With respect to the enzyme's specificity and the anomeric configuration of the glycosidic bond, the enzymatic assay proves to be a useful tool for assigning the β configuration to all the inhibitors prepared. In addition to the chemical and spectral evidence, the selectivity of cytidine deaminase for the β anomers constitutes additional proof for the β configuration assigned to these nucleosides. In our hands, only β-cytidine, the natural substrate, is deaminated. α-Cytidine, with the opposite configuration, was neither a substrate nor an inhibitor. This indicates that only nucleosides with the β configuration fit the enzyme's receptor site.

The combination of these inhibitors with cytidine analogues possessing antitumor properties (e.g., cytosine arabinoside) and the study of the biological consequences of total depletion of cytidine deaminase activity constitute fruitful areas for additional antitumor drug research.

Victor E. Marquez,* Paul S. Liu, James A. Kelley, John S. Driscoll
Laboratory of Medicinal Chemistry and Biology
National Cancer Institute, National Institutes of Health
Bethesda, Maryland 20205

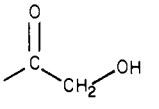
John J. McCormack
Department of Pharmacology, College of Medicine
University of Vermont, Burlington, Vermont 05401
Received April 4, 1980

Prostaglandins and Congeners. 25.[1] Inhibition of Gastric Acid Secretion. Replacement of the Carboxylate Moiety of a Prostaglandin with a Hydroxymethylketo Functional Group

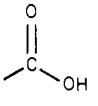
Sir:

In testing various prostaglandin congeners for their ability to inhibit histamine-induced gastric acid secretion in the dog, we observed, as have others,[2] that several 15-deoxy-16-hydroxy-16-methyl analogues were orally active at doses which did not produce the gastrointestinal side effects characteristic of the natural prostaglandins. These β (C_{13}–C_{20}) chain modifications at C-15 and C-16 apparently render these analogues more resistant to metabolic degradation by prostaglandin 15-dehydrogenase[3] with retention of biological activity. Insofar as fatty acid β oxidation is also one of the important deactivation routes for the prostaglandins,[3] we have further sought to enhance duration and potency through chemical modification of the α chain, specifically by substitution of a functional group which would mimic the carboxylate moiety with respect to receptor interaction while conferring greater metabolic stability.

