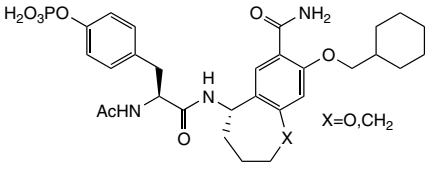
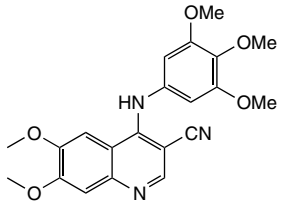
structure-based design and synthesis, Shakespeare and coworkers (ARIAD Pharmaceuticals, Cambridge, MA, USA) have identified a short series of bicyclic non-peptide inhibitors for the Src SH2 domain[5]. The resulting compounds, **(iii)**, represent some of the strongest binding inhibitors known for this target SH2 domain, and have promise for



(iii)

future inhibitors with increased cell penetration and *in vivo* activity. In related studies, the preparation and SARs of a series of Src tyrosine kinase inhibitors has been reported by Wang and coworkers[6] (Wyeth-Ayerst Research, Pearl-River, NY, USA). A series of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines were prepared and tested for inhibition of Src kinase activity, from which compound **(iv)** emerged as the most potent (ATP competitive) inhibitor (IC_{50} = 35 nM).



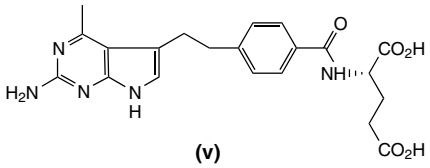
(iv)

5 Shakespeare, W.C. *et al.* (2000) Structure-based design of novel bicyclic nonpeptide inhibitors for the Src-SH2 domain. *J. Med. Chem.* 43, 3815–3819

6 Wang, Y.D. *et al.* (2000) Inhibitors of Src tyrosine kinase: the preparation and structure–activity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines. *Bioorg. Med. Chem. Lett.* 10, 2477–2480

A potent dual inhibitor of thymidylate synthase and dihydrofolate reductase

Inhibitors of folate metabolism, such as thymidylate synthase (TS) and dihydrofolate reductase (DHFR) inhibitors, have provided important clinical agents for cancer chemotherapy owing to their inhibition of the biosynthesis of nucleic acid precursors. Gangjee and coworkers have reported the design and synthesis of a potent dual inhibitor of TS and DHFR [**(v)**; Ref. 7]; evaluation of compound **(v)** in the National Cancer Institute (Bethesda, MD, USA) *in vitro* preclinical screening program afforded GI_{50} values in the nanomolar range against several human tumour cell lines (of leukaemic, non-small cell lung, colon, CNS and renal origin).



(v)

7 Gangjee, A. *et al.* (2000) Design, synthesis, and X-ray crystal structure of a potent dual inhibitor of thymidylate synthase and dihydrofolate reductase as an antitumor agent. *J. Med. Chem.* 43, 3837–3851

Andrew Westwell
Cancer Research Laboratories
University of Nottingham
Nottingham, UK NG7 2RD
tel: +44 (0)115 951 3419
fax: +44 (0)115 951 3412
e-mail: andrew.westwell@nottingham.ac.uk

Drug delivery

PEG-anhydride prodrugs and mucoadhesive polymers

Mucoadhesive polymer drug-delivery systems adhere to mucosal surfaces, such as the surface of the eye, and facilitate localized drug delivery. Mucoadhesion is thought to occur by hydrogen bonding of the mucoadhesive polymer to mucin, a glycoprotein that coats the mucosal surface. Several polymers have been used as mucoadhesive carriers, including poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA), with PAA being used the most extensively. Polyethylene glycol (PEG) and PAA at low pH form hydrogen-bonded complexes between the carboxylic acid groups of PAA and the ether oxygens of PEG. These formulations have higher viscosities than PAA itself, and it has been shown that this higher viscosity retards the removal of the polymer from the mucosal surface.

Another use of PEG in drug delivery is its covalent attachment to drugs to yield a prodrug conjugate. PEGylated drugs provide reduced toxicity and immunogenicity, low uptake by the reticuloendothelial system, and prolonged blood circulation. Drug molecules are usually conjugated to PEG via ester or amide bonds. A PEG prodrug will not be readily absorbed via the gastrointestinal mucosa, and PEG ester and amide bonds hydrolyze relatively slowly under physiological conditions. Given that mucin turnover times at various mucosal sites are ~1–4 h, the typical PEG prodrug strategy cannot be used for mucosal delivery.

Indomethacin is a non-steroidal anti-inflammatory that is being evaluated as an ocular anti-inflammatory. Lele and colleagues have recently reported the potential for mucosal drug delivery using hydrogen-bonded complexes of PAA and PEGylated indomethacin. In place of the usual ester or amide bond, the drug was conjugated, via the carboxyl group, to the PEG by a relatively easily hydrolyzable anhydride bond, the first known example of a PEG-anhydride–drug linkage[1]. Upon mixing acidic solutions of PEG-indomethacin and PAA, a hydrogen-bonded complex precipitated as a gummy mass, which was lyophilized before further study. Several different molecular weights of PAA were examined. The release of indomethacin within dialysis tubing (MW cutoff of 3500 Da) from these complexes was compared with the release of free drug from PEG-indomethacin alone. Greater than 60% of the total drug was released from PEG-indomethacin in 50 min, compared with 80 min when PEG-indomethacin was complexed with PAA (250 kDa). The release rate of indomethacin decreased with an increase in the MW of PAA in the complex. Thus, although 60% of the

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drug was released from the 250 kDa PAA complex in 80 min, it took 135 min and 240 min for 60% of the drug to be released from the 450 kDa and 750 kDa PAA complexes, respectively. Overall release rates of the drug from the complexes were within the typical 1–4 h time periods of mucin turnover. Mucosal delivery is often limited by low bioavailability of the drug, but by combining a new, easily hydrolyzable PEG prodrug linkage with a mucoadhesive drug carrier, these complexes could be useful for mucosal delivery of potent drugs that are effective at low concentrations.

