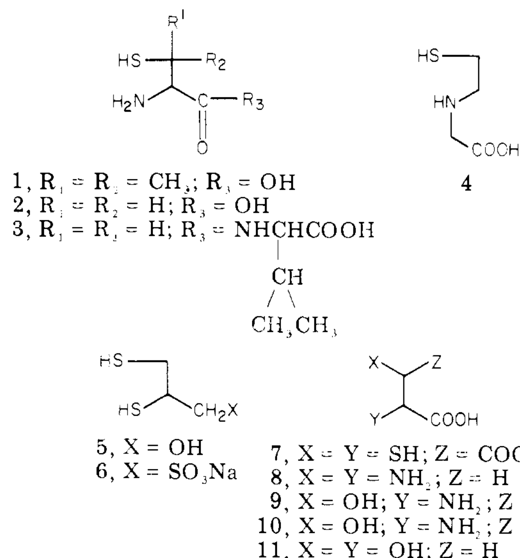
Structural Requirements for the Sequestration of Metabolically Generated Acetaldehyde

Herbert T. Nagasawa,* James A. Elberling, and Eugene G. DeMaster

Medical Research Laboratories, Veterans Administration Medical Center, and the Department of Medicinal Chemistry, University of Minnesota, Minneapolis, Minnesota 55417. *Received September 26, 1979*

Of a series of polyfunctional compounds containing amino, hydroxyl, or mercapto groups in conjunction with the carboxyl group, only the 1,2- or 1,3-disubstituted aminothiols, namely, D-(−)-penicillamine (**1**), L-cysteine (**2**), L-cysteinyl-L-valine (**3**), mercaptoethylglycine (**4**), and DL-homocysteine (**12**), showed any propensity to sequester acetaldehyde (AcH) when tested in vitro in a buffered system at pH 7.5. In vivo, however, only D-(−)-penicillamine (**1**) was effective in lowering ethanol-derived blood AcH in rats that had been treated with disulfiram and ethanol. These results suggest that, in addition to the functionality in the molecule, pharmacokinetic and metabolic factors must also be considered when designing AcH-sequestering agents for use in vivo.

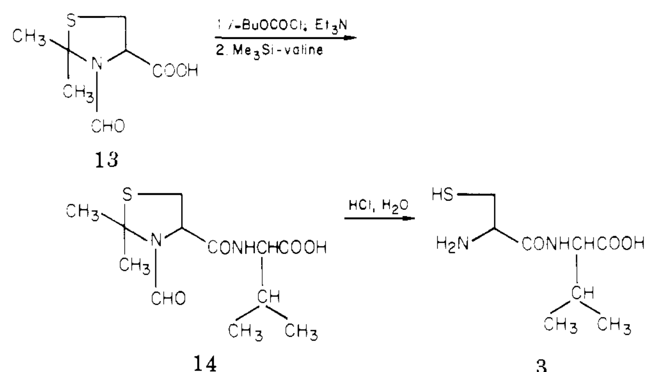
In previous communications,[1] we have presented evidence for a directed detoxication mechanism for acetaldehyde (AcH), the toxic first metabolic product of ethanol, wherein this ethanol-derived AcH is trapped as a thiazolidinecarboxylic acid and diverted to excretory pathways by administered D-(−)-penicillamine (**1**). Although **1**, a trifunctionalized sulfhydryl amino acid, is a highly effective agent for the sequestration of blood AcH from ethanol-treated animals,[2] it is known to exhibit certain toxic manifestations in humans on long-term administration, for example, in the treatment of rheumatoid arthritis.[3] For this reason, we have been seeking other polyfunctional agents that might be less toxic than **1** as in vivo trapping agents for metabolically generated AcH.



Rationale

The product of the condensation of AcH and **1** is the water-soluble 2,5,5-trimethylthiazolidine-4-carboxylic acid which is readily excreted by the kidneys.[1] This product water solubility is an important criterion for a detoxication role assigned to the AcH-sequestering agent; otherwise, the condensation product would be recirculated by renal tubular reabsorption mechanisms with the possibility of AcH release after further metabolism. An acidic functional group such as –COOH or $-SO_3H$ in the molecule is therefore a primary requirement. In addition, 1,2-vicinal substitution or 1,3 disubstitution in the molecule with amino, hydroxyl, or thiol groups (or combinations thereof) that would favor the formation of cyclic 5- or 6-membered ring condensation products with AcH at physiological pH's would be highly desirable. With these structural parameters in mind, we systematically undertook the evaluation of a series of such polyfunctional compounds as AcH-sequestering agents, using an in vitro test system as a preliminary screen followed by a more rigorous in vivo test for those compounds that showed promising activity in vitro.

