opnMe by Boehringer Ingelheim

Beta-3 adrenergic receptor agonist

BI-2800

Boehringer Ingelheim

Table of contents

Summary 2
Chemical Structure 2
Highlights 3
Target information 3
In vitro activity 4
In vitro DMPK and CMC parameters 5
Negative control 6
Selectivity 6
Reference molecule(s) 6
Supplementary data 6
References 7

Summary

The beta-3 adrenergic receptor agonist BI-2800 is a highly potent stimulator of lipolysis in human adipocytes. BI-0962 is available as a negative control.

Chemical Structure

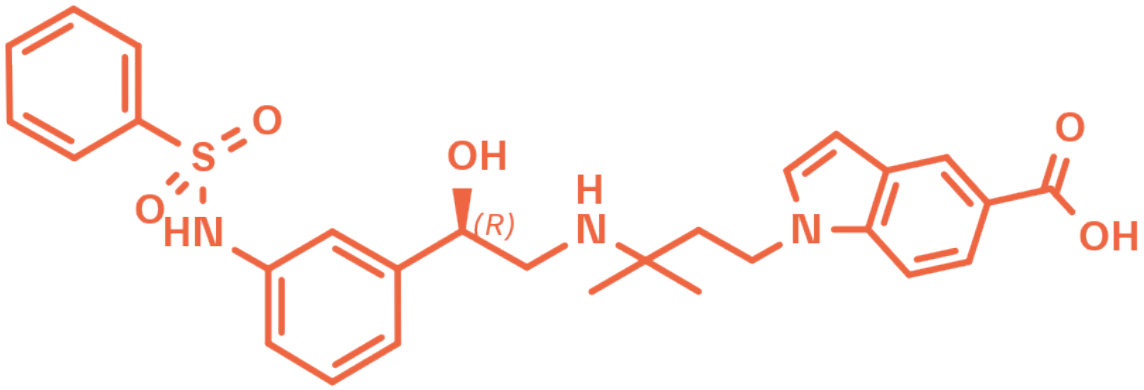

Figure 1: 2-D structure of BI-2800, a beta-3 adrenergic receptor

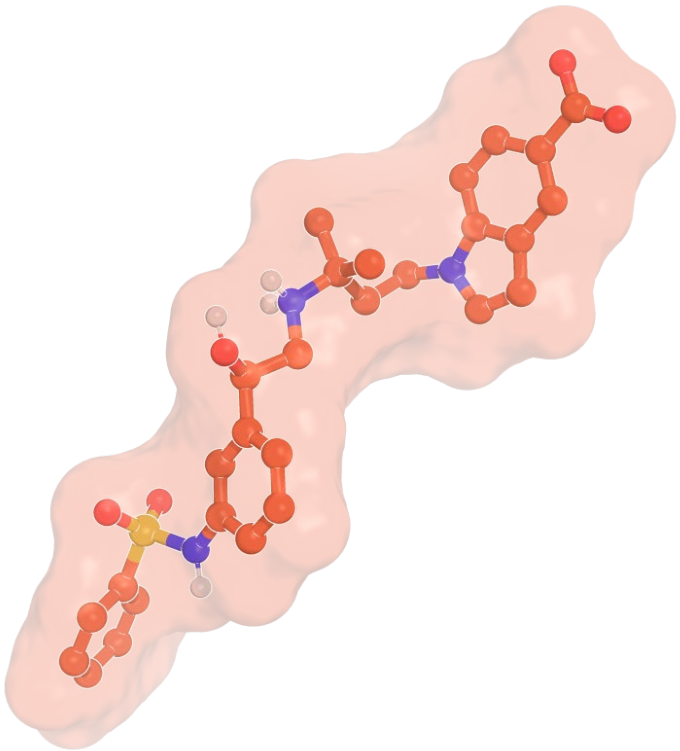

Figure 2: BI-2800, 3D low energy conformation

Highlights

BI-2800 is a highly potent β3 adrenergic receptor agonist. It binds to β1, β2 and β3 adrenergic receptors but shows high functional selectivity by only activating β3, where it has longer residence times and shows resistance to antagonist activity, while antagonizing β1 and β2. Accordingly, BI-2800 demonstrated continued activation of the β3 adrenergic receptor in the presence of excess antagonists and continued adipocyte lipolysis.