A terminal hydroxymethylketo functional group (1),



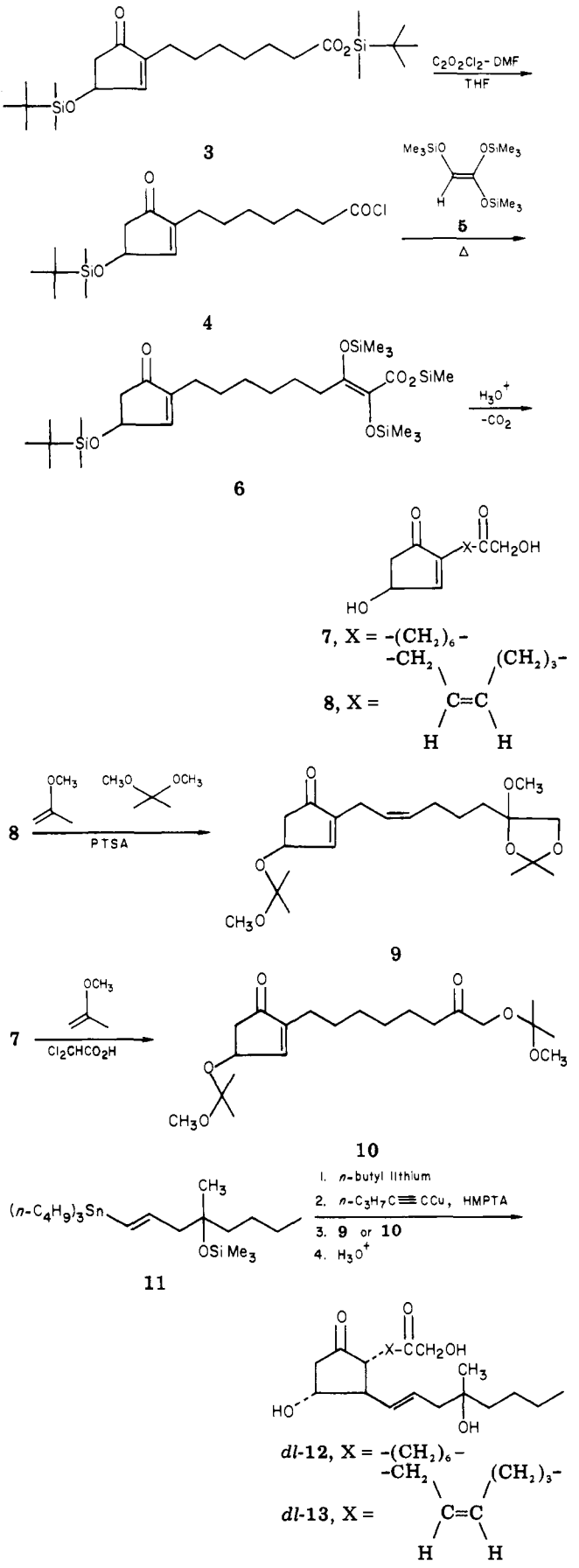
1



2

which differs from a carboxylate group (2) in having a methylene group interposed between the carbonyl and hydroxy functions, may have the potential for forming hydrogen bonds in a manner similar to that of a carbox-

Scheme I



(1) For Paper 24 in this series, see C. V. Grudzinskas, J. S. Skotnicki, S.-M. L. Chen, M. B. Floyd, W. A. Hallett, R. E. Schaub, G. J. Siuta, A. Wissner, M. J. Weiss, and F. Dessy, *ACS Symp. Ser.*, **no. 118**, 301 (1980).
(2) P. W. Collins, E. Z. Dajani, D. R. Driskill, M. S. Bruhn, C. J. Jung, and R. Pappo, *J. Med. Chem.*, **20**, 1152 (1977).
(3) B. Samuelsson, E. Granstrom, K. Green, and M. Homberg, *Ann. N.Y. Acad. Sci.*, **180**, 138 (1971).

0022-2623/80/1823-0715$01.00/0

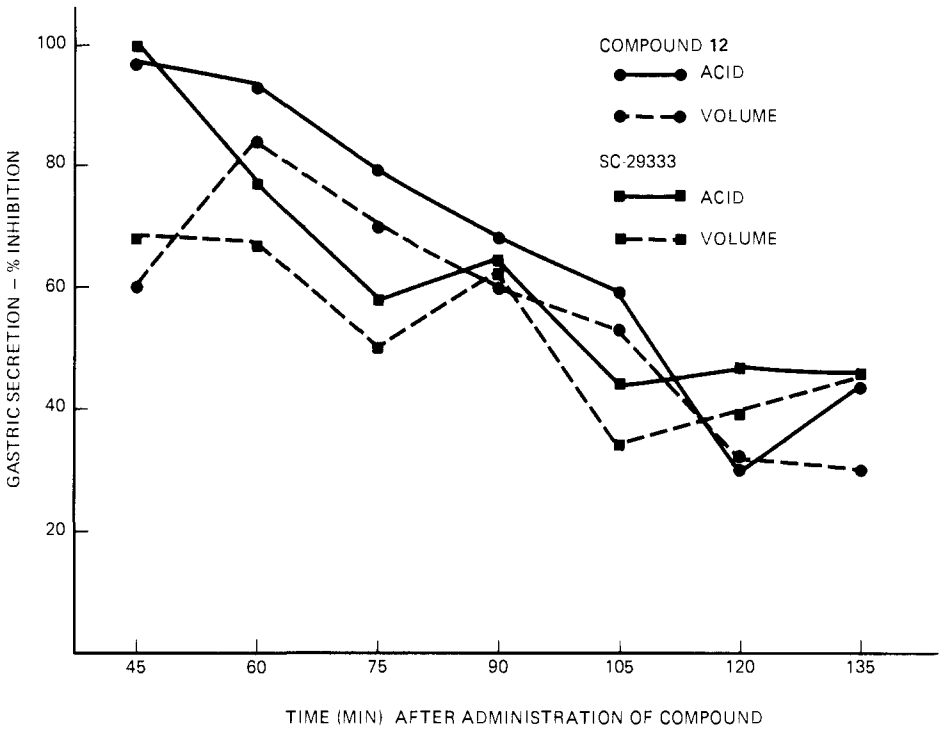


Figure 1. Effect of **12** and 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 methyl ester (SC-29333) on gastric acid secretion in the dog fistula preparation. Methods are as described in Table I. Each of two dogs was treated intragastrically with 10 μg/kg of test compound (n = 3 or 4) or vehicle control (n = 13). The average volume and acid output during each 15-min period is considered relative to the average control output during the corresponding period.

ylate moiety and conceivably might confer greater metabolic stability to the prostaglandin. Consequently, we have prepared a variety of prostaglandin congeners in the 15-deoxy-16-hydroxy-16-methyl series embracing this structural modification. This report describes the gastric antisecretory activity of two such analogues, *dl*-11α,16α,β-dihydroxy-1,9-dioxo-1-(hydroxymethyl)-16-methyl-13-*trans*-prostene (**12**), and the corresponding PGE_2 congener **13**. The gastric antisecretory activity of compound **12** was also compared to our reference standard 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 methyl ester (SC-29333), as this compound has been previously reported to be a potent inhibitor of gastric secretion.[2] These compounds were prepared by the conjugate addition approach[4] as shown in Scheme I.

