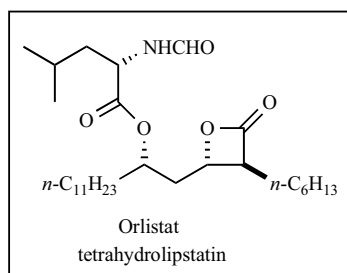


Molecule of the Month

A new "Alli" in weight loss. The FDA recently approved the country's first over-the-counter weight loss drug, appropriately named Alli (Orlistat), providing a readily available tool for the estimated 60 million Americans who are battling obesity [1]. Orlistat, first approved for prescription use in 1998, is a reversible inhibitor of gastric and pancreatic lipases, and causes a partial blockade of dietary fat absorption [2,3]. The compound, tetrahydrolipstatin, is derived from an endogenous lipostatin isolated from *Streptomyces toxytricini* [2]. Human studies showing that orlistat enhances weight loss in obese subjects were first reported in 1992 [4]. In conjunction with a low-calorie diet and moderate exercise, orlistat has been shown in double-blind, placebo-controlled studies to reduce fat mass significantly more than diet and exercise alone [2,3]. Additional



benefits of orlistat include reduced incidence of type 2 diabetes, lessening of risk factors for cardiovascular disease, and beneficial effects on blood pressure [2,3]. While Xenical, the prescription version of orlistat, is sold in 120 mg capsules, the nonprescription dose of Alli will be 60 mg. Studies performed by GlaxoSmithKline, which will manufacture Alli, indicate that the lower dose provides 85% of the weight loss benefit observed with the prescription dose [1]. While orlistat has a generally good safety record, many patients experience adverse gastrointestinal side effects due to an excess of excreted fat [2,3]. In addition, orlistat can reduce the absorption of fat-soluble vitamins and a handful of prescription drugs [2,3]. However, because very little drug is absorbed systemically, its negative drug interactions and potential for harmful systemic effects are minimal, making it relatively safe for nonprescription sale [1-3].

In addition to inhibiting gastrointestinal lipases, Orlistat is also an irreversible inhibitor of fatty acid synthase

(FASN), an enzyme that synthesizes long-chain fatty acids from acetyl-CoA, malonyl-CoA, and nicotinamide adenine dinucleotide phosphate (NADPH) [5]. Because FASN is minimally expressed in noncancerous cells, but is upregulated in many types of cancer cells, it has been identified as a possible therapeutic target for several types of cancer. Inhibitors of FASN, such as Orlistat and other β -lactones, have anti-proliferative and pro-apoptotic effects in cultured cancer cells expressing high levels of FASN, although the mechanisms underlying these effects are not well characterized. While Orlistat has no effect on non-cancerous cultured cells, cytotoxic effects have been observed against prostate, breast, colon, stomach, and ovarian cancer cells in culture [5]. Orlistat has also been shown to prevent tumor growth in a mouse xenograft model without obvious general toxicity, providing further evidence that it could be used to treat certain types of cancer [6]. Unfortunately, the low bioavailability of Orlistat would limit its application in human cancers to gastrointestinal tumors [5]. The synthesis of similar β -lactones with increased bioavailability and comparable levels of FASN inhibition could significantly enhance the therapeutic potential of Orlistat-like compounds.

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