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Communications to the Editor

Esters of N,N-Disubstituted 2-Hydroxyacetamides as a Novel Highly Biolabile Prodrug Type for Carboxylic Acid Agents

Sir:

A promising approach to improve drug delivery is chemical transformation of the active drug substances into per se inactive derivatives (prodrugs) that convert to the parent compounds by virtue of enzymic or chemical lability within the body system.[1-3] A major problem for the general application of this principle is, however, the limited availability of chemical derivative types satisfying the prodrug requirements, the most prominent of these being reconversion of the prodrug to the parent drug in vivo.[4] The best known prodrugs are probably esters of drugs containing carboxyl or hydroxyl groups, a major reason for this being the ready availability of enzymes in the organism capable of hydrolyzing most esters.

Sometimes, however, many aliphatic or aromatic esters are not sufficiently labile in vivo to ensure a sufficiently high rate and extent of prodrug conversion. For example, simple alkyl and aryl esters of penicillins are not hydrolyzed to the active free penicillin acid in vivo[5,6] and therefore have no therapeutic potential. Similarly, the much reduced antiinflammatory activity observed for the methyl or ethyl esters of naproxen[7] and fenbufen[8] relative to the free acids may be ascribed to the resistance of the esters to be hydrolyzed in vivo. In the field of angiotensin-converting enzyme inhibitors ethyl esters have been developed as prodrugs for the parent active carboxylic acid drugs in order to improve their oral bioavailability. Enalapril is such a clinically used ethyl ester prodrug of enalaprilic acid.[9] Plasma enzymes do not hydrolyze the ester and the necessary conversion of the ester to the free acid takes predominantly place in the liver.[10,11] As recently suggested,[11] liver function may thus be a very important determinant for the bioactivation of enalapril and hence its thereapeutic effect. Furthermore, the limited susceptibility of enalapril to undergo enzymatic hydrolysis in vivo has been shown to result in incomplete availability of the active parent acid.[9] Pentopril is another ethyl ester prodrug of an angiotensin-converting enzyme inhibitor[12,13] which also is highly stable in human plasma.[14] In this case less than 50% of an oral dose of the prodrug ester appears to be deesterified in vivo to the active parent acid.[14,15]

As has been demonstrated in the case of penicillins,[16,17] these shortcomings of some ester prodrugs may be overcome by preparing a double ester type, (acyloxy)alkyl or [(alkoxycarbonyl)oxy]alkyl esters, which in general show a higher enzymatic lability than simple alkyl esters. Although being of considerable importance, the utility of this double ester concept in prodrug design is, for some drugs, limited by the poor water solubility of the esters and their limited stability in vitro. In many cases such esters are oils, thus creating pharmaceutical formulation problems.

In attempting to explore new generally applicable ester prodrug types possessing a high susceptibility to undergo enzymatic hydrolysis in plasma or blood, we discovered that esters of certain 2-hydroxyacetamides (glycolamides) are cleaved with remarkable speed in human plasma. In this paper we report that such rather simple esters may be a promising prodrug type for drugs containing a carboxylic acid function and that it is feasible to obtain ester derivatives with almost any desired hydrophilicity or lipophilicity and still maintain a high rate of enzymatic hydrolysis.

With use of benzoic acid as a model acid, a series of benzoate esters of various N-substituted glycolamides (**1–24**) was synthesized by reacting (benzoyloxy)acetyl chloride,[18] prepared from benzoylglycolic acid[19] and thionyl chloride, with the appropriate amine in benzene or by esterifying benzoic acid with the appropriate 2-chloro-

