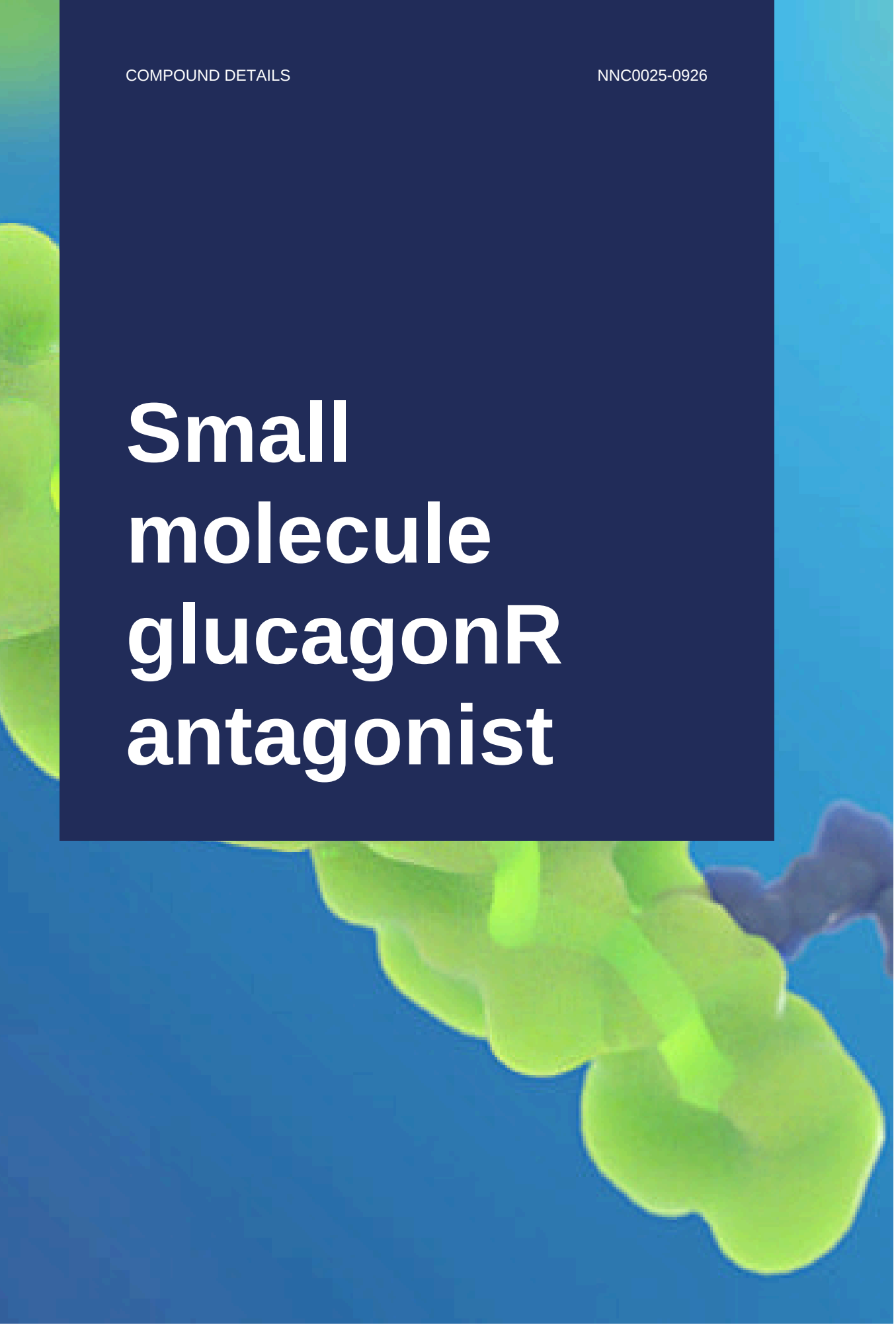
COMPOUND DETAILS NNC0025-0926

Small molecule glucagonR antagonist



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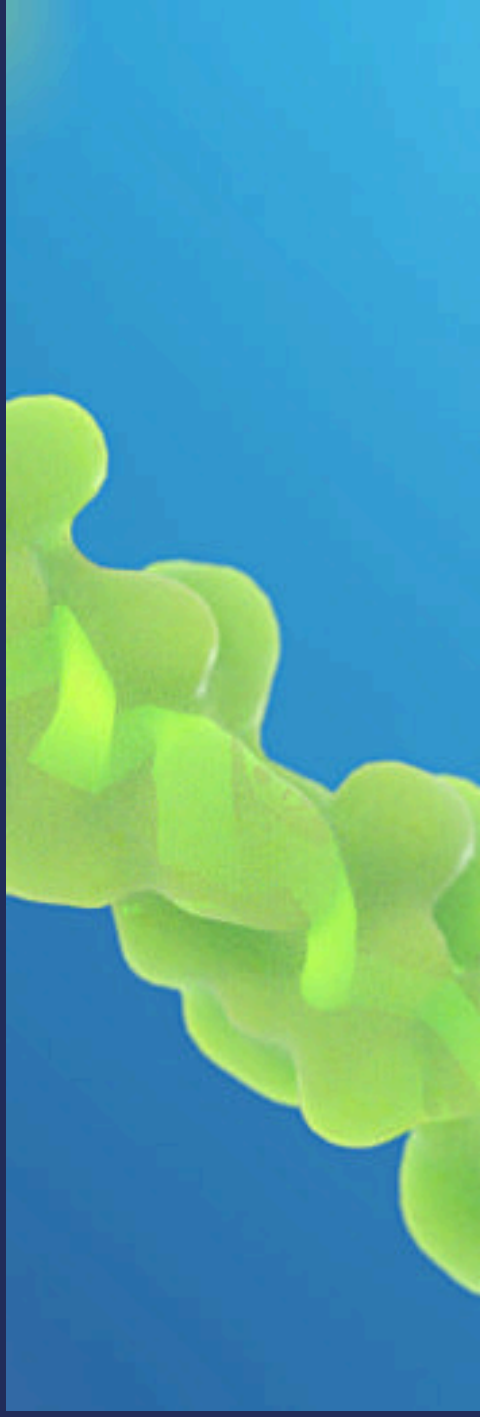
Content



