Some Notes on the Chlorogenic Acids.
1. Numbering and Nomenclature
Version 5 January 2017
with table margins corrected

Mike Clifford
Emeritus Professor of Food Safety
University of Surrey,
Guildford GU2 5XH, Surrey, UK

and

Dr Laszlo Abranko
Associate professor
Szent István University, Faculty of Food Science, Department of Applied Chemistry
1118 Budapest, Hungary

Contents

	Referees	**Page 2**
	Objectives	**Page 3**
	Summary and Recommendations for Nomenclature	**Page 3**
1.	**A brief history of Chlorogenic Acids**	**Page 4**
2.	**Trivial names applied to acyl-quinic acids**	**Page 5**
3.	**IUPAC and non-IUPAC numbering**	**Page 9**
4.	**Chlorogenic acids and the CIP sequence rules**	**Page 12**
5.	**Electronic Databases and Chemicals Suppliers' Catalogues**	**Page 19**
6.	**Examples from the published literature of confusion regarding numbering and configuration**	**Page 31**
7.	**The extended Chlorogenic Acids Family**	**Page 35**
8	**Structures**	**Page 43**
9	**References**	**Page 61**

Referees

The following chlorogenic acid researchers are thanked for taking the time to read and comment upon the content of this document before its uploading to Researchgate

Professor Gary Williamson	**University of Leeds, UK**
Dr Asimina Kerimi	**University of Leeds, UK**
Dr Dimitrina Zheleva-Dimitrova	**Medical University of Sofia, Bulgaria**
Dr Edwin Madala	**University of Johannesburg, South Africa**

Objectives

These notes are designed to draw attention to the complexity of the chlorogenic acids and confusion surrounding their naming, characterisation and identification. They have been placed on Researchgate to make them freely available, and have been reviewed by the undermentioned chlorogenic acid researchers in an attempt to ensure that no errors of fact have crept through, and that the information is presented clearly. Please notify us of any errors that are found and these notes will be updated as necessary.

Summary and Recommendations for Nomenclature

The plural term 'chlorogenic acids' now embraces a large number of structurally related compounds. These are best described as acyl derivatives of quinic acid enantiomers and diastereomers, and close relatives thereof (including shikimic acids and other cyclitols), where the one to four acyl moieties are drawn from one or more of the following groups: cinnamic acids, dihydrocinnamic acids, benzoic acids, phenylacetic acids, dicarboxylic aliphatic acids, formic or acetic acid. Further isomerisation arises through variation in the position(s) of the acyl residue(s), and the geometry of the cinnamic acid(s) if present.

Further complexity arises through two methods of numbering the quinic acid carbon skeleton, several different ways of describing its configuration, plus the ability of the quinic acid moiety to adopt several conformations in solution. The use of trivial names exacerbates this complexity.

In order to avoid confusion, it is essential to have clarity and consistency of nomenclature and drawing of structures. These notes attempt to illustrate the complications surrounding chlorogenic acids nomenclature in order to minimize the potential for confusion and error which is illustrated by examples from the electronic and printed sources. Recommendations to this end are as follows:

1. It is recommended that IUPAC numbering be adopted and a statement included to make it abundantly clear that this has been done.
2. In the introduction, the list of reagents used, and the discussion, it is essential that all data are expressed using only this system. This requires that suppliers' descriptions of commercial standards, and data from previous publications, are amended to the IUPAC numbering system if necessary, and a clear statement made to this effect.
3. If it is not possible to define which system has been used in a previous publication then this should be clearly noted when discussing that data along with a statement that the numbering and name have been left unchanged.

4. Revised recommendations for the nomenclature of chlorogenic acids have been prepared, and appear below. These have been communicated to IUPAC and a response is awaited.

Recommendations

1. (±)-Quinic acid and (±)-epi-quinic acid

The minimum requirement for unambiguous description of (±)-quinic acid and (±)-epi-quinic acid is:

a)	L-(–)-quinic acid	3*R*, 5*R*-(1α, 3α, 4α, 5β)
b)	D-(+)-quinic acid	3*S*, 5*S*-(1α, 3α, 4α, 5β)
c)	L-(–)-*epi*-quinic acid	3*R*, 5*R*-(1α, 3α, 4β, 5β)
d)	D-(+)-*epi*-quinic acid	3*S*, 5*S*-(1α, 3α, 4β, 5β)

2. *Meso*-quinic acids

To avoid ambiguity, particularly when describing acyl-*meso*-quinic acids, a convention, such as follows, is essential:

> Clockwise numbering should be used for *meso* forms, when the formula is drawn in such a way that the OH group at C1 is above the plane of the ring.

The minimum requirement for unambiguous description of the meso-quinic acids is:

a)	*muco*-quinic acid	3*S*, 5*R* (1α, 3β, 4α, 5β)
b)	*cis*-quinic acid	3*R*, 5*S* (1α, 3α, 4α, 5α)
c)	*neo*-quinic acid	3*S*, 5*R* (1α, 3β, 4β, 5β)
d)	*scyllo*-quinic acid	3*R*, 5*S* (1α, 3α, 4β, 5α)

1. A brief history of the chlorogenic acids

The origin of the term 'chlorogenic acid' is probably the use of '*chlorogen acid*' by Payen in 1846 *(1, 2)*. Payen reported the isolation of a crystalline potassium caffeine chlorogenate that formed up to 5% of green coffee beans, proposed an empirical formula of $C_{14}H_8O_7$ (now known to be $C_{16}H_{18}O_9$), and described its conversion to a green pigment on alkaline oxidation. In 1932 Fischer and Dangschat *(3)* proposed that this substance was 3-*O*-caffeoylquinic acid (3-CQA). Although the structure assignment made by Fischer and Dangschat *(3)* has stood the test of time, the numbering system they adopted was revised by IUPAC in the 1976 recommendations for the numbering of the carbon atoms of cyclitols *(4)*. In this system, Fischer and Dangschat's 3-CQA becomes 5-CQA IUPAC *(3, 4)*.