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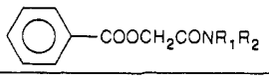
Table I. Properties of Various *O*-Benzoylglycolamides



compd	R_1	R_2	mp, °C	$t_{1/2}$,[a] min	k_{OH},[b] M^{-1} min^{-1}	S,[c] mg mL^{-1}	log P[d]
1	H	H	120.5–121	31	79.1	4.1	0.69
2	CH_3	H	111–112	9.3	85.0	3.7	0.99
3	C_2H_5	H	105–107	11.5	65.7	1.2	1.28
4	C_3H_7	H	89–90	11.2	52.1	0.64	1.88
5	t-C_4H_9	H	112–113	4.2	51.3	0.32	2.26
6	CH_2CONH_2	H	151–152	25	95.9	7.5	0.09
7	CH_3	CH_3	81–82	0.15	19.5	8.8	1.07
8	C_2H_5	C_2H_5	63–64	0.04	16.4	2.0	2.06
9	C_3H_7	C_3H_7	~20	0.14	14.2	1.1	2.65
10	i-C_3H_7	i-C_3H_7	105–106	0.08	10.7	0.12	2.56
11	C_4H_9	C_4H_9	~25	3.1	11.3	0.08	3.91
12	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	42–43	0.08	18.4	0.71	2.34
13	CH_3	CH_2CH_2OH	78–80	0.20	16.1	19.3	0.58
14	C_2H_5	CH_2CH_2OH	79–80	0.16	16.4	10.8	0.93
15	CH_2CH_2OH	CH_2CH_2OH	80–82	0.42	13.8	720	0.17
16	CH_3	CH_2CONH_2	101–102	0.13	23.5	30.2	0.08
17	CH_3	$CH_2COOC_2H_5$	39–40	0.22	15.6	6.0	1.56
18	CH_3	CH_2COOH	160–161	104	15.0	1.4[e]	0.67[f]
19	CH_3	C_6H_{11}	100–101	0.54	15.7	0.14	2.99
20	CH_3	$CH_2CH_2N(CH_3)_2$[g]	158–159	0.12	17.8	>200	
21	piperidinediyl		87–89	2.5	17.6	0.78	1.95
22	morpholinediyl		103–104	4.9	18.7	4.2	0.90
23	L-prolinamide		194–195	2.3	25.9	1.5	0.20
24	1-methylpiperazinediyl		227–228[g]	12.7	21.4	>200	

[a] Half-lives of ester hydrolysis in 50% human plasma (pH 7.40) at 37 °C. [b] Second-order rate constant for hydroxide ion catalyzed hydrolysis at 37 °C and $\mu = 0.5$. [c] Solubility in water at 22 °C. [d] Partition coefficients between octanol and water at 22 °C. [e] Solubility in 0.01 M HCl. [f] Partition coefficient between octanol and 0.01 M HCl. [g] HCl salt.

acetamide in dimethylformamide solutions.[20] The esters were found to be hydrolyzed in 50% human plasma solutions at 37 °C quite rapidly but with vastly different rates.[21] As can be seen from the data in Table I the N,N-disubstituted glycolamide esters are hydrolyzed particularly rapidly. The *N,N*-diethyl- and *N,N*-diisopropyl-substituted glycolamide esters showed the highest reactivity with a half-life of hydrolysis of only 2–5 s. In pure buffer solutions of the same pH (7.4) and at 37 °C, the half-lives of hydrolysis of these esters were estimated to be 1.2×10^3 h (**8**) and 1.8×10^3 h (**10**). The simple methyl and ethyl esters of benzoic acid were hydrolyzed much more slowly in 50% human plasma solutions, the half-lives being 1.8 and 4 h, respectively. At initial concentrations of about 10^{-4} M the progress of hydrolysis of the esters did not follow first-order kinetics. As seen from Figure 1 the rate initially followed zero-order kinetics and as the substrate depleted it changed to follow first-order kinetics. This behavior indicates the occurrence of a specific enzyme catalyzed reaction. By analyzing the progress curves according to the integrated form of the Michaelis–Menten equation,[22] a reasonable fit of this equation to the curves was obtained, indicating that the enzymatic hydrolysis followed Michaelis–Menten kinetics. This also was confirmed by measuring the initial rates of hydrolysis as a function of plasma concentration and plotting the data according to the Lineweaver–Burk equation. To give an impression of the values of the rate parameters K_m and V_{max}, the figures obtained in 50% human plasma solutions for a few compounds can be given: $V_{max} = 510$ μmol/min/L, $K_m = 1.1 \times 10^{-4}$ M (**7**); $V_{max} = 240$ μmol min^{-1} L^{-1}, $K_m = 2.7 \times 10^{-5}$ M (**8**); $V_{max} = 8$ μmol min^{-1} L^{-1}, $K_m = 1.3 \times 10^{-4}$ M (**3**). At a low substrate concentration, i.e., similar to the conditions prevailing in vivo for prodrug hydrolysis, the enzymatic reaction is first order with the rate equal to V_{max}/K_m. The half-lives given in Table I refer to this rate, i.e., $t_{1/2} = 0.693/(V_{max}/K_m)$.

