

Product Data Sheet

Product Name: GNE-781

Cat. No.: GC32081

Chemical Properties

Cas. No. 1936422-33-1

SMILES O=C(N1CCC(N(C2CCOCC2)N=C3N4CCCC5=C4C=C(C(F)F)C(C6=CN(C)N=C6)=C5)=C3C1)NC

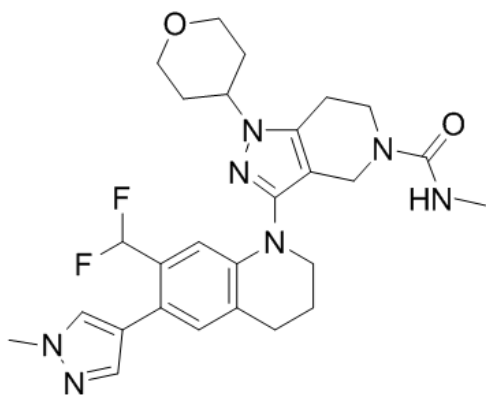
Formula $C_{27}H_{33}F_2N_7O_2$ M.Wt 525.59

Solubility DMSO : 100 mg/mL (190.26 mM) 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.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

**Animal
experiment:**

Mice[1] Twelve female CD-1 mice are used. All animals are 6-9 weeks old at the time of study and weighed between 20 and 35 g. Animals (n=3 per dosing route) are dosed with 10 or GNE-781 at 1 mg/kg iv (in propyl ethylene glycol 400 (35% v/v) and water (65% v/v)) or 5 mg/kg po (suspended in 0.5% w/v methylcellulose, 0.2% w/v Tween 80). Food and water are available ad libitum to all animals. Serial blood samples (15 µL) are collected by tail nick at 0.033, 0.083, 0.25, 0.5, 1, 3, 8, and 24 h after the intravenous administration and 0.083, 0.25, 0.5, 1, 3, 8, and 24 h after the oral administration. All blood samples are diluted with 60 µL of water containing 1.7 mg/mL EDTA and kept at -80 °C until analysis[1]. Rats[1] Twelve male Sprague-Dawley rats are used. All animals are 6-9 weeks old at the time of study and weighed between 200 and 300 g. Animals (n=3 per dosing route) are dosed with 10 or GNE-781 at 1 mg/kg iv (in propyl ethylene glycol 400 (35% v/v) and water (65% v/v)) or 5 mg/kg po (suspended in 0.5% w/v methylcellulose, 0.2% w/v Tween 80). Food and water are available ad libitum to animals in the iv groups. Animals in po groups are fasted overnight and food withheld until 4 h postdose. Approximately 250 µL of blood are collected via the catheter at 0.033, 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 h after the intravenous or oral administration. All blood samples are collected into tubes containing 5 µL of 0.5 M K2EDTA and processed for plasma. Samples are centrifuged (2500g for 15 min at 4°C) within 1 h of collection, and plasma samples are kept at -80 °C until analysis[1].

References:

[1]. Romero FA, et al. GNE-781, A Highly Advanced Potent and Selective Bromodomain Inhibitor of Cyclic Adenosine Monophosphate Response Element Binding Protein, Binding Protein (CBP). J Med Chem. 2017 Nov 22;60(22):9162-9183.

Background

GNE-781 is a highly potent and selective CBP inhibitor with an IC₅₀ of 0.94 nM in TR-FRET assay. GNE-781 also inhibits BRET and BRD4(1) with IC₅₀s of 6.2 nM and 5100 nM, respectively.

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

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

GNE-781 is a highly advanced potent and selective bromodomain inhibitor of cyclic adenosine monophosphate response element binding protein, binding protein (CBP). GNE-781 reduces FOXP3 (forkhead box P3) transcript levels. Examination of a subset of bromodomains reveals that GNE-781 is exquisitely selective for CBP/P300 and is remarkably selective for CBP (5425-fold) and P300 (4250-fold). GNE-781 demonstrates an appropriate balance of cell potency, selectivity (5425-fold over BRD4(1)) [1].

GNE-781 is a highly potent and selective CBP inhibitor that is efficacious in a MOLM-16 AML xenograft model. GNE-781 displays antitumor activity in an AML tumor model and is also shown to decrease Foxp3 transcript levels in a dose dependent manner. GNE-781 shows moderate to low clearance in vivo in all species evaluated, with acceptable oral bioavailability. The effect of GNE-781 is determined in an in vivo PK/PD experiment using a MOLM-16 (adult AML cell line) xenograft mouse model. Single doses of GNE-781 are given at dose levels between 3 and 30 mg/kg in MOLM-16 tumor-bearing animals, and samples are collected at time points covering 2-24 h. Tumor RNA is generated and used to assess MYC transcript by quantitative RT-PCR relative to vehicle-treated animals. Suppression of MYC is observed at doses as low as 3 mg/kg at 2 and 8 h, with maximal suppression observed at 10 and 30 mg/kg at 2 h (87% and 88% inhibition, respectively). To evaluate the in vivo efficacy of GNE-781, MOLM-16 AML xenografts are established in SCID beige mice. Upon tumor establishment, dosing of GNE-781 is initiated with po doses of 3-30 mg/kg, twice daily (BID). Single-agent efficacy is observed at all doses, as evidenced by inhibition of MOLM-16 tumor growth. Tumor growth inhibition (%TGI) is 73%, 71%, and 89% at 3, 10, and 30 mg/kg, respectively. All doses of GNE-781 are well tolerated over the 21-day dosing window, with a maximal body weight loss of 3.7%[1].

[1]. Romero FA, et al. GNE-781, A Highly Advanced Potent and Selective Bromodomain Inhibitor of Cyclic Adenosine Monophosphate Response Element Binding Protein, Binding Protein (CBP). J Med Chem. 2017 Nov 22;60(22):9162-9183.

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

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA