NPY2R Antagonist | BIIE0246

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Summary

BI0246 is a highly potent, non-peptide, competitive neuropeptide Y (NPY) Y2 receptor selective antagonist. A low-affinity congener is available as a negative control.

Chemical Structure

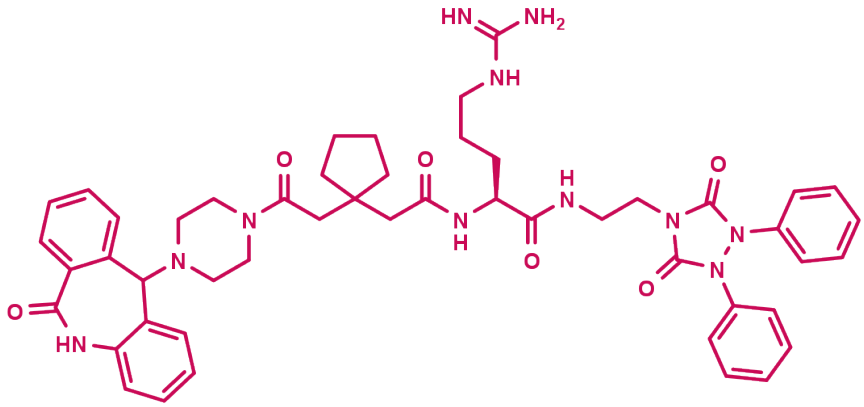

Figure 1: 2-D structure of BIIE0246, a non-peptide NPY2R antagonist.

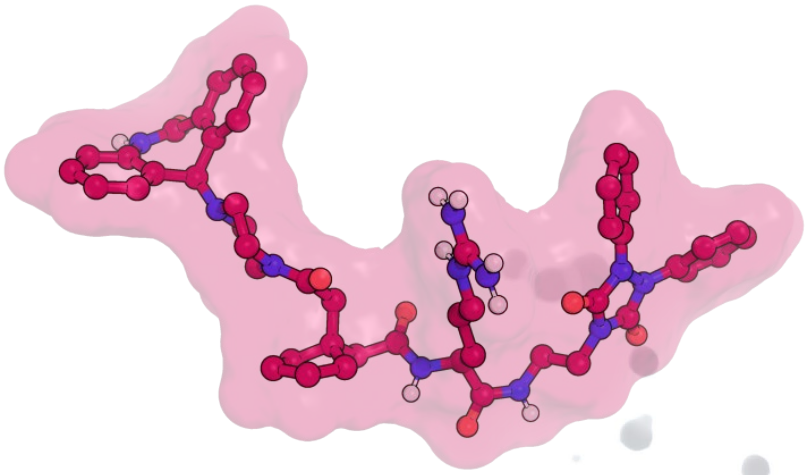

Figure 2: 3-D structure of BIIE0246, a non-peptide NPY2R antagonist.

Highlights

Since its introduction in 1999, BIIE0246 became the gold standard as pharmacological tool for the *in vitro* and *in vivo* study of Y2 receptor mediated effects. Its use has been documented in over 100+ scientific publications. It is offered together with its negative control, BIIE0212, a congeneric analogue with 400-fold lower affinity towards the Y2 receptor than BIIE0246.

Target information

The neuropeptide Y Y2 receptor (Y2R) is a member of the neuropeptide Y (NPY) receptor family which in humans consists of the four rhodopsin-like (class A) GPCRs: Y1, Y2, Y4, and Y5.

NPY receptors are activated by a family of structurally related tyrosine-rich polypeptides, namely NPY, PYY (peptide tyrosine-tyrosine) and PP (pancreatic polypeptide) having a common length of 36 amino acids and an amidated C-terminus.

Y2 receptors are expressed in both the peripheral and central nervous system where they predominantly are located on presynaptic neurons. Brain regions with high expression levels of Y2 receptors are hippocampus, thalamus, hypothalamus and amygdala.