Scheme I



Although L-cysteine (**2**), the naturally occurring sulfhydryl amino acid of protein origin, is a good AcH-trapping agent in vitro,[4] it is totally ineffective in vivo[1] due, presumably, to its rapid catabolism.[5] We envisioned that a dipeptide of cysteine, such as L-cysteinyl-L-valine (**3**) wherein the cysteine is N terminal, would be metabolized at a slower rate and we wished to evaluate its potential as an AcH-trapping agent in vivo. Other trifunctional compounds and the rationale for their selection are as follows. Mercaptoethylglycine (**4**), as its ester derivative, is known to condense with AcH to give a thiazolidineacetic acid derivative,[6] while 2,3-dimercaptopropanol (BAL, **5**) has

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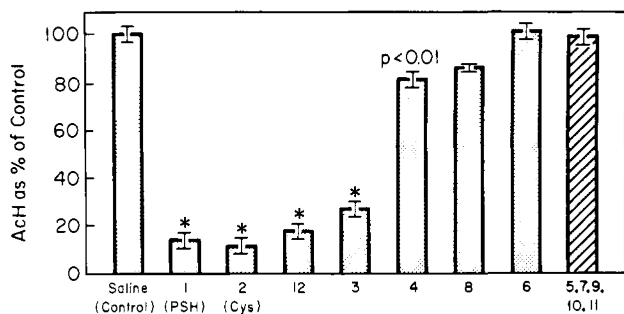

Figure 1. Ability of 1,2- and 1,3-difunctionalized agents to sequester AcH in vitro at pH 7.50. The details of the assay can be found under Experimental Section. The bar inserts are plus or minus SEM; where marked with asterisks, the p values (vs. saline control) are <0.001. PSH = D-penicillamine (1).

been reported to protect against aldehyde toxicity in methanol-treated rats.[7] The sodium salt of 2,3-dimercaptopropane-1-sulfonic acid (Dimaval, 6) is a water-soluble and less toxic analogue of BAL,[8] while *meso*-2,3-dimercaptosuccinic acid (7) is another water-soluble 1,2-dithiol. Theoretically, 2,3-diaminopropionic acid (8) can condense with AcH to form an imidazolidinecarboxylic acid, and L-serine (9) and L-threonine (10) can give the corresponding 1,3-oxazolidine-4-carboxylic acid, while DL-glyceric acid (11), a 1,2-glycol, can form a cyclic acetal. Although we have previously shown that L-cysteine (2) and DL-homocysteine (12) were not effective in sequestering AcH in vivo,[1,2a] they were included here to complete the structural series for our in vitro test system.

Results and Discussion

Since the literature revealed no convenient synthesis for L-cysteinyl-L-valine (3), we prepared 3 via a three-step procedure (Scheme I) starting with N-formyl-2,2-dimethylthiazolidine-4-carboxylic acid (13), where the amino and sulfhydryl groups are internally protected.[9] Mercaptoethylgycine (4) was prepared according to published procedures.[6] This compound was 95.3% in the expected free sulfhydryl form based on iodometric titration. The corresponding disulfide (4a) was prepared by oxidation of 4 with I_2.

A physiologically buffered system that mimics the conditions of analysis of AcH in blood samples taken from experimental animals is described under Experimental Section. In this test system, a tenfold molar excess of a polyfunctionalized, potential AcH-sequestering agent is equilibrated with AcH in a closed system at pH 7.5. After a prescribed period, the head space is monitored by GLC for free AcH that had not combined with the trapping agent. It can be seen (Figure 1) that of the various polyfunctional substances tested, only the 1,2- or 1,3-disubstituted *amino thiols* showed any AcH-sequestering ability. DL-Homocysteine (12) was nearly as effective as D-(−)-penicillamine (1) under these conditions, a result which is at variance with the observation that 12, like 2, was totally ineffective in vivo.[1b] The 1,2-amino alcohols, 1,2-diamines, 1,2-dithiols, and 1,2-glycols showed no propensity

