3050 Spruce Street, St. Louis, MO 63103 USA
Tel: (800) 521-8956 (314) 771-5765 Fax: (800) 325-5052 (314) 771-5757
email: techservice@sial.com sigma-aldrich.com

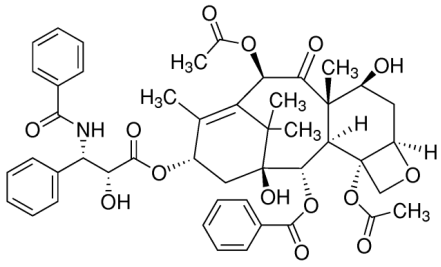
Product Information

Paclitaxel

Catalog Numbers **T1912 and T7402**
Storage Temperature 2–8 °C

CAS RN 33069-62-4
Synonyms: Taxol®, Taxol A, NSC 125973, BMS 181339-01

Product Description



Molecular formula: $C_{47}H_{51}NO_{14}$
Formula weight: 853.91
$E^{M,1}$: 29,800 (227 nm, methanol)
$E^{M,1}$: 1,700 (273 nm, methanol)

Paclitaxel is isolated from *Taxus brevifolia* (Catalog NumberT7402) and *Taxus yannanensis* (Catalog NumberT1912). It is a complex diterpene and antitumor agent with antitumor activity against ovarian, breast, lung, and prostrate cancer,[2,3] and acts as a promoter of tubulin polymerization and stabilizes microtubules to depolymerization by different agents, both *in vitro* and *in vivo*.[4,5] Microtubules, an integral component of eukaryotic cells, are involved in many cellular functions, including mitosis, maintenance of cell shape, cell motility, and transport between organelles within the cell. Paclitaxel alters the normal equilibrium between tubulin dimers and microtubules, and, therefore, disrupts cell division, i.e., stabilization of the microtubules interferes with the G_2 and M phases of the cell cycle and those cellular activities involving microtubules.[6] The paclitaxel-stabilized microtubules are resistant to depolymerization upon exposure to calcium ions and cold temperatures, and do not require the presence of GTP, a natural cofactor necessary for polymerization initiation.[2,5] Unlike other spindle poisons, which prevent polymerization of the monomer, paclitaxel has a binding site on the microtubule.[2] Characterization of the binding site of paclitaxel to the microtubule can be elucidated with taxol photoaffinity labels.[6]

The proposed preliminary mechanisms of action, metabolism, structure-activity relationships, and pharmacokinetics have been reported.[2,4,7-13] Analogs having greater biological activity have been prepared.[2,3,6,7,12,14,15] The antitumor potency of paclitaxel encapsulated in liposomes (phospholipid vesicles composed of phosphatidylglycerol and phosphotidylcholine) was retained or slightly enhanced.[16]

Paclitaxel, as low as 0.05 μM, promoted microtubule assembly *in vitro* even in the absence of GTP or microtubule-associated proteins (MAPs).[17] Studies with HeLa cells and fibroblasts treated with paclitaxel (0.25 or 10 μM) have shown paclitaxel blocked cells in the G_2 and M phase of the cell cycle.[18]

Paclitaxel effected the stimulation of MAP-2 kinase activity and blocked processes important for invasion and metastases in PC-3ML prostate tumor cells (induced inhibition of collagenase secretion).[6] It inhibited the locomotion of Walker 256 carcinoma cells; the intracellular transportation of steroids in MLTC-1 cells; and the immunoreactivity of τ-MAPs in neurons.[7] A 1.5-fold increase in cisplatin sensitivity in cisplatin-sensitive A2780 human ovarian cancer cell lines was induced by paclitaxel.[19] It (3–10 nM) inhibited mitotic progression of HCT116 human colon carcinoma cells and induced formation of micronuclei.[20]

In nonmalignant cells paclitaxel inhibited specific functions such as chemotaxis, migration, and cell spreading. It inhibited the slow transportation of tubulin, actin, and polypeptides in axons[7] and the proliferation of stimulated lymphocytes, decreased tumor necrosis factor-α (TNF-α) receptors, induced (at 1–30 μM) murine macrophages to express TNF-α mRNA and genes associated with the LPS-induced macrophage activation, and induced protein tyrosine phosphorylation.[7,21,22] Paclitaxel inhibited secretory functions of specialized cells, i.e., insulin secretion in isolated rat islets of Langerhans,[17] catecholamine from adrenal medullary cells, plasma proteins from rat liver cells, and prothrombinase from platelets.[7] Paclitaxel activated the GADD153 promoter through a cellular injury response element containing an essential Sp1 binding site.[23]

Paclitaxel induced assembly of 12-protofilament microtubules in *Drosophila* during microtubule nucleation step.[24] Paclitaxel-induced microtubule asters in mitotic extracts of *Xenopus* eggs require phosphorylation and cytoplasmic dynein.[25] The viability of chick embryos was decreased and malformed live embryos were produced by paclitaxel.[26]

Precautions and Disclaimer
This product is for R&D use only, not for drug, household, or other uses. Please consult the Material Safety Data Sheet for information regarding hazards and safe handling practices.

