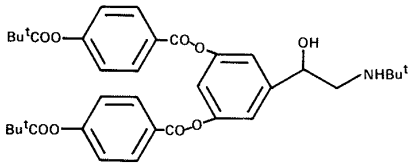
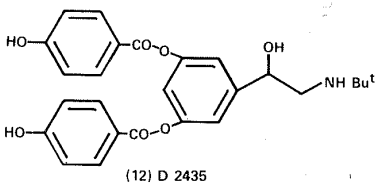
rate or pulse amplitude were noted and there was no difference in the incidence of subjective side-effects, both ibuterol and terbutaline being relatively free of side-effects at the bronchodilating dose. Human serum esterase hydrolysis [27] of a series of differently acyl-substituted mono- and diesters of terbutaline have been studied. The esterase-catalysed hydrolysis (Table 1) in this series was shown to be sensitive to steric hindrance in the acyl group of the ester. Increased branching in the acyl moiety lowered the rate of hydrolysis.

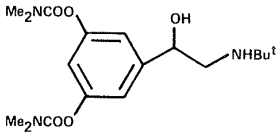
Two different types of terbutaline ester prodrugs have been evaluated by Svensson and co-workers [28] in their continuing quest for β-stimulants having a prolonged duration of action, reduced side-effects and increased bioavailability. D 2438 (11) was designed to function in the following way: the pivaloyl-phenol ester linkage, A, was less stable than the benzoyl-phenol ester linkage, B. Type A ester linkages, as seen in ibuterol (10b), have a half-life of 3 seconds in human serum, whereas type B ester linkages, as measured for D 2435 (12), have a half-life of 1.5 hours in human serum. Thus, first-pass hydrolysis and conjugation may operate preferentially on the outer ester linkage type A, still leaving terbutaline protected.



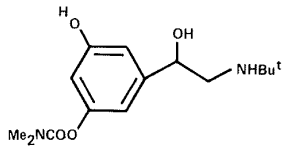
(11) D 2438



(12) D 2435



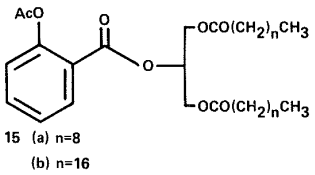
(13) KWD 2183



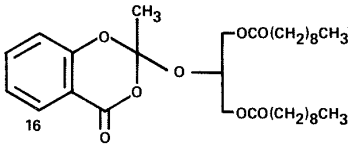
(14) KWD 2439

The nitrogen-isostere of ibuterol, KWD 2183 (13), was also synthesised and evaluated. This prodrug (13) produced sustained blood levels ($\approx$ 24 hours) of the parent drug in dog following a single oral dose. The biological persistence of this compound was attributed to the stability of the amide function and to the fact that KWD 2183, as well as the monourethane KWD 2439 (14), inhibited their own hydrolysis by reversibly binding to non-specific plasma esterases. Both D 2438 (11) and KWD 2183 (13) showed a dose-dependent inhibition of histamine-induced bronchospasm in unanaesthetised guinea-pigs by both the oral and local aerosol route. The ester prodrugs 11 and 13 showed less cardiovascular side-effects than the parent drug terbutaline when administered orally to the dog. Thus, the prodrugs showed improved bioavailability, prolonged duration of action and reduced cardiovascular toxicity relative to the parent terbutaline.

Although decreased gastric irritation has been demonstrated for both compounds 15a and 16, there is no proof that these derivatives are true prodrugs of aspirin (acetyl salicylic acid) rather than of salicylic acid. Only blood salicylate levels and anti-inflammatory assay data were presented and, as salicylic acid is known to be a potent anti-inflammatory agent [36], anti-inflammatory data cannot be taken as evidence for the systemic presence of acetyl salicylic acid (aspirin). A series of activated methylthiomethyl, methylsulphinylmethyl and methylsulphonylmethyl (17a – c) activated esters were synthesised and reported to be true prodrugs of aspirin (acetyl salicylic acid). As aspirin is a far more potent analgesic than salicylic acid, the detection of systemic acetyl salicylic, even though this was a transient species in in vivo biological systems, was considered to be a significant advance. No analgesic data nor gastric irritancy data were presented to support such claims.