In 1950 Barnes *et al*. *(5)* reported the presence in coffee of the isomer 5-*O*-caffeoylquinic acid (5-CQA) (now known as 3-CQA IUPAC), and over the next 15 years further acyl quinic acids were characterised. These included Cynarin(e) from globe artichoke (*Cynara scolymusI*) originally reported as 1,4-diCQA in 1954, now known to be 1,3-dicaffeoylquinic acid IUPAC *(6)*, plus galloyl *(7, 8)*, *p*-coumaroyl *(9, 10)*, feruloyl *(11)*, caffeoyl-feruloyl *(12)*, caffeoyl-succinoyl *(13)* and sinapoyl *(14)* esters of (–)-quinic acid. The relevant structures are illustrated below in Tables 2 to 9.

A recent survey of nearly 1100 papers concerned with the botanical distribution of chlorogenic acids, and their transformation during processing, has identified well over 300 acyl-quinic acid derivatives, and this number is certain to grow.

The study of chlorogenic acids is beset by a confusing trivial nomenclature (see Table 1), two systems of numbering the carbon atoms and numerous systems of defining the configuration of the quinic acid moiety, none of which are entirely satisfactory.

Further complexity, and hence likely confusion, arises because in attempting to present a dynamic three dimensional structure in two dimensions usage is made, quite reasonably and correctly, of two chair forms for each enantiomer plus two cyclic representations, one viewed 'from in front' and the other 'from behind' — see Table 5.

While this document was in preparation some aspects of this problem, particularly the failure of authors to indicate the orientation of substituents in the cyclohexane ring, have been discussed by Kremr *et al*. (2016).*(15)*

2. Trivial names applied to acyl-quinic acids

Table 1 summarises the various trivial names associated with the chlorogenic acids and where possible provides a systematic name using the IUPAC numbering.

Trivial Name	**Introduced**	**Current Interpretation with IUPAC numbering**	**Notes**
Band 510	Sondheimer 1958 *(16)*	4-Caffeoylquinic acid	
Burkinabins	Ouattara *et al.* 2004 *(17)*	Divanilloylquinic acids	
Castusic acid	Kirmizibekmev and Demir 2016 *(18)*	4-*p*-hydroxybenzoyl-5-caffeoylquinic acid	
Chlorogen acid or chlorogenic acid	Payen 1846 *(1, 2)*	5-Caffeoylquinic acid	The original isolate subsequently described as 3-caffeoylquinic acid and now known as 5-caffeoylquinic acid IUPAC
Chlorogenic acids			Used in the plural to denote the extended family of structurally related compounds — see text
Cryptochlorogenic acid	?	4-Caffeoylquinic acid	
Cynarin(e)	Panizzi *et al*. 1954 *(6, 19)*	1,3-Dicaffeoylquinic acid	Rapidly formed from 1,5-dicaffeoylquinic acid in aqueous media
Dactylifric acid	Maier *et al*. 1964 *(20)*	5-Caffeoylshikimic acid	

Dattelic acid	Wada *et al*. 1988 *(21)*	5-Caffeoylshikimic acid	
Hauschild's substance	Hauschild 1935 *(22)*	3-Caffeoylquinic-1,5-γ-lactone	This report was possibly of an artefact formed during extraction, but now known in roasted coffee and maté
Irbic acid	Antognoni *et al.* 2011 *(23)*	3,5-dicaffeoyl-4-malonoyl-quinic acid	This name was applied first to a compound isolated from cultured cells of *Centella asiatica* but subsequently found in the whole plant *(24, 25)*. This compound had been known from at least 2007.*(26)*
Isochlorogenic acid	Barnes *et al*. 1950 *(5)*	A mixture of at least three dicaffeoylquinic acids	Originally described as 5-caffeoylquinic acid using non-IUPAC numbering, contaminated with the associated lactone. Prefix 'iso' used to indicate 'isomer'.
Isochlorogenic acid a, b and c, or A, B and C	Scarpati and Guiso 1964, Corse *et al*., 1965 *(12, 27)*	Coffee bean dicaffeoylquinic acids	The two groups used the descriptors a, b and c, or A, B and C, differently and it is thus very difficult to tell which letter applies to which regio-isomer in later usage. As originally published A = c = 3,4-diCQA, and C = b = 3,5-diCQA IUPAC. Logically B = a = 4,5-diCQA IUPAC but there remains an unexplained difference in specific rotation of the two isolates.*(12)*

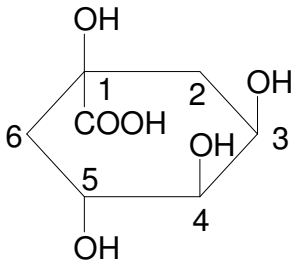
Macranthoin F and G	Chen *et al*. 1994 *(28)*	Methyl 4,5-dicaffeoylquinate and methyl 3,5-dicaffeoyl-quinate, respectively	Note that the term 'macranthoin' refers to constituents of *Lonicera macranthoides* regardless of whether or not they are chlorogenic acids.
Mumeic acid	Nakamura *et al*. 2013 *(29)*	4-benzoyl-5-caffeoylquinic acid	
n-Chlorogenic acid	Maier and Grimsehl 1982 *(30)*	5-Caffeoylquinic acid	Prefix '*n*' used to distinguish 5-caffeoylquinic acid from total chlorogenic acids
Neochlorogenic acid	Corse 1953 *(31)*	3-Caffeoylquinic acid	
Origanine A–C	Liu *et al*. (2012)*(32)*	Derivatives of 1,3,4,5- and 1,3,5,6-tetra-carboxy-shikimic acid	Reported in *Origanum vulgare* L. Biosynthetic origin unknown and possibly different from (–)-quinic and (–)-shikimic acids.
Pistafolins	Hou *et al*. 2000 *(33)*	Galloylquinic acid depsides	Term applied to some galloylquinic acids of *Pistacia lentiscus*
Podospermic acid	Zidorn *et al*. 2005 *(34)*	1,3,5-tri-dihydrocaffeoylquinic acids	Some close relatives, such as di-dihydrocaffeoyl-feruloylquinic acids, may also be included in the trivial name.*(35)*
Pseudochlorogenic acid	Uritani and Miyano 1955 *(36)*	1-Caffeoylquinic acid	Probably the original isolate was a poorly defined mixture of caffeoylquinic and dicaffeoylquinic acids

Salicornate	Kim *et al.* 2011 *(37)*	Methyl 4-caffeoyl-3-dihydrocaffeoyl-quinate
Theogallin	Roberts 1958 *(38)*	5-Galloylquinic acid
Tuntungmadic acid	Chung *et al*. 2005 *(39)*	4-Dihydrocaffeoyl-5-caffeoylquinic acid
Viarum acids	Wu *et al*. 2012 *(40)*	5-caffeoyl-[4-(1β-[6-(5-caffeoyl) quinate]gluco-pyranosyl)]quinic acid and 3-malonyl-5-caffeoyl-[4-(1β-[6-(5-caffeoyl)-quinate]glucopyranosyl)]quinic acid

3. IUPAC and non-IUPAC numbering

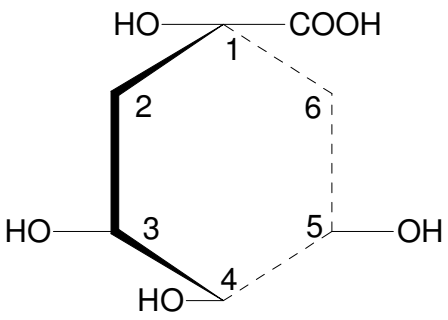
In 1976 IUPAC published their views on how best to define the configuration of cyclitols, cycloalkanes with one hydroxyl on each of at least three ring carbons. Special procedures were required because cyclitols possess features of relative and absolute configuration that are not clearly displayed by general methods of stereochemical nomenclature. It was recognised that the Cahn–Ingold–Prelog (CIP) sequence rule system for absolute stereochemistry could be used, but that the sequence rule procedure was complex in this application, a view also held by Corse and Lundin.*(41)* IUPAC considered the Maquenne fractional system, the Posternak system, the Fletcher, Anderson and Lardy system, and the Angyal and Gilman system, but recommended the adoption of the McCasland fractional system with prefixes.

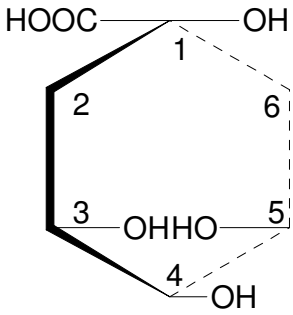
Accordingly, IUPAC recommended *inter alia* that the most common naturally occurring quinic acid should be described as L-1(OH),3,4/5-tetrahydroxy-cyclohexanecarboxylic acid with the trivial names (–)-quinic acid or L-quinic acid, as below.*(4)* For quinic acids, according to IUPAC recommendations, the lowest carbon number (i.e. C1) is applied to the substituent '*other than an unmodified hydroxyl group*'. Note also, that the application of the IUPAC recommendations to a pair of enantiomers, e.g. (+)-quinic acid and (–)-quinic acid or (+)-*epi*-quinic acid and (–)-*epi*-quinic acid, results in one enantiomer being numbered clockwise and the other being numbered anticlockwise.



As discussed by Corse and Lundin,*(41)* clockwise and anticlockwise numbering can make certain tasks extremely difficult, and in discussions of routes of chemical synthesis they preferred to use the Maquenne fractional system to avoid this complication. However, the Maquenne system uses non-IUPAC numbering, but does permit a convenient distinction between (–)-quinic acid, which is (–)-(3/145) tetrahydroxy-cyclohexane carboxylic acid, and (+)-quinic acid, which is the (+)-(5/134) isomer, with the fraction indicating which hydroxyls are *cis* to the carboxyl (drawn above the plane of the cyclohexane ring) and which are *trans*.

For the absolute configuration IUPAC stated that a Fischer–Tollens projection should be used with C1 at the top and C2 and C3 at the front edge of the ring. The configuration is D if the lowest numbered chiral centre projects to the right, and L if it projects to the left, see below. The prefix D or L, followed by a hyphen, is itself followed by the compound name. A numeral may precede the prefix to identify the defining centre of chirality. Omission of a prefix, or preferably the use of the prefix DL, identifies a meso form.





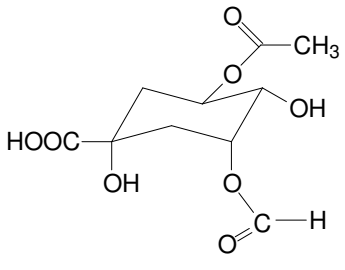
Fischer–Tollens Projections

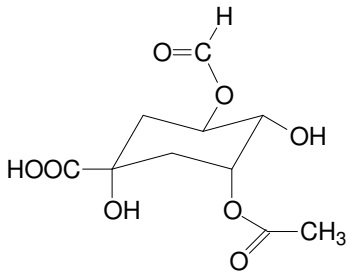
1L-Quinic Acid
(–)-Quinic Acid

1D-Quinic Acid
(+)-Quinic Acid

Note that Eliel advises that strictly the term 'chiral centre' is incorrect and should be replaced by 'centre of chirality'.*(42)*

