agents that demonstrate significant activity against MRSA bacterial strains. Through analogue generation, we have determined the gross structural feature of this series necessary for activity and used that information to construct several compounds with in vitro potencies comparable to that of vancomycin against MRSA strains. Efforts to further improve the potency and pharmacological profiles of these compounds may lead to drug candidates for the treatment of infectious diseases.

Experimental Section

Characteristic analytical data of a selected compound:

Cyanostilbene 41: IR (film): $\tilde{\nu}_{max}$=3379, 2963, 2343, 1763, 1609, 1453, 1373, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$ (s, 1H), 7.80 (s, 1H), 7.55 (d, $J = 8.8$ Hz, 2H), 7.06 (s, 1H), 6.91 (d, $J = 8.8$ Hz, 2H), 6.33 (d, $J = 9.7$ Hz, 1H), 5.71 (s, 1H), 5.64 (d, $J = 9.7$ Hz, 1H), 1.45 (s, 6H), 1.34 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.5$, 149.4, 143.2, 135.6, 130.7, 127.7, 127.6, 127.5, 125.7, 124.6, 122.4, 121.5, 120.7, 118.7, 115.8, 110.2, 34.5, 31.3, 28.2; HR-MS (MALDI-FT-MS): *m/z*: calcd for $C_{24}H_{25}NO_2$ [$M+H^+$]: 360.1958, found: 360.1951.

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Cyberpills

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Despite several decades of developing improved therapies and prevention mechanisms, infectious pathogens remain a major cause of morbidity and mortality for humans worldwide.[1] A potential solution to this predicament is arising through the development of regimented treatment programs such as multi-drug therapies.[2] While effective in clinical studies, execution of these programs can be problematic for the patient.[3] Often this problem can only be solved by in-patient treatment or by associated training programs. Clearly, these treatments—and pharmaceutical therapy in general—would benefit from an information network that allows the patient and his physician to monitor the progress of a pharmaceutical therapy.[4]

Medical communication networks, online medicine, and electronic patient databanks[5] are now available through developments in the fields of e-medicine, telemedicine, and telepharmacy. These resources aid physicians by expediting their diagnostic workload (for example, a growing number of radiographic examinations can be accessed through online networks).[6] When approved by the patient, information from these systems can also be compiled into databanks, therein providing a powerful resource and research tool. Collection of this information is critical in learning how to control the evolution of drug resistance.

Currently, the administration of pharmaceuticals is rarely monitored, and when conducted, its process requires extensive clinical visits and laboratory analyses. The information transacted by these examinations, like radiographic methods,[6] could be adapted to remote networks through the development of noninvasive sensing systems. Methods exist that monitor

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pharmaceuticals in or through skin by using a combination of visible, infrared, and electromagnetic radiation.[7] These tools can be used to monitor the consumption of a pharmaceutical either by analyzing an active component or additive. For example, Roche recently disclosed a wristwatch system to monitor the fluorescence of a nontoxic food coloring, Brilliant Blue FCF.[7a] In this disclosure, the ingestion of a fluorescent dye was determined by using a 1.5-mW He – Ne laser, a fiber optic network, and a light diode or semiconductor light detector. While effective for the model given, this system was limited to a single preparation. Here we describe a universal method to monitor the oral administration of pills, caplets, and tablets.

Pills are currently identified by using an imprint code. Using these codes, pharmacists, physician, and trained patients can collect information about a medicine: name, strength (or dose), manufacturer, and formulation. A network could be developed in which the patient is required to enter this code each time he has taken a pill.[8] This data could easily be transmitted from a personal computer, palm pilot, or cellular phone. In so doing, the patient builds a log of his own regiment. This system, however, is restricted to literate patients and would be further limited by the occasional typographic error.[9] While this error could be reduced by using graphical prompts (e.g., a picture of the pill), such systems would be further complicated by the number of different preparations offered by producers. Most importantly, this system fails to provide a means to verify the patient's consumption.

