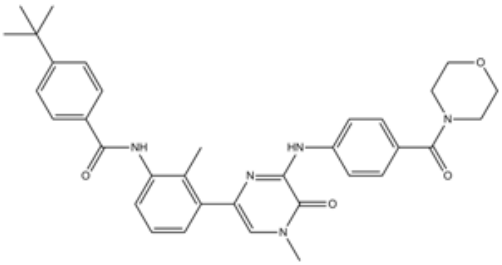
Product Data Sheet

Product Name: CGI-1746
Cat. No.: GC13365

Chemical Properties

Cas. No.	910232-84-7		
Chemical Name	4-tert-butyl-N-[2-methyl-3-[4-methyl-6-[4-(morpholine-4-carbonyl)anilino]-5-oxopyrazin-2-yl]phenyl]benzamide		
SMILES	CC1=C(C=CC=C1NC(=O)C2=CC=C(C=C2)C(C)(C)C)C3=CN(C(=O)C(=N3)NC4=CC=C(C=C4)C(=O)N5CCOCC5)C		
Formula	$C_{34}H_{37}N_5O_4$	M.Wt	579.71
Solubility	≥ 29 mg/mL in DMSO, ≥ 6.72 mg/mL in EtOH with ultrasonic and warming	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

Cell experiment [1]:

Cell lines Human B cells

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Preparation method	The solubility of this compound in DMSO is > 29 mg/mL. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below - 20 °C for several months.
Reacting condition	0.003 ~ 10 μM
Applications	In human B cells, CGI-1746 potently inhibited anti-IgM-induced phosphorylation of Btk Tyr223, Btk Tyr551 and PLCγ2 Tyr1217, with an average IC50 value of 2.9 nM. In addition, CGI-1746 lowered the basal phosphorylation levels of Btk Tyr551 and Tyr223, but not the basal phosphorylation of PLCγ2 Tyr1217.

Animal experiment [1]:

Animal models	Collagen-induced arthritis (CIA) mouse model
Dosage form	100 mg/kg; s.c.; b.i.d., from day 12 to day 26
Applications	CGI-1746 significantly inhibited overall clinical arthritis scores (97% inhibition). Moreover, CGI-1746 substantially reduced anti-collagen II (CII) titers.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

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References:

[1]. Di Paolo JA, Huang T, Balazs M, et al. Specific Btk inhibition suppresses B cell- and myeloid cell-mediated arthritis. Nat Chem Biol, 2011, 7(1): 41-50.

Background

CGI-1746 is a selective and potent inhibitor of Bruton's tyrosine kinase (BTK) with IC50 value of 1.9 nM [1][2].
Bruton's tyrosine kinase (BTK) is a member of the Tec tyrosine kinase family and plays an important role in differentiation, proliferation and development of B cells. It is an attractive target for the treatment of immunological disorders such as B-cell malignancies, rheumatoid arthritis (RA), multiple sclerosis (MS) and lupus [3].
CGI-1746 potently inhibits both auto- and transphosphorylation of BTK. It binds to un-phosphorylated BTK and stabilizes it in an inactive enzyme state. In cellular assays, CGI-1746 blocks BCR-mediated B-cell proliferation and suppresses the production of IL-6, IL-1βand TNF in macrophages [1].
In experimental mouse models, CGI-1746 shows a robust anti-arthritic activity [1]. In B10.RIII mice model, CGI1746 resulted in a significant inhibition (97%) of clinical arthritis scores, which were better than dexamethasone treatment (56% inhibition) [2].

References:

[1]. Akinleye A, Chen Y, Mukhi N, et al. Ibrutinib and novel BTK inhibitors in clinical development. J Hematol Oncol, 2013, 6: 59.
[2]. Di Paolo JA, Huang T, Balazs M, et al. Specific Btk inhibition suppresses B cell- and myeloid cell-mediated arthritis. Nat Chem Biol, 2011, 7(1): 41-50.
[3]. Young WB, Barbosa J, Blomgren P, et al. Potent and selective Bruton's tyrosine kinase inhibitors: discovery of GDC-0834. Bioorg Med Chem Lett, 2015, 25(6): 1333-1337.