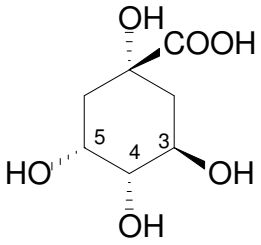
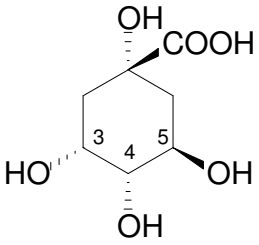
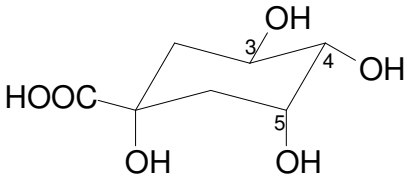
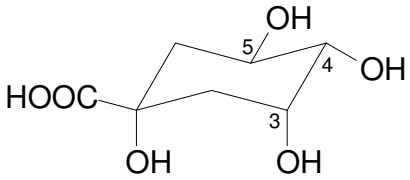
However, it has since become apparent that the IUPAC system applied to quinic acid derivatives is not without its problems, with some basic IUPAC priority rules being flouted. If one considers, for example, a 3,5-disubstituted formyl-acetylquinic acid, the acetyl group has higher priority than the formyl group. Hence, two obviously very different compounds would have the same recommended name, 3-*O*-acetyl-5-*O*-formylquinic acid, as below. Nomenclature software will always suggest this numbering.





To avoid this problem the original numbering of the quinic acid parent compound must be maintained in all quinic acid derivatives. This is a practical problem encountered with many chlorogenic acid derivatives, with lactones, produced for example during the roasting of coffee and maté,*(43, 44)* presented as a troublesome example. Following strict IUPAC rules the quinide formed from internal esterification of the IUPAC C5 OH group changes the priority of this carbon, now becoming IUPAC C3 of the lactone. Again to avoid such confusion it is recommended that the basic quinic acid numbering is maintained in all quinic acid derivatives despite flouting the IUPAC rules**,** and this approach is used throughout these notes.

The term 'chlorogenic acid' is still used, particularly by chemicals suppliers, as a synonym for Fischer and Dangschat's 3-CQA which is known in the IUPAC numbering system as 5-caffeoylquinic acid IUPAC (5-CQA IUPAC). The numbering systems for the quinic acid carbons used by Fischer and Dangshcat and that recommended by IUPAC *(4)* are illustrated below.

Non-IUPAC	**IUPAC 1976**
	
	

IUPAC and non-IUPAC numbering of 1L-1(OH),3,4/5-tetrahydroxy-cyclohexanecarboxylic acid [(–)-quinic acid].

4. Chlorogenic acids and the CIP sequence rules

The complications inherent in defining the configuration of quinic acid were addressed again in 1997 by Eliel and Ramirez,*(45)* who drew attention to two problems, inconsistencies in reference compendia, and a problem arising from the use of CIP sequence rules. The configuration of (–)-quinic acid can be defined by the use of the α,β system designed to denote the configuration of the hydroxyl substituents relative to the carboxyl. If substituents *trans* to the carboxyl are designated α, and those *cis* are designated β, then (–)-quinic acid is either 1α,3α,4α,5β or 1α,3β,4α,5α depending on which way the ring carbons are numbered. They pointed out that *Dictionary of Organic Compounds* (6th edition 1966) specifies that the *cis* hydroxyl is on C3, consistent with *Beilsteins Handbuch der Organischen Chemie* (3rd supplement 1971 and 4th supplement 1983), thus favouring 1α,3β,4α,5α. Unfortunately, *Chemical Abstracts* uses 1α,3α,4α,5β, and this is perpetuated by the RSC's Chemspider.[1] Spresiweb describes the quinic acid moiety of chlorogenic acid as 1*S*-(1'α,3'β,4'α,5'α), and presents four different structures for the same compound.[2]

Fortunately, because the hydroxyl at C1 must be *trans* to the carboxyl in any quinic acid or acyl-quinic acid it is possible to deduce which α,β system is being used even if it is not stated explicitly.

The second problem to which Eliel and Ramirez *(45)* drew attention arises from the use of the CIP sequence rules — specifically that incorrect configurational descriptors were applied to C1 and C4 of (–)-quinic acid in several reference compendia.[3]

While Eliel and Ramirez concur that using the CIP sequence rules establishes the C3 and C5 configuration as *R*, they point out that neither C1 nor C4 are centres of chirality because two of the branches attached to these atoms are identical (–CHOH for C4 and $–CH_2$ for C1). Accordingly C1 and C4 cannot be assigned an *R* or *S* priority under the CIP sequence rules as published in 1964,*(46)* but both C1 and C4 are reflection invariant and prochiral, i.e. can be converted to a chiral atom by a single modification.

Never the less, in a footnote to this paper, Eliel and Ramirez following discussion with the Dr J.E. Blackwood, editor of Chemical Abstracts, modify their opinion. They accept that (–)-quinic acid, (+)-quinic

[1] http://www.chemspider.com/Chemical-Structure.10246715.html?rid=6cb65cf3-03b5-4bae-8eb3-9696a069e9c9
[2] http://spresi.cds.rsc.org/cgi-bin/spdisp?dbtype=0001002&username=ipdefault&password=ipdefault&LOGINTYPE=ip
[3] Note that the structures in the electronic version of this paper must be viewed at high magnification in order to visualise clearly the subtle differences in configuration.

acid, (–)-*epi*-quinic acid and (+)-*epi*-quinic acid all differ in their descriptors at C1 and C4 if the sequence rule *seqcis>seqtrans* (i.e. as though the *cis* substituent had a larger atomic number than the *trans* substituent), as later proposed by Cahn *et al*.,*(47)* is utilised, amply illustrating IUPAC's opinion that the CIP system is complex in this particular application. However, the comment by Blackwood notwithstanding, Eliel and Ramirez recommended that (–)-quinic acid should be defined as 1α,3*R*,4α,5*R*-tetrahydroxycyclohexane carboxylic acid, i.e. with α defining a *trans* substituent.