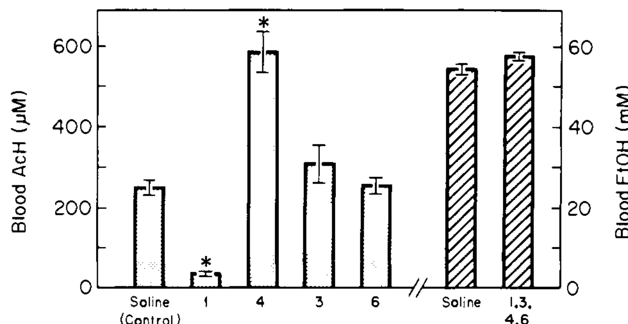

Figure 2. The effect of potential AcH-sequestering agents on blood AcH and blood EtOH in rats treated with disulfiram–ethanol combinations. The protocol is given under Experimental Section. Compound 6 was toxic by the ip route, and the data shown are for equivalent oral doses. The bar inserts are plus or minus SEM; where marked with asterisks, the p values (vs. saline control) are <0.001. The number of animals (N) per group are: 14 for controls, 9 for 1, 4, and 6 (blood AcH), and 6 for all others.

for combining with AcH at near physiological pH. Thus, the mere presence of functional groups capable of forming Schiff bases or hemithioacetals, alone without the proximity of the other, is not sufficient to sequester AcH.

Based on these results, L-cysteinyl-L-valine, mercaptoethylglycine (4), and sodium 2,3-dimercaptopropanesulfonate (6) were selected for in vivo evaluation in rats. Although 6 was not effective as an AcH-trapping agent in the in vitro test system (Figure 1), its water solubility and BAL-like therapeutic effects and its extensive clinical use for the treatment of heavy metal poisoning in the USSR and Eastern Europe[8] warranted the testing of this compound for possible efficacy in vivo. These results, which are summarized in Figure 2, have reconfirmed our earlier finding[1,2] that, to date, the *only* agent that effectively sequesters AcH in vivo is D-(−)-pencillamine (1). The high activities of 3, 4, and 12 in vitro (Figure 1) were not reflected in vivo and can be likened to the experience with L-cysteine (2).[1,2a] While the formation in vitro of thiazolidines from 3 and 4 and a 1,3-thiazane derivative from 12 is only inferred (the synthetic route to 3 involved the thiazolidine intermediate, 14), the absence of in vivo AcH-sequestering ability by these compounds did not warrant any attempts to pursue the synthesis of the cyclized products for possible identification as excretion products. Sodium 2,3-dimercaptopropanesulfonate (6) at equimolar doses with 1 was toxic by the ip route; however, oral doses of 6 failed to reduce the level of blood AcH in rats treated with ethanol. Blood ethanol levels were not affected by these compounds (Figure 2).

The in vitro and in vivo results with mercaptoethylglycine (4) were both disappointing and perplexing. Ester derivatives of 4 are known to cyclize to thiazolidines when reacted with aldehydes,[6] although under conditions more vigorous than the conditions described here. The sluggishness of 4, a β-mercapto secondary amine, to sequester AcH at physiological pH and temperature may have mechanistic significance in terms of the intermediacy of a Schiff base or a hemithioacetal in the cyclization reaction.[4] The augmentation by 4 of the disulfiram-mediated increase in blood AcH to near double the usual values without significantly affecting blood ethanol levels (Figure 2) is not due to any intrinsic activity of 4 as an aldehyde dehydrogenase inhibitor, since administration of 4 alone followed by an acute ethanol dose did not elevate blood AcH. The formation in vivo of the disulfide of 4, viz., 4a, or of a mixed disulfide of 4 and diethyldithiocarbamate are possibilities that may explain this potentiated action. However, the administration of 4a to rats did not enhance

(6) Bulavin, L. *Zh. Org. Khim.* 1971, 7, 2086; *J. Org. Chem. USSR (Engl. Transl.)* 1971, 7, 2168. The discrepancies in the melting points that we observed for 4·HCl and for 4a·HCl with that reported in this reference, though not explainable, are listed for the record. Our NMR data, together with the method of preparation, are in accord with the proposed structures.
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the disulfiram-mediated acetaldehydemia, suggesting the latter as the more likely possibility. This avenue was not further pursued, as the goal of the present investigation was to discover agents that sequester—not elevate—ethanol-derived blood AcH.