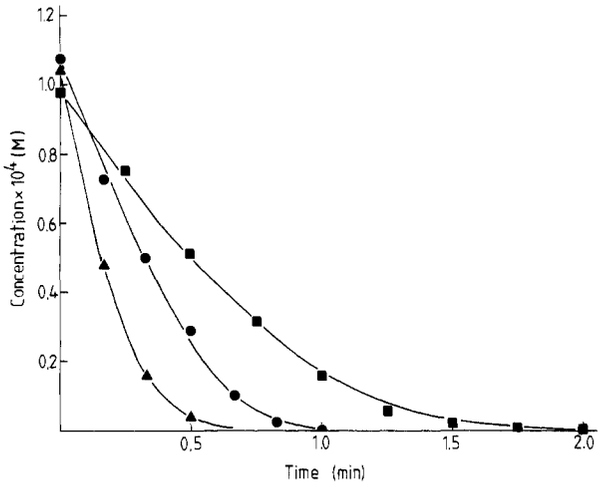


Figure 1. Plots showing the rate of hydrolysis of compound **8** (●), compound **14** (■), and compound **26** (▲) in 50% human plasma solutions at 37 °C. Compound **26** is the *N,N*-dimethylglycine ester of compound **13**, i.e., 2-(benzoyloxy)-*N*-methyl-*N*-[[(*N,N*-dimethylglycyl)oxy]ethyl]acetamide.

The enzyme in human plasma that so rapidly hydrolyzes the N,N-disubstituted glycolamide esters is most likely cholinesterase (E.C. 3.1.1.8; also called pseudocholinesterase or butyrylcholine esterase). Evidence for this was obtained from various findings, e.g., total inhibition of the plasma-catalyzed hydrolysis by 10^{-3} M physostigmine and comparison of the rates of ester hydrolysis by a purified butyrylcholinesterase preparation and by plasma.[23] Thus

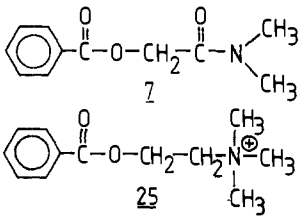
(20) Spectral and elemental analysis of all the compounds were consistent with their structures. Melting points are given in Table I.

(21) The rates of hydrolysis were followed by reversed-phase HPLC methods with mixtures of MeOH and dilute H_3PO_4 as eluants (UV detection). The plasma samples were deproteinized with MeOH. Benzoic acid was in all cases produced in quantitative amounts.

(22) Orsi, B. A.; Tipton, K. F. *Methods Enzymol. (Part A)* **1979**, *63*, 159–183.

for compound 8 such a comparison showed that cholinesterase could account for more than 90% of the observed enzymatic ester hydrolysis by plasma.

Considering the high reactivity of the N,N-disubstituted glycolamide esters toward cholinesterase, it is of particular interest to note the structural similarity between these esters and choline esters, e.g., benzoylcholine (**25**). It has



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recently been shown[24] that the binding subsite of acetylcholinesterase for the trimethylammonium group of acetylcholine may be better considered an uncharged trimethyl site rather than an "anionic" site as commonly considered. The enzymatic reactivity appears primarily related to the volume of the β-substituent and its fit in the trimethyl site as well as the hydrophobicity of its surface.[24] The different enzymatic reactivity of the glycolamide esters is seen to be in good accordance with this view, considering the similarity of the active centers in acetylcholinesterase and cholinesterase.[25] A good fit to the trimethyl binding site should certainly require an N,N-disubstituted amide group rather than an unsubstituted (compound **1**) or monosubstituted group (compounds **2–6**). A closer analysis of the relation between structure and enzymatic reactivity encompassing further ester derivatives will be made in a future paper.

