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Introducing Lipophilicity to (Polyhydroxyalkyl)thiazolidine Carboxylic Acids Via Acylation

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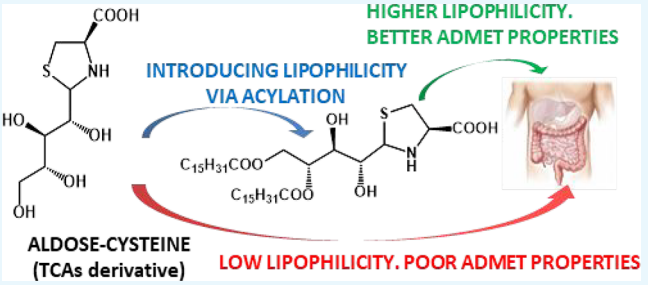
ABSTRACT: The therapeutic efficacy of bioactive compounds is related to their bioavailability. In turn, the bioavailability depends on the equilibrium between the hydrophilicity and the lipophilicity. 2(*R*,*S*)-(Polyhydroxyalkyl)thiazolidine-4(*R*) carboxylic acids (TCAs), obtained from the condensation of L-cysteine and an aldose, have been recognized as nontoxic precursors of glutathione with important preventive and therapeutic effects. The bioavailability of these compounds can be improved by enhancing their lipophilicity. This can be achieved by the introduction of some acyl groups derived from fatty acids via esterification of the aldose hydroxyl groups. With this purpose four new compounds were synthesized through a selective palmitoyl acylation of D-(−)-ribose and D-(+)-glucose and subsequent condensation with L-cysteine. In addition, the log P of the new compounds was calculated as a measure of the lipophilicity, and in vitro 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) tests were performed as a measure of the antioxidant capability.



INTRODUCTION

The addition of bioactive compounds, with preventive and therapeutic properties, to foods is gaining popularity. Bioactive compounds in foods have health benefits above their normal roles as nutrients.[1,2] The high lipophilic character of some foods, mainly fat- or oil-rich foods, allows one to use fat-soluble bioactive compounds in food supplementation.[3] Modifications of the chemical structure of bioactive compounds are usually performed with the main objectives of enhancing the solubility and bioavailability of these compounds.[4] Lipophilicity contributes to the absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics of compounds.[5,6] Log *P* is a parameter that serves to experimentally determine the lipophilicity. According to Lipinski et al. (2001),[7] a limit of log $P < 5$ is a desirable lipophilicity range for compound absorption and permeability. Improving the bioavailability of bioactive food compounds is fundamental to improving their bioefficacy. However, high lipophilicity (log $P > 5$) is linked with a rapid metabolic turnover, low solubility, and poor absorption. The importance of the lipophilic partition lies in the ability of compounds to cross a cell membrane and avoid not only rapid excretion but also the hydrophilic part to enhance the solubility of those compounds in aqueous conditions and to interact with molecular targets.

Bioactive compounds must be solubilized into mixed micelles so that they are available for absorption in the gastrointestinal tract (GIT). The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability;[8] consequently, equilibrium between lipophilicity and hydrophilicity needs to be achieved.

Cysteine prodrugs are compounds synthesized to release L-cysteine, the rate-limiting amino acid in the synthesis of glutathione (GSH).[9] Acetylation of the amino residue of L-cysteine is one approach to increase lipophilicity in L-cysteine. The resulting compound, *N*-acetylcysteine (NAC), is a good source of thiol groups able to stimulate GSH synthesis to promote detoxification and directly scavenge reactive oxygen species (ROS).[10] However, *N*-acetylcysteine administration has been limited by several drawbacks, including low membrane penetration and low systemic bioavailability.[11,12] Chemical modifications on the carboxyl group of L-cysteine have been performed in attempting to ameliorate the bioavailability drawbacks. New esters including alkyl esters, glycollamide esters, and acyloxymethyl esters have also been synthesized, with the thiol group protected as an S-benzoyl ester or S-benzoylcarbamate ester.[13]

Moreover, thiazolidine derivatives with masked sulfhydryl and amino groups of L-cysteine have been described as prodrugs. The thiazolidine prodrugs including aldoses in the 2-

