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Glycolamide esters of 6-methoxy-2-naphthylacetic acid as potential prodrugs – physicochemical properties, chemical stability and enzymatic hydrolysis

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Abstract

Various glycolamide ester prodrugs of 6-MNA (**I**), an active metabolite of nabumetone (**II**), were synthesised to obtain NSAIDs with improved therapeutic index. To assess their suitability as prodrugs, these derivatives were evaluated for physicochemical properties, chemical stability and enzymatic hydrolysis in 80% human plasma. A number of these ester derivatives possessed physicochemical properties required for oral absorption (log $P \geq 2$, solubility ≥ 10 μg/ml). These esters were sufficiently stable in 0.05 M phosphate buffer of pH 7.4 at 37°C (half-lives 16–473 h). The disubstituted glycolamide esters **XII–XXII** were more stable than monosubstituted glycolamide esters **IV–XI**. Compound **XII** was also subjected to hydrolytic studies over the pH range 1.2–9.0 at 70°C and from the pH-rate profile, the pH of maximum stability was found to be 4.34 (4–5). At pH 4.5 compound **XII** showed a shelf life of 1.12 years at 20°C as determined from accelerated studies using the Arrhenius equation. The ester derivatives were quantitatively converted to 6-MNA very rapidly in human plasma at 37°C and pH 7.4 Comparison with chemical stability data shows that the intrinsic reactivity of esters has no effect on their enzymatic reactivity. The chemically most stable *N,N*-disubstituted glycolamide esters were better substrates for plasma enzymes (half-lives 7–83 s) compared to the monosubstituted glycolamide esters (half-lives 168–809 s). It is concluded that these derivatives possess many of the ideal properties of prodrugs and esterification of 6-MNA with substituted 2-hydroxyacetamides may be a potentially useful prodrug approach.

Keywords: 6-Methoxy-2-naphthylacetic acid; Prodrug; Enzymatic hydrolysis; Lipophilicity; NSAID; Chemical stability

1. Introduction

6-Methoxy-2-naphthylacetic acid 6-MNA (**I**), is the major active metabolite of nabumetone (**II**), a newly developed nonsteroidal antiinflammatory agent (Friedal and Todd, 1988). However, nabumetone is not converted to 6-MNA quantitatively because many interrelated pathways occur simultaneously, forming a number of other metabolites (Haddock et al., 1984). These metabolic pathways include *O*-demethylation, reduction of the keto group to an alcohol and oxidation of the butanone side chain to form

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6-MNA. 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 (Haddock et al., 1984).

These types of oxidative metabolic transformations put a burden on the oxidative enzyme systems and result in the formation of a number of potentially active metabolites, which have different binding, distribution and elimination properties (Bodor, 1982). The overall result is that, depending on the other compounds requiring the same enzyme systems, as well as on the activity level of the specific individual's enzymes, a variety of combinations of active compounds will be formed in different individuals making the safe and effective dosing of these agents practically impossible (Bodor, 1982, 1984).

In this type of situation, the drug of choice should be one of these active metabolites if activity and pharmacokinetic considerations permit it. In doing so, it would often be possible to end up with a product showing less variability, less complex biotransformations and better therapeutic performance (Faigle, 1987). Although there are a number of examples of active metabolites being introduced as independent drugs, it is not possible to use 6-MNA as such because of its severe gastrointestinal side effects. 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 (Jeremy et al., 1990; Price and Fletcher, 1990).

An alternate approach is to use the promising prodrug concept to mask the carboxyl group of 6-MNA temporarily (Jones, 1985; Buge, 1986). These prodrugs will thus possess the potential to avoid 6-MNA mediated direct acidic gastrointestinal damage, while maintaining their efficacy via the systemic action of the active metabolite 6-MNA. 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 (Brett et al., 1990). Glycolamide esters have been reported as potentially useful biolabile and chemically stable prodrugs of carboxylic acid drugs (Bundgaard and Nielsen, 1987; Nielsen and Bundgaard, 1988). These observations prompted us to prepare and to evaluate glycolamide esters of 6-MNA as potential prodrugs. In this paper, we report the physicochemical properties, chemical kinetics and enzymatic hydrolysis in 80% human plasma of glycolamide esters of 6-MNA **III–XXII**. The synthesis and chemical characterisation of these derivatives have been communicated elsewhere (Wadhwa and Sharma, 1995).