Y2 receptors are involved in the modulation of various (patho-) physiological processes including memory retention, anxiety, arousal, alcohol consumption and energy homeostasis. In particular, the appetite suppressant effect elicited by the activation of Y2 receptors expressed in the arcuate nucleus of the hypothalamus attracted considerable attention.

Recently, Beck-Sickinger et al. proposed a structural model for the binding mode of BIIE0246 in the Y2R binding site based on mutagenesis data and computational docking[2].

In vitro activity

BIIE0246 displaced radiolabelled neuropeptide Y from NPY2R sites on SMS-KAN cells expressing the hY2R, with an IC_{50} of 3.3 nM[1]. In addition, BIIE0246 displayed an IC_{50} of 7.5 nM for the displacement of [^{125}I]-NPY from Y2R binding sites in preparations from rabbit kidney[3].

The antagonistic properties of BIIE0246 were demonstrated by a concentration dependent right shift for the dose-response curve of the endogenous agonist NPY in the rat *vas deferens* assay – a functional bioassay for the Y2 receptor[1,4].

The low nanomolar binding affinity as well as the antagonistic potency of BIIE0246 was confirmed in several different cellular and tissue/isolated organ-based assays reported in various scientific papers[5-9].

PROBE NAME / NEGATIVE CONTROL	BIIE0246	BIIE0212
MW [Da]	896.07	665.88
Radioligand binding hY2R (IC_{50}) [nM][a]	3.3	NA
Radioligand binding rabbit Y2R (IC_{50}) [nM][b]	7.5	3300
Radioligand binding rY1R IC_{50}) [nM][c]	>10,000	NA
Radioligand binding rY2R IC_{50}) [nM][c]	15	NA
Radioligand binding rY4R IC_{50}) [nM][c]	>10,000	NA
Radioligand binding rY5R IC_{50}) [nM][c]	>10,000	NA
Y2 antagonistic activity in rat *vas deferens* bioassay (pA_2)[d]	8.1	NA

[a] Displacement of radiolabelled NPY from SMS-KAN cells expressing human NPY2R[1].
[b] Displacement of radiolabelled NPY from Y2R binding sites in rabbit kidney membrane preparations[3].
[c] Displacement of radiolabelled ligands binding to HEK 293 cells transfected with rat Y1, Y2, Y4, and Y5 receptor cDNA, respectively. For details see lit.[4]
[d] Alteration of NPY-induced inhibition of the twitch response in electrically stimulated rat *vas deferens* preparations by an Y2 antagonist[4].

In vitro DMPK and CMC parameters

BIIE0246 is a large and flexible peptidomimetic molecule with rather poor drug-like properties, displaying low permeability, high plasma protein binding and moderate microsomal stability. Accordingly, for *in vivo* investigations BIIE0246 is best administered via parenteral routes.

PROBE NAME / NEGATIVE CONTROL	BIIE0246	BIIE0212
logD (pH 2)	2.21	1.51
Solubility @ pH 2.2 | 4.4 | 6.8 [µg/ml]	206 | 26 | 20	166 | 82 | –
PAMPA permeability [10^{-6} cm · s^{-1}]	0.005	0.01
CACO permeability @ pH 7.4 [10^{-6} cm · s^{-1}]	<0.86	3.5
CACO efflux ratio	>1.1	1.3
MDCK permeability @ 1µM [10^{-6} cm · s^{-1}]	P_{a-b}: <0.2 P_{b-a}: 0.22	P_{a-b}: <0.23 P_{b-a}: 0.26
MDCK efflux ratio	>1.1	>1.1
Microsomal stability (h/m/r) [% Q_H]	62 / 40 / 66	74 / 61 / 79
Hepatocyte stability (h/m/r) [% Q_H]	5 / 26 / 38	15 / 61 / 54
Plasma protein binding (h/r) [%]	99.0 / 99.4	99.1 / 99.4
hERG (IC_{50}) [µM]	> 0.1	> 0.3
CYP 3A4 (IC_{50}) [µM]	3.24	8.61
CYP 2C8 (IC_{50}) [µM]	10.9	18.9
CYP 2C9 (IC_{50}) [µM]	> 50	46.7
CYP 2C19 (IC_{50}) [µM]	> 50	> 50
CYP 2D6 (IC_{50}) [µM]	20.4	24.1