If the rule *seqcis>seqtrans* as introduced in 1966 *(47)* is applied to (–)-quinic acid, then C4 is clearly *S* and C1 appears to be *R* because $–CH_2–$CHOH *wit*h *cis* OH at C3 IUPAC is deemed larger than the $–CH_2–$CHOH *wit*h *trans* OH at C5 IUPAC. Accordingly (–)-quinic acid becomes 1*R*,3*R*,4*S*,5*R*, and fortuitously this designation is valid for both IUPAC and non-IUPAC numbering.

Although use of the *seqcis>seqtrans* rule apparently resolves the problem associated with (–)-quinic acid IUPAC it produces another when *muco*-quinic or *cis*-quinic acid are considered. Inversion at C3 (*muco*-quinic acid) or C5 (*cis*-quinic acid) produces isomers where C4 has two identical substituents (i.e. either both *cis* or both *trans*), and this is maintained if the substituents are extended further (i.e. to C2 and C6 which are both methylenes), and further extension brings C1 into play for each of these substituents. The analogous situation occurs with *neo*-quinic acid (inverted at C3 and C4) and *scyllo*-quinic acid (inverted at C4 and C5).

However, in these four compounds, C3 and C5 never have the same CIP designation, i.e. one is R and the other is *S*. Accordingly, this complication can be accommodated by invoking the rule that '*a ligand with the descriptor* R *has priority over its enantiomorph with the descriptor* S'.*(47)*

Inversion only at C4 ((–)-*epi*-quinic acid) reverses the *cis* and *trans* substituents relative to C4 in (–)-quinic acid but because the position from which the substituents are observed also changes, the nett result is no change and (–)-*epi*-quinic acid has the same description as (–)-quinic acid, creating another complication. Corse and Lundin also noted this anomaly and circumvented it by incorporating the Maquenne fractional formula into the name, thus describing (–)-quinic acid IUPAC as '*(1*R*;3*R*:4S;5*R*)-3/1,4,5-*

tetrahydroxycyclohexane-1-carboxylic acid'[4] and then state '*(–)*-epi-*quinic acid is probably (1*R*;3*R*:4*S*;5*R*)-3,4/1,5-tetrahydroxycyclohexane-1-carboxylic acid*',*(41)* but unfortunately using non-IUPAC numbering.

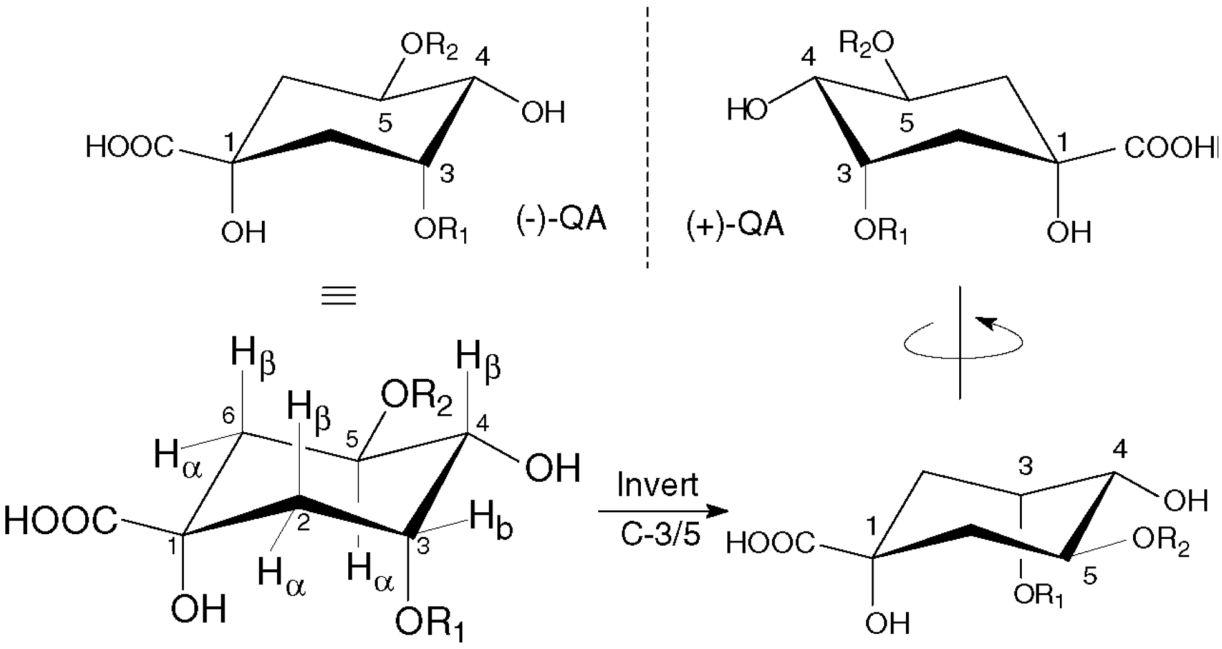
With IUPAC numbering (–)-quinic acid becomes (1*R*,3*R*,4*S*,5*R*)-5/1,3,4-tetrahydroxycyclohexane-1-carboxylic acid and (–)-epi-quinic acid is (1*R*,3*R*,4*S*,5*R*)-4,5/1,3-tetrahydroxycyclohexane-1-carboxylic acid.

Inversion at C1 yielding (+)-quinic acid reverses the description at C1 and C4 leading to 1*S*,3*S*,4*R*,5*S* and this appears to be the description also for (+)-*epi*-quinic acid, and there does not seem to be a CIP rule to resolve the (+)- and (–)-enantiomers.

