



β 2AR agonist | BI-167107

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Short Summary

BI-167107 was used to support crystallization of active state β 2AR 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 β 2-agonists and shows very high potency and slow dissociation from the target.

Chemical Structure

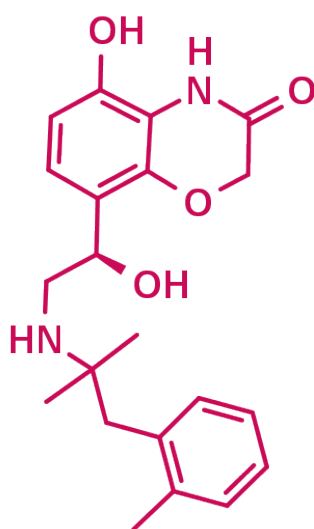


Figure 1: 2-D structure of BI-167107, a β 2AR agonist

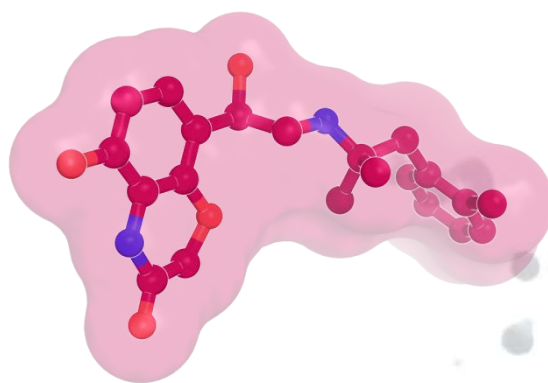


Figure 2: 3-D structure of BI-167107

Highlights

β 2 adrenergic receptor (β 2AR) agonists have been used as bronchodilating agents for the last decades for the treatment of pulmonary diseases like asthma. BI-167107 was synthesized during a campaign to develop third generation of β 2-agonists. Due to its high potency and slow dissociation from the target BI-167107 was subsequently used to support crystallization of active state β 2AR and β 2AR-G-protein complexes. Interestingly BI-167107 is also very active agonist of the β 1AR ($IC_{50} = 3.2$ nM) and shows some activity as α 1A antagonist ($IC_{50} = 32$ nM). Therefore the compound could be employed for the crystallization of other receptors.¹⁻⁵ BI-167107 should be used only as a tool to support crystallization studies und will be shipped free of charge in 2 mg batches to researchers.

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. β 2AR is a member of the class A family of GPCRs. Besides rhodopsin it is the best characterized member of that family.

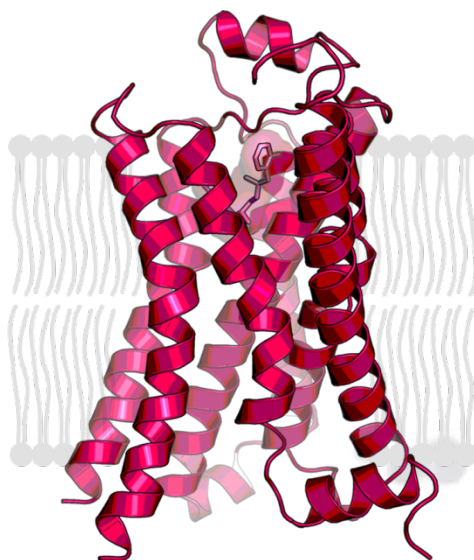


Figure 3: Human beta2 adrenoceptor in the active state, in complex with BI-167107 (PDB code: 3p0g).

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]	370.4
K_D^1 [nM]	0.084
B_{max}^1	2238
EC ₅₀ cAMP accumulation ¹ [nM]	0.05
$t_{1/2}$ (dissociation half-life) ¹ [h]	30

For further information on assays please refer to reference 1.

Selectivity

BI-167107 is not a selective beta2 agonist.

A Cerep screen revealed several hits >70% inhibition at 10 μ M and IC₅₀s were consequently measured for eight targets. Two showed strong activity in the low nanomolar range: β 1(h) (agonist radioligand) (IC₅₀ = 3.2 nM), α 1A(h) (antagonist radioligand) (IC₅₀ = 32 nM). BI-167107 showed weaker activity on the other targets: 5-HT transporter (h) (antagonist radioligand) (IC₅₀ = 6.1 μ M), 5-HT1A(h) (agonist radioligand) (IC₅₀ = 1.4 μ M), 5-HT1B (antagonist radioligand) (IC₅₀ = 0.25 μ M), D2S(h) (agonist radioligand) (IC₅₀ = 5.9 μ M), dopamine transporter(h) (antagonist radioligand) (IC₅₀ = 7.2 μ M), μ (MOP) (h) (agonist radioligand) (IC₅₀ = 6.5 μ M).

The data is available for download.

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 beta2 adrenoceptor
4LDE	Structure of beta2 adrenoceptor bound to BI-167107 and an engineered nanobody
3SN6	Crystal structure of the beta2 adrenergic receptor-Gs protein complex

Summary

β 2 adrenergic receptor (β 2AR) agonists have been used as bronchodilating agents for the last decades for the treatment of pulmonary diseases like asthma. BI-167107 was synthesized during a campaign to develop third generation of β 2-agonists suitable for a once a day regimen. Due to its high potency and slow dissociation from the target it was subsequently used to support crystallization of active state β 2AR and β 2AR-G-protein complexes. The compound could potentially be employed for the crystallization of other beta receptors.¹⁻⁵

Efforts to obtain an agonist-bound active-state GPCR structures have proven difficult due to the inherent instability of this state in the absence of a G protein. Here, BI-167107 has proven itself to be a valuable tool: the compound is an ultra-high affinity agonist with a dissociation half-life of more than 30 h ensuring that the β 2AR would be occupied by an agonist at all times.¹ BI-167107 was subsequently used in various studies in β 2AR structure and dynamics. BI-167107 may also prove useful as a tool for the study of other isoforms. BI-167107 should be used only as a tool to support crystallization studies.

References

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