reduction in viral titer compared with untreated mice. In addition, treatment with an unrelated cholesterol-reducing agent had no antiviral effect and lovastatin had no antiviral effect on vaccinia virus. Finally, no reduction in serum cholesterol was observed during the time the mice were treated.

These results are promising and suggest that an already approved class of drugs could be used in the battle against certain viral diseases, such as RSV. It is hoped that future experiments will determine if lovastatin does act by reducing the plasma membrane expression of RhoA.

4 Gower, T.L. and Graham, B.S. (2001) Antiviral activity of lovastatin against respiratory synceytial virus *in vivo* and *in vitro*. *Antimicrob. Agents Chemother.* 45, 1231–1237

PARP-1 as a potential anti-HIV target

Infection by HIV-1 requires the integration of a DNA copy of the viral genome into the host DNA. Integration is achieved by a multi-step mechanism involving processing of the 3′-ends of double stranded viral DNA by clipping off two nucleotides and inserting the processed ends into the host genome. This pathway leads to an intermediate with gaps at either end of the integrated DNA. These gaps are repaired by an enzyme, or enzymes, which have yet to be identified. A recent publication[5] by researchers from John Hopkins University (Baltimore, MD, USA) suggests that one of the enzymes involved in gap repair is PARP-1 [poly(ADP-ribose) polymerase-1; EC2.4.2.3.0], a host enzyme. PARP-1 is a nuclear enzyme that is activated by DNA strand breaks and, as such, might be activated by the integration intermediate already described. To test this hypothesis, the John Hopkins team looked at the infection of fibroblasts isolated from PARP-1 knockout mice by a pseudotyped HIV virus. As expected, the virus infected normal fibroblasts (PARP-$1^{+/+}$) but not the knockout fibroblasts (PARP-$1^{-/-}$). If PARP-1 is involved in HIV integration, as these results suggest, then PARP inhibitors might be useful in treating HIV-1 infection.

5 Ha, H.C. *et al.* (2001) Poly(ADP-ribose) polymerase-1 is required for efficient HIV-1 integration. *Proc. Natl. Acad. Sci. U. S. A.* 98, 3364–3368

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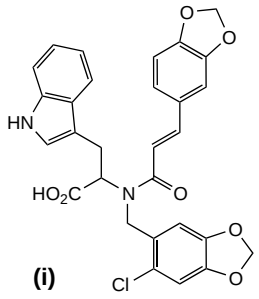
Combinatorial chemistry

Endothelin receptor antagonists

Endothelin (ET-1) is a potent vasoconstrictor consisting of 21 amino acids. ET-1, as well as two other structurally and functionally related vasoconstricting peptides (endothelin-2 and endothelin-3), interacts with two known G-protein coupled receptors (ET_A and ET_B) and induces vasoconstricting effects. ET_A, ET_B and the more recently discovered ET_C, are tissue specific and displayed preferentially in varying proportions on different cell types. ET_A is found in vascular smooth-muscle tissue and is mainly responsible for vasoconstriction of smooth muscle cells, whereas ET_B, which is found in nonvascular smooth-muscle tissues, has been implicated in the release of endothelin-derived relaxing factors. Elevated levels of endothelin are found in patients suffering from a variety of diseases, including hypertension, pulmonary hypertension and cerebral vasospasm, and evidence is accumulating that newly discovered ET antagonists could not only provide a novel therapy for the treatment of such patients but also help in understanding the precise physiological roles of endothelins. In an effort to discover new ET antagonists, a library of 15 individual peptoid compounds was synthesized[1]. Screening of these compounds revealed their affinity for endothelin receptors in terms of their ability to competitively inhibit ET. One of the most potent compounds discovered was **(i)**, which possessed an IC_{50} of 660 nM against ET_B and 13-fold selectivity over ET_A. This library has been successful in providing novel peptoids possessing a range of ET_A and ET_B receptor affinities. Future work could be directed at comparing biophore mapping of this series with the energy-minimized three-dimensional model of other active compounds from the literature, which could aid in the design of further compounds with improved activity.



(i)

1 Dasgupta, F. *et al.* (2001) Peptoids as endothelin receptor antagonists. *Bioorg. Med. Chem. Lett.* 11, 555–557

Dopamine D_4 receptor partial agonists

Recent advances in molecular cloning techniques have led to the characterization of several dopamine receptor subtypes, which can be divided into the D_1- and D_2-like families. The D_1-like family comprises the D_1 and D_5 subtype, whereas the D_2-like family consists of the D_2, D_3 and D_4 receptors. Because of the preferred expression of mRNA for dopamine receptors in the frontal cortical and mesolimbic areas, considerable interest has been focused on selective D_4 antagonists. According to recent neuropathological and genetic studies[2] selective dopamine D_4 receptor agonists, partial agonists or antagonists, might be of interest for the treatment of neuropsychiatric disorders including attention-deficient hyperactivity, mood disorders and Parkinson's disease[3].