At this point it seems appropriate to draw attention to a comment made by Pauli *et al*,*(48)* as follows:

'*Although covered by a 1976 IUPAC recommendation, the ring numbering scheme and therefore the relative stereochemistry of the caffeoyl quinic acids can easily cause stereochemical confusion. Therefore, it should be noted that the formula drawing of the (+)-enantiomer of the naturally occurring (–)-quinic acid (QA) turns out to be identical to the structure obtained after inversion of the chirality at both centers C-3 and C-5. Consequently, because the revised IUPAC and the old numbering scheme only differ in the numbering of these two centers, their parallel use even in the most recent literature is equivalent to an improper distinction of enantiomers which cannot be achieved by non-chiral NMR*'.

[4] Note that there is a typographical error in the paper by Corse and Lundin with the carboxyl of (–)-quinic acid described as at C3 rather than C1 as correctly given by them for (–)-*epi*-quinic acid.



1 chlorogenic acid (R_1 = H, R_2 = *trans* caffeic acid)

2 neochlorogenic acid (R_1 = *trans* caffeic acid, R_2 = H)

3 quinic acid (R_1 = R_2 = H)

This figure is taken from Pauli *et al.,* 1999 who use IUPAC numbering and α to denote a substituent *trans* to the carboxyl.*(48)*

Conclusions regarding the adequacy of the CIP rules and other nomenclature systems

After careful consideration we have concluded that none of the existing systems provide an unambiguous description that can be applied to the eight quinic acids and their acyl derivatives. Our reasoning is set out below.

1) **In the cases of L and D quinic acids or L and D *epi*-quinic acids (i.e., in the case of ones with "chiral centres")** In order to distinguish between the enantiomers, it is not sufficient to provide only the *cis/trans* orientations of the hydroxyls relative to the carboxyl because both L and D enantiomers of quinic acid are identical — 1*α*, 3*α*, 4*α*, 5*β* — if IUPAC numbering is applied.

   Similarly, both L and D enantiomers of *epi*-quinic acid are identical 1*α*, 3*α*, 4*β*, 5*β* — if IUPAC numbering is applied.

   To enable these enantiomers to be distinguished it is necessary to apply the CIP descriptors to the *meta*-hydroxyls (i.e C3 and C5) which in the case of L-enantiomers are both *R* and in the case of D-enantiomers are both *S.*

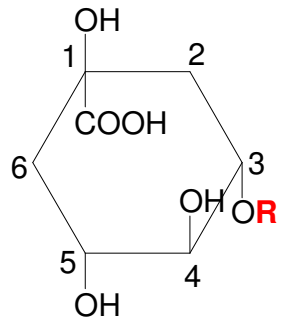
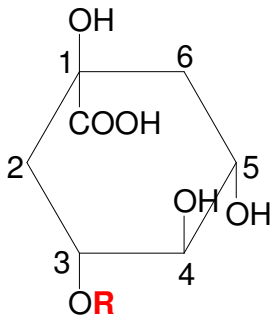
2) **In the case of *meso* forms** (*cis*-quinic acid, *muco*-quinic acid, *scyllo*-quinic acid and *neo*-quinic acid) **the indication of the *cis/trans* orientations of the OH groups relative to the COOH group is sufficient to distinguish between all species, but not if they are asymmetrically substituted because this creates new *R / S* enantiomers.**

   For the avoidance of doubt the asymmetrical derivatives would include 3-acyl and 5-acyl derivatives, and 3,5-diacyl derivatives where two different acyl residues are present. Further examples are given in section 7.3.

   If such acyl derivatives were synthesized from 1L-(–)-quinic acid the derivative would have a negative rotation, but if synthesized from 1D-(+)-quinic acid would have a positive rotation. The position of acylation would then be defined by the 1976 IUPAC rule applied to the precursor:

"…when the formula is drawn in a way that the substituent (i.e. OH group) on the lowest numbered asymmetric carbon atom is above the plane of the ring, and the numbering is clockwise, the compound is L; if anti-clockwise, it is D",

but the 3-acyl-*meso*-quinic acid prepared from 1L-(–)-quinic acid would appear to be very different from the 3-acyl-*meso*-quinic acid prepared from 1D-(+)-quinic acid, see below, when in fact they should be a pair of enantiomers. This is exactly the problem encountered and discussed by Corse and Lundin,*(41)* in connection with chemical synthesis.

	
3-Acyl derivative prepared from 1L-(–)-quinic acid	3-Acyl derivative prepared from 1D-(+)-quinic acid

Accordingly, a convention must be defined so that a *meso*-quinic acid, whether or not it is substituted, is numbered independently of its actual or perceived precursor. Corse and Lundin favoured the Maquenne system, but that uses non-IUPAC numbering and therefore we suggest;

"Clockwise numbering should be used for *meso* forms, when the formula is drawn in such a way that the OH group at C1 is above the plane of the ring".

Adoption of this convention then permits distinct and unambiguous descriptions for all eight quinic acids and their acyl derivatives, as presented below:

4.1.. (±)-Quinic acid and (±)-epi-quinic acid

The minimum requirement for unambiguous description of (±)-quinic acid and (±)-epi-quinic acid is:

a) L-(–)-quinic acid 3*R*, 5*R*-(1α, 3α, 4α, 5β)

b) D-(+)-quinic acid 3*S*, 5*S*-(1α, 3α, 4α, 5β)

c) L-(–)-*epi*-quinic acid 3*R*, 5*R*-(1α, 3α, 4β, 5β)

d) D-(+)-*epi*-quinic acid 3*S*, 5*S*-(1α, 3α, 4β, 5β)

4.2. *Meso*-quinic acids

To avoid ambiguity, particularly when describing acyl-*meso*-quinic acids, a convention, such as follows, is essential:

> Clockwise numbering should be used for *meso* forms, when the formula is drawn in such a way that the OH group at C1 is above the plane of the ring.

