Synthesis and biological evaluation of glycolamide esters as potential prodrugs of some non-steroidal anti-inflammatory drugs

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Glycolamide ester prodrugs of some frequently used NSAIDs have been prepared by condensing them with N,N-disubstituted-2-chloroacetamides. These compounds were evaluated for their GI toxicity in rats, which was markedly reduced in comparison to their parent moieties, their anti-inflammatory and analgesic activities were comparable to the parent drugs.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications in the world. In 1988, it was estimated that 100 million prescriptions were written for NSAIDs annually in the United States alone\(^1\). The major limiting side effects of chronic NSAIDs are gastrointestinal (GI) symptoms and complications. Prevalence studies have demonstrated that gastric or duodenal ulcers are present in 15-20% of patients taking NSAIDs chronically\(^1\). The incidences of significant gastrointestinal complications (bleeding, perforation, or gastric outlet obstruction) have been estimated to be 1-4% per year from population studies\(^2\). Even though the incidences of significant complications seem small, the large number of patients at risk make NSAID-induced GI complications a significant health hazard.

In addition to the increased morbidity and mortality, these GI complications contribute considerably to the cost of care. Database studies have suggested that the direct cost of treating GI symptoms and complications comprise 31-40% of the total cost of care for arthritis patients\(^3\) and that adverse event occurs in 25% of patients. Numerous perspective studies have identified a prevalence of 15-20% for gastric ulcers and 5-8% for duodenal ulcers after 12 weeks of therapy\(^4\).

Viewing the above important factors the present studies were undertaken to modify the existing NSAIDs associated with GI toxicities by the prodrug approach so as to alleviate these undesirable effects. In the present studies, the free acidic group in these drugs was temporarily masked by a promoiety so as not to expose stomach's mucosa to this free carboxylic acidic group. The glycolamide ester prodrugs of ibuprofen 1, diclofenac 2, naproxen 3, mefenamic acid 4 and indomethacin 5 were synthesised. The glycolamide esters have been reported to be bioreversible and chemically stable prodrugs of carboxylic acid drugs\(^9\). These prodrugs were synthesised by condensing these NSAIDs with N,N-disubstituted-2-chloroacetamides by following the Scheme I. Their ulcerogenic potential was determined in rats and compared with parent drugs. These prodrugs were also evaluated for their anti-inflammatory and analgesic activities to find out their efficacy in comparison to the parent compounds.

**Biological Evaluations**

**Anti-inflammatory activity**

Anti-inflammatory activity was determined by the method of Winter et al.\(^12\) against carrageenan induced rat paw edema. Percentage reduction in edema at 3 hr in comparison to control is presented in Table I. All the glycolamide ester prodrugs showed activity comparable to their parent drugs, however, prodrugs 2a and 2b of diclofenac 2 showed improved activity over their parent moiety.

**Analgesic activity**

Analgesic activity was determined in mice by acetic acid induced writhing method\(^13\). The decrease in number of writhings expressed as percentage protection with reference to control is given in Table I. These prodrugs were found to be more active than their parent drugs. Prodrugs 3a and 3b of naproxen 3 and 4a and 4b of mefenamic acid 4 in particular showed a marked increase in activity. All
other glycolamide esters showed activity comparable to their parent drugs.

**Gastrointestinal toxicity**

Subacute gastrointestinal toxicity studies were done by the method of Wilhemi et al. The animals were divided into groups with six animals in each group. Control group was given only 0.5% CMC suspension. Compounds were administered orally once in a day for 10 days. The animals were fasted for 8 hr prior to dosing and for 4 hr post dosing. Food was available at all other times, free access to water.
was provided throughout the experiment. Four hr after the last dose, the animals were sacrificed using chloroform. The abdomen was opened at the midline and the stomach and the first 3cm of the duodenum were removed. The stomach was opened along the larger curvature and washed with distilled water. The mucus was wiped off and the numbers of ulcers were examined by means of a magnifying glass. All ulcers were counted and recorded as average number of ulcers per animal and assessed as score [No ulcers (0.0), less than 2 ulcers (1.0), 2-5 ulcers (2.0), 5-10 ulcers (3.0), more than 10 ulcers (4.0)]. The results are given in Table 1. All the synthesised glycolamide esters considerably reduced GI toxicity as compared to their parent drugs. Prodrugs 3a and 3b showed 70-88% less ulceration than naproxen 3 while prodrugs 1a, 1b and 5a, 5b were found to be less ulcerogenic by 75-84% in comparison to their parent drugs 1 and 5. Prodrugs of 2 and 4 were less ulcerogenic by 66-80%.