2. Materials and methods

2.1. Chemicals

6-MNA was synthesised starting from 2-naphthol using methylation with dimethyl sulphate (Vogel, 1968) followed by Friedal-Crafts acylation (Arsenijevic et al., 1973), Willgerodt-Kindler modified reaction (Ormancey and Horeau, 1955) and alkaline hydrolysis. Substituted 2-chloroacetamides required for the synthesis of glycolamide esters of 6-MNA were prepared according to reported methods (Speziale and Hamm, 1956; Harkins, 1965). Reagents used for the preparation of the buffers were of analytical reagent grade. Fresh triple-distilled water from all-glass apparatus was used in the preparation of all the solutions. HPLC mobile phase was prepared from HPLC-grade acetonitrile and methanol (E. Merck). Human plasma was procured from the blood bank of the Post Graduate Institute of Medical Education and Research, Chandigarh, India.

2.2. Preparation of glycolamide esters of 6-MNA (III–XXII)

A mixture of 6-MNA (0.01 mol), appropriate 2-chloroacetamide (0.011 mol), sodium iodide (0.001 mol), triethylamine (0.011 mol) and DMF (10 ml) was stirred at 90°C for 3 h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3×50 ml). The combined organic extract was washed successively with aqueous sodium thiosulphate (2%, 50 ml),

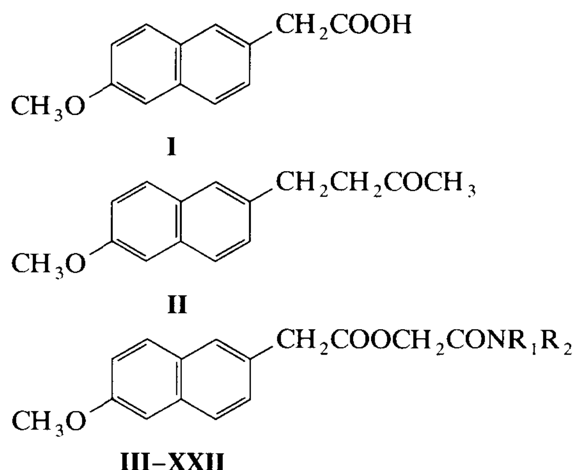
aqueous sodium bicarbonate (2%, 50 ml) and water (3 × 50 ml). The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield a solid residue which was recrystallised from ethyl acetate-hexane mixture, giving glycolamide esters (**III–XXII**) of 6-MNA.

2.3. HPLC procedure for the analysis of ester prodrugs of 6-MNA

Glycolamide ester prodrugs and 6-MNA were determined by isocratic reversed-phase HPLC procedures using a Waters equipment consisting of two M501 pumps controlled by an automated gradient controller 680, a Waters 484 tunable UV detector, Waters 746 data module and a 20 μl Rheodyne loop injection valve. For analysis, a reversed-phase μBondapack C_{18} (30 cm × 3.9 mm; 10 μm particles) column in conjunction with Guard-Pak precolumn module with μBondapack C_{18} insert was eluted with mixtures of methanol or acetonitrile and 0.02 M phosphate buffer (pH 3.5–4.5). The compositions of the eluant and pH of the buffer were adjusted for each compound in order to provide an appropriate retention time and separation of ester prodrugs and 6-MNA. The flow rate of 1 ml/min was maintained and column effluent was monitored at 230 nm. Quantification of the compounds was carried out by measuring the peak areas or peak heights in relation to those of standards chromatographed under the same conditions.

2.4. Determination of solubility

The solubility of prodrugs **III–XXII** was determined in 0.05 M phosphate buffer of pH 7.4 at 25°C. Excess amount of the powdered prodrug was added to 2–5 ml of the buffer in screw-capped test tubes. The suspension was vortexed for 10 min and kept in a shaking incubator maintained at 25°C for 24 h. The suspension was transferred to a 10 ml glass syringe maintained at 25°C and filtered through a 0.45 μm membrane filter in a warm test tube. After appropriate dilutions in the same buffer, 20 μl of the solution was injected for HPLC analysis. The concentration of the compound was calculated from the standard plot obtained on the same day under similar conditions. Determinations were performed in triplicate for each compound.



