Forget chugging chalky Kaopectate when your next bout of diarrhea hits. A newly synthesized pyridopyrimidine derivative (shown) may one day be used to halt diarrhea caused by toxin-producing strains of the bacteria *Escherichia coli*. The novel compound, identified by pharmacologist Ferid Murad and coworkers at the University of Texas Health Science Center, prevents the heat-stable enterotoxin (STa) secreted by *E. coli* from stimulating the buildup of fluids in the intestine and causing diarrhea.

Unlike current therapies, which reduce fluids already accumulated, the bromophenyl-substituted pyridopyrimidine derivative synthesized by Murad’s team prevents the accumulation of cyclic guanosine monophosphate (cGMP) and therefore the efflux of fluid into the intestines (Proc. Natl. Acad. Sci. USA 2008, 105, 8440). STa binds to the transmembrane guanylyl cyclase type C receptor in intestinal cells, causing intracellular concentrations of cGMP to spike. The increase in cGMP triggers an influx of sodium ions and water to the intestines, which leads to diarrhea. Murad identified the pyridopyrimidine derivative by screening a library of compounds for ones that prevent accumulation of cGMP. The compound can be synthesized in a one-step condensation reaction and purified by flash chromatography.
Thick-Shelled Quantum Dots Blink Less

Fluctuations in the emission intensity of individual fluorophores, a phenomenon known as blinking, can be a problem when those fluorophores are used as labels in single-molecule experiments. In a study led by Jean-Pierre Hermier and Benoit Dubertret, both with France's National Center for Scientific Research, researchers have found that semiconducting nanocrystals—known as quantum dots (QDs)—that have thick shells blink less than thinner shelled ones (Nat. Mater., DOI: 10.1038/nmat2222). Separately, a team led by Jennifer A. Hollingsworth of Los Alamos National Laboratory has also reported reduced blinking with thick-shelled QDs (J. Am. Chem. Soc. 2008, 130, 5026). The French team synthesized 13-nm-diameter QDs with a 2.5-nm CdSe core and a layered CdS shell and detected the fluorescence of individual QDs using a charge-coupled device camera. At 30-millisecond exposure times per frame, two-thirds of the QDs emit continuously for five minutes without blinking. At longer exposure times even more of the QDs don't blink. The nonblinking behavior depends on the thickness of the CdS shell. "Well-designed shells are the key parameter for obtaining nonblinking QDs," the French researchers write.

Designing With DNA Made Easy

This tail-flipping dolphin, made of DNA, was designed with origami software.

DNA is more than just the basic building block of life. It has also become a basic building block of nanostructures, winding its way into nanoscale cubes, cages, and tetrahedra. In 2006, scientists developed "DNA origami" as a method for creating complex two-dimensional DNA nanostructures such as maps and snowflakes (C&EN, March 20, 2006, page 10). The technique, in which hundreds of short oligonucleotides fold and fasten a long single strand of DNA into a predetermined shape, requires some complex chemical design strategies. Now, Jørgen Kjems of Denmark's University of Aarhus and colleagues have developed a user-friendly software package (www.cdna.dk/origami) that makes designing DNA origami structures easier (ACS Nano 2008, 2, 1213). To demonstrate the program, Kjems's team designed and built a DNA dolphin that measures roughly 150 nm nose to tail. The researchers created the dolphin with a flexible tail that can be bent (shown) with the tip of an atomic force microscope. Such flexibility, they note, might be exploited in future DNA origami structures for use as nanorobotic arms or nanocantilevers.

Mass Spec Reveals NeuroAIDS-Related Metabolites

A mass spectrometry analysis of the cerebrospinal fluid (CSF) of macaques that are infected with simian immunodeficiency virus (SIV) and that develop neurological disorders has revealed clues about mechanisms of the nervous system diseases and could lead to new therapeutic treatments (J. Clin. Invest., DOI: 10.1172/JCI34138). SIV in monkeys or human immunodeficiency virus in people can infiltrate the central nervous system and cause "neuroAIDS" conditions such as dementia and encephalitis. Howard S. Fox, Gary Siuzdak, and coworkers William R. Wikoff and Gurudutt Pendyala at Scripps Research Institute used capillary reversed-phase liquid chromatography and electrospray ionization MS to analyze the CSF metabolites of SIV-infected macaques. Only one other such MS-based metabolomics study has ever been carried out. The researchers found increased levels of carnitines, fatty acids, and phospholipids that were specific to macaques that developed SIV-induced encephalitis. In related work, they observed increased expression of phospholipases, including one that catalyzes fatty
acid production. "The identification of specific metabolites, as well as mechanisms of their increase, illustrates the potential of mass-based metabolomics" to study nervous system biochemistry and virology and neurodegenerative diseases, the researchers note.