Molecular screening systems analyze bioinformatic inquiries by arraying colorimetric or fluorimetric assays over a two-dimensional surface.[10] We extended this approach to provide a multicolor assay for human α-amylase,[11] a constituent in saliva (Figure 1). Pigment **1** contained two dyes: one that was red and a second that was either blue or yellow (Figure 2).[12] These pigments were further derivatized with a fatty acid ester in order to reduce their solubility in saliva. Upon contact with saliva, the carbohydrate moiety in **1** (**1Y** contains the yellow tag, and **1B** the blue tag) was cleaved, releasing the red label in water-soluble **2**. This process left water-insoluble pigment **3** (identified herein as **3Y** for yellow, and **3B** for blue). In phosphate-buffered saline (PBS) containing 30% DMSO, cleavage of **1B** and **1Y** by human α-amylase was comparable, demonstrating K_m values of 75 ± 3 μM and 69 ± 2 μM, respectively.

Pigments **1B** and **1Y** were formulated into respective blue and yellow inks. Using an ink jet printer,[13] 0.4-mm square pixels were printed on the surface of a plastic transparency. These pixels contained either yellow from **1Y**, blue from **1B**, or green from a 1:1 mixture of **1Y** and **1B**. After drying, printed regions contained ca. 2 pmol of pigment (Figure 3). Eight pixels were printed for each palette. The resulting palette was cut from the transparency such that it lay on an end of a 2 mm × 80 mm applicator strip (Figure 3a). Each applicator contained a palette with two rows of four 0.4-mm square pixels (Figure 3b). The applicator strip was then attached to a pill, tablet or capsule by molding the palette, face-up, in a gelatin coating (Figure 3c).

The user took this "cyberpill" by placing the medicated end in his mouth by holding the other end (arrow in Figure 3a) of the applicator (i.e., like a lollipop). As the gelatin coating dissolved in the mouth, the pill was released from the applicator strip. This took less than a minute. The applicator strip was removed from the mouth, and the pill was swallowed with the aid of water. Following incubation at room temperature for two minutes and washing with tap water (to remove **2**), the color in the palette was uploaded into a personal computer using either a scanner or digital camera. The resulting scan was then displayed on a personal computer by using a variety of graphic programs.

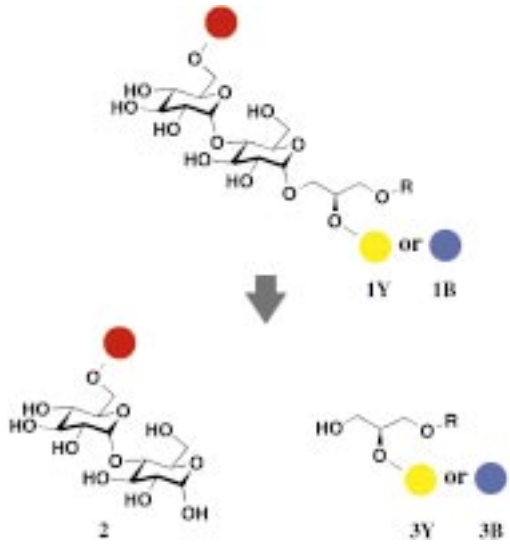

Figure 1. *Pigments and color processing. A colorimetric switch was built into a pigment by using a glycerol template. A red label was attached through a glycosidic linkage to one of the glycerol template's primary hydroxy groups. The other primary hydroxy group was protected as an oleic ester (R = cis-$CH_3(CH_2)_6CH_2{=}CH_2(CH_2)_5CH_2$-). This functionality prevented pigments **1** and **3** from dissolving in saliva. Alternatively, this position could be used to covalently attach the template to a surface. A second color scheme was built onto the secondary hydroxy group. This position contained either yellow or blue label, and served as the identifier. Before exposure to saliva, pixels printed with pigments **1** had a reddish hue. Cleavage of the carbohydrate moiety in **1** was accompanied by release of the red dye in water-soluble **2**. After washing away **2** with water, the surface contained only water-resistant pigments **3** displaying either the yellow or blue label.*