From these results we can conclude that, although AcH sequestration in a model system at physiological pH's is an absolute requirement, this criterion alone does not guarantee that an agent will be effective in trapping AcH in vivo. Pharmacokinetic and metabolic consequences must be considered in assessing in vivo activities. Our in vitro observations, however, are in complete harmony with the results reported by Cederbaum and Rubin[4,10] on the structural parameters required for protection of hepatic mitochondrial function from AcH inhibition. These investigators noted that, whereas cysteine, D-(−)-penicillamine and mercaptoethylamine protected against mitochondrial injury elicited by added AcH in an in vitro system, dithiothreitol, glycine, alanine, *N*-acetylcysteine, or *S*-methylcysteine offered no protection, while mercaptoethanol, thioglycerol, and glutathione gave marginal protection. The concomitant disappearance of the free sulfhydryl groups of the β-mercaptoethylamines in the presence of AcH suggested to these authors also that the protective effect of these compounds was due to the formation of thiazolidines.

The most promising direction for further work along these lines, therefore, appears to be with latentiated derivatives (prodrug forms) of D-(−)-penicillamine (1) or of L-cysteine (2), and/or with structural analogues thereof. Such investigations are in progress.

Experimental Section

Melting points were determined on a Mettler FP-2 melting point apparatus that had been calibrated to reference standards. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Infrared spectra were taken on a Beckman IR-10 infrared spectrophotometer and the NMR spectra in D_2O on a Varian T-60A NMR spectrometer using sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standard.

Sodium 2,3-dimercaptopropanesulfonate (Dimaval, 6) was a product of Heyl and Co., Berlin, West Germany, purchased through Aldrich Chemical Co., Milwaukee, WI. D-(−)-Penicillamine (1), 2,3-dimercaptopropanol (BAL, 5), 2,3-dimercaptosuccinic acid (7), 2,3-diaminopropionic acid (8), L-serine (9), L-threonine (10), D-glyceric acid (11), and L-homocysteine (12) were all commercial products.

***N*-(3-Formyl-2,2-dimethyl-L-thiazolidine-4-carboxy)-L-valine (14).** To a suspension of L-valine (10.54 g, 0.090 mol) in acetonitrile (145 mL) was added bis(trimethylsilyl)trifluoroacetamide (23.17 g, 0.090 mol), and the mixture was heated under reflux for 2 h. The solution was cooled to −10 °C and was then quickly added with stirring into a cold (−10 °C) preformed mixture of the mixed anhydride prepared over 40 min at −10 °C from 3-formyl-2,2-dimethyl-L-thiazolidine-4-carboxylic acid[9] (17.03 g, 0.090 mol), triethylamine (9.08 g, 0.090 mol), and isobutyl chloroformate (12.28 g, 0.090 mol) in methylene chloride (180 mL).

The reaction mixture was kept cold for 1 h and allowed to stand at room temperature for 18 h. The mixture was then extracted with 2 N HCl (4 × 100 mL), and the organic phase was separated, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from CH_2Cl_2–hexane to give 14.28 g (58% yield) of white crystals: mp 172–173 °C; $[\alpha]^{25}_D$ −111.9° (*c* 1.0, dioxane); IR (KBr) 3300 (w, NH), 1750 (COOH), 1650 (amide I), 1550 cm^{-1} (amide II). Anal. ($C_{12}H_{20}N_2O_4S$) C, H, N.

L-Cysteinyl-L-valine Hydrochloride (3·HCl). Compound 14 (14.42 g, 0.050 mol) was dissolved in a mixture of 165 mL of 0.4 N HCl and 100 mL of dioxane, and the mixture was heated in a N_2 atmosphere for 4 h. After lyophilization to remove solvent, the residue was dissolved in 50 mL of MeOH and the solution decolorized with charcoal. The filtrate was evaporated under reduced pressure to a light syrup, which was gently heated in a N_2 atmosphere and diluted with ether until the cloud point was reached. The excess ether was evaporated and the clear solution was set aside at 0 °C for crystallization. After 18 h, the product which crystallized as a mass of colorless needles was collected under N_2 and recrystallized again from MeOH–ether as above. This product was dried under vacuum at 65 °C for 20 h to give 7.70 g (60% yield) of 3; $[\alpha]^{25}_D$ −10.3° (*c* 1.0, 1 N HCl). Anal. ($C_8H_{27}N_2O_3SCl$) C, H, N, S.