### Vanadium-B-12 Bioconjugates Lower Blood Glucose

Nicola E. Brasch and Derek S. Damron of Kent State University and colleagues report the synthesis of the first vanadium-vitamin B-12 bioconjugates (Chem. Commun., DOI: 10.1039/b806598e). These complexes could lead to novel orally active therapeutics for lowering high blood glucose levels associated with diabetes, the researchers suggest. Diabetics who must take insulin to regulate carbohydrate and lipid metabolism are often reluctant to inject the protein hormone several times per day, and even when they take their injections, they may still experience swings in blood sugar levels. Researchers are therefore trying to develop alternative oral treatments to work around these problems. Over the past decade, vanadium salts have shown promise in lab studies, but toxicity due to their poor absorption in the body became evident during clinical trials with type 1 and type 2 diabetics. Brasch's team reasoned that attaching a vanadium complex to a common vitamin should improve absorption by taking advantage of the body's vitamin uptake mechanisms. With this approach other B–12 conjugates have been successfully developed for medical uses, including chemotherapy and imaging. The researchers combined sodium metavanadate with a derivative of vitamin B–12 to make a mixture of mono and bis conjugates. The mixture was more effective at reducing glucose levels in diabetic rats than sodium metavanadate alone, they found.

### Why Anesthetics Sometimes Cause Pain

![Propofol](image1.png)  ![Isoflurane](image2.png)

General anesthetics are welcomed for their ability to banish pain during surgery, but some of these drugs increase postsurgical pain and inflammation. Pharmacologist Gerard P. Ahern of Georgetown University and colleagues believe they have found a possible explanation (Proc. Natl. Acad. Sci. USA 2008, 105, 8784). Using cell cultures and mouse studies, the researchers discovered that certain anesthetics activate the TRPA1 receptor on nerve cells. This ion channel protein, which also responds to irritants found in hot peppers and mustard, plays a key role in the biochemical pathways for pain and inflammation. The researchers showed that intravenous anesthetics such as propofol and inhaled anesthetics such as isoflurane activate and sensitize nerve cells. This activation can lead to nerve-mediated inflammation. Although some general anesthetics don't activate the TRPA1 receptor, they might not be as effective as the irritating anesthetics, Ahern says. "This tells us that there is room for improvement in these drugs," he adds. "We hope these findings are ultimately helpful in providing more comfort to patients."
Peptide Backbone's Folding Role

Modifying elements of a peptide's backbone yields nonnatural peptides that reproduce the three-dimensional structure of the original amino acid sequence, a strategy that could help in designing protein mimics (Proc. Natl. Acad. Sci. USA, DOI: 10.1073/pnas.0801135105). Researchers have long studied how the side chains of amino acids affect peptide folding, but little is understood about the influence of a peptide's backbone. To gain new insight on the backbone's role, Samuel H. Gellman and coworkers at the University of Wisconsin, Madison, substituted selected α-amino acid residues in a very stable four-helix protein with β-amino acid counterparts without changing the side-chain sequence. Despite the extra atoms introduced into the backbone with the β-residues, several substitution patterns closely approximated the original protein's helical structure, as determined by X-ray crystallography. The best replicas contained cyclic β-residues to make certain segments of the backbone more rigid. "Gellman and coworkers have taken another important step in the development of an expanded set of building blocks to engineer proteins," says William F. DeGrado, a protein design expert at the University of Pennsylvania.

Accelerated Electron Transfer Observed In Model Protein

In biological systems, electron flow often occurs very quickly between distant redox centers in electron-transfer proteins. Researchers have proposed that charge transfer in such proteins is accelerated by redox-active amino acid residues that act as donors or acceptors to relay electrons between the redox centers. But experimental evidence for this proposal has been indirect and inconclusive. A collaborative team based at Cornell University, California Institute of Technology, and the University of London has now obtained the best direct experimental evidence for the proposal so far by assessing the influence of an intervening tryptophan residue on the rate of electron transfer between redox centers in a semisynthetic model protein (Science 2008, 320, 1760). The team found that electron transfer between distant redox centers in an azurin protein mutant occurs about 300 times faster when the tryptophan residue is present than when it is absent. Researchers believe such expedited electron transfers can potentially be exploited in the design of new energy-yielding devices, among other applications.