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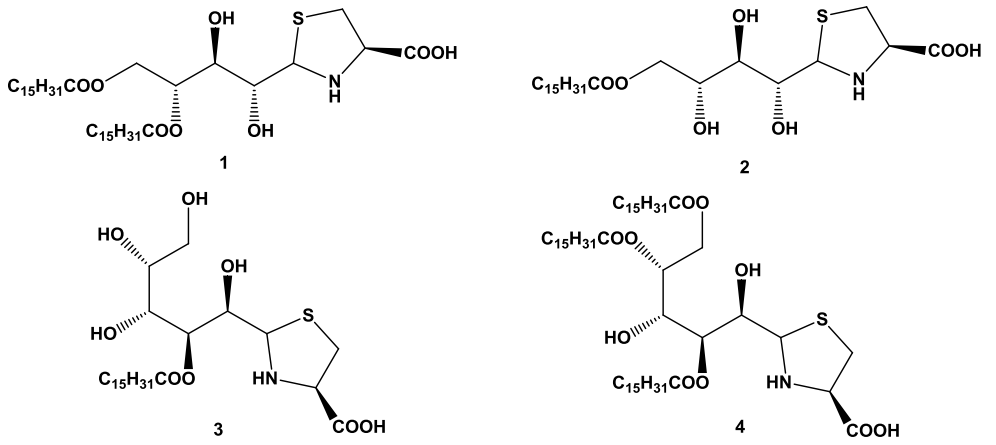
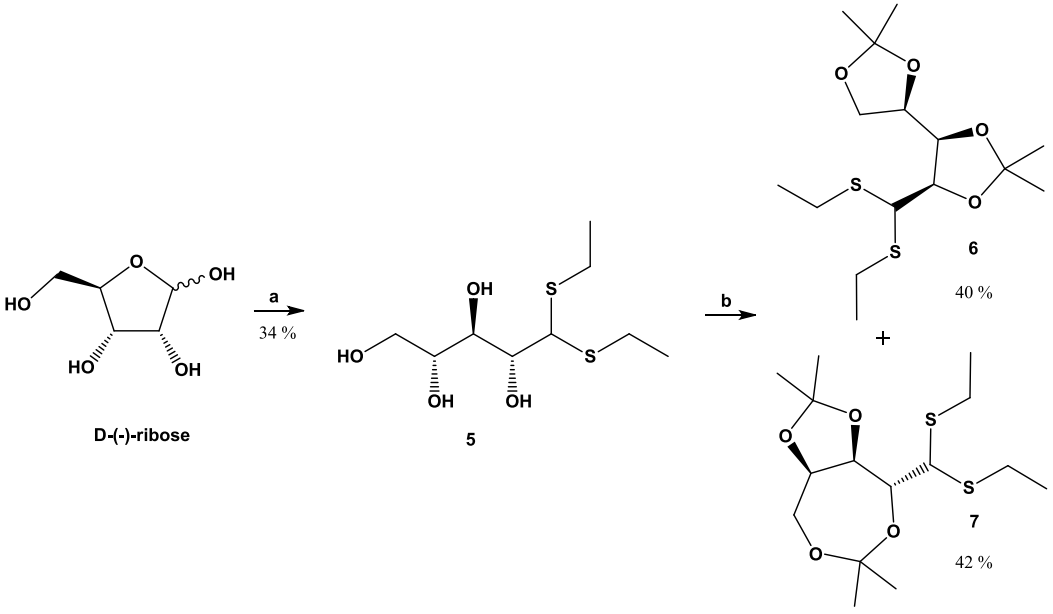


Figure 1. Proposed acyl (polyhydroxyalkyl)thiazolidin carboxylic acids derived from D-(−)-ribose (**1**, **2**) and from D-(+)-glucose (**3**, **4**).

Scheme 1. Carbonyl Group Protection and the Isopropylidenation of the Hydroxy Groups of D-(−)-Ribose[a]



[a]Conditions: (a) ethanethiol, 37% HCl, rt, 2 h; (b) dry acetone, H_2SO_4, rt, 16 h. The yield for each step is expressed as a percentage.

position have been already described.[14] These compounds are highly polar, water-soluble compounds due to the presence of multiple hydroxy groups and have the advantage that they do not deliver toxic compounds in vivo by hydrolysis, as it was hypothesized that they might be rapidly excreted by the kidneys. To enhance lipid solubility, the sugar hydroxy groups were acetylated. The biological evaluation of these novel thiazolidines indicated extreme toxicity;[15] this may result from the early dissociation into the respective acetylated sugars before the deacetylation took place.

