opnMe by Boehringer Ingelheim

β2AR agonist

BI-167107

Boehringer Ingelheim

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Summary

BI-167107 was used to support crystallization of active state β2AR complexes and can be employed as a tool for the crystallization of other beta receptors.

The compound was synthesized during a campaign to develop third generation of β2-agonists and shows very high potency and slow dissociation from the target.

Chemical Structure

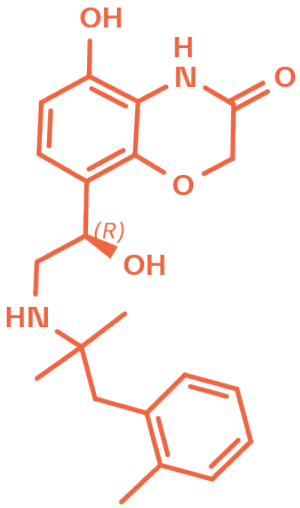

Figure 1: 2D structure of BI-167107, a β2AR agonist

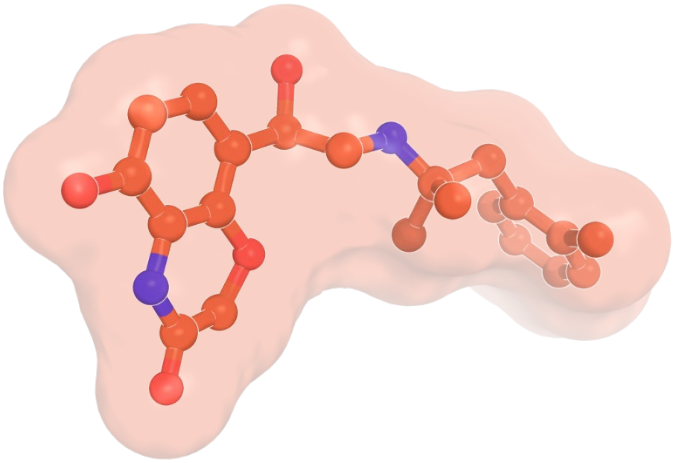

Figure 2: 3D structure of BI-167107

Highlights

BI-167107 is a highly potent and long-acting β2 adrenergic receptor (β2AR) agonist. As a result, BI-167107 was used to support the crystallization of the active state of the β2AR and β2AR-G-protein complexes. It is not a selective β2-agonist, so its only recommended use is as a tool to support crystallization studies of other beta receptors[1-5], such as β1AR.

Target information

G-protein-coupled receptors (GPCRs) are integral membrane proteins that have an essential role in human physiology, yet only recently we started to understand the molecular processes through which they bind to their endogenous agonists and activate effector proteins. β2AR is a member of the class A family of GPCRs. Besides rhodopsin it is the best characterized member of that family.

β2 adrenergic receptor (β2AR) agonists have been used as bronchodilating agent for the last decades for the treatment of pulmonary diseases like asthma. BI-167107 was synthesized during a campaign to develop third generation of β2-agonists. Interestingly BI-167107 is also very active agonist of the β1AR (IC_{50} = 3.2 nM) and shows some activity as α1A antagonist (IC_{50} = 32 nM).

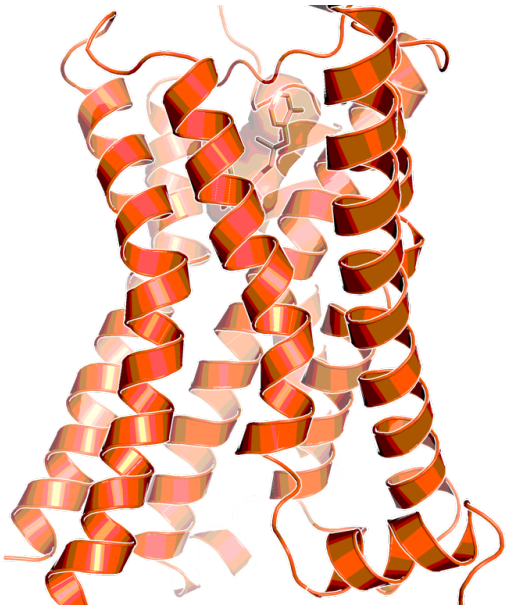

Figure 3: Human β2AR in the active state, in complex with BI-167107 (PDB code: 3p0g).

In vitro activity

We recommend using this compound only to support the crystallization of beta receptors.

BI-167107 is a potent and long-acting beta agonist with a K_D of 84 pM.

PROBE NAME	BI-167107
MW [Da, free base][a]	370.4
β2AR K_D [nM][b]	0.084
β2AR B_{max} [nM][b]	2238
EC_{50} cAMP accumulation [nM][b]	0.05
$t_{½}$ (dissociation half-life) [h][b]	30

[a] For the salt form you will get, please refer to the label on the vial and for the molecular weight of the salt, please refer to the FAQs
[b] For further information on assays please refer to reference 1.

Selectivity

BI-167107 is not a selective β2 agonist.

A Eurofins Safety Panel 44™ screen revealed several hits >70% inhibition at 10µM and IC_{50}s were consequently measured for eight targets. Two showed strong activity in the low nanomolar range: β1(h) (agonist radioligand) (IC_{50} = 3.2 nM), α1A(h) (antagonist radioligand) (IC_{50} = 32 nM). BI-167107 showed weaker activity on the other targets: 5-HT transporter (h) (antagonist radioligand) (IC_{50} = 6.1 µM), 5-HT1A(h) (agonist radioligand) (IC_{50} = 1.4 µM), 5-HT1B (antagonist radioligand) (IC_{50} = 0.25 µM), D2S(h) (agonist radioligand) (IC_{50} = 5.9 µM), dopamine transporter(h) (antagonist radioligand) (IC_{50} = 7.2 µM), µ (MOP) (h) (agonist radioligand) (IC_{50} = 6.5 µM).

SELECTIVITY DATA AVAILABLE	BI-167107
SafetyScreen44™ with kind support of eurofins	Yes
Invitrogen®	No

DiscoverX®	No
Dundee	No

Co-crystal structures of the BI probe compound and the target protein

PDB ID	TITLE
3P0G	Structure of a nanobody-stabilized active state of the β2AR
4LDE	Structure of β2AR bound to BI-167107 and an engineered nanobody
3SN6	Crystal structure of the β2AR-Gs protein complex

References

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