Target information

The beta-3 adrenergic receptor (β_3-adrenoceptor or ADRB3) is predominantly expressed on the cell surface of adipocytes and smooth muscle cells, in particular the detrusor muscle in the bladder wall. It is stimulated by the endogenous ligands adrenaline and noradrenaline and has been explored as a drug target for several indications, mostly in the context of lipolysis and thermogenesis. Of note is the related, but different ADRB3 agonist mirabegron that has even obtained regulatory approvals for treatment of overactive bladder syndrome in some (but not all!) countries, among them the US and Japan. In rodents, activation of the beta-3 adrenergic receptor also stimulates thermogenesis in brown adipose tissue, which may represent a potential strategy for treating metabolic disorders. There is also data suggesting a potential stimulation of thermogenesis in human brown adipose through the application of mirabegron[2], albeit to a lesser extent due to lower expression levels than in rodents. In addition, some of the effects observed with mirabegron may be due to stimulation of beta-1 and/or beta-2 adrenergic receptor, whereas BI-2800 selectively activates the beta-3 adrenergic receptor. However, a role of BI-2800 in the context of thermogenesis has never been established so far.

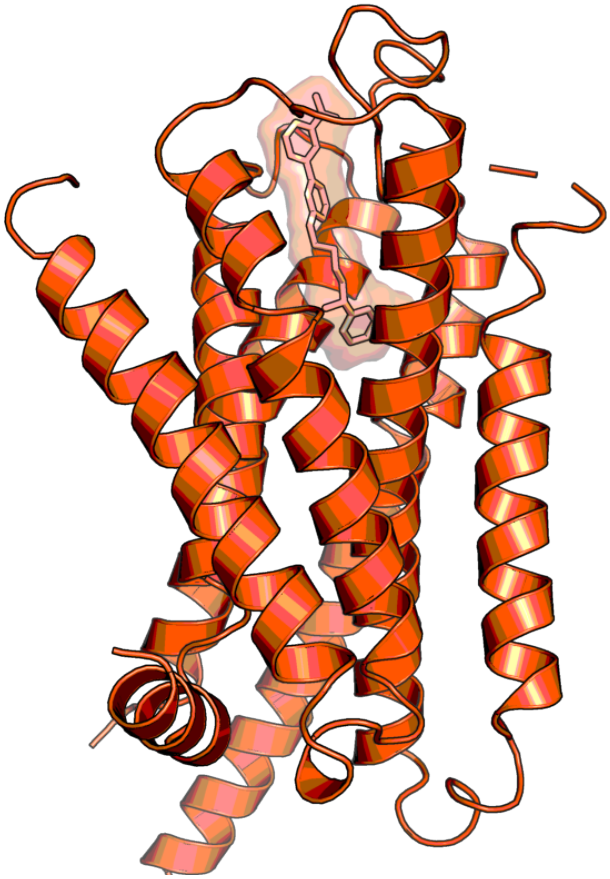

Figure 3: X-ray structure of the dog beta-3 adrenergic receptor with solabegron, an agonist structurally related to BI-2800 (PDB code: 7XJI)

In vitro activity

BI-2800 shows an EC_{50} of 4 nM in a cAMP-based beta-3 adrenergic receptor assay in CHO cells. Furthermore BI-2800 behaves as an antagonist in similar assays for beta-1 and beta-2 adrenergic receptors.

An atypical beta-3 adrenergic receptor agonist, BI-2800 is structurally similar, but different to the compounds examined by Hamilton and Doods[1], and has a long residence time on the beta-3 adrenergic receptor.

Accordingly BI-2800 showed continued activation the beta-3 adrenergic receptor in the presence of excess antagonists, continued rat adipocyte lipolysis after extensive washing and continued stimulation of rat adipocyte lipolysis after fat extraction.