The purpose of this work is the synthesis of four novel thiazolidine derivatives (1−4) with increased lipophilicity using fatty acids instead of acetic acid. The new structures are based on the partial esterification of the carbohydrate skeleton with C16 acyl chains maintaining some free hydroxyl groups. The selected aldoses were D-(−)-ribose and D-(+)-glucose, as representative aldopentose and aldohexose (Figure 1).

The lipophilic part of the modified thiazolidines would come from the partial esterification of some of the sugar hydroxy groups, whereas carbohydrate and thiazolidine moieties exhibit hydrophilic characteristics. This esterification would incrementally change the lipophilicity of the modified thiazolidines, whereas the free hydroxyl groups of the carbohydrate and thiazolidine moieties will confer the hydrophilic character on the compounds.

In addition, the lipophilicity using log *P* values and in vitro antioxidant properties, based on a 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) test, were assessed for the four new compounds.

RESULTS AND DISCUSSION

Synthesis of Compounds. As stated in the Introduction, the properties of thiazolidine-derived compounds are dependent on the size, functionality, and polarity of the groups of these compounds. In the present work, the synthesis of different thiazolidine ester derivatives (Figure 1) of (a) D-(−)-ribose and (b) D-(+)-glucose, an aldopentose and an aldohexose, respectively, is described. In addition to producing mixtures, the direct acylation of 2(*R*,*S*)-(polyhydroxyalkyl)

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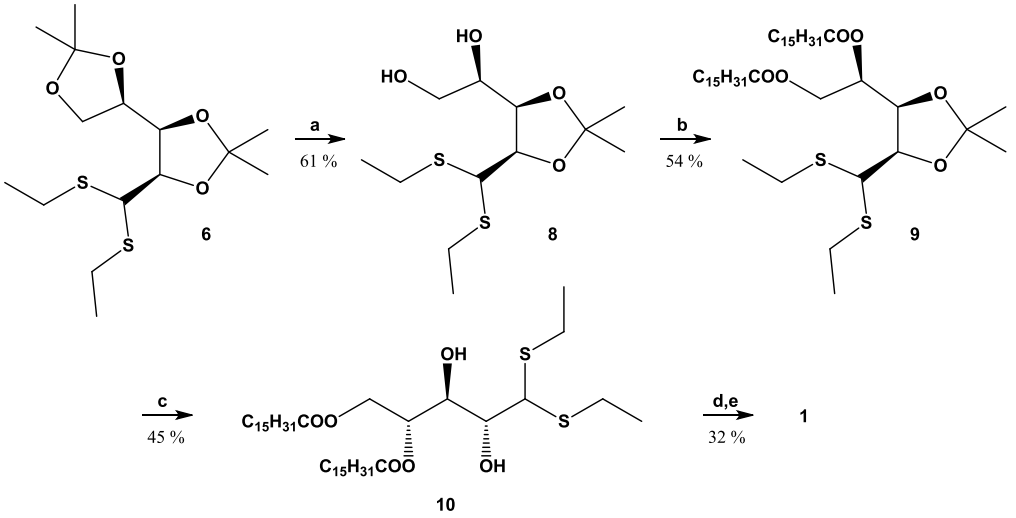
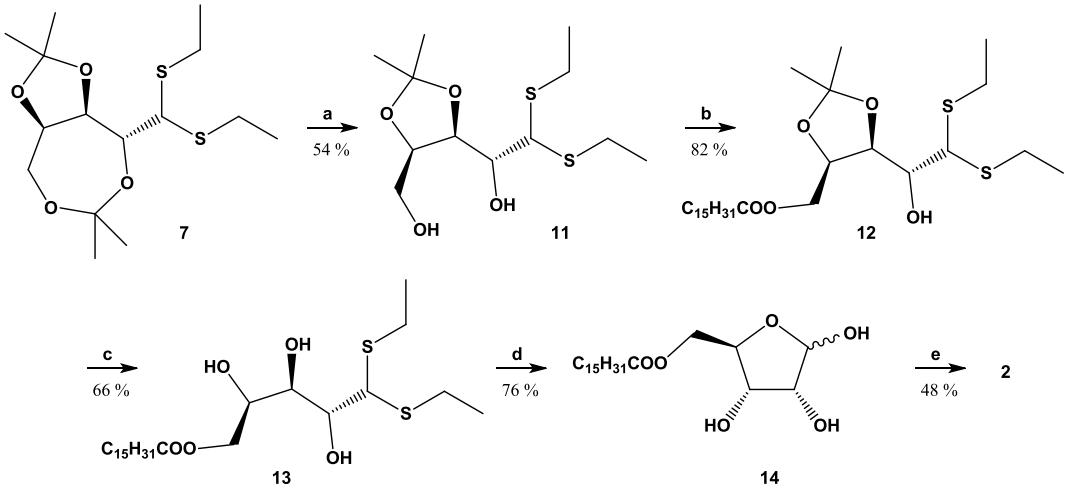
Scheme 2. Synthesis of Compound 1 from Compound 6[a]