As it appears from Table I the glycolamide esters of benzoic acid are crystalline compounds with reasonable (i.e., not too high) melting point. The latter property is important in terms of solubility behavior. The solubility and octanol–water partition data show that it is readily feasible to select esters with greatly varying water solubilities and lipophilicities[26] and still obtain a high rate of enzymatic conversion. Thus, compound **15** (derived from diethanolamine) is soluble in water to an extent of more than 70% w/v although it is a neutral compound with a positive log P value. The availability of a hydroxyl group in compounds **13–15** makes it possible to further modify the physicochemical properties, e.g., by esterification with an amino acid. Thus, compound **13** was esterified with *N,N*-dimethylglycine to give a highly water-soluble derivative (**26**) (isolated as a fumarate salt, mp 127–127.5 °C), which was rapidly ($t_{1/2}$ = 5 s) hydrolyzed to benzoic acid in 50% plasma solutions.

Glycolic acid esters have previously[27] been proposed as prodrugs of amino acids. We found that these double esters were more resistant to enzymatic hydrolysis by plasma than the parent glycolamide esters, and furthermore, glycolic acid esters of most carboxylic acids are liquids with a slight water solubility.

Table II. Half-Lives ($t_{1/2}$) of Hydrolysis of Esters of Various Drugs and Compounds Containing a Carboxylic Acid Function in 80% Human Plasma[a]

	$t_{1/2}$	
acid	methyl ester	*N,N*-diethylglycolamide ester
salicylic acid	17.6 h	0.08 min
4-aminobenzoic acid	>100 h[b]	0.6 min
naproxen	20.1 h[b]	0.6 min
ketoprofen	>20 h	0.5 min
fenbufen	4.7 h	3.8 min
tolmetin	19 h	13.4 min
tolfenamic acid	100 h	5.0 min
indomethacin	150 h	25 min
L-phenylalanine	29 min	0.2 min
L-tyrosine	59 min[b]	0.5 min
4-hydroxybenzoic acid	>50 h	1.8 min
tranexamic acid	4.0 h[c]	1.2 min[d]

[a] At pH 7.4 and 37 °C. [b] Value for ethyl ester. [c] Value in human blood at 37 °C.[28] [d] Value for the *N,N*-dimethylglycolamide ester.

The observed great reactivity of the glycolamide esters of benzoic acid was found to be valid for other acids as well. Table II shows the hydrolysis data for the *N,N*-diethylglycolamide esters of various acids. As expected the structure of the acyl moiety has an influence on the enzymatic reactivity, but in all cases a quite rapid rate of hydrolysis in plasma was observed, the rate being several-fold larger than the rate of hydrolysis of the corresponding simple methyl or ethyl esters.

A further illustration of the great susceptibility of the esters to undergo enzymatic hydrolysis is provided by the behavior of esters of acetylsalicylic acid. Thus, the *N,N*-diethylglycolamide ester was found to be cleaved in plasma solutions to form acetylsalicylic acid in large amounts (>50%) whereas the methyl and other simple esters of acetylsalicylic acid exclusively undergo deacetylation to yield the corresponding salicylic acid ester.[29]

In conclusion, esters of N,N-disubstituted glycolamides are shown to be a potentially useful biolabile prodrug type for carboxylic acid agents. The esters combine a high susceptibility to undergo enzymatic hydrolysis in plasma with a high stability in aqueous solution.[30] The new ester prodrug type is further characterized by providing ample possibilities for varying the water and lipid solubilities of the derivatives with retainment of the favorable enzymatic/nonenzymatic hydrolysis index. Studies on the applicability of the novel prodrug approach to increase the oral and topical bioavailability or reduce the gastrotoxicity of various carboxylic acid agents are presently being performed. The latter aspect may be of particular importance for nonsteroid antiinflammatory drugs since it has been reported[31] that esterification of such carboxylic acid agents suppresses their gastric ulcerogenic activity. In contrast to the methyl esters previously investigated,[31] the glycolamide esters described herein have a high capacity to release the parent active drugs following absorption[32] and