**Experimental Section**

Melting points were taken in open capillaries and are uncorrected. $^1$H NMR spectra were recorded in CDCl$_3$ on a Bruker 300 MHz instrument using TMS as internal standard. Chemical shift values are reported in ppm (δ). Purity of the compounds were checked by TLC on silica gel plates and the spots were located by exposure to iodine vapours. Microanalyses of all these compounds were within ±0.4%.

**General method of synthesis of N,N-disubstituted-2-chloroacetamides.**

To a solution of the appropriate NSAID (0.01 mole) in ethyl acetate (40 mL) were added triethylamine (0.01 mole; 1.53 mL), sodium iodide (0.01 mole) and N,N-diisopropyl-2-chloro-acetamide (0.01 mole). The mixture was refluxed for 3 hr on a water-bath, cooled and filtered. The filtrate was washed with 2% sodium thiosulphate solution, 2% sodium bicarbonate and water, dried and ethyl acetate removed under reduced pressure. A semi-solid mass so obtained was purified on a column of silica gel and crystallised from ethanol to give TLC pure crystalline compounds.

**N,N-Diethylcarbamoylmethyl 2-(4-isobutylphenyl) propionate 1a:** Yield 2.6 g (81%), semi-solid (Found: C, 71.23; H, 9.28; N, 4.18. C$_{16}$H$_{19}$NO, requires C, 71.44; H, 9.15; N, 4.38 %). $^1$H NMR (CDCl$_3$): δ 80.9 (d, 6H, -CH(CH$_3$)$_2$); 1.12 and 1.13 (t, 3H each, 2×N(CH$_2$CH$_2$)$_3$); 1.5 (d, 3H, >CH-CH$_3$); 1.83 (m, 1H, -CH(CH$_3$)$_2$); 2.4 (d, 2H, CH$_2$); 3.19 and 3.35 (q, 2H each, 2×N(CH$_2$CH$_3$)$_3$); 3.83 (q, 1H, >CH-CH$_3$); 4.6 and 4.7 (d, 1H each, OCH$_2$CO), 7.07 and 7.12 (d, 2H each, aromatic).

**N,N-Diisopropylcarbamoylmethyl 2-(4-isobutylphenyl)-propionate 1b:** Yield 2.8 g (80%), semi-solid (Found: C, 72.21; H, 9.64; N, 3.89. C$_{16}$H$_{20}$NO, requires C, 72.58; H, 9.57; N, 4.03%). $^1$H NMR (CDCl$_3$): δ 0.8 (d, 6H, -CH(CH$_3$)$_2$); 1.1 and 1.3 (m, 6H each, 2×N(CH$_2$CH$_3$)$_3$); 1.45 (d, 3H, >CH-CH$_3$); 1.7 (m, 1H, -CH(CH$_3$)$_2$); 2.35 (d, 2H, CH$_2$); 3.39 and 3.5 (m, 1H each, 2×N(CH$_2$CH$_3$)$_3$); 3.79 (q, 1H, >CH-CH$_3$); 4.4 and 4.6 (d, 1H each, OCH$_2$CO), 7.0 and 7.1 (d, 2H each, aromatic).

**N,N-Diethylcarbamoylmethyl 6-methoxy-a-naphthyl acetate 2a:** Yield 3.5 g (85.7%), yellow crystals, m.p. 80-92° (Found: C, 58.42; H, 5.51; N, 6.58. C$_{15}$H$_{13}$NO requires C, 58.69; H, 5.42; N, 6.84%). $^1$H NMR (CDCl$_3$): δ 1.12 and 1.17 (t, 3H each, 2×N(CH$_2$CH$_3$)$_3$); 3.2 and 3.7 (q, 2H each, 2×N(CH$_2$CH$_3$)$_3$); 3.9 (s, 2H, CH$_2$); 4.77 (s, 2H, OCH$_2$CO); 6.5 (dd, 1H, H3); 6.86 (s, 1H, NH); 6.96 (m, 2H, H4, H5); 7.1 (dt, 1H, H4'); 7.25 (dd, 1H, H6); 7.31 (d, 2H, H3', H5').