[a]Conditions: (a) AcOH 70%, rt, 12 h; (b) $C_{15}H_{31}COCl$, dry DCM, triethanolamine (TEA), 4-dimethylaminopyridine (DMAP), rt, 16 h; (c) 50% TFA, rt, 16 h; (d) HgO, $HgCl_2$, acetone, H_2O, rt, 2 h; (e) L-cysteine, MeOH, pyridine, reflux, 4 h. The yield for each step is expressed as a percentage.

Scheme 3. Synthesis of Compound 2 from Compound 7[a]



[a]Conditions: (a) 70% AcOH, rt, 12 h; (b) $C_{15}H_{31}COCl$, dry DCM, TEA, DMAP, rt, 16 h; (c) 50% TFA, rt, 1 h; (d) HgO, $HgCl_2$, acetone, H_2O, rt, 2 h; (e) L-cysteine, MeOH, pyridine, reflux, 4 h. The yield for each step is expressed as a percentage.

thiazolidine-4(*R*) carboxylic acids (TCAs) would also change the thiazolidine moiety, so the sugars were peracylated before their incorporation into the thiazolidine structure.

Carbohydrate chemistry is complex due to the presence of multiple reactive hydroxy groups,[16] thus requiring additional steps of protection and removal of protecting groups to modify specific hydroxyl groups. An initial protection step was performed to allow us to regioselectively esterify the hydroxyl groups, avoiding the formation of polyesters as byproducts.[17] Prior to the acetylation of hydroxy groups, the aldehyde functionality was protected as a diethyl dithioacetal. The partial esterification of some hydroxy groups of the sugar was performed using palmitoyl chloride. Then the esterified sugars were unprotected, and the final thiazolidine synthesis was accomplished by a condensation step of the unprotected esterified sugars with L-cysteine. As stated above, the direct esterification of the thiazolidines was not an option if the formation of mixtures of products is to be avoided.

Synthesis of Thiazolidines Derived from D-(−)-Ribose. The first step consisted of the protection of the carbonyl group of D-(−)-ribose to avoid the reactivity of the carbonyl group while maintaining its functionality until the cyclization step with L-cysteine. The aldehyde protection was performed with ethanethiol and 37% HCl (Scheme 1) to achieve the corresponding open-chain derivative of D-(−)-ribose **5** with the free hydroxyl groups.[18,19] The low yield after recrystallization from acetone was in accordance with the literature.[15]

The following step consisted of a standard isopropylidenation to selectively protect the vicinal hydroxyl groups.[20,21] Isomeric acetonides **6** and **7** were obtained using acetone and H_2SO_4 as a catalyst. These compounds have already been described.[22,23]

Compound **6** was the starting material for the synthesis of thiazolidine derivative **1**, which contained two acyl chains. A selective 4,5-*O*-isopropylidene hydrolysis was performed using mild acid conditions to afford the diol **8** (Scheme 2). The

