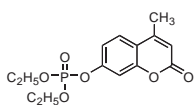


## Diethylumbelliferyl phosphate (UBP; DEUP): Cholesteryl ester hydrolase inhibitor

Prod. Code **D 7692**



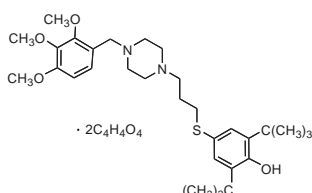
An effective inhibitor of the cholesteryl ester hydrolase in intact MA-10 Leydig tumor cells ( $IC_{50} = 11.6 \mu\text{M}$  in (Bu)<sub>2</sub>cAMP-stimulated, cholesteryl ester-loaded MA-10 cells) [1]. Blocks steroidogenesis mainly by preventing cholesterol transport into the mitochondria of steroidogenic cells [1]. In Fu5AH cells, UBP caused a 72% decrease in the cellular free cholesterol/cholesteryl ester and inhibition of triglycerides (TG), but did not interfere with esterified cholesterol and TG synthesis nor did it cause cellular toxicity in doses up to 120  $\mu\text{g/ml}$  [2,3]. Inhibitors of cholesterol esterase are anticipated to limit the absorption of dietary cholesterol [4].

### References

1. Gocze, P.M., et al., A cholesteryl ester hydrolase inhibitor blocks cholesterol translocation into the mitochondria of MA-10 Leydig tumor cells. *Endocrinology*, **131**, 2972-2978 (1992).
2. Delamatre, J.G., et al., Evidence that a neutral cholesteryl ester hydrolase is responsible for the extralysosomal hydrolysis of high-density lipoprotein cholesteryl ester in rat hepatoma cells (Fu5AH). *J. Cell Physiol.*, **157**, 164-168 (1993).
3. Kellner-Weibel, G., et al., Evidence that newly synthesized esterified cholesterol is deposited in existing cytoplasmic lipid inclusions. *J. Lipid Res.*, **42**, 768-777 (2001).
4. Heidrich, J.E., et al., Inhibition of pancreatic cholesterol esterase reduces cholesterol absorption in the hamster. *BMC Pharmacol.*, **4**, 5 (2004).

## S-15176 difumarate salt: Carnitine palmitoyltransferase (CPT-1) inhibitor; antioxidant and anti-ischemic agent

Prod. Code **S 5944**



$IC_{50}$  for carnitine palmitoyltransferase (CPT-1) in heart homogenate is 16.8  $\mu\text{M}$ . Inhibits *in vitro* lipid peroxidation (0.3  $\mu\text{M}$ ) in liver from animals subjected to 2 hr of liver injury induced by warm ischemia-reperfusion. The shift from fatty acid to glucose oxidation

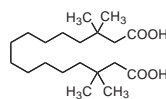
may contribute to anti-ischemic effect. Also used to inhibit mitochondrial permeability transition and to prevent onset of apoptosis by preventing collapse of the electrochemical gradient across the mitochondrial membrane.

### References

1. Hamdan, M., et al., Inhibition of mitochondrial carnitine palmitoyltransferase-1 by a trimetazidine derivative, S-15176. *Pharmacol. Res.*, **44**, 99-104 (2001).
2. Rupp, H., et al., The use of partial fatty acid oxidation inhibitors for metabolic therapy of angina pectoris and heart failure. *Herz*, **27**, 621-636 (2002).
3. Settaf, A., et al., S-15176 reduces the hepatic injury in rats subjected to experimental ischemia and reperfusion. *Eur. J. Pharmacol.*, **406**, 281-292 (2000).
4. Eliadi, A., et al., S-15176 inhibits mitochondrial permeability transition via a mechanism independent of its antioxidant properties. *Eur. J. Pharmacol.*, **468**, 93-101 (2003).

## MEDICA 16: ATP-citrate lyase inhibitor; potent triacylglycerol-lowering agent

Prod. Code **M 5693**



ATP-citrate lyase is the main enzyme responsible for supplying acetyl-CoA to many tissues, and most notably in adipose tissue and liver where *de novo* synthesis of fatty acids is very active, especially when glucose is in excess [1].

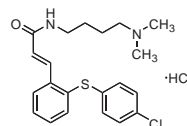
Because ATP-citrate lyase is involved in both the fatty acid and cholesterol synthesis pathways, it has been suggested that inhibition of this enzyme may be a drug target for hyperlipidemia [1]. One compound that supports this suggestion is MEDICA 16. When MEDICA 16 was given to JCR:LA-cp rats (0.25% (wt/wt)) starting at weaning up to three weeks of age, (JCR:LA-cp rats develop extreme obese/insulin-resistant syndrome by 12 weeks of age), their plasma lipids decreased dramatically and their food intake and body weight returned to normal levels by 8 weeks of age [2]. In addition, insulin levels were significantly decreased, and plasma triacylglycerol concentrations were maintained at the same level as the control lean rats [2].

### References

1. Groot, P.H.E., et al., ATP-citrate lyase: A potential target for hypolipidemic intervention. *Curr. Med. Chem. Immunol. Endocr. Metab. Agents*, **3**, 211-217 (2003).
2. Russell, J.C., et al., Development of insulin resistance in the JCR:LA-cp rat: role of triacylglycerols and effects of MEDICA 16. *Diabetes*, **47**, 770-778 (1998).

## A-350619 hydrochloride: Novel, soluble guanylyl cyclase activator

Prod. Code **A 6604**



The soluble guanylyl cyclase (sGC) receptor is a major receptor for nitric oxide (NO). Guanylyl cyclase converts GTP to cyclic GMP affecting such physiological processes as smooth muscle relaxation, neurotransmission, inhibition of platelet aggregation and immune response. A-350619, an activator of

sGC, modulates the catalytic properties of sGC [increases  $V_{max}$  from 0.1 to 14.5  $\mu\text{mol/min/mg}$  (145-fold increase), lowers  $K_m$  from 300 to 50  $\mu\text{M}$  (6-fold decrease)]. A-350619 has also been shown to relax rabbit corpus cavernosum tissue strips in a dose-dependent manner with  $EC_{50}$  of 80  $\mu\text{M}$  (vs 50  $\mu\text{M}$  for another sGC inhibitor, YC-1). Moreover, A-350619 has been shown to induce penile erection in a conscious rat model (1  $\mu\text{mol/kg}$ ) suggesting that activation of sGC could be used as an alternate method of enhancing the effect of NO for the treatment of sexual dysfunction.

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### Reference

1. Miller, L.N., et al., A-350619: a novel activator of soluble guanylyl cyclase. *Life Sci.*, **72**, 1015-1025 (2003).

### Related Products

Product Name	Descriptor	Prod. Code
Isoliquiritigenin	Guanylyl cyclase activator	I 3766
NS 2028	Guanylyl cyclase inhibitor	N-211
ODQ	Guanylyl cyclase inhibitor	O 3636
YC-1	Guanylyl cyclase activator	Y-102