Compound	R_1	R_2
III	H	H
IV	H	CH_3
V	H	CH_2CH_3
VI	H	$CH_2CH_2CH_3$
VII	H	$CH(CH_3)_2$
VIII	H	$CH_2CH_2CH_2CH_3$
IX	H	$CH(CH_3)CH_2CH_3$
X	H	$C(CH_3)_3$
XI	H	cyclohexyl
XII	CH_3	CH_3
XIII	CH_2CH_3	CH_2CH_3
XIV	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$
XV	$CH(CH_3)_2$	$CH(CH_3)_2$
XVI	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$
XVII	cyclohexyl	cyclohexyl
XVIII	$-CH_2CH_2CH_2CH_2-$	
XIX	$-CH_2CH_2OCH_2CH_2-$	
XX	CH_3	CH_2CH_2OH
XXI	CH_2CH_3	CH_2CH_2OH
XXII	CH_2CH_2OH	CH_2CH_2OH

2.5. Determination of lipophilicity parameters

The apparent partition coefficients (P) of the ester derivatives of 6-MNA were determined in

octanol-buffer system at 25°C. The aqueous phase was a 0.05 M phosphate buffer of pH 7.4. The buffer solution and octanol were mutually saturated before use. The traditional shake flask method (Leo et al., 1971) was used, and concentrations were determined by HPLC to afford rapid evaluation and better reliability (Hairsine, 1989; Stopher and McClean, 1990). The compounds were dissolved in octanol (2 ml) in 10 ml screw-capped test tubes. After addition of buffer (5 ml), the two phases were mixed on a cyclo-mixer for 15 min and kept in a shaking water bath maintained at 25°C for 8 h. The tubes were centrifuged at 3000 rpm for 30 min. The octanol layer (1 ml) was removed, diluted, 20 μl of the resulting solution was injected into the HPLC column and the peak area was measured (AUC_{oct}). The buffer solution was also removed, 20 μl of this solution was injected and corresponding peak area was obtained (AUC_{buffer}). The partition coefficient (P) was determined from the following expression:

$$P = (AUC_{oct}/AUC_{buffer}) \times \text{dilution factor} \quad (1)$$

The lipophilicity of these prodrug derivatives was also evaluated by means of reversed-phase HPLC capacity factors (Chou and Jurs, 1980). In this method, the capacity factor (k') of a solute was taken as a measure of the relative lipophilicity and was calculated as:

$$k' = (t_R - t_0)/t_0 \quad (2)$$

where t_R is the retention time of the solute and t_0 denotes the elution time of the solvent. The k' values were determined using methanol/phosphate buffer (0.02 M, 4.0 pH) in 80:20 ratio. The flow rate was maintained at 1 ml/min and column effluent was monitored at 230 nm.

2.6. Chemical hydrolysis

Hydrolysis of ester prodrugs of 6-MNA was studied under near physiological conditions at pH 7.4 in 0.05 M phosphate buffer at 37°C. The reaction was initiated by adding 50–100 μl of the stock solution (in CH_3CN) of the ester to 20 ml of preheated buffer solution in screw-capped test tubes. The final concentration of the compounds was in the range of 1.8×10^{-6}–2.0×10^{-5} M. The solutions were kept in a water bath at constant temperature and at appropriate intervals samples were withdrawn and chromatographed.

In the case of prodrugs, where the rate of hydrolysis was found to be very slow in preliminary studies, 2-ml aliquots of the ester solution were transferred to glass ampoules, flame sealed and kept immersed in the water bath maintained at 37°C for the entire study. Several of these ampoules were refrigerated immediately after flame sealing and were later used as controls for the initial time points. At known time intervals, ampoules were removed from the water bath and refrigerated. All the ampoules were removed from the refrigerator at the end of the study, allowed to attain room temperature and analysed on the same day by HPLC. Pseudo-first-order rate constants for the hydrolysis of the derivatives were determined from the slopes of linear plots of the logarithms of residual derivative against time.