(23) This approach is based on previous studies on cholinesterase- and plasma-catalyzed hydrolysis of various esters: Lockridge, O.; Mottershaw-Jackson, N.; Eckerson, H. W.; La Du, B. N. *J. Pharmacol. Exp. Ther.* **1980**, *215*, 1–8. Valentino, R J.; Lockridge, O.; Eckerson, H. W.; La Du, B. N. *Biochem. Pharmacol.* **1981**, *30*, 1643–1649. Myers, C.; Lockridge, O.; La Du, B. N. *Drug Metab. Dispos.* **1982**, *10*, 279–280.

(24) (a) Cohen, S. G.; Elkind, J. L.; Chisti, S. B.; Giner, J.-L. P.; Reese, H.; Cohen, J. B. *J. Med. Chem.* **1984**, *27*, 1643–1647. (b) Cohen, S. G.; Chisti, S. B.; Elkind, J. L.; Reese, H.; Cohen, J. B. *J. Med. Chem.* **1985**, *28*, 1309–1313.

(25) Järv, J. *Bioorg. Chem.* **1984**, *12*, 259–278.

(26) Benzoic acid has a solubility of 3.1 mg/mL in 0.01 M HCl and a log P value of 1.91.

(27) Wermuth, C. G. *Chem. Ind.* **1980**, 433–435.

(28) Svahn, C. M.; Merenyi, F.; Karlson, L.; Widlund, L.; Grälls, M. *J. Med. Chem.* **1986**, *29*, 448–453.

(29) The hydrolytic behavior of a large number of acetylsalicylic acid esters will be described in a separate paper.

(30) Temperature-accelerated studies thus showed that compound **7** has a shelf-life (i.e., the time for 10% degradation) of more than 5 years in aqueous solution (pH 4.0) at 20 °C.

(31) Whitehouse, M. W.; Rainsford, K. D. *J. Pharm. Pharmacol.* **1980**, *32*, 795–796.

possess physicochemical properties favorable for peroral absorption. Thus, preliminary experiments in rabbits with various glycolamide esters of naproxen have shown that these are completely absorbed upon peroral administration and that only the parent naproxen is detectable in the blood, indicating very rapid ester hydrolysis in vitro in accordance with in vitro plasma hydrolysis studies.

(32) Preliminary studies indicate that the N,N-disubstituted glycolamide esters are stable to gastrointestinal enzymes (e.g., α-chymotrypsin).

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A New Thienylpyrazoloquinoline: A Potent and Orally Active Inverse Agonist to Benzodiazepine Receptors

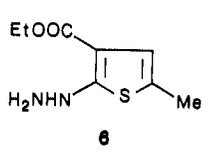
Sir:

Benzodiazepine (BZ) receptor inverse agonists[1] that possess pharmacological effects opposite to those of the benzodiazepines such as diazepam have recently been attracting attention. One such agent, methyl β-carboline-3-carboxylate (β-CCM), has been shown to enhance performance in learning and memory tasks in animal models.[2] The disadvantage of β-CCM is that it evokes clonicotonic convulsions in mice.[1a] However, β-CCE (an ethyl ester analogue of β-CCM) has been found to be an inverse agonist that does not generate convulsions,[1b,d] although its activity decreases after oral administration. The orally effective BZ antagonist 2-phenyl-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (CGS 8216)[3] has an inverse agonistic character but weak intrinsic activity.[1e,4]

Here we report on a new thienylpyrazoloquinoline compound, **5** (S-135), which is a potent and orally active inverse agonist with high affinity to BZ receptors but produces no convulsions by itself. Furthermore, its regioisomer **7**, also having a high affinity to BZ receptors, is classified as an agonist.

