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Nabumetone (47) is a recently developed NSAID with proven efficacy and safety\textsuperscript{83}. It is nonacidic and after absorption gets rapidly metabolised to form a major metabolite, 6-methoxy-2-naphthylacetic acid (6-MNA, 48) which is mainly responsible for the activity of nabumetone\textsuperscript{84}. Nabumetone, as a bioprecursor type of prodrug, possesses the potential to avoid NSAID-mediated direct acidic gastrointestinal damage, while maintaining the efficacy as an antiinflammatory agent via the peripheral action of its active metabolite, 6-MNA\textsuperscript{85}.

Haddock et al.\textsuperscript{41} studied the metabolism of nabumetone and reported that three different interrelated pathways (Figure 5) involving O-demethylation, reduction of the ketone group to an alcohol and oxidation of the butanone side chain to form 6-MNA occurred in all species, but the ratio of the end products tended to be species dependent. The latter process is of primary importance for the production of 6-MNA, which is responsible for the activity of nabumetone, although other metabolites also possess various levels of activity.

These types of oxidative metabolic transformations put a burden on the oxidative enzyme systems, and result in a number of potentially active metabolites which have different binding, distribution and elimination properties\textsuperscript{86}. The overall result is that depending on the other compounds requiring the same enzyme system, as well as
Figure 5: Biotransformation of nabumetone.
on the activity level of the specific individual’s enzymes, a variety of combinations of the active species will be present in different individuals making the safe and effective dosing of these compounds practically impossible\textsuperscript{86,87}.

In this type of situation, the drug of choice should be one of these active metabolites, if activity and pharmacokinetic considerations permit it\textsuperscript{88}. Although there are many examples of active metabolites being introduced as independent drugs (vide supra), it was not possible to use 6-MNA as such because of its severe gastrointestinal side effects. However, it has been observed that systemically 6-MNA does not markedly inhibit gastroprotective prostanoids, and therefore gastric damage induced by this agent largely results from the direct local effect caused by its free carboxyl (-COOH) group\textsuperscript{85,89}.

A short account given in the introduction, highlighting the importance of prodrug approach in reducing toxic and unwanted side effects of drugs, prompted us to use this promising approach to modify 6-MNA. The objective was to mask the carboxylic group of 6-MNA temporarily which may result in the development of improved and safer NSAIDs. Additionally, it has been found that 6-MNA is not subject to significant enterohepatic circulation, and this will contribute to overall better gastrointestinal tolerance of its prodrugs\textsuperscript{90}. 
It has been suggested that while designing prodrugs hydrolytic mechanisms should be used, as much as possible, for bioconversion\textsuperscript{86} (vide supra). It is important to note that nonspecific esterases have no important role in the basic biochemical processes; their main function is exactly to get rid of a variety of xenobiotics\textsuperscript{86}. Moreover, distribution of esterases is ubiquitous, and several types are present in blood, liver and other organs and tissues\textsuperscript{91-94}. This has been the main reason behind the fact that the best known prodrugs are esters of drugs containing carboxyl or hydroxyl groups. A variety of esters of acidic NSAIDs have been developed in order to reduce their gastrointestinal toxicity\textsuperscript{95,96}.

Recently, esters of certain $N,N$-disubstituted glycolamides (93) have been reported as potentially useful biolabile prodrugs for carboxylic acid agents. This is because of their high susceptibility to undergo enzymatic hydrolysis to the parent active acid (94) in plasma due to the presence of pseudocholinesterases (Figure 6)\textsuperscript{97}. At the same time these glycolamide esters are highly stable in aqueous solutions\textsuperscript{97}. Furthermore, it is feasible to obtain

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\text{RCOCH}_2\text{CON}_2^{R_1} \xrightarrow{\text{enzymatic}} \text{RCOOH} + \text{HOCH}_2\text{CON}_2^{R_1}
\]

\textbf{Figure 6: Single step quantitative conversion of glycolamide ester to parent acid.}

39
these ester derivatives with almost any desirable water solubility or lipophilicity, without affecting their enzymatic hydrolysis significantly, just by changing the substituents on the nitrogen\textsuperscript{97,98}.

Based on these observations, it was decided to prepare various glycolamide esters of 6-MNA (96) as potentially useful biolabile and chemically stable prodrugs, which were expected to undergo enzymatic hydrolysis releasing the parent active acid 6-MNA quantitatively in a single step. The specific aims of this study were:

1. To synthesise a series of glycolamide esters of 6-MNA as potentially useful prodrugs, and to confirm their structures using the combined techniques of spectroscopy and elemental analysis.
2. To synthesise a series of simple alkyl esters of 6-MNA and to confirm their structures.
3. To investigate these prodrug derivatives of 6-MNA with regard to their physicochemical properties, namely solubility, partition coefficient and capacity factor.
4. To assess the chemical stability of these prodrugs in aqueous solutions.

5. To determine the rate of enzymatic hydrolysis in human plasma and rat liver homogenate to assess the prodrug potential of these derivatives.