The pH-hydrolysis profile of **XII** was determined over the pH range 1.2–9.0 to determine the pH of maximum stability. The buffers used were hydrochloric acid, acetate, phosphate, and carbonate buffers. A constant ionic strength of 0.5 was maintained for each buffer by adding a calculated amount of potassium chloride. Temperature accelerated studies for the same ester **XII** were also performed at 80–90°C at pH of high stability to predict the shelf-life at 20°C.

2.7. Enzymatic hydrolysis

The hydrolysis of the ester prodrugs of 6-MNA having solubility of more than 5 μg/ml, was studied in human plasma diluted to 80% with 0.05 M phosphate buffer at pH 7.4 at 37°C. The reaction was initiated by adding 20–50 μl of the stock solution of ester in acetonitrile to 2–5 ml of preheated plasma solution, the final concentration of the compound being 4.2×10^{-5}–1×10^{-4} M. The solution was kept in water bath at 37°C. At appropriate time intervals samples of 100–250 μl were withdrawn and added to 1000–5000 μl of cold acetonitrile or methanol in order to deproteinise the plasma. After immediate mixing and

centrifugation for 5 min at 7000 rpm, 20 μl of the clear supernant was analysed by HPLC for remaining ester prodrug and the values of rate constants and half-lives were calculated as described above.

3. Results and discussion

3.1. Solubility and lipophilicity of prodrugs III–XXII

It is generally recognized that solubility and lipophilicity play an important role in governing the overall biological performance of drugs. For orally administered drugs it has been mentioned that drugs having octanol-water partition coefficient of 100 or more ($\log P \geq 2$) are well absorbed provided they have a minimum solubility of 10 μg/ml (Wakita et al., 1986). To assess this potential, the solubility of the ester prodrugs **III–XXII** was determined in 0.05 M phosphate buffer at pH 7.4 (25°C). The values are listed in Table 1.

Table 1
Solubilities (S), partition coefficients (P) and chromatographic capacity factors (k') for 6-MNA and various ester prodrugs

Compound	S (μg/ml)	log P	log k'
I	20.14 [a]	2.82 [b]	–
III	15.58	1.88	−0.4102
IV	46.77	2.19	−0.3276
V	37.98	2.65	−0.2581
VI	7.95	3.10	−0.1713
VII	15.43	2.89	−0.1883
VIII	3.54	3.57	−0.0659
IX	18.63	3.31	−0.1009
X	15.97	3.60	−0.0621
XI	1.55	3.99	0.0443
XII	45.44	2.23	−0.2640
XIII	145.07	3.05	−0.1260
XIV	5.06	4.04	0.0751
XV	0.53	3.89	0.0572
XVI	6.66	3.67	−0.0369
XVII	neg.	> 6	0.6568
XVIII	47.11	2.71	−0.1665
XIX	20.74	2.13	−0.2978
XX	196.17	1.58	−0.3900
XXI	129.71	1.98	−0.3276
XXII	567.63	1.41	−0.4676

S, solubility in 0.05 M phosphate buffer of pH 7.4 at 25°C; P, apparent partition coefficient in octanol/0.05 M phosphate buffer of pH 7.4; k', capacity factor in mobile phase methanol/0.02 M phosphate buffer of pH 4.0 (80:20).
[a] Solubility in 0.1 M HCl solution.
[b] Partition coefficient in octanol/0.1 M HCl system.

The apparent partition coefficients (P) were determined between octanol and 0.05 M phosphate buffer of pH 7.4. The log P values obtained are listed in Table 1.

The lipophilicity of the ester derivatives was also evaluated by means of reversed-phase HPLC capacity factors (k') in methanol : 0.02 M phosphate buffer of pH 4.0 (4 : 1) as mobile phase. The k' values are listed in Table 1. As has been observed with many different types of compounds (Hafkenscheid and Tomlinson 1983; Fort and Mitra, 1987), a linear relationship existed between log k'

$$\log P = 5.0603 \log k' + 3.7632$$

$$r = 0.985 \quad n = 19 \quad (3)$$

and log P. This relationship would very likely allow extrapolation to other esters in the series.