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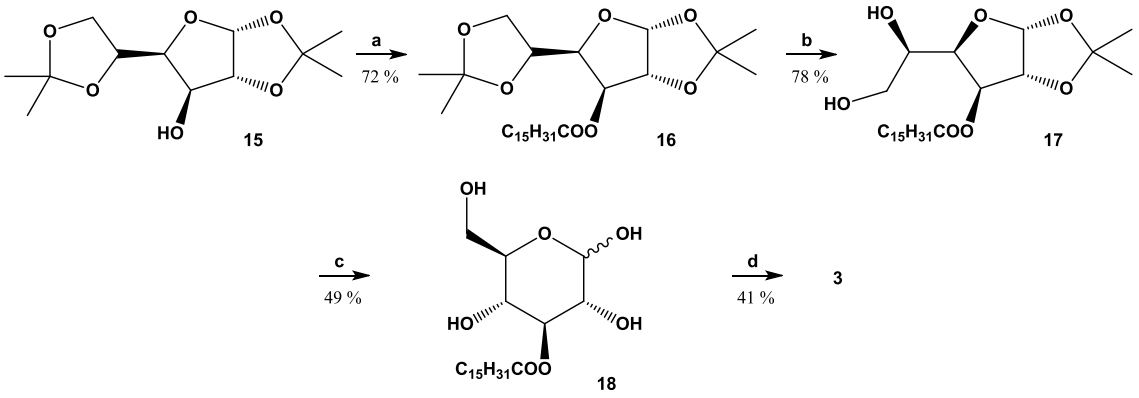
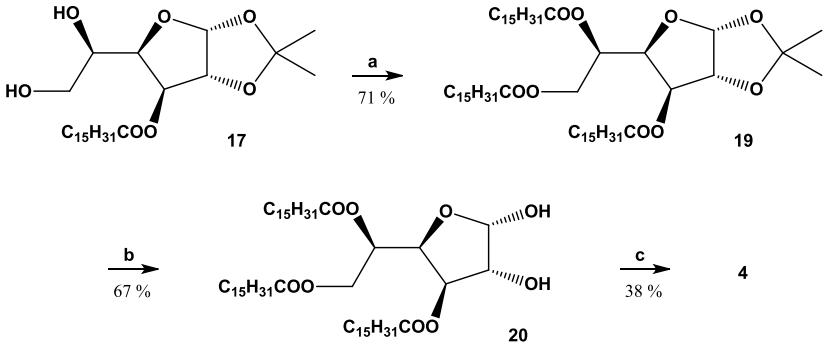
Scheme 4. Synthesis of Compound 3 from Compound 15[a]



[a]Conditions: (a) $C_{15}H_{31}COCl$, dry DCM, TEA, DMAP, rt, 16 h; (b) 70% AcOH, rt, 12 h; (c) TFA 70%, 40 °C, 16 h; (d) L-cysteine, MeOH, pyridine, reflux, 4 h. The yield for each step is expressed as a percentage.

Scheme 5. Synthesis of Compound 4 from Compound 17[a]



[a]Conditions: (a) $C_{15}H_{31}COCl$, dry DCM, TEA, DMAP, rt, 16 h; (b) 70% TFA, 40 °C, 16 h; (c) L-cysteine, MeOH, pyridine, reflux, 4 h. The yield for each step is expressed as a percentage.

reaction progress for this regioselective unprotection was followed by thin-layer chromatography (TLC) to ensure that there was no hydrolysis of the 2,3-*O*-isopropylidene. Acetonide **8** was obtained in a moderate yield (61%) similar to what is described in the literature.[24]

Acylation of acetonide **8** was performed at OH-4 and OH-5 with palmitoyl chloride to obtain the diester **9**, which has not previously been reported. The structure of the acylated compound **9** was confirmed by ^{13}C NMR. The chemical shifts for the carbons of the carboxylic group appeared at δ 172.8 and 173.6. Hydrolysis of the remaining 2,3-*O*-isopropylidene group was performed in stronger conditions than the previous one. Compound **10** was obtained after a treatment with 50% trifluoroacetic acid (TFA) at room temperature instead of 70% acetic acid.[25]

The cleavage of the diethyl dithioacetal group was performed using mercuric oxide (HgO) and mercuric chloride ($HgCl_2$).[26,27] The resulting aldehyde was immediately submitted to cyclization with L-cysteine. That reaction was performed using methanol and pyridine under reflux.[28,29] As previously reported, the cyclization reaction implies the formation of a new chiral center at C-2 without any stereoisomeric control leading to a diastereomeric mixture.

