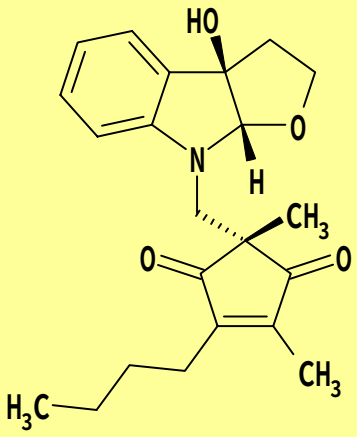
(+)-Madindoline A

Cat.# BLS0480

Structure



Origin: synthetic

CAS Registry Number: 184877-64-3

CA Index Name: [(2R), 3aR, 8aS]-8-[4-(n-Butyl)-2,5-dimethyl-1, 3-dioxo-2-(4-cyclopentyl)-methyl]-3, 3a, 8,8a-tetrahydro-3a-hydroxy-2*H*-furo[2,3-*b*]indole

Appearance: Light Greenish solid

Molecular Formula/ Weight: $C_{22}H_{27}NO_4$=370.20

Melting Point: 81-86℃ | **Purity:** >97.5% by HPLC

Solubility: Soluble in MeOH, DMSO, Chloroform, EtOH, EtOAc, Acetone, Acetonitrile
Insoluble in water, Hexane

Background Information:

Madindolines A was isolated from *Streptomyces nitrosporeus* K93-0711, as selective inhibitors of IL-6. Madindolines A specifically inhibited the growth of the IL-6-dependent MH60 cell line (IC_{50} values of 8 microM), but they did not affect the IL-6-independent MH60 cell line. More detailed biological studies showed that Madindolines A dose-dependently suppressed IL-6 and IL-11-induced osteoclastogenesis. Furthermore, madindoline A markedly inhibited bone resorption in ovariectomized (OVX) mice *in vivo*.
Madindolines A binds to gp130 and inhibits actions of IL-6 without formation of the trimeric complex. Therefore, the mechanism of this action involves binding to gp-130 site 2, the site for IL-6 site III, and inhibiting gp130 homodimerization, resulting in inhibition of IL-6 activity.

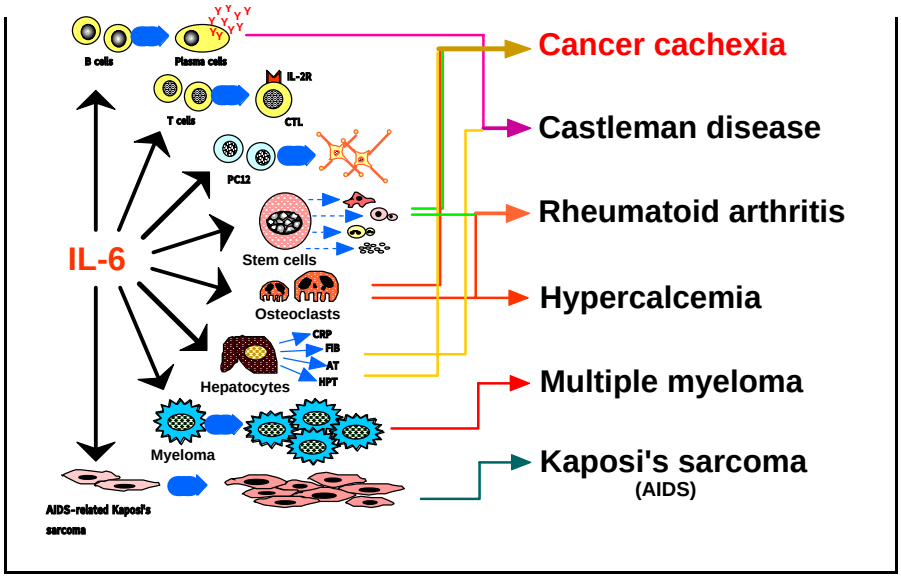
Handling and Storage:

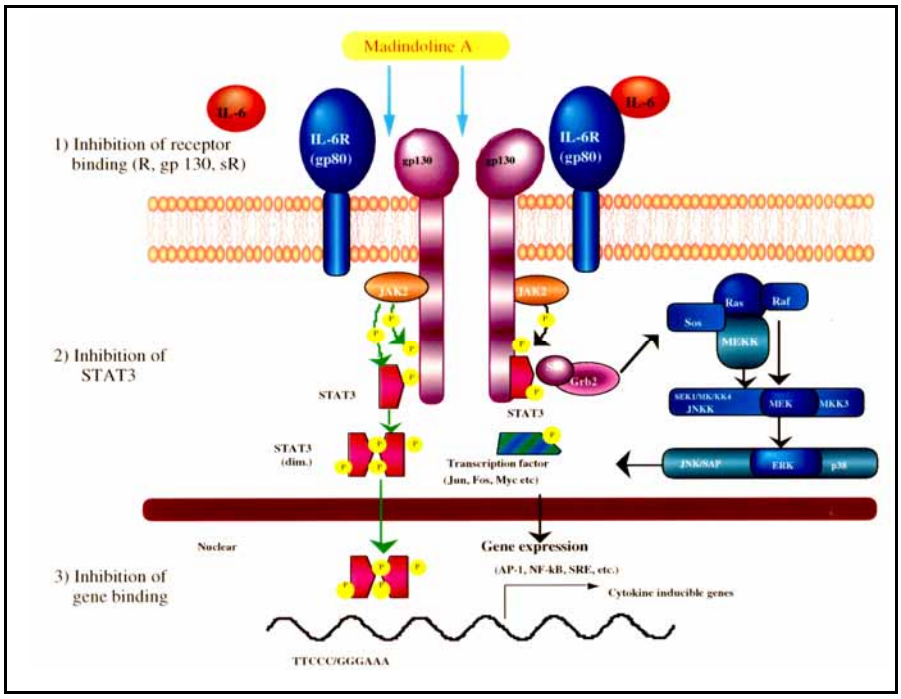
Store at -20℃.