The solubility and log P data (Table 1) show that ester derivatives **III–V, VII, IX, X, XII, XIII, XVIII–XXII** possess optimum physicochemical properties required for oral absorption. Compounds **IV, V, XII, XIII** and **XVIII–XXII** are even more soluble than 6-MNA (20.14 μg/ml), the parent drug.

3.2. Chemical stability of 6-MNA esters

Prodrug derivatives should be sufficiently stable so that they can be formulated in a stable dosage form. To assess stability, hydrolysis of the ester derivatives **III–XXII** was studied in 0.05 M phosphate buffer of pH 7.4 at 37°C. The degradation of glycolamide ester prodrugs displayed strict pseudo-first-order kinetics over several half-lives. Fig. 1 represents pseudo-first-order cleavage of **VI, X, XII** and **XIX**. For all compounds, parent 6-MNA was formed in stoichiometric amounts. The pseudo-first-order rate constants and half-lives observed for hydrolysis at pH 7.4 and 37°C are listed in Table 2.

It can be seen from Table 2 that monosubstituted glycolamide esters **IV–XI** are less stable (half-lives 16–40 h) as compared to disubstituted glycolamide esters **XII–XXII** (half-lives 42–473 h). Bundgaard and Nielsen (1987) reported the same trend while studying glycolamide esters of benzoic acid. It was mentioned that lower reactivity of *N,N*-disubstituted glycolamide ester prodrugs compared to *N*-monosubstituted glycolamide esters may be due to increased steric hinderance to nucleophile OH^- in the case of the former. This is further strengthened by the fact that compounds **XV** and **XVII** having maximum steric hindrance are most stable.

The stability of **XII** was further investigated over the pH range 1.2–9.0 at 70°C to evaluate the effect of pH on degradation rate and to determine the pH of maximum stability. The influence of pH on the rate of hydrolysis of **XII** at 70°C is shown in Fig. 2, in which the logarithms of the observed pseudo-first-order rate constants (k) are plotted against pH. The U shaped pH-rate profile indicates the occurrence of specific acid-catalysed (k_H) neutral or water-catalysed (k_0) and specific base-catalysed (k_{OH}) processess according to the following rate expression:

$$k_{obs} = k_H a_H + k_0 + k_{OH} a_{OH} \quad (4)$$

where a_H and a_{OH} are the hydrogen ion and hydroxide ion activities, respectively, at the reaction temperature (Connors et al., 1986). The latter was calculated from the measured pH at 70°C according to the equation:

$$\log a_{OH} = \mathrm{pH} - 12.82(70°\mathrm{C}) \quad (5)$$

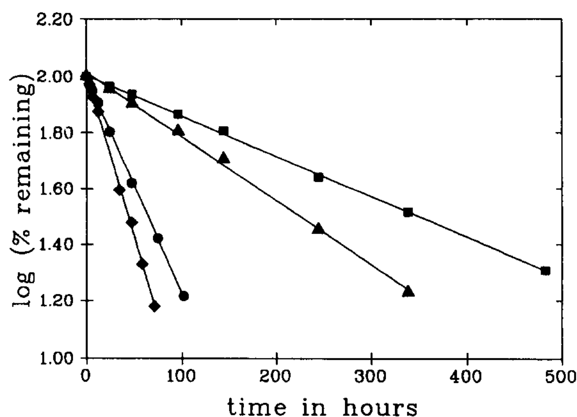


Fig. 1. Pseudo-first-order plots for the hydrolysis of **VI** (◆), **X** (●), **XII** (■) and **XIX** (▲) in 0.05 M phosphate buffer of pH 7.4 at 37°C.