Preparation Instructions
Paclitaxel is soluble in DMSO (50 mg/ml). A 0.01 M solution of paclitaxel in DMSO was stored as aliquots until use and further diluted to 10^{-10} M with medium.[27]

Paclitaxel is soluble in methanol (50 mg/ml). It undergoes hydrolysis and transesterification in methanol, losing ~30% of the peak signal at 227 nm by HPLC in two weeks at room temperature. Paclitaxel is rapidly destroyed in weakly alkaline, methanolic solutions and in strongly acidic methanolic solutions (1:1 of methanol:concentrated HCl). A sample with 0.1% acetic acid added to methanol showed no signs of degradation for seven days at room temperature or three months at 4 °C (presumably due to the ability of the acetic acid to neutralize traces of alkali in the methanol).[28]

Paclitaxel is also soluble in ethanol and acetonitrile. It is soluble in a mixture of 50% Cremophor® EL and 50% anhydrous ethanol. This solution can be diluted with saline to give a final concentration of 0.03–0.60 mg/ml in paclitaxel.[2]

Paclitaxel has poor solubility in water and is rapidly destroyed in weakly alkaline, aqueous solutions.[28] The least amount of degradation in aqueous paclitaxel solutions occurred in the pH range of 3–5. Paclitaxel solutions at 0.1 and 1 mg/ml in 5% dextrose injection or 0.9% sodium chloride injection remained active for at least three days at 4, 22, or 32 °C.[29] Paclitaxel (20 μg/ml) is remains more active in cyclodextrin solutions (10–20%) than in buffer solutions of comparable pH. There was less than 1% decomposition of paclitaxel in the cyclodextrin solutions stored for one month at 37 °C. Solubility in water is increased in the presence of cyclodextrin.[30]

Storage/Stability
Store the product desiccated at 2–8 °C and protected from the light.

References

1. *Merck Index*, 12th ed. #7117, 1996.
2. Vyas, D.M., and Kadow, J.F., *Prog. Med. Chem.*, **32**, 289, 1995.
3. Wall, M.E., and W., M.C., *Cancer Res.*, **55**, 753, 1995.
4. Carlier, M.-F., and Pantaloni, D., *Biochem.*, **22**, 4814, 1983.
5. Schiff, P.B. et al., *Nature (Lond.)*, **277**, 665, 1979.
6. Georg, G.I. et al., *The Medicinal Chemistry of Taxol*, Chap. 13, Taxol: Science and Applications, Suffness, M., ed., CRC Press, Inc., 1995.
7. Nicolaou, K.C. et al., *Angew. Chem. Int. Ed. Engl.*, **33**, 15, 1994.
8. Han, Y. et al., *Biochem.* **35**, 14173, 1996.
9. Horwitz, S.B., *Trends Pharmacol. Sci.* **13**, 134, 1992.
10. Suffness, M., *Annu. Rep. Med. Chem.* **28**, 305, 1993.
11. Horwitz, S.B. et al., *Monogr. Natl. Cancer Inst.* **15**, 55, 1993.
12. Kingston, D.G.I., ACS Symposium Series 583, *Taxane Anticancer Agents*, 203, Georg, G.I. et al., eds, Chap. 15, American Chemical Society, 1995.
13. Rowinsky, E.K. et al., *J. Natl. Cancer Inst.*, **82**, 1247, 1990.
14. Kant, J., *The Chemistry and Pharmacology of Taxol and Its Derivatives*, 22, 255, Farina, V. ed., Pharmochemistry Library, Elsevier, New York, 1995.
15. Boge, T.C. et al., *J. Med. Chem.*, **37**, 3337, 1994.
16. Straubinger, R.M. et al., Chap. 8 ACS Symposium Series 583, *Taxane Anticancer Agents*, 111, Georg, G.I. et al, eds., American Chemical Society, 1995.
17. Rowinsky, E.K., and Donehower, R.C., *Pharmac. Ther.* **52**, 35, 1991.
18. Schiff, P.B., and Horwitz, S.B., *Proc. Natl Acad. Sci.*, **77**, 1561, 1980.
19. Parker, R.J. et al., *J. Natl. Cancer Inst.*, Monographs No. 15, 83, 1993.
20. Guenard, D. et al., *Current Pharmaceutical Design*, **1**, 95, 1995.
21. Ding, A.H. et al., *Science*, **248**, 370, 1990.
22. Manthey, C.L. et al., *J. Immunol.*, **149**, 2459, 1992.
23. Gately, D.P., and Howell, S.B., *J. Biol. Chem.,* **271**, 20588, 1996.
24. Mogensen, M.M., and Tucker, J.B., *J. Cell Science*, **97**, 101, 1990.
25. Verde, F. et al., *J. Cell Biol.*, **112**, 1177, 1991.
26. Scialli, A.R. et al., *Teratogenesis, Carcinog. Mutagen.,* **14**, 23, 1994.
27. Adler, L.M. et al., *Cancer*, **74**, 1891, 1994.
28. Richheimer, S.L. et al., *Anal. Chem.,* **64**, 2323, 1992.
29. Xu, Q. et al., *Am. J. Hosp. Pharm.*, **51**, 3058, 1994.
30. Dordunoo, S.K., and Burt, H.M., *Int. J. Pharmaceu.*, **133**, 191, 1996.

KEK,ARO,MAM 06/09-1