Probe name / Negative control	BI-2800	BI-0962
MW [Da]	521.6	521.6
cAMP[a] CHO-ADRB1 (EC_{50}) [nM] (isoprenaline)	Antagonist IC_{50} = 70	n.a.
cAMP CHO-ADRB2 (EC_{50}) [nM] (isoprenaline)	Antagonist IC_{50} = 88	n.a.
cAMP CHO-ADRB3 (EC_{50}) [nM] (IA isoprenaline)	4 (0.8)	344 (0.6)

[a] cAMP generated by the cells was detected using the LANCE™ cAMP 384 kit (PerkinElmer) according to manufacturer's instructions. When testing for antagonism, the compound was incubated 20 min before addition of isoprenaline for 30 min.

In vitro DMPK and CMC parameters

Probe name / negative Control	BI-2800	BI-0962
logD @ pH 11	-0.79	0.2
Solubility @ pH 7 [µg/ml]	400	47
CACO permeability @ pH 7.4 [$*10^{-6}$ cm/s]	1.0	0.9
CACO efflux ratio	3	7.9
CYP 3A4 (IC_{50}) [µM]	37	n.a.
CYP 2C9 (IC_{50}) [µM]	>50	>50
CYP 2C19 (IC_{50}) [µM]	9.0	>50
CYP 2D6 (IC_{50}) [µM]	>50	>50
Cytotoxicity (IC_{50}) [µM]	>200	n.a.

Negative control

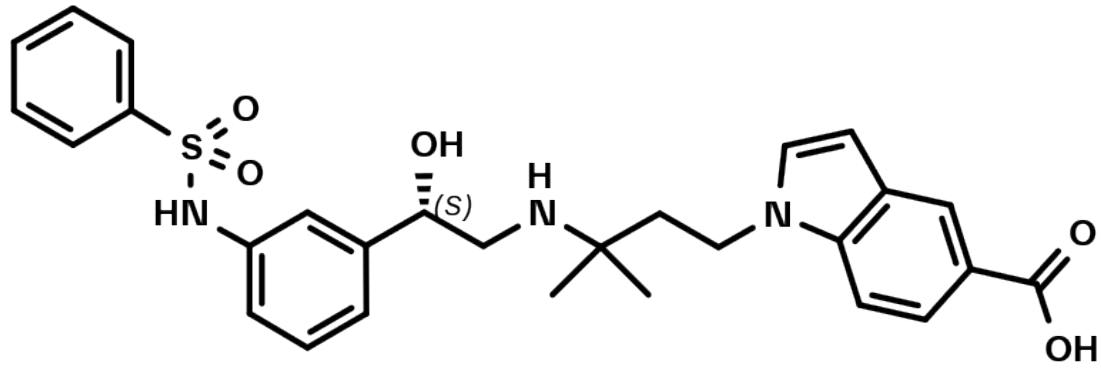

Figure 4: BI-0962, which serves as a negative control

Selectivity

BI-2800 was tested against a panel of 72 receptors at 10µM concentration. BI-2800 showed antagonistic activity on beta-1 adrenergic receptor (IC_{50} = 70nM), beta-2 adrenergic receptor (IC_{50} = 88 nM) and 5-HT1A receptor (IC_{50} = 2350 nM).

The negative control BI-0962 hit 3 out of 44 targets (>50% of control at 10 µM, 5HT2B/H, BETA1/HUM, BETA2/HUM).

Selectivity data available	BI-2800	BI-0962
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Reference molecule(s)

mirabegron (YM178)

Supplementary data

2-D structure files can be downloaded free of charge from opnMe.

References

1. Hamilton B.S., Doods H.N. Identification of potent agonists acting at an endogenous atypical β_3-adrenoceptor state that modulate lipolysis in rodent fat cells *Eur J Pharmacol.* **2008**, 580(1-2), 55-62. DOI: 10.1016/j.ejphar.2007.10.065, PubMed.

2. Chen K. Y., Brychta R. J., Israni N. S., Jiang A., Lea H. J., Lentz T. N., Pierce A. E., Cypess A. M. Activating Human Adipose Tissue with the β3-Adrenergic Agonist Mirabegron *Methods Mol Biol.* **2022**, 2448: 83-96. DOI: 10.1007/978-1-0716-2087-8_5, PubMed