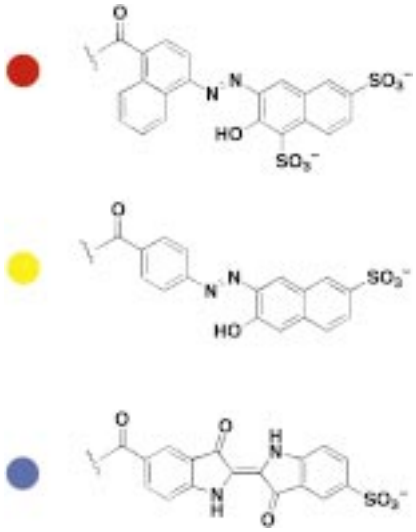

Figure 2. *Chemical structures of the dyes. Each dye was attached through an ester linkage (see Figure 1).*

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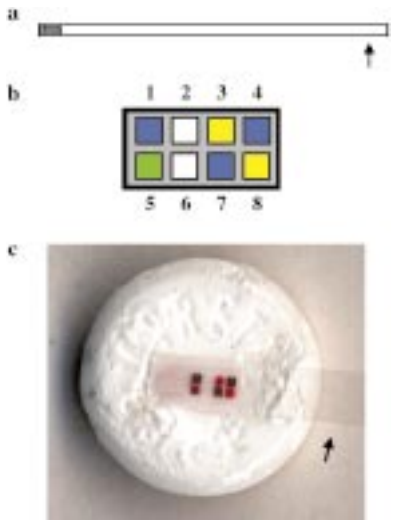

Figure 3. *Schematic representation of the physical system. a: An applicator stick was constructed by printing a color palette on a transparency. The left end of the applicator holds the palette. The applicator, given by an arrow, provided a handle. b: The palette contained two rows of four 0.4-mm square pixels. Each pixel was either colorless, yellow, blue, or green (by printing a 1:1 mixture of blue and yellow* ***1****). c: The cyberpill was prepared by fusing the applicator with its palette face-up on a tablet, pill, or capsule. The cyberpill shown here contained 100 mg of glucose in a corn starch/lactic acid matrix. The applicator was affixed with gelatin containing 1% glycerol.*

The pill's identity was encoded by the color and orientation of pixels in the palette (Figure 4a). Incubation of the palette with saliva converted **1** to **2** and **3** (Figure 1). This reaction was not limited by the enzyme reactivity (that is, the cleavage of 2 pmol of pigment by 1 U of α-amylase theoretically takes 120 μs), but rather by the transfer of enzyme to the surface. After washing with water, pixels were colorless, yellow (from **3Y**), blue (from **3B**), or green (from the mixture of **3Y** and **3B**) (Figure 4b).

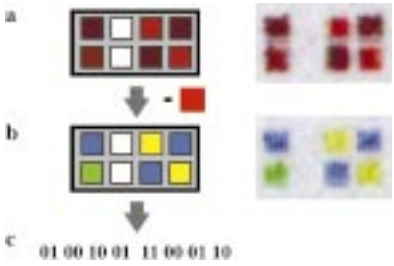

Figure 4. *Color processing. a: Pixels printed with* ***1*** *had reddish hue. The color in this palette is hard to distinguish. b: After exposure to saliva, the red color vanishes leaving colorless, yellow, blue, or green pixels. c: Each of these pixels was then converted into a digital counterpart, beginning at the upper left and ending at the lower right. Colorless wells were given the two-digit code 0 0, yellow 1 0, blue 0 1, and green 1 1. Here, the first digit was indicative of yellow and the second of blue. As shown, 0 was given if the color was present and 1 if not.*

The coloring in these pixels presented a two-digit code. The first digit described the presence of yellow, and the second the presence of blue (Figure 4c). A digit of 1 was given if color was seen and 0 if not. Using this system a colorless pixel was given by 0 0, a yellow pixel by 1 0, a blue pixel by 0 1, and a green pixel by 1 1. The 8 pixels were read from top left to bottom right into a 16-digit transcript. This transcript provided a unique digital name for a pharmaceutical or pharmaceutical preparation. Using this system, over 65 000 preparations (i.e., 2^{16}) could be encoded in a 4-mm^2 tag. This tag served as a primitive memory device.