Table 2
Rate data for the hydrolysis of various ester prodrugs of 6-MNA in 0.05 M phosphate buffer solution and 80% human plasma at 37°C and pH 7.4

Compound	First-order rate constants		Half-lives	
	Buffer (h^{-1})	80% human plasma (s^{-1})	Buffer (h)	80% human plasma (s)
III	1.640×10^{-2}	8.043×10^{-4}	42.26	862
IV	2.105×10^{-2}	4.126×10^{-3}	32.96	168
V	2.186×10^{-2}	1.493×10^{-3}	31.70	464
VI	2.660×10^{-2}	8.569×10^{-4}	26.05	809
VII	2.405×10^{-2}	1.770×10^{-3}	28.82	392
VIII	2.959×10^{-2}	–	23.42	–
IX	2.813×10^{-2}	1.067×10^{-3}	24.64	649
X	1.770×10^{-2}	2.606×10^{-3}	39.14	266
XI	4.184×10^{-2}	–	16.56	–
XII	3.324×10^{-3}	9.930×10^{-2}	208.48	7
XIII	2.838×10^{-3}	8.266×10^{-2}	244.19	8
XIV	2.641×10^{-3}	2.587×10^{-2}	262.40	27
XV	1.464×10^{-3}	–	473.36	–
XVI	3.331×10^{-3}	2.586×10^{-2}	208.04	27
XVII	1.514×10^{-3}	–	457.73	–
XVIII	3.855×10^{-3}	1.184×10^{-2}	179.77	59
XIX	5.272×10^{-3}	8.334×10^{-3}	131.45	83
XX	8.115×10^{-3}	6.461×10^{-2}	85.39	11
XXI	1.025×10^{-2}	8.395×10^{-2}	67.63	8
XXII	1.614×10^{-2}	4.388×10^{-2}	42.92	16

Values of the second-order rate constants k_H and k_{OH} were determined from the straight line portions of the pH-rate profile at low and high pH values after adjusting the slope to -1 and $+1$, respectively. The value for the first-order rate constant for spontaneous hydrolysis (k_0) was obtained from Eq. 4, using the best-fit method. In Fig. 2, the points shown are the log k_{obs} values and the solid curve is constructed from the derived rate constants using Eq. 4.

The pH where the rate of hydrolysis is minimum (pH_{min}) was found by differentiating Eq. 4 and setting the derivative equal to zero (Connors et al., 1986). The pH_{min} and values for rate constants at 70°C are given below:

$$k_H = 2.4203 \ \mathrm{M}^{-1} \ \mathrm{h}^{-1}$$

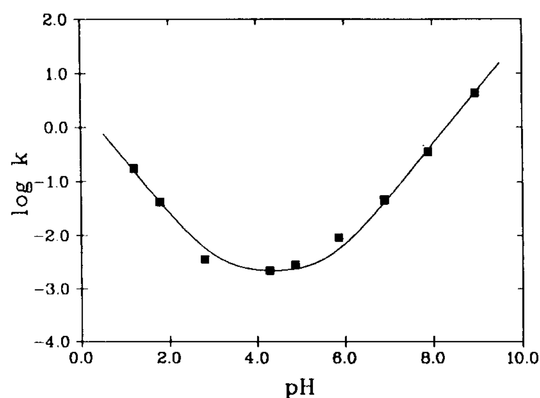


Fig. 2. The pH-rate profile for the hydrolysis of **XII** in aqueous buffers ($\mu = 0.5$) at 70°C.

$k_0 = 0.002\ h^{-1}$

$k_{OH} = 33198.85\ M^{-1}\ h^{-1}$

$pH_{min} = 4.34(pH\ 4\text{–}5)$.

The effect of temperature (80–90°C) on the rate of hydrolysis of **XII** was also studied at pH 4.5 (stable range) to determine the shelf-life ($t_{10\%}$, time required to degrade 10% of the compound) at 20°C. The rate constants obtained at different temperatures were plotted according to Arrhenius equation:

$$\log k = \log A - E_a/2.303RT \quad (6)$$

where E_a is the energy of activation, A denotes the frequency factor, R is the gas constant and T represents absolute temperature. On the basis of Eq. 6, the shelf-life of **XII** was estimated to be 1.12 years at 20°C.

