



# Beta-3 adrenergic receptor agonist | BI-2800

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## 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

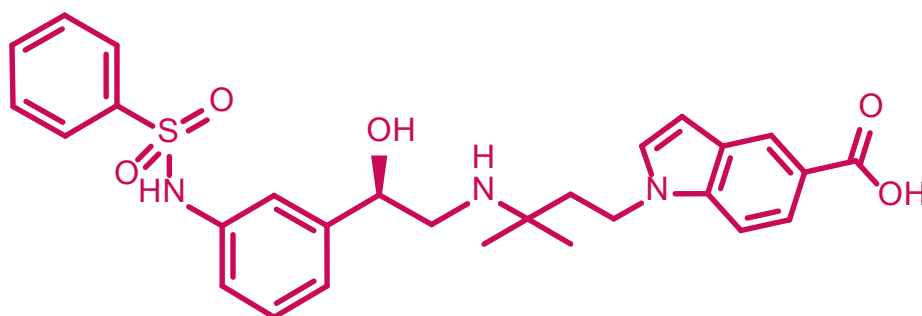


Figure 1: 2-D structure of BI-2800, a beta-3 adrenergic receptor

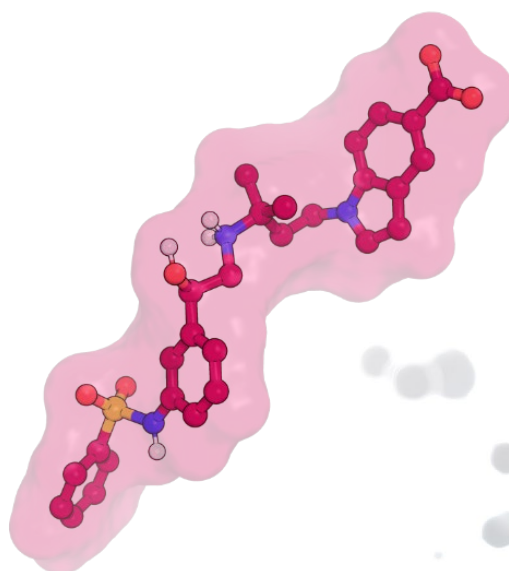


Figure 2: BI-2800, 3D low energy conformation

## Highlights

BI-2800 is a highly potent  $\beta_3$  adrenergic receptor agonist. It binds to  $\beta_1$ ,  $\beta_2$  and  $\beta_3$  adrenergic receptors but shows high functional selectivity by only activating  $\beta_3$ , where it has longer residence times and shows resistance to antagonist activity, while antagonizing  $\beta_1$  and  $\beta_2$ . Accordingly, BI-2800 demonstrated continued activation of the  $\beta_3$  adrenergic receptor in the presence of excess antagonists and continued adipocyte lipolysis.

## Target information

The beta-3 adrenergic receptor ( $\beta_3$ -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<sup>2</sup>, 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<sub>50</sub> 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<sup>1</sup>, 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]	558.1	635.7
cAMP <sup>a</sup> CHO-ADRB1 (EC <sub>50</sub> ) [nM] (isoprenaline)	Antagonist IC <sub>50</sub> = 70	n.a.
cAMP CHO-ADRB2 (EC <sub>50</sub> ) [nM] (isoprenaline)	Antagonist IC <sub>50</sub> = 88	n.a.
cAMP CHO-ADRB3 (EC <sub>50</sub> ) [nM] (IA isoprenaline)	4 (0.8)	344 (0.6)

<sup>a</sup> 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 2, 7.4, 11	n.a. / 0.5 / -0.79	1.1 / n.a. / -0.77
Solubility @ pH 6.8 [ $\mu\text{g}/\text{ml}$ ]	90	47
CACO permeability @ pH 7.4 [ $*10^{-6} \text{ cm/s}$ ]	1.0	0.9
CACO efflux ratio	3	7.9
CYP 3A4 ( $\text{IC}_{50}$ ) [ $\mu\text{M}$ ]	37	>50
CYP 2C8 ( $\text{IC}_{50}$ ) [ $\mu\text{M}$ ]	>50	>50
CYP 2C9 ( $\text{IC}_{50}$ ) [ $\mu\text{M}$ ]	>50	>50
CYP 2C19 ( $\text{IC}_{50}$ ) [ $\mu\text{M}$ ]	9.0	>50
CYP 2D6 ( $\text{IC}_{50}$ ) [ $\mu\text{M}$ ]	>50	>50
Cytotoxicity ( $\text{IC}_{50}$ ) [ $\mu\text{M}$ ]	>200	n.a.

## Negative control

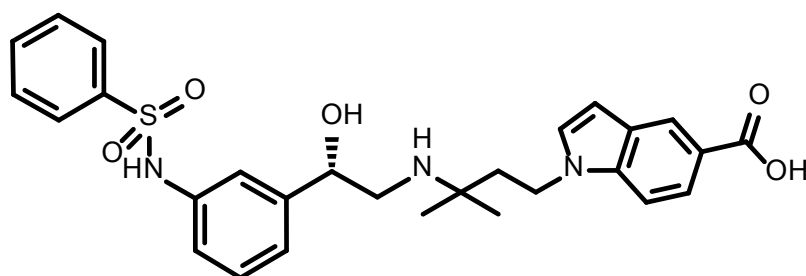



Figure 4: BI-0962, which serves as a negative control

## Selectivity

BI-2800 was tested against a panel of 72 receptors at 10 $\mu$ M 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  $\mu$ M, 5HT2B/H, BETA1/HUM, BETA2/HUM).

SELECTIVITY DATA AVAILABLE	BI-2800	BI-0962
SafetyScreen44™ with kind support of 	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 [openMe](https://openme.org).

## References

1. Hamilton B.S., Doods H.N. Identification of potent agonists acting at an endogenous atypical  $\beta_3$ -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](https://doi.org/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  $\beta_3$ -Adrenergic Agonist Mirabegron *Methods Mol Biol.* **2022**, 2448: 83-96. [DOI: 10.1007/978-1-0716-2087-8\\_5](https://doi.org/10.1007/978-1-0716-2087-8_5), [PubMed](#)