Batefenterol

Cat. No.: HY-12980

CAS No.: 743461-65-6

Molecular Formula: $C_{40}H_{42}ClN_5O_7$

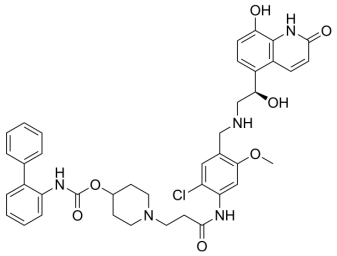
Molecular Weight: 740.24

Target: Adrenergic Receptor; mAChR

Pathway: GPCR/G Protein; Neuronal Signaling

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (135.09 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.3509 mL	6.7546 mL	13.5091 mL
5 mM	0.2702 mL	1.3509 mL	2.7018 mL
10 mM	0.1351 mL	0.6755 mL	1.3509 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (3.38 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (3.38 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Batefenterol (GSK961081;TD-5959) is a novel muscarinic receptor antagonist and β_2-adrenoceptor agonist; displays high affinity for hM2, hM3 muscarinic and hβ_2-adrenoceptor with K_i values of 1.4, 1.3 and 3.7 nM, respectively.

IC_{50} & Target

mAChR2	mAChR3

In Vitro

Batefenterol is a novel first-in-class inhaled bifunctional compound possessing both muscarinic antagonist (MA) and β_2-adrenoceptor agonist (BA) properties (MABA). In competition radioligand binding studies at human recombinant receptors, batefenterol displays high affinity for hM2 (K_i=1.4 nM), hM3 muscarinic receptors (K_i=1.3 nM) and hβ_2-adrenoceptors (K_i=3.7 nM). Batefenterol behaves as a potent hβ_2-adrenoceptor agonist (EC_{50}=0.29 nM for stimulation of cAMP levels) with 440- and

	320-fold functional selectivity over hβ_1- and hβ_3-adrenoceptors, respectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In the guinea pig bronchoprotection assay, inhaled Batefenterol produces potent, dose-dependent inhibition of bronchoconstrictor responses via MA (ED_{50}=33.9 μg/mL), BA (ED_{50}=14.1 μg/mL), and MABA (ED_{50}=6.4 μg/mL) mechanisms. Significant bronchoprotective effects of Batefenterol are evident in guinea pigs via MA, BA, and MABA mechanisms for up to 7 days after dosing[1]. In guinea pig isolated trachea expressing native muscarinic M3 and β_2, batefenterol produces smooth muscle relaxation through a dual mechanism involving competitive antagonism of the M3 receptor (EC_{50}=50 nM) and agonism of the β_2 receptor (EC_{50}=25 nM). The combined effect on both muscarinic receptors and β_2 receptors is more potent than either function working alone (EC_{50}=10 nM). Batefenterol exhibits a rapid rate of clearance and short half-life[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	CHO-K1 cells stably transfected with each receptor subtype are incubated with increasing concentrations of batefenterol for 20 minutes at 37°C. The cells are stimulated with an EC_{90} concentration of the muscarinic agonist oxotremorine. Oxotremorine elicits a Gq-mediated calcium-release event, which in turn caused the calcium-sensitive dye to bind to calcium and fluoresce upon stimulation with a 488 nm laser light source. The change in fluorescence is measured by the FLIPR for 3 minutes, and the peak height in fluorescence is taken as the maximal response to generate the concentration-response curve for batefenterol[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Guinea pigs: Batefenterol is dissolved in water. Guinea pig trachea is dissected and isolated. The tracheal rings are initially tensioned to 1 g and allowed to equilibrate for 1 hour before evoking contraction with a submaximal concentration of either methylcholine (MCh; 10 μM), in the presence of propranolol (10 μM), or histamine (HIS; 30 μM) to assess relaxant effects via MA and BA mechanisms, respectively. Relaxation through the MABA mechanism is evaluated in tissues precontracted with MCh in the absence of propranolol. After the contractile tone attained a plateau, the batefenterol (0.1 nM to 100 μM) is added cumulatively in half log increments, with each concentration being added after achieving a steady-state relaxation response to the previous concentration. After the last concentration of test compound, theophylline (2.2 mM) is added to establish maximum relaxation[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Hegde SS, et al. Pharmacologic characterization of GSK-961081 (TD-5959), a first-in-class inhaled bifunctional bronchodilator possessing muscarinic receptor antagonist and β2-adrenoceptor agonist properties. J Pharmacol Exp Ther. 2014 Oct;351(1):190-9.

[2]. Hughes AD, et al. Discovery of (R)-1-(3-((2-chloro-4-(((2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-5-methoxyphenyl)amino)-3-oxopropyl)piperidin-4-yl [1,1'-biphenyl]-2-ylcarbamate (TD-5959, GSK961081, batefenterol): first-in-class dual pharmacology multivalent muscarinic antagonist and β? agonist (MABA) for the treatment of chronic obstructive pulmonary disease (COPD). J Med Chem. 2015 Mar 26;58(6):2609-22.

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