Small molecule glucagonR antagonist

Glucagon is a 29 amino acid peptide hormone liberated in the alpha cells of the islets of Langerhans. Glucagon has in general been viewed as the counter regulatory hormone to insulin in peripheral tissues, predominantly to the liver. An important contributor to the development of hyperglycemia in type 2 diabetes is inappropriately high glucose production from the liver. The primary physiological effect of glucagon is to stimulate hepatic glucose production by increasing both gluconeogenesis and glycogenolysis.

NNC0025-0926 was developed as an oral bioavailable small molecule capable of antagonizing glucagon signaling and thereby shut down the contribution from glucagon to hyperglycemia in T2DM.

Category	Glucagon
ID	NNC0025-0926
Amount pr. vial	20 mg

Calculated properties

Compound	NNC0025-0926
MW (Da)	582.49
Sum formula	$C_{30}H_{29}Cl_2N_3O_5$

Proton-NMR (DMSO-d6): d 1.50-1.80 (4H, m), 2.08-2.38 (4H, m), 3.36-3.65 (2H, m), 4.14-4.24 (1H, m), 4.96 (2H, m), 6.17 (1H, t), 7.14 (1H, t), 7.18 (2H, d), 7.35 (2H, d), 7.42 (2H, d), 7.63 (2H,d), 7.78 (2H, d), 8.48 (1H, t), 8.55 (1H, s).

Analytical chiral HPLC: Chiralcel OF 250x4.6 mm. Isocratic eluent; isopropanol:n-heptane: TFA: 80:20:0.1, Rt = 67.3 min. Purity > 99.5 % ee

Structural information

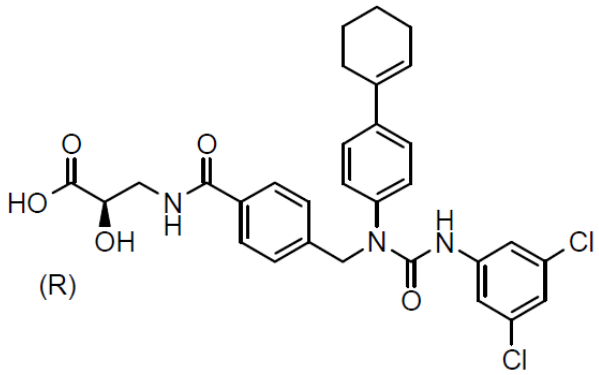


Figure 1

Figure 1

2D sketch of NNC0025-0926. (R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl] benzoylamino}-2-hydroxypropionic acid.

In vitro data

Receptor	Affinity of NNC0025-0926 (IC50, nM)
Rat GCGR;	43
Rat GIPR;	501
Human GCGR;	3.9
Human GIPR;	359

GIPR: GIP receptor; GCGR: glucagon receptor

See the Kodra et al. 2008 reference listed in the reference section for further details.

In vivo data

To examine the effects *in vivo*, NNC0025-0926 was tested in a glucagon-challenged rat model. The compound dose-dependently inhibited the glucagon-stimulated rise in blood glucose (see figure 3 in the Kodra et al. 2008 reference listed in the reference section). The minimum effective i.v. dose for NNC0025-0926 was 3 mg/kg.

Parameter	NNC0025-0926
Species	Rat
Oral bioavailability (%)	32
Half-life after i.v. dose (min)	53
CL (ml/min/kg) i.v.;	26
Vz (l/kg) i.v.;	0.91

CL: clearance; Vz: volume of distribution.

Reference Compound

No reference compound available

Compound handling instructions

Please note that the vial contains app. 20 mg and you need to check the exact amount in each vial. Follow the below guide to make a 3 mg/mL oral solution of NNC0025-0926. Hydroxypropyl--cyclodextrin (HBCD) stock solution: Dissolve HBCD in MilliQ water using magnet stirring to form a 20% w/w HBCD stock solution. NNC0025-0926 suspension: Suspend NNC0025-0926 in PEG 400 at a concentration of 15 mg/mL. Formulation: Mix 20% v/v NNC0025-0926 suspension with 50% v/v HBCD stock solution to form a suspension. Add 5% v/v 1.0 M NaOH to the NNC0025-0926 suspension to obtain a transparent solution (sonication may be used to wet NNC0025-0926). Add 20% 0.1 M phosphate buffer pH 7.2 and adjust pH to 7.2 with 1 M NaOH or 1 M HCl (less than 5% v/v used). Add 0.1 M phosphate buffer pH 7.2 to obtain the final volume of formulation, a transparent solution should be obtained. The formulation can be stored for 1 week at 5C without risk of precipitation and/or degradation of NNC0025-0926 in solution.

PEG: polyethylene glycol

References

1. Kodra JT et al.
Novel glucagon receptor antagonists with improved selectivity over the glucose-dependent insulinotropic polypeptide receptor

J. Med. Chem., 2008, 51, 5387–5396