1 Lele, B.S. *et al.* (2000) Mucoadhesive drug carriers based on complexes of poly(acrylic acid) and PEGylated drugs having hydrolysable PEG-anhydride–drug linkages. *J. Control. Release* 69, 237–248

Enhanced sulpiride absorption via synchronized release of sulpiride and sodium decanoate

The oral bioavailability of poorly absorbed drugs can be increased by coadministration of a penetration enhancer. If the drug and the enhancer possess different solubility properties, dissolution of the two will occur at different rates and an immediate release dosage form will not, therefore, be advantageous. However, any sustained release dosage form must be carefully designed, such that the drug and the penetration enhancer are released at similar rates. Sulpiride, a substituted benzamide, is an antipsychotic drug used for the treatment of depression, schizophrenia, migraine, vertigo and gastrointestinal (GI) disorders. It has poor water solubility, and absorption in the GI tract is slow and erratic. The oral bioavailability of sulpiride is 30% in man, and 15% in the rat. Sodium decanoate is a well-recognized penetration enhancer with a transient effect on the paracellular pathway. The absorption of sulpiride in the human intestine can be improved by concomitant dosing of a penetration enhancer such as sodium decanoate, but if it is coadministered in an immediate release dosage form, little advantage is actually realized because of the different solubilities of sodium decanoate and sulpiride.

Baluom and colleagues have recently reported the development of a formulation of sulpiride and sodium decanoate, which was designed so that sulpiride and sodium decanoate are released at similar rates (synchronized release)[2]. Tablets containing sulpiride and sodium decanoate within a hydroxypropylmethyl cellulose (HPMC) matrix were prepared. The HPMC matrix was chosen because previous studies indicated that sodium decanoate and drug are released at synchronous rates from this matrix when drug and sodium decanoate are both present throughout the tablet. The HPMC matrix dissolves by surface erosion. As each layer of the tablet dissolves, the drug contained within the matrix is released. Tablets with higher percentages of HPMC in the formulation take a longer time to erode. In this study, three different HPMC matrices containing sulpiride and sodium decanoate throughout the tablet were designed so that the erosion times of the tablets were 1, 2 and 4 h (synchronous release or S-formulations). A formulation that contained sulpiride and sodium decanoate but no HPMC was prepared to investigate the effect of immediate release (I-formulation). Finally, a set of tablets consisting of two HPMC matrix layers, one containing sulpiride and the other containing sodium decanoate, were prepared to study the effect of non-synchronous release (NS-formulations).

In vitro release kinetic studies confirmed that sodium decanoate and sulpiride were released from the S-formulations at synchronous rates over the course of the 1, 2 or 4 h erosion time of the tablet. The I-formulation released both sodium decanoate and sulpiride quickly over 20 min, whereas an NS-formulation, designed to erode over 4 h, released sodium decanoate quickly, in ~1 h, and sulpiride was released over the course of 4–5 h. The effect of the synchronous release of sulpiride and sodium decanoate was then studied *in vivo*. When the S-formulation designed for a 1 h synchronous release was compared with the I-formulation, it was apparent from measured plasma levels of sulpiride that sodium decanoate is required to increase sulpiride bioavailability. It was also found that synchronized release of sulpiride and sodium decanoate greatly increases bioavailability.

When plasma levels of sulpiride from these two formulations were measured, the area-under-curve (AUC) of sulpiride was two-fold larger for the 1 h S-formulation compared with the AUC of sulpiride for the I-formulation. The C_{max} of sulpiride for the 1 h S-formulation was 21.5 μg ml^{-1} at 1 h, and the C_{max} for the I-formulation was 9.4 μg ml^{-1} at 1 h. A similar enhancement of bioavailability of sulpiride was observed for corresponding longer release formulations, where observed plasma levels of sulpiride were higher for S-formulations versus NS-formulations with the same erosion times. The bioavailability of sulpiride is increased in the presence of sodium decanoate, and these studies indicate that tablets designed for synchronous release of sulpiride and sodium decanoate from an HPMC matrix over several hours greatly increases the bioavailability of sulpiride, as compared with an immediate release or non-synchronous release formulation. This approach could be useful for other poorly absorbed drug and penetration-enhancer combinations.

2 Baluom, M. *et al.* (2000) Synchronized release of sulpiride and sodium decanoate from HPMC matrices: a rational approach to enhance sulpiride absorption in the rat intestine. *Pharm. Res.* 17, 1071–1076

John Weidner
Parallel Synthesis
Medicinal Chemistry, Emisphere Technologies
765 Old Saw Mill River Rd, Tarrytown,
NY 10591, USA
tel: +1 914 785 4792
fax: +1 914 593 8250
e-mail: jweidner@emisphere.com