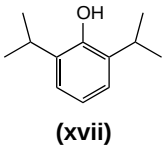
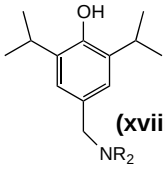
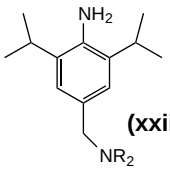


(xvii)



(xviii–xxii)



(xxiii–xxv)

NR_2 **(xviii)** = Morpholine
(xix) = Thiomorpholine
(xx) = Ethyl isonipecotate
(xxi) = N-acetylpiperazine
(xxii) = N-methylbenzylamine

NR_2 **(xxiii)** = Morpholine
(xxiv) = Thiomorpholine
(xxv) = Ethyl isonipecotate

Water-soluble analogues of the anaesthetic propofol

Propofol **(xvii)** is a widely used intravenous anaesthetic, whose mechanism of action involves the positive allosteric modulation of the neurotransmitter γ-aminobutyric acid (GABA) at $GABA_A$ receptors. The main advantages of propofol are favourable operating conditions (induction of anaesthesia is rapid and maintenance can be achieved by continuous infusion) and a rapid recovery. However, the compound shows cardiovascular side-effects and its injection is painful[13]. Recently, it has been suggested that propofol analogues containing a *para* substituent still retain good activity at the $GABA_A$ receptor[14].

On this basis, Cooke and coworkers[15] have synthesized several *para*-alkylamino-substituted analogues of propofol **(xviii–xxii)**, with the aim of obtaining water-soluble compounds with good anaesthetic activity. All the compounds were tested *in vivo* and *in vitro* as their hydrochloride salts. The anaesthetic potency of the compounds was determined upon their intravenous administration to mice when their hypnotic $dose_{50}$ (HD_{50}) was determined: propofol (HD_{50} = 68 μM kg^{-1}) was used as a positive control. All the *para* compounds compared favourably with propofol, the most potent being **(xx)**, which has an HD_{50} value of 19 μM kg^{-1}. To explore the SARs of this series further, several compounds **(xxiii–xxv)**, that have an amino group instead of the phenolic group at position 1, were synthesized and tested. They all showed good hypnotic potency, the most interesting being **(xxv)**, which had an HD_{50} value of 14.4 μM kg^{-1}.

However, further modifications of the amino group (e.g. removal, conversion to an amide or mono- or dimethylation) were not tolerated. The *in vitro* effect of the compounds at $GABA_A$ receptors was assessed by determining their ability to inhibit [^{35}S]-tert-butyl-bicyclophosphorothionate (TBPS) binding to rat whole-brain membranes. However, most of the compounds were found to be weakly active or inactive, which suggests that their *in vivo* anaesthetic activity is mediated by a non-GABAergic mechanism.

13 Trapani, G. *et al.* (2000) Propofol in anaesthesia. Mechanism of action, structure–activity relationships, and drug delivery. *Curr. Med. Chem.* 7, 249–271

14 Trapani, G. *et al.* (1998) Propofol analogues. Synthesis, relationships between structure and affinity at $GABA_A$ receptor in rat brain, and differential electrophysiological profile at recombinant human $GABA_A$ receptors. *J. Med. Chem.* 41, 1846–1854

15 Cooke, A. *et al.* (2001) Water-soluble propofol analogues with intravenous anaesthetic activity. *Bioorg. Med. Chem. Lett.* 11, 927–930

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Drug delivery

System for time and/or site-specific oral drug delivery

Time and/or site-specific drug delivery can be advantageous in the treatment of certain diseases. The symptoms of bronchial asthma and rheumatoid arthritis, for example, follow circadian rhythms, recurring primarily at night or in the early morning. A delayed-release formulation that can be taken before bedtime is advantageous in these cases. Delayed release is typically achieved through osmotic mechanisms, with tablets that contain a drug-loaded core which is surrounded by outer layers that slowly erode and then release the core. Alternatively, site-specific release is often used as a method to achieve drug delivery into specific regions of the gastrointestinal (GI) tract. In this regard, colon-specific release has some potential advantages as a strategy for improvement of the oral bioavailability of peptide drugs. The local concentration of peptidases is lower in the colon than in the small intestine. Although physiologically it is not the ideal site for absorption when compared to the small intestine, the colon is the site of significant absorption, and some of the absorptive disadvantages are offset by the long residence time. In addition, colon-specific delivery of drugs represents an advantageous approach for the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease. To date, several different strategies have been used to achieve colon-specific delivery. Most of these strategies rely on prodrugs or polymers, designed to selectively degrade under the microbiological or pH conditions unique to the colonic environment versus the other portions of the GI tract and/or the relative reproducibility of small intestinal transit time (SITT).