Thiazolidine derivative **2** obtained from D-(−)-ribose was synthesized from compound **7** with a similar synthetic pathway. The first step was the selective cleavage of 2,5-*O*-isopropylidene in mild acid conditions to obtain compound **11** (Scheme 3). Then, a selective esterification at OH-5 performed with palmitoyl chloride (1 equiv) in dry dichloromethane (DCM) was performed.

The following steps consisted of the unprotection of the isoproylidene and diethyl dithioacetal groups. The hydrolysis of the isopropylidene was performed in an aqueous solution of TFA, as in the previous synthetic pathway, to obtain compound **13**. The cleavage of the diethyl dithioacetal and the subsequent cyclization afforded compound **14**, 5-palmitoyl-D-ribofuranose, in good yield (76%). The structure of **14** was confirmed by ^{1}H and ^{13}C NMR spectra.[30,31]

The last step was the condensation with L-cysteine in the same conditions previously reported for compound **1**. The thiazolidine derivative **2** was analyzed by ^{1}H and ^{13}C NMR spectroscopy, but proton identification was difficult because of overlapping signals. High-resolution mass spectra confirmed the new thiazolidine derivative compound. The ratio of diastereomers in the mixture favored the (2*R*,4*R*)-epimer (2*S*,4*R*/2*R*,4*R*, 4.5:5.5) according to the ratio of peak areas of the ^{1}H NMR spectrum (see the Supporting Information).

A hydrolysis under mild conditions removed the 5,6-*O*-isopropyilidene, whereas the 2,3-*O*-isopropylidene remained stable. For most carbohydrates, the spiro-fused isopropylidene moiety was more stable than the terminal isopropylidene moieties.[32] In the previous case (synthesis of compound **8**), 2,3-*O*-isopropylidene was found to be more difficult to remove than 4,5-*O*-isopropylidene, although a great instability was observed under mild acid conditions. A chemoselective pattern was observed in di-*O*-isopropylidene compounds in which all

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terminal isopropylidenes are preferably deprotected under mild conditions. Compound **17** was obtained after a treatment with acetic acid. The spiro-fused isopropylidene was removed by a treatment with 70% TFA at 40 °C to obtain 3-palmitoyl-D-glucopyranose **18**.

Compound **18** was cyclized after the acetal protection was removed to obtain a mixture of isomers.

Finally, the thiazolidine monoester derived from D-(+)-glucose **3** was obtained (Scheme 4) after the condensation of **18** with L-cysteine, yielding 41% of the desired compound. The ratio of diastereomers in the mixture favored the (2*R*,4*R*)-epimer (2*S*,4*R*/2*R*,4*R*, 4.1:5.9)) according to the ratio of peak areas of the ^{1}H NMR spectrum (see the Supporting Information).

Triester thiazolidine derivative **4** was synthesized starting from compound **17**, which has already been reported.[33] The diol was completely acylated with palmitoyl chloride to obtain compound **19** in good yield (71%). The unprotection of isopropylidene afforded compound **20**, which maintained the furanose form due to the esterification at OH-5 (Scheme 5). The coupling constant of the protons of C-1 and C-2 was 4 Hz, indicating a *cis* orientation of the protons and an α-furanose conformation. In ^{13}C NMR, the signal at δ 96.89 indicates the α-furanose conformation. Additionally, the presence of minor signals in the ^{13}C NMR spectrum suggested some formation of a β-furanose structure.

Finally, the cyclization with L-cysteine in methanol allowed us to synthesize thiazolidine derivative **4** in a moderate yield (38%). The compound was obtained as a diastereomeric mixture, but the diastereomeric ratio could not be determined.

Measurement of Lipophilicity, Log P. To assess the lipophilicity of new compounds, log *P* values were measured. When log *P* values exceed 4, the octanol−water partitioning system cannot be applicable. In these cases, log *P* is estimated by using the retention time of the compounds in reversed-phase high-performance liquid chromatography (HPLC) and calculating the capacity factor k', because there is a linear relationship among them.[34,35] Table 1 shows the values for thiazolidine derivatives based on D-(−)-ribose and D-(+)-glucose.