Mercaptoethylglycine Hydrochloride (4·HCl). Mercaptoethylglycine ethyl ester[11] (4.65 g, 0.28 mol) in 20 mL of air-free 2 N HCl was heated under reflux in a N_2 atmosphere for 18 h. The reaction mixture was evaporated to dryness under reduced pressure, and the resulting solid residue was recrystallized three times from EtOH–ether. The product was dried under vacuum at 60 °C for 24 h to yield 1.60 g (33% yield) of 4·HCl: colorless flakes; mp 141.5–143.5 °C (reported[6] mp 101–102 °C). Iodometric titration[12] gave a free SH value of 95.3%: NMR (D_2O; from DSS) δ 3.97 (s, 2 H, NCH_2CO), 3.33 (t, 2 H, J = 6 Hz, $-CH_2S$), 2.87 (t, 2 H, J = 6 Hz, $-CH_2N$). Anal. ($C_4H_{10}NO_2SCl$) C, H, N.

Mercaptoethylglycine Disulfide (4a). A solution of mercaptoethylglycine ethyl ester[11] (8.02 g, 0.078 mol) in 50 mL of 2 N HCl was allowed to evaporate to dryness over 24 h on a steam bath, and this operation was repeated three times with new portions of acid following the procedure of Bulavin.[6] The residue was an orange syrup which was soluble in EtOH but did not crystallize on evaporation of the solvent as reported.[6] TLC on silica gel (*n*-PrOH–H_2O, 4:1) showed that at least five components were present. Heating this mixture under reflux for 18 h in 50 mL of 6 N HCl reduced the number of spots on TLC to two, but the major spot had an R_f similar to unchanged 4. This material was, therefore, chemically oxidized by addition of a solution of 0.3 M I_2 in EtOH dropwise until a permanent color was obtained. The reaction mixture was evaporated to 10 mL, the concentrate was applied to a column of Dowex 50W X-12 (50–100 mesh, 80 g), and the column eluted with H_2O until the eluate was chloride free (250 mL). The column was then eluted with 2 N NH_4OH. The six 250-mL fractions obtained, being similar by TLC criterion, were combined and evaporated to about 5 mL. Dilution with EtOH precipitated some solids, which were collected and recrystallized from H_2O–EtOH. The colorless crystals obtained were dried under vacuum at 65 °C for 18 h to give 1.03 g (4.9% yield) of 4a: mp 240–242 °C; NMR (D_2O) δ 3.63 (s, 4 H, NCH_2CO), 3.45 (m, 4 H, $-CH_2S$), 3.05 (m, 4 H, $-CH_2N$). A Na_2SO_3–$(NH_4)_2MoO_4$ spot test for disulfides[13] was positive. Anal. ($C_8H_{16}N_2O_4S_2$) C, H, N.

A few milligrams of the disulfide 4a in 5% ethanolic HCl was reduced with Raney nickel alloy. The product was shown to be 4, by identity on TLC (silica gel, *n*-PrOH–H_2O, 4:1). The –SH group was visualized using a 2,2′-dithiobis(5-nitropyridine) spray reagent.[14] A sample of 4a in 6 N HCl was evaporated to dryness to give 4a·HCl: mp 204–206 °C dec (reported[6] mp 158–160 °C); NMR (D_2O; from DSS) δ 3.97 (s, 4 H, NCH_2CO), 3.52 (m, 4 H, $-CH_2S$), 3.08 (m, 4 H, $-CH_2N$).

Model in Vitro System for the Evaluation of AcH Sequestration by Polyfunctional Agents. In a 20-mL glass septum vial were placed AcH and the AcH-trapping agent in a pH 7.50 phosphate buffer such that the final concentration in a total volume of 1.2 mL was 0.04 mM in AcH and 0.4 mM in trapping agent. The vial was immediately sealed with a rubber septum and equilibrated for 30 min in a shaking water bath at 37 °C. The vial was then placed in a separate water bath maintained at 55 °C and agitated for 10 min. A 2.0-mL sample of head space volume was then withdrawn and analyzed for AcH by gas chromatography as described previously.[2a]

Measurement of Ethanol-Derived Blood AcH in Rats after Administration of 3, 4, and 6. Male Sprague–Dawley rats (Gibco

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Animal Resources Laboratories, Madison, WI) weighing 180–230 g were divided into four groups of at least six rats each and fasted 24 h before administration of 2.0 mmol/kg (po) of disulfiram. Twenty-four hours after the administration of disulfiram, the separate groups were administered 8.0 mmol/kg of the AcH-sequestering agents **3**, **4**, **6**, or saline (control) ip, followed 1 h later by ethanol (43.5 mmol/kg, ip, as a 20% aqueous solution). The animals were sacrificed by cervical dislocation 1 h after ethanol, and blood was collected by open-chest cardiac puncture. Blood AcH, as well as blood ethanol, was measured using the head-space gas chromatographic procedure as above.