The minimum requirement for unambiguous description of the meso-quinic acids is:

a) *muco*-quinic acid 3*S*, 5*R* (1α, 3β, 4α, 5β)

b) *cis*-quinic acid 3*R*, 5*S* (1α, 3α, 4α, 5α)

c) *neo*-quinic acid 3*S*, 5*R* (1α, 3β, 4β, 5β)

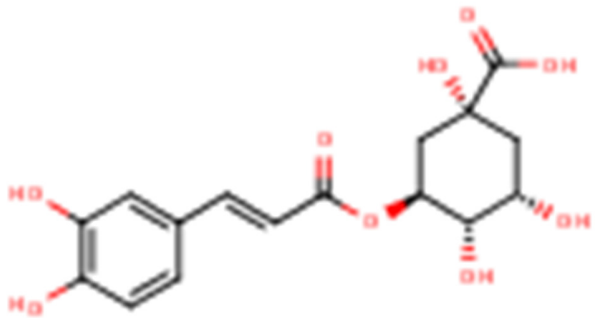
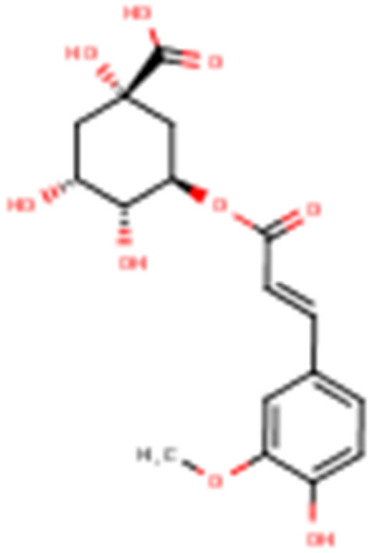
d) *scyllo*-quinic acid 3*R*, 5*S* (1α, 3α, 4β, 5α)

5. Electronic Databases and Chemicals Suppliers' Catalogues

Despite the multiple methods of describing and drawing the structure of quinic acids, acyl-quinic acids and related compounds, one would hope that any single database would use the same structure for (–)-quinic acid IUPAC on every occasion. This is patently not the case as described below.

The Phenol-Explorer database uses IUPAC numbering and provides structures for the commoner chlorogenic acids with the majority correct. There are three errors as follow:

Chlorogenic acid, i.e. 5-Caffeoylquinic acid IUPAC, is shown incorrectly as (+)-quinic acid derivative with clockwise IUPAC numbering,[5] clearly different from the other structurally related compounds in this database as shown below.

Phenol-Explorer structures for 5-caffeoylquinic acid (incorrect) and 5-feruloylquinic acid (correct)	
	
5-Caffeoylquinic acid IUPAC shown incorrectly as 5-caffeoyl-(+)-quinic acid as presented by Phenol-Explorer	**5-Feruloylquinic acid IUPAC with correct quinic acid configuration as presented by Phenol-Explorer**

[5] http://phenol-explorer.eu/compounds/475

Pseudochlorogenic acid is shown correctly as 1-CQA.[6] The structure shown for 4-*p*-coumaroylquinic acid does not explicitly show the orientation of the quinic acid carboxyl,[7] and the use of different representations of the quinic acid moiety, even when correct, only adds to confusion.

Wikipedia uses non-IUPAC numbering for 'chlorogenic acid' with an incorrect CIP description, and non-IUPAC numbering for 'neochlorogenic acid'. In contrast, IUPAC numbering is used for 'cynarine' but probably because they still believe that it is 1,5-diCQA.[8] Bizarrely, it states '*The epimer at position 1 has not yet been reported*' and cites Clifford *et al*. 2003 *(49)* in support — that paper does not use the term 'epimer', and the statement made in that publication is '*In coffee, esterification occurs at positions 3, 4, and 5 of the quinic acid moiety, but not at position 1*' and indicates that Wikipedia have confused 'epimer' and 'isomer', and have assumed that all other plants have the same chlorogenic acids profile as coffee.

Chemdraw 13.0. The ChemACX database within ChemDraw Pro 13.0 provides structures for quinic acid, shikimic acid and several caffeoylquinic and dicaffeoylquinic acids, as follows:

Quinic acid is correct for (–)-quinic acid IUPAC viewed from in front, and shikimic acid is correct for (–)-shikimic acid IUPAC viewed from behind.

3-CQA — Non-IUPAC numbering — this is 5-caffeoylquinic acid IUPAC, but orientation of C1-OH not explicitly shown.

4-CQA — This is 4-caffeoyl-(+)-quinic acid.

5-CQA — Non-IUPAC numbering — this is 3-caffeoylquinic acid IUPAC, except that the orientation of the quinic acid carboxyl is not explicitly shown.

3,4-diCQA — Non-IUPAC numbering — this is 4,5-diCQA IUPAC, but orientation of quinic acid carboxyl not explicitly shown.

3,5-diCQA — correct but orientation of quinic acid carboxyl not explicitly shown.

4,5-diCQA — Incorrect — this is 3,4-dicaffeoylquinic acid IUPAC, but orientation of quinic acid carboxyl not explicitly shown.

---

[6] http://phenol-explorer.eu/compounds/524
[7] http://phenol-explorer.eu/compounds/456
[8] https://en.wikipedia.org/wiki/Chlorogenic_acid

Dicaffeoylquinic acid — this is correct for 1,5-dicaffeoylquinic acid IUPAC, with all orientations shown.