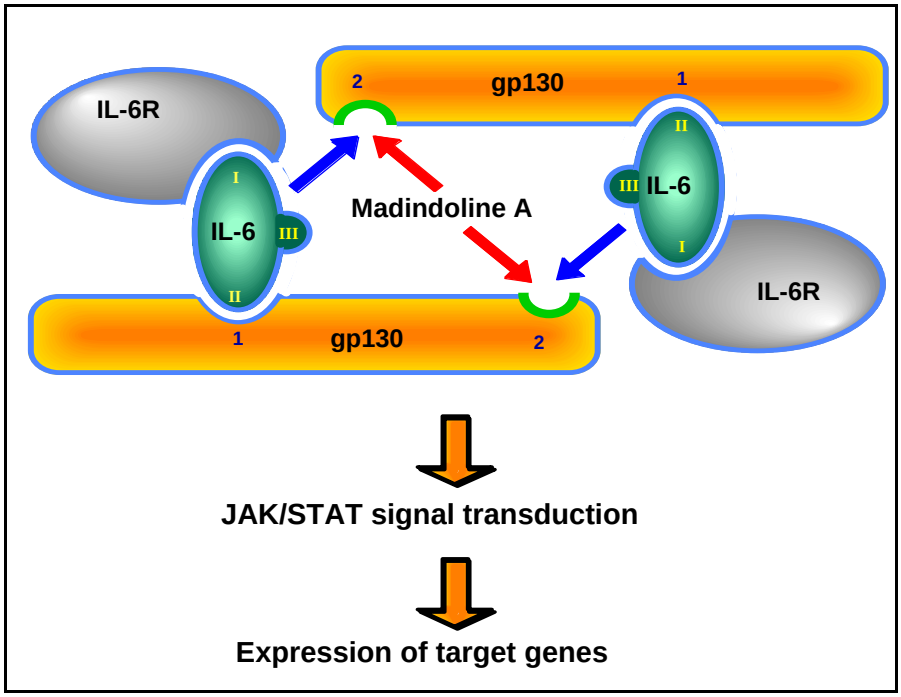
References:

1. M. Hayashi et al., J. Antibiot., **49**, 1091 (1996).
2. S. Takamatsu et al., J. Antibiot., **50**, 1069 (1997).
3. T. Sunazuka et al., J. Am. Chem. Soc., **122**, 2122 (2000).
4. T. Hirose et al., Organic Letters, **4**, 501 (2002).
5. M. Hayashi et al., Proc. Natl. Acad. Sci. USA, **99**, 14728 (2002).
6. T. Hirose, T. Sunazuka, T. Shirahata, D. Yamamoto, Y. Harigaya, I. Kuwajimaand, S. Ōmura, “Total Synthesis of (+)-Madindoline A
7. D. Yamamoto, T. Sunazuka, T. Hirose, N. Kojima, E. Kaji and S. Ōmura. “Design, synthesis, and biological activities of madindoline

Synthesized by Organic Chemistry Group, The Kitasato Institute.


B cells
Plasma cells
T cells
IL-2R
CTL
PC12
IL-6
Stem cells
Osteoclasts
CRP
FIB
AT
HPT
Hepatocytes
Myeloma
AIDS-related Kaposi's sarcoma
Cancer cachexia
Castleman disease
Rheumatoid arthritis
Hypercalcemia
Multiple myeloma
Kaposi's sarcoma
(AIDS)


Madindoline A
IL-6
IL-6R (gp80)
gp130
1) Inhibition of receptor binding (R, gp 130, sR)
JAK2
2) Inhibition of STAT3
STAT3
STAT3 (dim.)
Grb2
Ras
Raf
Sos
MEKK
MEK
MKK3
JNKK
JNK/SAP
ERK
p38
Transcription factor (Jun, Fos, Myc etc)
Nuclear
Gene expression
(AP-1, NF-kB, SRE, etc.)
Cytokine inducible genes
3) Inhibition of gene binding
TTCCCGGGAAA


IL-6R
gp130
2
1
I
II
III
IL-6
Madindoline A
IL-6R
JAK/STAT signal transduction
Expression of target genes