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Halogenated L-Fucose and D-Galactose Analogues: Synthesis and Metabolic Effects[1]

Janice R. Sufrin, Ralph J. Bernacki, Michael J. Morin, and Walter Korytnyk*

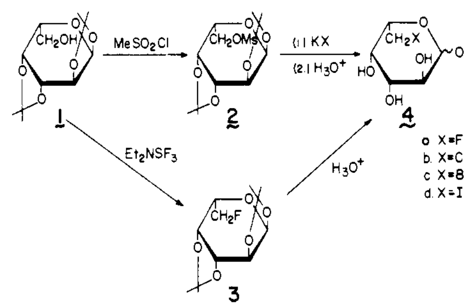
Grace Cancer Drug Center, Department of Experimental Therapeutics, Roswell Park Memorial Institute, New York State Department of Health, Buffalo, New York 14263. *Received April 2, 1979*

Several new analogues of L-fucose modified in the 2 position and the 5-methyl group have been synthesized as potential plasma-membrane glycoconjugate inhibitors or modifiers, and their biological effects have been studied. 2-Chloro-, 2-bromo-, and 2-iodo-2-deoxy-L-fucose (**9a**, **9b**, and **13**, respectively) have been prepared by addition of the appropriate halogen to 3,4-di-*O*-acetyl-L-fucal, followed by hydrolysis of the anomeric halogen and the acetyl groups. A series of four halogenated 5-methyl analogues of L-fucose (**4**, X = F, Cl, Br, and I) have been obtained starting from 1,2:3,4-di-*O*-isopropylidene-L-galactose. The synthesis of this latter compound has been improved. A corresponding series of 6-deoxy-6-halo-D-galactose analogues, which are enantiomers of the 5-(halomethyl)-L-fucose analogues, has also been synthesized. Analogues **4b**, **4c**, and **9b** at 1×10^{-3} M specifically inhibited the incorporation of L-[^{3}H]fucose into macromolecular components of SW613 human mammary tumor cells. Analogue **13** inhibited the growth of L1210 murine leukemic cells with an IC_{50} of 6×10^{-5} M in culture. 6-Deoxy-6-fluoro-D-galactose and its enantiomer **4a** were found to be effective inhibitors of D-[^{3}H]galactose and L-[^{3}H]fucose incorporation, respectively, into macromolecular components of human mammary tumor cells. The effectiveness of inhibition was reduced with an increase in size of the halogen atom. Analogue **4a** and its enantiomer have been tritiated at C-1 and both were found to be activated to a nucleotide sugar, which was followed by incorporation into the macromolecular fraction of SW613 human mammary tumor cells in vitro.

The plasma membrane is involved in a number of cellular properties which are implicated in neoplasia, such as increased invasiveness, breakdown in cell to cell communication, impairment of differentiation, and antigenic modulation. Extensive investigation has shown that changes occur in the plasma membrane following oncogenic transformation in terms of its modified properties and composition.[2-4] Many, if not most, of these changes involve cell-surface glycoconjugates. These molecules, and particularly their carbohydrate moieties, appear to develop structural and functional differences potentially exploitable for chemotherapeutic attack.

L-Fucose is a terminal sugar and, hence, an inviting target for chemotherapeutic intervention, especially since Seltzer et al.[5] have shown that following its continuous intravenous infusion a decrease in mammary tumor size occurred in rats. In addition, Wassenaar and Tator[6] have demonstrated that both L-fucose and D-galactose are preferentially taken up in brain tumor.

Scheme I



A consideration of the intermediates of L-fucose metabolism and the pathways that lead to GDP–L-fucose has provided a basis for the rational design of its potential inhibitors or modifiers. GDP–L-fucose in cells is synthesized either from appropriate D-mannose precursors by a de novo pathway or from L-fucose starting with phosphorylation of its anomeric carbon, followed by condensation of the resulting 1-phosphate sugar with GTP. Thus, while L-fucose analogues are likely to affect the latter ("salvage") pathway, analogues of D-mannose are potential inhibitors of the de novo biosynthetic pathway.

In the present study, the synthesis and biological activities of several L-fucose analogues, modified at the 2 and 6 positions, are described. These compounds may interfere with the salvage pathways utilizing fucose. Modification of the 6 position should not greatly affect the substrate activity for appropriate enzymes, such as L-fucose kinase, enabling conversion to nucleotide sugars and incorporation into glycoconjugates. Conversely, modification of the 2 position, because of its proximity to the anomeric center,

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