15 (a) n=8
(b) n=16



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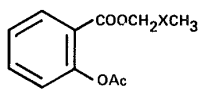
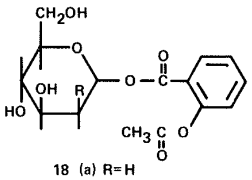
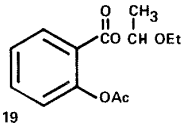


17 (a) X=S
(b) X=SO
(c) X=SO_2



18 (a) R=H
(b) R=OH



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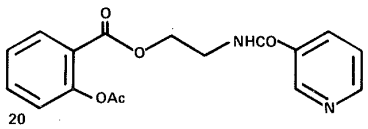

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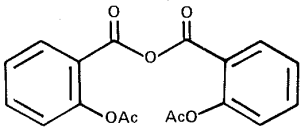
The synthesis of a crystalline α-D-deoxy glucopyranose derivative (18a) has been described recently [31]. This putative prodrug cleaves to aspirin in vitro in a reaction which is independent of pH, and has a half-life of 7 minutes at 37°C. The α-D-glucopyranose derivative (18b) slowly generates aspirin in solution. Although a number of simpler ester prodrugs of aspirin, including the 1′-ethoxy ethyl ester (19) [37], *N*-hydroxyethyl nicotinamide ester (20) [38], acyloxymethyl esters (21a,b) [39], and salicylamide ester (22) [40], have been described, little specific information regarding their biological properties is available. Decreased gastrointestinal irritation was claimed for both benorylate (23) [41] and the lysine salt of aspirin (24) [42];



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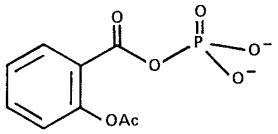

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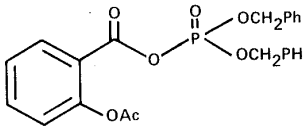

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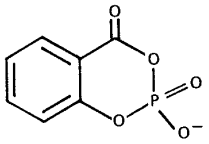

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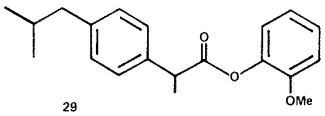
intestinal damage was assessed by measuring the rise in an acute-phase protein, α_1-acid glycoprotein, by an immunological assay of the serum. The concentration of α_1-acid glycoprotein has been shown to correlate well with the incidence and severity of gastric lesions, as determined by the usual visual method [46]. At equimolar doses, the 2-glyceride (30b) produced no significant change in the basal concentration of α_1-acid glycoprotein, while the 1-glyceride (30a) effected a small rise in the concentration of this protein. Comparison of the 2-glyceride (30b) with 2-(6-methoxy-2-naphthyl)-propionic acid for gastric irritation, as determined by the minimum chronic dose producing occult blood in either the faeces or urine in dog, gave a dose ratio in favour of the 2-glyceride of at least 3. The 2-triglycerides of in-



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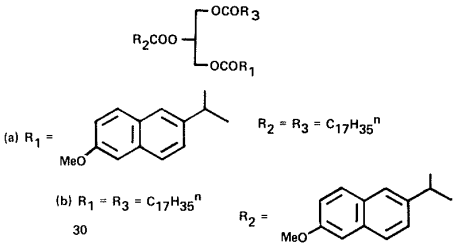

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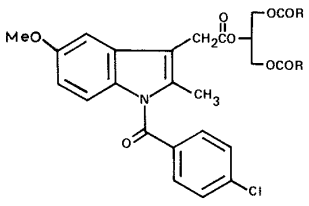
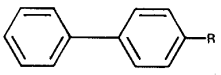
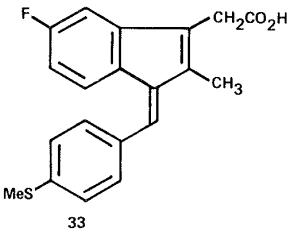


31 (a) R = CH_3
(b) R = $C_9H_{19}^n$



32 (a) R = $COCH_2CH_2CO_2H$
(b) R = $CHOHCH_2CH_2CO_2H$
(c) R = CH_2CO_2H

perties remain intact when compared at equimolar doses with the parent drug. Metabolic studies [51] indicate that suxibuzone was hydrolysed by esterases to give 4-hydroxymethylphenylbutazone (36b), which is considered to be labile [52] and to decompose spontaneously to phenylbutazone (36c) unless otherwise conjugated with glucuronic acid at the oxymethyl side-chain. Suxibuzone is considered to be less ulcerogenic than phenylbutazone (Table 2) because any suxibuzone remaining in the gastrointestinal tract is less harmful than phenylbutazone, since unchanged suxibuzone does not inhibit the function of either mitochondria or prostaglandin synthetase.