A routine was programmed to compile the aforementioned transcript into a sector that contained information on the date, time, place, physician, and patient associated with a given pill taking (Figure 5).[14] Over the period of three weeks, we simulated a treatment with a glucose placebo by using a web-based entry system (Figure 5a). All of 14 applications taken by the lead author returned the correct 16-digit transcript. This system compiled each reading into a 600-bit sector (as given by clicking on the buttons in the upper corner of Figure 5a) and linked all 14 sectors into a single file, glucose R2 (Figure 5b). This file was sent from a server to model workstations, networks, and databases, mimicking transmission and storage. This process rapidly offered a means to translate pharmaceutical treatments to the physician and pharmaceutical researcher. The information gained in this process provides a powerful tool for medicine as well as for the further pharmaceutical development and

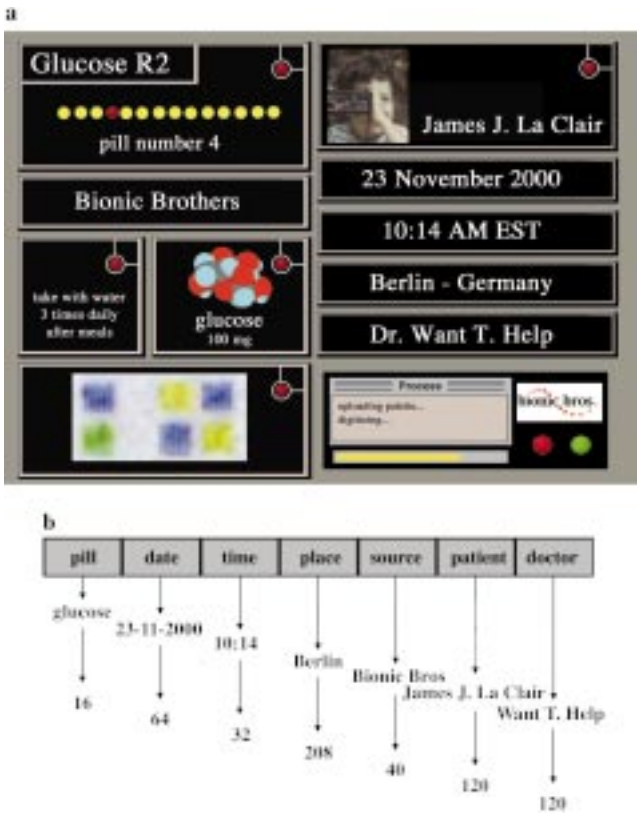

Figure 5. *The transcript from Figure 4c was compiled into a sector by using a Java-driven data entry. An example system was shown using a total of 600 bits. a: Data on the date (23 November 2000), time (10:14 AM EST), place (Berlin - Germany), source (Bionic Brothers), patient (James J. La Clair), and physician (Dr. Want T. Help) were entered by using a web-based system. This system also provided the patient with timely prompts and info on their medicine. It also could be adapted to provide access priorities. b: Data from this site was compiled into a sector beginning with the transcript. This was followed by: a 64-bit code for date – month – year, a 32-bit code for hour – minutes, a 40-bit code for the pharmaceutical's source, a 208-bit code for place or positioning, and a 120-bit identity for the patient and physician. The positioning code allowed one to include security systems that tracked misuse by including key codes from a tracking device such as global satellite positioning or licensing identifiers.*

regulation. Its method is simple, inexpensive and can be conducted using common computational devices. Efforts are now underway to tailor software and plastic electronics that enhance this interface.