The bis(*tert*-butyldimethylsilylated) enone **3**[5] was converted to the acid chloride **4** by treatment of a THF solution with oxalyl chloride (1.1 equiv) containing a catalytic quantity of DMF.[6] The reaction of **4** with tris[(trimethylsilyl)oxy]ethylene (**5**), a reagent developed specifically for this purpose,[7] either in the absence of solvent at 120 °C or preferably in refluxing chlorobenzene gave, after hydrolysis–decarboxylation of the presumed intermediate **6**, the enone **7** containing the hydroxymethylketo functionality [mp 56–61 °C; ^{1}H NMR (acetone-d_6) δ 7.10 (m, 1 H, CH), 4.80 (m, 1 H, C*H*OH), 4.10 (s, 2 H, CH_2OH), 3.60 (br s, 2 H, OH), 2.8–1.0 (m's, 14 H, CH_2's); yields have varied between 30 and 60% based on **3**]. In a similar manner, the PGE_2 precursor **8** was obtained. The dioxolane derivative **9** was prepared by the *p*-toluenesulfonic acid catalyzed reaction of **8** with a mixture of 2-methoxypropene and 2,2-dimethoxypropane. Prepared in this manner, **9** required chromatographic purification due to the formation of a large quantity of aldol products derived from the reagents. It was subsequently discovered that the ketone moiety need not be protected for a successful conjugated addition reaction. Consequently, **10** was prepared by the reaction of **7** with a 2-methoxypropene using dichloroacetic acid as the catalyst; these mild conditions avoided decomposition of the reagent. The reaction of enones **10** or **9** with an excess of the cuprate reagent derived from vinylstannane **11**,[4] followed by hydrolysis with

Table I. Effect of 12 and 13 on Gastric Acid Secretion[a] in the Dog Fistula Preparation[b]

treatment	dose, μg/kg ig	n[c]	cumulative 75-min gastric secretion[d] vol, mL	cumulative 75-min gastric secretion[d] acid output, mequiv of H^+
control		20	130 ± 11	17.2 ± 1.6
12	10	6	59 ± 19 ($p < 0.02$)	6.9 ± 2.8 ($p < 0.02$)
13	10	6	76 ± 16 ($p < 0.02$)	7.5 ± 2.1 ($p < 0.005$)

[a] After a 26-h fast, gastric acid secretion was submaximally stimulated, beginning 45 min after treatment, using a constant intravenous infusion of histamine acid phosphate [40 (μg/kg)/h]. Gastric secretions were collected at 15-min intervals. [b] See ref 9. [c] Each of three dogs was treated six to seven times with vehicle (control) and one to three times with each compound; n is the number of experiments conducted with each treatment. [d] Total secretion from 45 to 120 min following intragastric (ig) administration of 12, 13, or vehicle. Mean effects of treatment were compared to control means by Student's t test.

(4) For pertinent references, see S.-M. L. Chen, R. E. Schaub, and C. V. Grudzinskas, *J. Org. Chem.*, 43, 3450 (1978).
(5) Compound **3** was prepared from the unprotected cyclopentenone [G. Piancatelli and A. Scettri, *Tetrahedron Lett.*, 1131 (1977) and references therein] using *tert*-butyldimethylchlorosilane and imidazole; see ref 6.
(6) A. Wissner and C. V. Grudzinskas, *J. Org. Chem.*, 43, 3972 (1978).
(7) (a) A. Wissner, *Tetrahedron Lett.*, 2749 (1978). (b) A. Wissner, *J. Org. Chem.*, 44, 4617 (1979).

aqueous acetic acid–THF, gave the prostaglandin congeners **12** and **13**, respectively. The ^{13}C NMR spectra obtained for **12** and **13** clearly indicate that they are both mixtures of two C_{16} epimers, in approximately equal amounts.[8]

As indicated in Table I, **12** and **13** are potent inhibitors of histamine-induced gastric acid secretion in the dog gastric fistula preparation.[9] As illustrated in Figure 1, the activity and duration of **12** appear to be comparable to that of 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 methyl ester (SC-29333), a compound previously reported on by Collins et al.[2] Additional studies, to be reported subsequently, have demonstrated that the compounds are antisecretory in the rat, where they also protect against the formation of a variety of experimental ulcers. Intragastric doses of **12** as great as 100 times those required for antisecretory activity were well tolerated acutely and chronically in the dog. On the basis of this activity profile, the PGE_1 analogue **12** is now undergoing development as a therapeutic agent for the treatment of gastrointestinal ulcers and other hypersecretory states in man.