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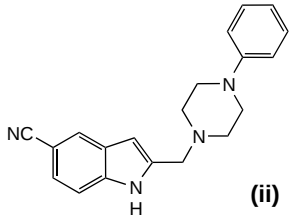
A small library of 13 compounds was synthesized on solid phase. One of the most potent compounds isolated was **(ii)**, which possessed a K_i value of 0.52 nM for human D_4 affinity, and 25000-, 6000-, 550- and 3300-fold selectivity over the bovine D_1, human D_{2long}, human D_{2short} and human D_3 receptors, respectively. This library has been successful in generating highly potent and selective D_4 receptor-binding compounds, which could serve as an interesting tool for the treatment of various neuropsychiatric disorders.



(ii)

2 Smalley, S.L. *et al.* (1998) Evidence that the dopamine D_4 receptor is a susceptibility gene in attention-deficient hyperactivity disorder. *Mol. Psychiatry* 3, 427–430

3 Gmeiner, P. *et al.* (2000) Cyanoindole derivatives as highly selective dopamine D_4 receptor partial agonists: solid-phase synthesis, binding assays, and functional experiments. *J. Med. Chem.* 43, 4563–4569

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Drug delivery

A drug delivery system for the treatment of periodontitis

Gum disease is a common medical problem, affecting up to 75% of adults over the age of 35. Periodontitis is one of the more severe forms of gum disease and is characterized by the formation of periodontal pockets. These pockets are lesions between the teeth and junctional epithelium resulting from a localized pathogenic bacterial infection below the gum line. Periodontal pockets are easily accessed through the mouth and are a convenient site for using a localized drug delivery system (LDDS). Currently, the commercially available subgingival LDDSs are designed to deliver a single antibacterial agent into the gingival crevicular fluid (GCF), for up to seven days. The effectiveness of subgingival LDDSs could be increased if they: (1) were capable of delivering a range of antibacterial agents; (2) exhibited controlled release over an extended period of time; (3) had limited swelling in GCF and; (4) possessed adhesive properties that prolonged the retention time on the surface of the tooth.

Recently, Bromberg and colleagues have reported an *in vitro* investigation of an LDDS that possesses all of the above characteristics[1]. This LDDS is composed of a composite wafer with an adhesive surface layer and a bulk layer, which consists of antibacterial agents, biodegradable polymers and matrix polymers. *In vitro* investigations of drug release from the wafer into human serum, scanning electron microscope (SEM) studies and measurements of the adhesive properties on calf's teeth, indicate that this wafer composition is promising as an LDDS for the treatment of periodontitis.

Periodontal LDDS wafers were prepared from polylactic-co-glycolic acid (PLGA), ethyl cellulose and an active ingredient mixture (chosen from silver nitrate, benzylpenicillin and tetracycline) using a compression-molding technique. Subsequently, the sheets were cut into ~4 × 4 × 0.5 mm wafers. Previous periodontal LDDSs, composed entirely of biodegradable and water-soluble components, have a tendency to swell considerably in GCF, leading to possible reduced residence time in the periodontal pocket[2]. Ethyl cellulose was found to decrease the swelling of the wafer, and the maximum swelling decreased with an increased content of ethyl cellulose. LDDS wafers with a 9–12% ethyl cellulose content swelled to a maximum of ~250%, whereas wafers with a 15% cellulose content swelled to a maximum of ~200%, a range that is comparable to some commercially available periodontal LDDS wafers. Wafers with 0–3% ethyl cellulose swelled the most, with a maximum swelling of >600%. The amount of silver nitrate in the wafer (12–24%) had little effect on the swelling characteristics of the LDDS.

LDDS wafers composed of 67% PLGA, 9% ethyl cellulose and 24% of an antibacterial agent (chosen from silver nitrate, benzylpenicillin and tetracycline) were prepared and their drug-release characteristics studied (in water). All formulations exhibited zero-order release of antibacterial agent, in water, over 30 days. The LDDS wafer that contained 24% silver nitrate was further studied for its drug-release characteristics in human serum (readily available and similar to GCF): the release of silver nitrate was measured for total silver by inductively coupled plasma atomic emission spectroscopy (ICP), and for bactericidal silver by an *E. coli* bioassay[2]. Again, zero-order release was observed over ~30 days. The measurement of total silver by ICP showed a cumulative release of ~80% of the silver nitrate from the matrix over 30 days. The cumulative release of bactericidal silver, as measured by the bioassay, only reached ~20%. The overall lower cumulative release of bactericidal silver, compared with total silver, is thought to be caused by the binding and/or redox reactions with serum proteins.

Another goal was to design an LDDS that would not require manual removal after a 30-day treatment. As a test for disintegration, wafers were kept in serum for 28 days and their degradation characteristics followed by SEM. The initially smooth surface of the wafers degraded to an irregular surface after 14 days as the PLGA in the matrix degraded and eroded. After 28 days in human serum, the wafers consisted of particles of ethyl cellulose ~1–10 μm in size, small enough for the residual wafer particles

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