Table 1. Log *P* Values from Thiazolidines Derived from D-(−)-Ribose and D-(+)-Glucose

compound	log *P*
1	9.23
2	2.78
3	3.11
4	14.34

The lipophilicity of the thiazolidine derivatives depends on the acyl chains and the presence of hydroxy groups in the carbohydrate and thiazolidine moieties. As expected, larger values of log *P* were achieved in thiazolidine derivatives including two or more acyl chains. The log *P* of thiazolidine derivative **1** (9.23) was greater than that of thiazolidine derivative **2** (2.78) due to the two C_{16} acyl chains. Log *P* values for the thiazolidine compounds derived from D-(+)-glucose **3** and **4** were 3.11 and 14.34, respectively, indicating that they are also highly lipophilic. Thiazolidine derivative **4** resulted as the most lipophilic compound of all the synthesized compounds due to the incorporation of three C_{16} acyl chains.

On the one hand, as stated in the Introduction, highly lipophilic compounds are associated with a rapid metabolic turnover, low solubility, and poor absorption in the GIT. On the other hand, the high hydrophilicity of thiazolidine derivatives is correlated with a rapid excretion. Compounds that display a log *P* value between 1 and 3 appear to be optimal for achieving appropriate physicochemical characteristics.[5] The log *P* of thiazolidine derivatives **2** and **3** is linked with this optimal range, improving the expected compound quality within desired ADMET parameters.

In Vitro Antioxidant Activity. To assess the antioxidant properties of the new compounds, two assays of the scavenging effect, namely, 2,2-diphenyl-1-picrylhydrazyl (DPPH) and ABTS, were performed.[36,37] The obtained results were compared to those for the sodium salts of the corresponding homologous compounds without acyl groups (Rib-Cys Na^+ and Glu-Cys Na^+) and also to the 1,3-thiazolidine-4(*R*)-carboxylic acid and its sodium salt (TCA-Na^+). While DPPH showed incongruent values (results not shown), probably due to the low solubility of the compounds in the solvents used to perform the test, the ABTS assay revealed the conservation of radical scavenging effects to a certain extent. Table 2 shows the Half Maximal Inhibitory Concentration (IC_{50}) of the compounds tested.

Table 2. IC_{50} Values from the New Compounds Compared with Nonacylated Derived Compounds

compound	IC_{50} (mg/L)
1	435
2	343
3	339
4	409
Rib-Cys Na^+	299
Glu-Cys**Na^+**	440
TCA	236
TCA-Na^+	>600

The acylation of the polyhydroxyalkyl thiazolidines resulted in some loss of radical scavenging capability in the ABTS test compared to TCA, used as reference. However, the values of new compounds are similar to those of the sodium salts of polyhydroxyalkyl thiazolidin carboxylic acids, being better for compounds **2** and **3**. For these compounds the in vitro lower antioxidant capability may be compensated with their better liposolubility.

CONCLUSIONS

New thiazolidine-4(*R*)-carboxylic acid derivatives were synthesized from L-cysteine and monosaccharides with some hydroxy groups esterified with C_{16} acyl chains. A protocol to obtain modified thiazolidines from two aldoses, D-(−)-ribose and D-(+)-glucose, was described. Changes in the aldose moiety, in the protecting groups used and in the employed catalysts, may result in variations in the obtained compounds or modifications in the reaction steps. Here, the common C_{16} acyl chain was used, but the protocol can be applied to other fatty acid chains.

Since lipophilicity has long been considered a crucial physicochemical parameter that strongly influences compound absorption, distribution, metabolism, excretion, and toxicity, log *P* values of the new thiazolidine derivatives were measured. As expected, log *P* values increased as more acyl chains were

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incorporated to the carbohydrate moiety. The increased hydrophobic character of these molecules would come from the incorporation of these acyl chains, whereas carbohydrate and thiazolidine moieties would contribute to the hydrophilic character. The thiazolidine compounds with one acyl chain in their structures showed suitable log *P* values according to those desirable for compound absorption and permeability. In addition, in vitro radical scavenging IC_{50} values obtained in the ABTS assay were similar to the ones corresponding to the sodium salt of the polyhydroxyalkyl thiazolidines with the same aldoses.

EXPERIMENTAL SECTION

The experimental methods, synthesis, log *P* measurements, antioxidant activity, characterizations, and NMR, Fourier transform infrared (FTIR), and high-resolution mass spectrometry (HRMS) spectra are thoroughly detailed in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c07078.

Full experimental methods, characterization data, and ^{1}H NMR, $^{13}C\{^{1}H\}$-NMR, FTIR and HRMS spectra of the synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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