1024
pI (calculated)	5.8	13.0
Fatty acid	C16-tetrazole	-
Linker	OEG	-
Sum formula	C96 H146 N28 O25	C50 H69 N15 O9
Extinction coefficient (calculated, 280 nm)	5500	5500

Selected calculated properties for NNC0070-0453 and MT-II (NNC0090-1735) are listed in the table.

Structural information

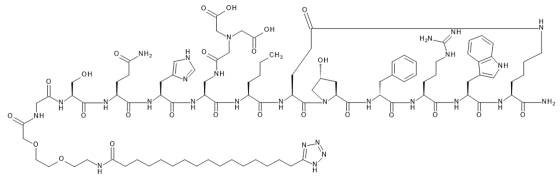


Figure 1

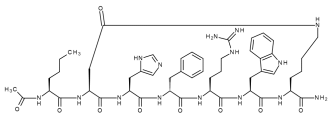


Figure 2

Figure 1

2D sketch of NNC0070-0453. The salt bridge in a-MSH between Glu5 and Lys11 is replaced with a lactam bridge. Gly-10 has been removed and the oxidative labile Met4 has been replaced with an isosteric norleucine (Nor). A fatty acid derivative (C16-tetrazole) is attached to the N-terminal.

Figure 2

2D sketch of the structure of MT-II (NNC0090-1735), a widely used reference for a-MSH used in the litterature.

In vitro data

Receptor	NNC0070-0453 (IC50, nM)	MT-II (IC50, nM)	NDP-a-MSH (IC50, nM)
hMC1R	22	0.74	0.18
hMC3R	4	7.6	0.22
hMC4R	0.57	0.56	0.29
hMC5R	N/A	N/A	N/A

hMC1R, hMC3R, hMC4R, hMC5R: human melanocortin receptor subtype 1,3,4, and 5, respectively.

New receptor binding data from scintillation proximity assays (SPA) binding assays (different from the previously published data) are listed in the table.

In vivo data

For NNC0070-0453 the mean $T_{1/2}$ in Sprague Dawley rats were 28 h after subcutaneous (s.c.) dosing. NNC0070-0453 and other long chain fatty acid analogues have an effect up to 48 h in an acute feeding study in male Sprague-Dawley rats after a single s.c. administration (see the Conde-Frieboes K et al., 2012, reference listed in the reference section further details).

Reference Compound

The reference compound is MT-II (NNC0090-1735), which is a short cyclic analogue of a-MSH. Please indicate (with a check mark at ‘Please add the reference compound if available) during your compound request if you would like to have MT-II (NNC0090-1735) included in your shipment.

Compound handling instructions

For in vitro experiments the compound can be dissolved in DMSO, 80/20% DMSO /MilliQ water or low salt buffer with neutral to basic pH. 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. Conde-Frieboes K et al.
Identification and in vivo and in vitro characterization of Long Acting and Melanocortin 4 Receptor (MC4-R) selective a-melanocyte-stimulating hormone (a-MSH) analogues

J Med Chem. 2012;55(5):1969-77

2. Royalty JE et al.
Investigation of safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple doses of a long-acting a-MSH analogue in healthy overweight and obese subjects

J Clin Pharmacol. 2014; 54(4): 394–404.

3. al-Obeidi F et al.
Design of a new class of superpotent cyclic a-melanotropins based on quenched dynamic simulations

J. Am. Chem. Soc. 1989, 111, 3413– 3416