In vivo pharmacology

BIIE0246 was used as a subtype selective pharmacological tool in several *in vivo* studies to investigate the (patho-) physiological role of Y2 receptor modulation in various tissues – including CNS[10-15]. However, the duration of action after i.v. or i.p. application is rather short (in mice a half-life of < 3h was estimated[15]). Central availability of BIIE0246 after systemic administration was shown to be limited (brain to plasma ratio: 0.2 % 30 min after i.p. dosing[16]); hence, for the study of central Y2R mediated effects BIIE0246 was administered intrathecally or injected directly into the brain region of interest[11].

Negative control

BIIE0212 is a congeneric analogue from the same series of L-argininamides with similar physicochemical properties but with a more than 400-fold lower affinity towards the Y2 receptor[3].

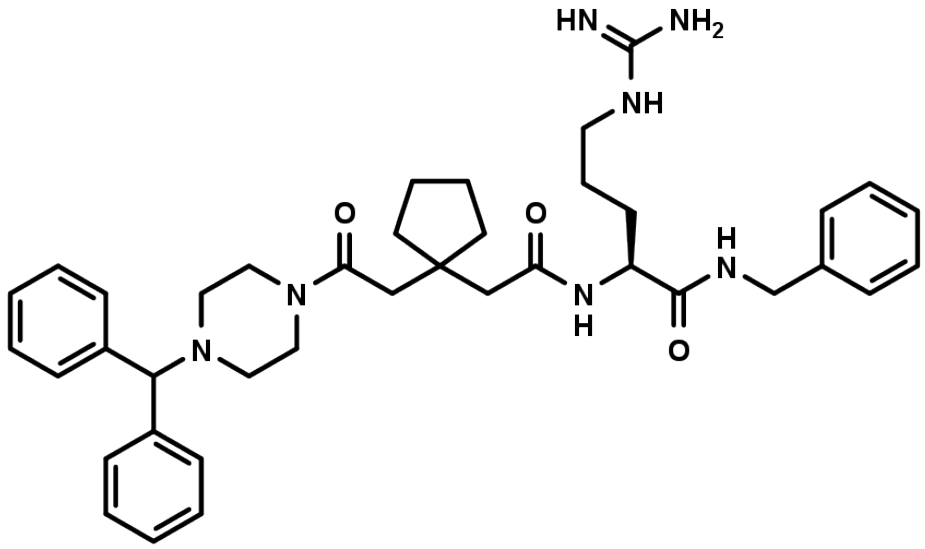

Figure 4: BIIE0212 which serves as a negative control

Selectivity

BIIE0246 features an excellent subtype selectivity as indicated by a >600 fold lower affinity in rat Y1, Y4 and Y5 radioligand binding assays. No bioactivity was seen in a panel of 60 other receptor types

or enzymes[1]. Screening against a panel of 40 CNS targets revealed submicromolar affinity only in case of the α1A adrenergic receptor and the μ- and κ-opiod receptors[16].

SELECTIVITY DATA AVAILABLE	BIIE0246	BIIE0212
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Reference molecules

Structurally BIIE0246 is an L-arginine derivative mimicking the C-terminal RQRYamide motif of the endogenous signal peptides NPY and peptide YY (PYY).

JNJ-5207787[17], JNJ31020028[18,19], [3H]UR-PLN196[20], Cpd. 36 (GSK)[21], Cpd. 2 (GSK)[22], CYM 9484 and CYM 9552[23], SF-11[24], ML052[25], and ML075[25] can serve as reference molecules.

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

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