Sangalli and colleagues have recently reported the application of a novel oral drug delivery system designed for delayed, colon-specific release[1]. The system

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consists of a drug-loaded core surrounded by two additional layers of coatings. For this study, the analgesic antipyrine was chosen as a model drug. This was selected because it is easily detectable by HPLC methods, and can be detected in the saliva of human subjects following administration. The drug-loaded core is first coated with hydroxypropylmethylcellulose (HPMC), which is responsible for a lag phase preceding the release of drug from the core. The HPMC layer is then coated with a gastroresistant film containing Eudragit L30D™ (Röhm America, Piscataway, NJ, USA), so the system is expected to remain intact as long as it remains in the stomach. The approach, therefore, relies on the relative consistency of the SITT, which is 3–5 h on average, independent of the fasted or fed condition of the subject. A pH change occurs with the passage of the system from the stomach to the duodenal environment, and the gastroresistant film then dissolves. The thickness of the now exposed HPMC coating determines the length of the lag phase before release of the drug in the core, and the thickness can be adjusted so that the lag phase corresponds to the SITT.

In vitro-release studies in a 24-paddle apparatus confirmed that the thickness of the HPMC coating had a direct correlation to the duration of the lag phase before release of antipyrine from the core. Drug-loaded cores with no coating released 100% of the antipyrine within the first hour. Cores coated with various thicknesses of HPMC exhibited a linear release of drug, with the longest release time (ca. 12 h) corresponding to the thickest HPMC coating. Tablets with the second, gastroresistant coating were demonstrated to withstand acidic pH; no drug was released in simulated gastric fluid. In simulated intestinal fluid, the gastroresistant film dissolves, and the drug-release time observed from these tablets was similar to tablets without the gastroresistant film, except for a correspondingly longer lag time associated with the dissolution time of the gastroresistant film.

The successful application of this system for delayed, colon-specific release of antipyrine was then demonstrated in a small group of healthy male volunteers (n = 4, age 36–45 years, weight 70–80 kg). The volunteers were dosed with the various formulations of coated antipyrine-loaded cores, and saliva samples were collected at 0, 0.5, 1–18, 24, 30, 36 and 48 h after dosing. Antipyrine in saliva was then quantified by HPLC. The uncoated antipyrine-loaded core exhibits essentially no lag phase. Antipyrine-loaded cores coated only with various thicknesses of HPMC coating led to a delayed appearance of antipyrine in saliva. The lag phase increases with the applied thickness of the HPMC layer, so that the thickest HPMC coating causes a lag time of ~4 h before the appearance of antipyrine. The area under the curve values for all the formulations are similar, but the corresponding peak saliva levels of antipyrine tend to decrease as the thickness of the HPMC layer increases. Antipyrine-loaded cores coated with both HPMC and the gastroresistant film exhibit similar release patterns, except for longer lag times. The enteric film prevents interaction between the HPMC coating and GI fluid until the system exits the stomach. The resulting increase in lag times was ~2 h for all formulations.

A gamma-scintigraphic study was also undertaken. Although the details will not be elaborated on here, the results of this study confirm that this drug-delivery system disintegrates and delivers drug in the caecum and/or ascending colon. These initial results show promise for the potential application of this drug-delivery system for the delayed release and/or colonic delivery of a model drug. If the application can be extended to other drugs, particularly those with low oral bioavailability or those used for the treatment of colonic disorders, it could be of significant use.

1 Sangalli, M.E. *et al.* (2001) In-vitro and in-vivo evaluation of an oral system for time and/or site-specific drug delivery. *J. Control. Release* 73, 103-110

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Errata

Please note a correction to 'A genomic perspective on human proteases as drug targets' by Christopher Southan published in *Drug Discovery Today* 6(13), 681–688. On page 684, first column, line five should have read '…the reported β-secretase (BACE) mRNA…'. Also, on page 685, the first line of the legend to Figure 1 should have read '…information available for β-secretase (BACE/ASP2).'

The Editorial team of *Drug Discovery Today* would like to apologize for this inaccuracy and for any confusion that we might have caused.

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