3.3. Bioconversion

In order to be useful as prodrugs of 6-MNA, the ester derivatives should be readily converted to the parent drug in vivo. To assess the biolability, the hydrolysis of the ester prodrugs of 6-MNA was studied in 80% human plasma (pH 7.4) at 37°C. At initial concentration of 4.2×10^{-5}–1×10^{-4} M, the progress of hydrolysis of all esters followed strict first-order kinetics over several half-lives as illustrated in Fig. 3 for ester prodrugs **III**, **IV**, **XII** and **XIX**. The half-lives and pseudo-first-order rate constants are given in Table 2. Under the conditions used, all esters were quantitatively hydrolysed to 6-MNA as revealed by HPLC analysis of the reaction solutions.

It is clear from the data that the glycolamide esters are hydrolysed quite rapidly (7–862 s) in 80% human plasma solutions. The enzymatic activity appears to depend on the number and size of substituents on the amide nitrogen atom. The unsubstituted glycolamide ester **III** was relatively slowly hydrolysed, whereas the monosubstituted glycolamide esters **IV–XI** were hydrolysed at a faster rate. However, *N,N*-disubstituted glycolamide esters **XII–XXII** were hydrolysed particularly rapidly. The same structural dependence was observed for the glycolamide esters of aromatic acid, benzoic acid (Nielsen and Bundgaard, 1988). The introduction of hydrophilic groups in the *N*-substituents (**XX–XXII**) and keeping the amide nitrogen in a cyclic structure (**XVIII, XIX**) do not affect the reactivity considerably.

The rapid rate of hydrolysis observed in plasma is important in view of the slow rates of hydrolysis in the absence of plasma under similar conditions in buffer solutions of pH 7.4 at 37°C (Table 2). Comparison shows that the intrinsic reactivity of esters has no effect on their enzymatic reactivity. The enzymatically most active *N,N*-disubstituted glycolamide esters show even a lower intrinsic chemical reactivity than the unsubstituted or monosubstituted esters. Nielsen and Bundgaard (1988) have reported that the enzyme responsible

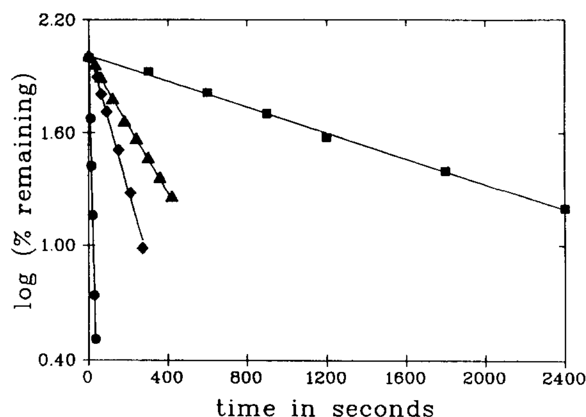


Fig. 3. Plots showing first-order kinetics of hydrolysis of the ester prodrugs **III** (■), **IV** (▲), **XII** (•) and **XIX** (♦) in 80% human plasma of pH 7.4 at 37°C.

for these glycolamide esters hydrolysis may be pseudocholinesterase (EC 3.1.1.8). The high reactivity of *N,N*-disubstituted glycolamide esters is due to the structural similarity between these esters and benzoylcholine. The carbonyl group in the amide moiety of glycolamide esters may be regarded as isosteric to the methylene group in choline esters. A good fit to the trimethyl binding site of the enzyme should require a *N,N*-disubstituted amide group rather than unsubstituted or monosubstituted group.

4. Conclusion

Glycolamide esters of 6-MNA fulfil most of the ideal requirements of prodrugs. They are chemically very stable to be presented in a proper dosage form. At the same time they get rapidly cleaved to parent 6-MNA, in 80% human plasma. Compounds **III–V, VII, IX, X, XII, XIII** and **XVIII–XXII** possess optimum physicochemical properties required for oral absorption and may be selected for further studies. These prodrugs will thus possess the potential to avoid 6-MNA mediated direct gastric damage while maintaining their efficacy via the systemic action of the active metabolite 6-MNA. It is concluded that esterification of 6-MNA with substituted 2-hydroxyacetamides may be a potential prodrug approach in order to get NSAIDs with improved therapeutic index.

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