The significance of active metabolites of therapeutic agents is discussed, and literature on active metabolites of nonsteroidal antiinflammatory drugs (NSAIDs) is reviewed. Various examples of active metabolites introduced as independent drugs are illustrated. The possibility of chemical modifications of such metabolites using prodrug approach, as a means of design and development of new and safer drugs, is discussed. The prodrug concept is also dealt with briefly.

In the present study, 6-methoxy-2-naphthylacetic acid (6-MNA), an active metabolite of nabumetone, was selected for structural modifications using prodrug approach. 6-MNA was synthesised by treating 2-naphthol with dimethyl sulphate, followed by Friedal-Crafts acylation and Willgerodt-Kindler modified reaction. Glycolamide ester prodrugs of 6-MNA were prepared by reacting the parent compound with the appropriate substituted 2-chloroacetamides. The required 2-chloroacetamides were synthesised by reacting chloroacetyl chloride with respective amines. Alkyl esters of 6-MNA were also prepared. Structures of these prodrugs were confirmed by the combined techniques of spectroscopy ($^1$H-NMR, $^{13}$C-NMR, MASS and IR) and elemental analysis.
A reversed-phase HPLC procedure was developed for the determination of purity, physicochemical and kinetic properties of various prodrug derivatives prepared.

The physicochemical properties namely, solubility, partition coefficient and capacity factor were determined. Partition coefficients were also calculated using Rekker fragmentation constants. Log $P_{cal}$ values were in good agreement with log $P_{obs}$ values. Correlations between capacity factors and partition coefficients, and between solubilities, melting points and partition coefficients were established.

Ester derivatives of 6-MNA were subjected to hydrolysis in phosphate buffer of pH 7.4 at 37 °C to assess their stability. The degradation of these esters followed pseudo-first-order reaction kinetics. Simple alkyl esters were most stable and monosubstituted glycolamide esters were least stable with disubstituted glycolamide esters having intermediate stability. One ester prodrug of each type was subjected to hydrolysis over a pH range of 1.2 to 9.0 to see the effect of pH on degradation rate and to determine the pH of maximum stability. The shelf-lives of these esters were estimated at pH 4.5 (stable range pH 4-5) using accelerated stability testing procedures. The results indicated that ester prodrugs possessed sufficient stability to be formulated in solid dosage forms. It might also be possible
to prepare stable liquid formulations of simple alkyl and disubstituted glycolamide ester prodrugs.

The ester prodrugs of 6-MNA possessing aqueous solubility more than 5 µg/ml were subjected to enzymatic hydrolysis in 80% human plasma at pH 7.4. These results indicated that bioconversion of the ester prodrugs to the parent 6-MNA was quantitative and fast. Disubstituted glycolamide esters showed highest reactivity followed by monosubstituted glycolamide esters and simple alkyl esters. Simple alkyl esters were also subjected to hydrolysis in 0.2% w/v rat liver homogenate.

The above mentioned in vitro evaluation results indicate that many of these ester derivatives may act as potential prodrugs of 6-MNA, which will get cleaved to 6-MNA quantitatively after absorption.