Experimental Section

Cyberpill preparation: Pigments **1 Y** and **1 B** were prepared from conventional food colorings and glycerol (Aldrich). Human α-amylase was used as purchased (Sigma). Pigments **1** were formulated as ink by dissolving them at 2 mM in ethanol and placed in an appropriate cartridge of a Stylus Color 740 (Epson) or DeskJet 990 CXI (Hewlett – Packard) ink jet printer.[13] Yellow ink with **1 Y** was loaded into the colored cartridge and blue ink **1 B** in the black. A 1200-dpi graphic template containing 5 columns of 40 palettes was created in PhotoShop (Adobe) on a Macintosh 1400 cs/133PowerBook (Apple Computer) and printed on an A4 ink jet transparency (Hewlett – Packard). This template was designed with the appropriate dimensions and color such that its printing generated 0.40 ± 0.04 mm square pixels containing ca. 2 pM of **1**. HPLC analysis indicated that green units contained between $46 \pm 7\%$ **1 B** and $41 \pm 6\%$ **1 Y**. The transparency was cut into individual 2 mm $\times$ 80 mm applicator strips (Figure 3 a). Each strip contained one palette (Figure 3 b). The strip was then placed, with the palette face pointing upward, on the surface of a pill or tablet and coated with gelatin. After hardening, the cyberpill was complete (Figure 3 c).

Execution: The cyberpill was taken by placing the pill end in the mouth and holding the applicator stick. The surface of the pill was processed in a manner that mimicked the consumption of a lollipop. This process freed the pill, at which point the applicator was removed and the pill swallowed with the assistance of water. The applicator was incubated for 2 min, washed under tap water, and air-dried. The applicator was then uploaded into the same PowerBook used to create the template, either through a scanner (Philips Vesta Pro Scan or AGFA SnapScan E50) or a digital camera (Sony Cybershot DSC P-1). The color code was compiled by using the routine in Figure 5 into a 600-bit sector.

[1] Among the most complex and daunting problems facing medical science lies the evolution of drug resistance. Recent studies now indicate that the appropriate use of antibiotics can delay and in many cases prevent the emergence of resistance. For instance, outbreaks of erythromycin-resistant Group A *Streptococci* and penicillin-resistant *Pneumococci* have been controlled by regulating the prescription of erythromycin and penicillin, respectively, as demonstrated in Japan and Hungary, and more recently in Finland and Iceland. Several authors have attributed these successes specifically to the development of better methods to regulate the consumption of antibiotics. Resistance has also been observed amongst other major human diseases such as human immunodeficiency virus (HIV) infections, tuberculosis (TB), malaria, and hepatitis B virus (HBV) infections. For further information, see: a) A. T. Pavia, *Semin. Pediatr. Neurol.* **1999**, *6*, 288; b) E. Bergogne-Berezin, *Drugs* **1999**, *58*, 51; c) I. M. A. Gould, *J. Antimicrob. Chemother.* **1999**, *43*, 459; d) K. Fujita, K. Murono, M. Yoshikawa, T. Murai, *Pediatr. Infect. Dis. J.* **1994**, *13*, 1075; e) R. Nowak, *Science* **1994**, *264*, 364; f) H. Seppala, *New Engl. J. Med.* **1997**, *337*, 441; g) V. A. Arason, *Br. Med. J.* **1996**, *314*, 313; h) D. J. Price, J. D. Sleigh, *Lancet* **1970**, *2*, 1213; i) K. S. Meyer, C. Urban, J. A. Eagan, B. J. Berger, J. J. Rahal, *Ann. Intern. Med.* **1993**, *119*, 353; j) S. Matsushita, *Int. J. Hematol.* **2000**, *72*, 20.

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[3] Some patients have difficulty understanding and maintaining multidrug programs. Once overwhelmed the patient either becomes noncompliant or hides his failure. This deficiency is further complicated by indirect factors, such as improper prescription or lack of bioavailability. See: a) J. M. Lange, *Antiviral Ther.* **1998**, *3*, 75; b) G. Carosi, C. Torti, L. Palvarini, E. Q. Roldan, *J. Biol. Regul. Homeost. Agents* **1999**, *13*, 163.

