

Product Data Sheet

Product Name: Tonabersat

Cat. No.: GC16494

Chemical Properties

Cas. No. 175013-84-0

Chemical Name N-[(3S,4S)-6-acetyl-3-hydroxy-2,2-dimethyl-3,4-dihydrochromen-4-yl]-3-chloro-4-fluorobenzamide

SMILES CC(=O)C1=CC2=C(C=C1)OC(C(C2NC(=O)C3=CC(=C(C=C3)F)Cl)O)(C)C

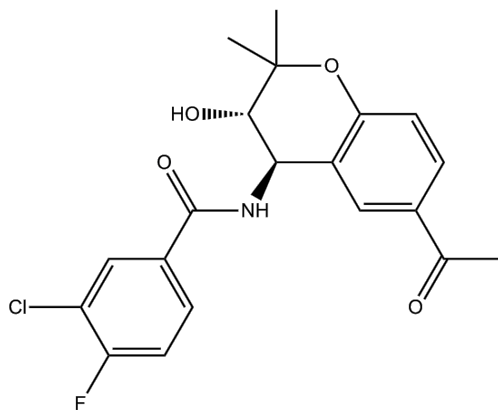
Formula $C_{20}H_{19}ClFNO_4$ M.Wt 391.82

Solubility DMF: 30 mg/ml, DMSO: 30 mg/ml, DMSO:PBS (pH 7.2)(1:9): 0.1 mg/ml, Ethanol: 20 mg/ml
Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Caution: Product has not been fully validated for medical applications. For research use only.

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Animal experiment: Mice[2] Athymic NCR nu/nu mice, Cr:NIH bg-nu-xid mice, B6129SF1/J, C57BL/6J-Tmem173gt/J 'golden ticket', and C57/BL/6J mice are used at 5-6 weeks of age. For inducible knockdown experiments, mice are given doxycycline hyclate in the drinking water (2 mg/mL) and the diet 14 days after injection of cancer cells. For drug treatment experiments, mice are intraperitoneally injected with Carboplatin (5 mg/kg per 5 days), Tonabersat (MedChem Express) (10 mg/kg per day), or meclofenamic acid sodium salt (20 mg/kg per day). Vehicle (10% DMSO in polyethylene glycol 400) is used in control mice. Quantification of tumour burden is by Bio-luminescent imaging (BLI), performed using an IVIS Spectrum Xenogen instrument and analysed using Living Image software v.2.50.

References:

- [1]. Silberstein SD, et al. Tonabersat, a gap-junction modulator: efficacy and safety in two randomized, placebo-controlled, dose-ranging studies of acute migraine. Cephalalgia. 2009 Nov;29 Suppl 2:17-27.
- [2]. Chen Q, et al. Carcinoma-astrocyte gap junctions promote brain metastasis by cGAMP transfer. Nature. 2016 May 18;533(7604):493-8.
- [3]. Kim Y, et al. Tonabersat Prevents Inflammatory Damage in the Central Nervous System by Blocking Connexin43 Hemichannels. Neurotherapeutics. 2017 May 30.

Background

Migraine is a common, recurrent and primary headache disorder. Optimisation of novel cis- and trans-4-(substituted-anfido)benzopyran-3-ol derivatives has led to the identification of Tonabersat (SB-220453) with potential antimigraine activity.

In vitro: Topiramate targets multiple cortical and subcortical loci, altering voltage-gated ion channels and chemical transmission to decrease abnormal brain excitability. Preclinical studies have identified four properties that may account for the drug's efficacy in epilepsy and migraine prophylaxis: (i) blockage of voltage-dependent sodium channels; (ii) augmentation of the activity of the neurotransmitter g-aminobutyric acid (GABA) at some subtypes of the GABA-A receptor; (iii)

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antagonism of the AMPA/kainate subtype of the glutamate receptor; and (iv) inhibition of the carbonic anhydrase enzymes, particularly isozymes II and IV [1].

In vivo: Tonabersat binds selectively to a unique site in the brain. Moreover, tonabersat could markedly reduce cortical spreading depression (CSD) and CSD-associated events and inhibit gap-junction communication between neurons and satellite glial cells in the trigeminal ganglion. Together, these findings indicate that tonabersat should have clinical application in preventing migraine attacks [2].

Clinical trial: Tonabersat showed a preventive effect on attacks of migraine aura but no efficacy on non-aura attacks, in keeping with its known inhibitory effect on CSD. The results support the theory that auras are caused by CSD and that this phenomenon is not involved in attacks without aura [3].

References:

- [1] Silberstein SD. Tonabersat, a novel gap-junction modulator for the prevention of migraine. Cephalalgia. 2009;29 Suppl 2:28-35.
- [2] Durham PL, Garrett FG. Neurological mechanisms of migraine: potential of the gap-junction modulator tonabersat in prevention of migraine. Cephalalgia. 2009;29 Suppl 2:1-6.
- [3] Hauge AW, Asghar MS, Schytz HW, Christensen K, Olesen J. Effects of tonabersat on migraine with aura: a randomised, double-blind, placebo-controlled crossover study. Lancet Neurol. 2009;8(8):718-23.

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