**N,N-Diisopropylcarbamoylmethyl 2-[(2', 6'-dichlorophenyl) amino] phenyl acetate 2b:** Yield 3.8 g (87%), yellow crystals, m.p. 110-115° (Found: C, 60.18; H, 5.73; N, 6.19. C$_{15}$H$_{13}$NO, requires C, 60.42; H, 5.99; N, 6.40%). $^1$H NMR (CDCl$_3$): δ 1.32 and 1.3 (m, 6H each, 2×N(CH$_2$CH$_3$)$_3$); 3.48 and 3.6 (m, 1H each, 2×N(CH$_2$CH$_3$)$_3$); 3.9 (s, 2H, CH$_2$); 4.73 (s, 2H, OCH$_2$CO); 6.52 (dd, 1H, H3); 6.87 (s, 1H, NH); 6.96 (m, 2H, H4, H5); 7.11 (dt, 1H, H4'); 7.2 (dd, 1H, H6); 7.32 (d, 2H, H3', H5').

**N,N-Diethylcarbamoylmethyl-6-methoxy-α-methyl-2-naphthyl acetate 3a:** Yield 2.8 g (82%), m.p. 52-54° (Found: C, 69.73; H, 7.18; N, 4.28. C$_{19}$H$_{20}$NO requires C, 69.95; H, 7.34; N, 4.08%). $^1$H NMR (CDCl$_3$): δ 1.05 and 1.12 (t, 3H each, 2×N(CH$_2$CH$_3$)$_3$); 1.52 (d, 3H, >CH-CH$_3$); 3.1 and 3.27 (q, 2H each, 2×N(CH$_2$CH$_3$)$_3$); 3.79 (s, 3H, -OCH$_3$); 3.91 (q, 1H, >CH-CH$_3$); 4.44 and 4.69 (d, 1H each, OCH$_2$CO); 7.0 (m, 2H, H5, H7); 7.33 (m, 1H, H3); 7.60 (m, 3H, H1, H4, H8).

**N,N-Diisopropylcarbamoylmethyl 6-methoxy-α-methyl-2-naphthyl acetate 3b:** Yield: 2.5 g (67%), semi-solid (Found: C, 71.25; H, 7.64; N, 3.49.
C_{22}H_{29}N_{4}O_{4} requires C, 71.13; H, 7.87; N, 3.77%.

{^1}H NMR (CDCl_{3}): 81.1 and 1.3 (m, 6H each, 2xN-CH(CH_{3})_{2}); 1.5 (d, 3H, >CH-CH_{3}); 3.39 and 3.56 (m, 1H each, 2xN-CH(CH_{3})_{2}); 3.7 (s, 3H, -OCH_{3}); 3.9 (q, 1H, >CH-CH_{3}); 4.6 (s, 2H, OCH_{2}CO); 7.12 (m, 2H, H5, H7); 7.43 (m, 1H, H3); 7.7 (m, 3H, H1, H4, H8).

N,N-Diethylcarbamoylmethyl 2-(2',3'-dimethylphenyl) amino benzoate 4a:

Yield 2.3g (65%), semi-solid (Found: C, 70.89; H, 7.14; N, 7.72. C_{21}H_{26}N_{2}O_{3} requires C, 71.16; H, 7.39; N, 7.90%); {^1}H NMR (CDCl_{3}): 81.06 and 1.14 (t, 3H each, 2xN(CH_{2}CH_{3}); 2.08 (s, 3H, CH_{3}); 2.24 (s, 3H, CH_{3}); 3.18 and 3.33 (q, 2H each, 2xN(CH_{2}CH_{3}); 4.89 (s, 2H, OCH_{2}CO); 6.5 (m, 2H, H4', H6'); 6.9 (dt, 1H, H5'); 7.04 (m, 2H, H3, H5); 7.20 (m, 1H, H4); 7.98 (m, 1H, H6); 9.0 (bs, 1H, NH).

N,N-Diisopropylcarbamoylmethyl 2-(2',3'-dimethylphenyl) amino benzoate 4b:

Yield 2.9g (76%), semi-solid (Found: C, 72.48; H, 7.68; N, 7.46. C_{23}H_{30}N_{2}O_{3} requires C, 72.22; H, 7.39; N, 7.90%); {^1}H NMR (CDCl_{3}): 81.14 and 1.14 (t, 3H each, 2xN(CH_{2}CH_{3}); 2.1 (s, 3H, CH_{3}); 2.2 (s, 3H, CH_{3}); 3.39 and 3.5 (m, 1H each, 2xN-CH(CH_{3})_{2}); 4.6 (s, 2H, OCH_{2}CO); 6.5 (m, 2H, H4', H6'); 6.9 (m, 1H, H5'); 7.05 (m, 1H, H3, H5); 7.2 (m, 1H, H4); 7.98 (m, 1H, H6); 9.0 (bs, 1H, NH).

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