[4] After decades of developing information systems for physicians and other healthcare professionals, increasing attention has been devoted to the development of online networks that link patients to health care providers. See: a) C. C. Carpenter, D. A. Cooper, M. A. Fischl, J. M. Gatell, B. G. Gazzard, S. M. Hammer, M. S. Hirsch, D. M. Jacobsen, D. A. Katzenstein, J. S. Montaner, D. D. Richman, M. S. Saag, M. Schechter, R. T. Schooley, M. A. Thompson, S. Vella, P. G. Yeni, P. A. Volberding, *J. Am. Med. Assoc.* **2000**, *283*, 381; b) A. Lazarus, J. Sanders, *Postgrad. Med.* **2000**, *108*, 71.

[5] Information technology and consumer health informatics are becoming an integral part of the modern concept of public health and national healthcare policy in many developed countries. These trends are partly the result of an effort to improve the patient's responsibility for his own health. Alternatively, online networks offer their users an electronic medium to store their own medical records and obtain medical care in the privacy of their own home. Electronic solutions have also become available for the transmission of pharmaceuticals. So-called online pharmacies now provide patients a means to examine and order their medicines with a few mouse clicks. These networks provide an ideal platform to monitor pharmaceutical treatments. See further: a) G. Eysenbach, *Br. Med. J.* **1999**, *319*, 385; b) A. R. Jadad, *Br. Med. J.* **1999**, *319*, 761; c) A. R. Jadad, A. Gagliardi, *J. Am. Med. Assoc.* **1998**, *279*, 611; d) R. Smith, *Br. Med. J.* **1997**, *314*, 1495; e) D. Pencheon, *Br. Med. J.* **1998**, *316*, 1665, f) A. Coulter, *Br. Med. J.* **1999**, *319*, 719; g) J. Wyatt, J. Keen, *Br. Med. J.* **1999**, *317*, 900; h) G. Eysenbach, T. L. Diepgen, *Lancet* **1998**, *352*, 1526; i) D. A. Lindberg, B. L. Humphreys, *J. Am. Med. Assoc.* **1995**, *273*, 1667.

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[9] The result of this error could be devastating. For instance, entering the code of 93 122 for the histidine H2 blocker Cimetidine accidentally as 93 129 would indicate that a patient took the oral hypnotic Estazolam.

[10] Color schemes are also commonly used to distinguish electronic, mechanical, and nutritional components. Each one of us has at one point examined a piece of hard candy based on its color (purple = grape, red = berry, yellow = lemon, white and red = mint, etc.). See further: a) D. Gerhold, T. Rushmore, C. T. Caskey, *Trends Biochem. Sci.* **1999**, *24*, 168; b) J. F. Cargill, M. Lebl, *Curr. Opin. Chem. Biol.* **1997**, *1*, 67.

[11] For comparable colorimetric methods, see: M. G. Cotenescu, J. J. La Clair, *J. Biotechnol.* **2000**, *76*, 33.

[12] This procedure uses color transfer in thermodynamic terms, wherein the color of the system lies either in **1** or in **2** – **3**.

[13] a) T. Okamoto, T. Suzuki, N. Yamamoto, *Nat. Biotechnol.* **2000**, *18*, 438; b) A. Roda, M. Guardigli, C. Russo, P. Pasini, M. Baraldini, *Biotechniques* **2000**, *2*, 492; c) A. P. Blanchard, R. J. Kaiser, L. E. Hood, *Biosens. Bioelectron.* **1996**, *11*, 687.

[14] The user is required to enter his name and his doctor's name (if desired). Information on the source is often indicated by conventional imprint codes and could also be included in our 16-bit transfer. The date and time (i.e., the CMOS microprocessor internal clock) and place of application (i.e., computer identity such as IP address) is given when the applicator is scanned or uploaded into a computer and/or computer network. While similar input could be generated by scanning conventional imprint codes, this approach could not verify if the user actually took the pill. The cyberpill described herein requires contact between the user's saliva and the pill. While this cannot exclusively verify consumption, it approaches it.

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