Chemistry. Our synthetic strategy involved joining an alkoxycarbonyl as a protecting group to the starting hydrazinothiophenes, which are extremely unstable when they have no electron-withdrawing groups adjacent to their hydrazino moiety.[5] Treatment of methyl 3-hydrazino-5-methylthiophene-2-carboxylate (**1**)[6] with ethyl 4-chloroquinoline-3-carboxylate (**2**)[7] in ethanol at room temperature gave adduct **3**, which was cyclized by sodium hydroxide in aqueous ethanol at room temperature to afford **4a**. Compound **4a** was hydrolyzed by heating with excess sodium hydroxide in aqueous ethanol to obtain an acid **4b**. Decarboxylation of **4b** with copper in quinoline at ca. 190 °C provided 2-(5-methylthien-3-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (**5**) [mp 293–295 °C dec. Anal. ($C_{15}H_{11}N_3OS$) C, H, N, S] (Scheme I).

A similar sequence using ethyl 2-hydrazino-5-methylthiophene-3-carboxylate (**6**)[8] as starting material led to 2-(5-methylthien-2-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]-quinolin-3-one (**7**) [mp 309–311 °C dec. Anal. ($C_{15}H_{11}N_3OS$) C, H, N, S].



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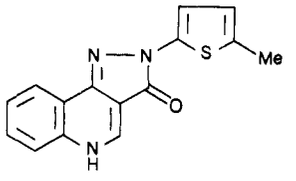

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Pharmacology. The pharmacological data are summarized in Table I, showing the activities of the agonists and the inverse agonists assessed on the basis of inhibition or facilitation of the pentylenetetrazole (PTZ) induced convulsions, respectively. Both **5** and **7** had a greater affinity for BZ receptors than diazepam. In the mouse PTZ test,[9] **7** prevented tonic convulsions and death induced by the PTZ challenge (125 mg/kg sc) 1 h after oral administration, while **5** facilitated the convulsions. These effects were completely antagonized by the BZ antagonist Ro 15-1788.[10] Therefore, **7** and **5** are classified as an agonist and an inverse agonist, respectively, in spite of their structural similarity. In the anticonflict test[9] in rats, **7** showed an ED_{50} value of 5.94 mg/kg 30 min after oral administration, whereas the corresponding value of diazepam was 1.05 mg/kg.

The proconvulsant effect of **5** was compared with those of known inverse agonists by the following procedure. The test compounds were administered to 8–16 male mice in

(1) (a) Braestrup, C.; Nielsen, M. *Nature (London)* **1981**, *294*, 472. (b) Cowen, P. J.; Green, A. R.; Nutt, D. J.; Martin, I. L. *Nature (London)* **1981**, *290*, 54. (c) Petersen, E. N.; Paschelre, G.; Kehr, W.; Nielsen, M.; Braestrup, C. *Eur. J. Pharmacol.* **1982**, *82*, 217. (d) Oakley, N. R.; Jones, B. J. *Eur. J. Pharmacol.* **1980**, *68*, 381. (e) Braestrup, C.; Nielsen, M.; Honorē, T.; Jensen, L. H.; Petersen, E. N. *Neuropharmacology* **1983**, *22*, 1451.

(2) Venault, P.; Chapouthier, G.; Prado de Carvalho, L.; Simiand, J.; Morre, M.; Dodd, R. H.; Rossier, J. *Nature (London)* **1986**, *321*, 864.

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(5) To our knowledge, hydrazinothiophenes without an electron-withdrawing group have not been synthesized.

(6) Huddleston, P. R.; Barker, J. M.; Admczewska, Y. Z. *J. Chem. Res. Synop.* **1980**, 238.

(7) Kaslow, E. E.; Clark, W. R. *J. Org. Chem.* **1953**, *18*, 55.

(8) Hentschel, M.; Gewald, K. *J. Prakt. Chem.* **1974**, *316*, 878.

(9) The method described by Sugasawa et al. was used: Sugasawa, T.; Adachi, M.; Sasakura, K.; Matsushita, A.; Eigyo, M.; Shiomi, T.; Shintaku, H.; Takahara, Y.; Murata, S. *J. Med. Chem.* **1985**, *28*, 699.

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