While the manner in which the hydroxymethylketo functional group modifies the metabolism of a prostaglandin still remains to be determined, we have demonstrated that this group is an effective replacement for the carboxylate group in this series of compounds. This observation might have utility outside the prostaglandin area.

Acknowledgment. We thank L. M. Brancone and his staff for microanalyses, W. Fulmor, G. O. Morton, and Dr. R. T. Hargreaves and staff for spectral data, W. Scruggs for his technical assistance in the gastric fistula secretion studies, and Dr. M. B. Floyd for helpful suggestions.

Allan Wissner,* Jay E. Birnbaum
Metabolic Disease Research Section
Medical Research Division
Lederle Laboratories
Pearl River, New York 10965

Donald E. Wilson
Department of Medicine, Section of Gastroenterology
University of Illinois
Abraham Lincoln School of Medicine
Chicago, Illinois 60612
Received December 26, 1979

(8) Satisfactory magnetic resonance, infrared, analytical or high-resolution mass spectral data were obtained for the prostaglandins reported herein.
(9) Three mongrel dogs (20–32 kg) were surgically prepared with stainless-steel cannulae. These were inserted into the most dependent portion of the ventral stomach and exteriorized through the abdomen for the collection of gastric secretions. The dogs were trained to stand quietly in a Pavlov support and were conscious during subsequent secretory studies.

Articles

Synthesis and Blood Pressure Lowering Activity of 3-(Substituted-amino)-1,2,4-benzothiadiazine 1-Oxide Derivatives

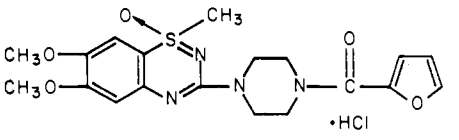
Robert D. Dillard,* Terence T. Yen, Paul Stark, and Donald E. Pavey

Chemical Research Division, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285.
Received October 22, 1979

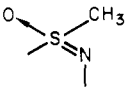
A series of (substituted amino)-1,2,4-benzothiadiazine 1-oxides has been synthesized and most members of the series have been shown to have blood pressure lowering effects in normotensive rabbits and in spontaneously hypertensive rats. The most active member of the series was 3-[4-(2-furoyl)-1-piperazinyl]-6,7-dimethoxy-1-methyl-1*H*-1,2,4-benzothiadiazine 1-oxide hydrochloride. This compound in animal tests was equipotent to the known antihypertensive Prazosin.

Our investigation of the synthesis of blood pressure lowering compounds has led to the development of a series of 3-amino-1,2,4-benzothiadiazine 1-oxides. These compounds have a unique structural relationship to a family of 4-aminoquinazolines with known blood pressure lowering properties.[1] One member of that series, "Prazosin"[1] is a clinically useful drug. In our series of compounds, the sulfoximine moiety replaced the amidine group in the quinazoline series.

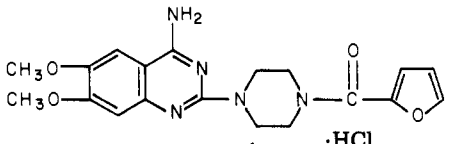
The 1,2,4-benzothiadiazine 1-oxide ring structure has been described by Cohnen and Mahnke[2] in 1972 and by Williams and Cram[3] in 1973. Sulfoximine compounds were reviewed by Kennewell and Taylor in 1975.[4]



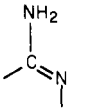
17f



sulfoximine



prazosin



amidine

Generally, the sulfoximine function is a basic group forming stable salts with strong acids with pK_a values in

(1) A. Scriabine, J. W. Constantine, H.-J. Hess, and W. K. McShane, *Experimentia*, **24**, 1150 (1968); Chas. Pfizer and Co., Inc., U.S. Patent 3511836; J. W. Constantine, W. K. McShane, A. Scriabine, and H.-J. Hess, *Postgrad. Med.*, **56**, 18 (1975).
(2) E. Cohnen and J. Mahnke, *Chem. Ber.*, **105**, 757 (1972).
(3) T. R. Williams and D. J. Cram, *J. Org. Chem.*, **38**, 20 (1973).
(4) P. D. Kennewell and J. B. Taylor, *Chem. Soc. Rev.*, **4**, 189 (1975).

0022-2623/80/1823-0717$01.00/0