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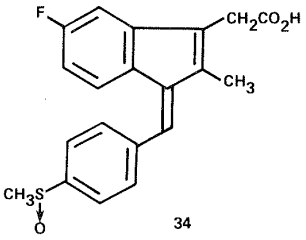

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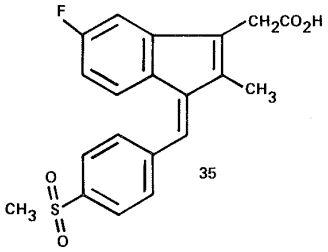

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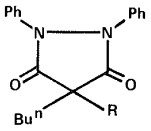
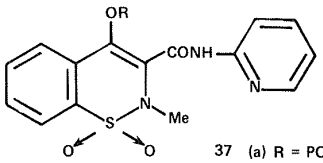


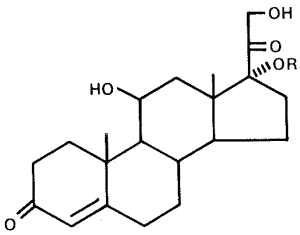
36 (a) R = $CH_2OCO(CH_2)CO_2H$
(b) R = CH_2OH
(c) R = H



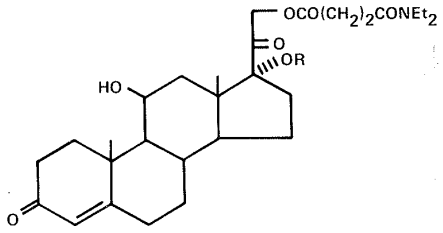
37 (a) R = PO_3^{2-}
(b) R = H

Piroxafos (37a) [53], the phosphoric ester of piroxicam (37b), was shown to have anti-inflammatory, antigranuloma and analgesic activity and was considered to be a prodrug of the parent anti-inflammatory agent. In comparison with indomethacin, aspirin and phenylbutazone, piroxafos was less active as an anti-inflammatory agent than indomethacin, but equiactive with the other two agents. Piroxafos was tolerated significantly better by the gastrointestinal tract than were the comparison drugs.

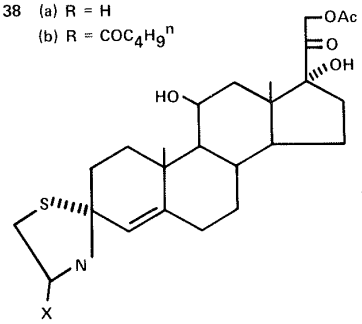
(39b) from the same series exhibited less systemic toxicity than its parent, hydrocortisone-17-valerate (39a), whilst retaining a portion of the local activity of the parent drug. The systemic toxicity was assessed by measuring the thymus weight of weanling rats, whilst the local toxicity was determined using hairless mice and measuring the double-fold skin thickness. The topical anti-inflammatory effect was assessed using the croton oil mouse ear irritation test. A further series of



38 (a) R = H
(b) R = $COC_4H_9^n$



39 (a) R = H
(b) R = $COC_4H_9^n$



40 (a) X = CO_2Et
(b) X = H

TABLE 3
Toxicity and Anti-inflammatory Potencies of Steroidal Prodrugs

Compound	% Reduction in thymus weight (systemic toxicity)	Skin thickness in XLO [4] ± S.E. (local toxicity)	Croton oil irritation ED_{50} (M)
38a	36	79 ± 2	0.0084
39a	39	94 ± 3[b]	–
38b	21	88 ± 5[c]	–
39b	16[a]	–	0.0019
40a	22[d]	88 ± 6	0.0033
40b	11[d]	87 ± 6	0.0055
Hydrocortisone-21-acetate	36	90 ± 7	0.016

a. $P < 0.01$ compared to 1a.
b. $P < 0.05$ compared to 1a.
c. Data from Ref. 56.
d. $P < 0.001$ compared to hydrocortisone-21-acetate.

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