CHEBI (**Chemical entities of biological interest**) displays 31 structures in response to a search for 'quinic'.[9]

The following structures are correct IUPAC although in some examples the orientation of the quinic acid carboxyl is not explicitly shown:

I. (–)-Quinic acid, (+)-quinic acid, (–)-quinate and 3-dehydroquinic acid
II. Chlorogenic acid (= 5-caffeoyl-(–)-quinic acid IUPAC)
III. *cis*-5-caffeoylquinic acid
IV. *trans*-4-caffeoylquinic acid
V. 3-pCoQA, 4-pCoQA and 5-pCoQA
VI. 3-SiQA, 4-SiQA and 5-SiQA
VII. 1-caffeoyl-4-deoxyquinic acid, 1,3-diCQA and 1,3,4,5-tetraCQA
VIII. 3,5-digalloyl-4-(digalloyl)-quinic acid
IX. *cis*-5-CQA
X. 3,5-dicaffeoyl-*muco*-quinic acid
XI. *trans* 4-CQA

The following structures are correct for (–)-quinic acid (L-quinic acid) derivatives except that the orientation of the quinic acid carboxyl is not shown:

I. methyl 3,5-dicaffeoylquinate
II. 3,5-diCQA
III. Theogallin
IV. Chlorogenic acid

The following structures are incorrect for the reasons given.

I. trans 5-*O*-(4-coumaroyl)-D-quinic acid is actually 5-*p*-coumaroyl-L-quinic acid
II. 4-*O*-feruloyl-D-quinate is actually 4-feruloyl-L-quinate

[9] https://www.ebi.ac.uk/chebi/advancedSearchFT.do;jsessionid=B6B2000E1835B5540C3D275EADBC8C9D

III. trans-5-*O*-caffeoyl-D-quinate is actually *trans*-3-caffeoyl-L-quinate

IV. 3-*O*-Feruloyl-D-quinic acid is actually 5-feruloyl-L-quinic acid

V. Tungtungmadic acid, i.e. 4-dihydrocaffeoyl-5-caffeoylquinic acid,*(39)* is incorrect because the orientation of the substituents is not shown.

VI. 1-caffeoyl-5-feruloylquinic acid is actually 1-caffeoyl-3-feruloylquinic acid.

The search term '*chlorogenic*' returns additionally[10] 'chlorogenate' which is presented correctly as 5-caffeoylquinate IUPAC, and 'isochlorogenic acid b' presented as 4,5-dicaffeoylquinic acid IUPAC.

Searching CHEBI for 'shikimic acid' displays 12 structures, only six of which are natural products.[11] These natural products are correct except for the structure described as '4-coumaroylshikimic acid' which is actually 5-*p*-coumaroyl-(–)-shikimic acid IUPAC.

Chemblink database returns 26 entries for the search term 'quinic'.[12] These include an entry described as D-(–)-quinic acid [13] which appears to be D-(+)-quinic acid IUPAC.

There are six entries for caffeoylquinic acids. Two for 5-caffeoylquinic acid IUPAC appear with non-IUPAC numbering and both are described as a D-quinic acid derivative. One of these is given an incorrect CIP description (1*S*,3*R*,4*R*,5*R*), and described as both 3-caffeoylquinic acid and 5-caffeoylquinic acid,[14] i.e. utilising both IUPAC and non-IUPAC numbering, although this is not explained, and the other as the hemi-hydrate, described as a D-quinic acid derivative when it should be L-quinic acid.[15] A third structure described as (–)-5-caffeoylquinic acid is actually 3-caffeoyl-(–)-*epi*-quinic acid correct for this compound, but is given the incorrect CIP description (1*S*,3*R*,4*R*,5*R*).[16] Neochlorogenic acid is shown correctly as 3-caffeoylquinic acid IUPAC but described as 5-caffeoylquinic acid and as a D-quinic acid derivative despite being given the correct CIP description (1*R*,3*R*,4*S*,5*R*).[17] Cryptochlorogenic acid [18] is shown incorrectly as 4-caffeoyl-(+)-quinic acid. 1-Caffeoylquinic acid, which is given the synonym '3,4-

[10] https://www.ebi.ac.uk/chebi/advancedSearchFT.do;jsessionid=C745BB7BB9E910D09EE1BB846488E1E8
[11] https://www.ebi.ac.uk/chebi/advancedSearchFT.do;jsessionid=7A696F8BEDD3AB82091D2FA32CB12C64
[12] http://www.chemblink.com/asp/searching.asp
[13] http://www.chemblink.com/products/77-95-2.htm
[14] http://www.chemblink.com/products/327-97-9.htm
[15] http://www.chemblink.com/products/6001-76-9.htm
[16] http://www.chemblink.com/moreProducts/more202650-88-2.htm
[17] http://www.chemblink.com/products/906-33-2.htm
[18] http://www.chemblink.com/products/905-99-7.htm

Dihydroxycinnamic acid (-)-1-carboxy-3,4,5-trihydroxycyclohexyl ester',[19] is shown correctly as 1-caffeoyl-(–)-quinic acid IUPAC except that the orientation of the C1-ester is not explicitly indicated.

Methyl-4-caffeoylquinate is presented correctly except that the orientation of the carboxyl is not explicitly indicated.[20] The structure described as methyl-3-caffeoylquinate is actually methyl-5-caffeoylquinate IUPAC except that the orientation of the carboxyl is not explicitly indicated.[21]

A structure described as 3-feruloylquinic acid[22] is 5-feruloyl-(+)-quinic acid IUPAC, whereas 4-feruloylquinic acid has an acceptable CIP description '(1α,3*R*,4α,5*R*)' and is correct for IUPAC numbering except that the orientation of the carboxyl is not explicitly shown.[23] The structure described as 3-*p*-coumaroylquinic acid is actually 3-*p*-coumaroyl-*epi*-quinic acid IUPAC, but is given the incorrect CIP description (1*S*,3*R*,4*R*,5*R*).[24]

A compound described as theogallin is actually shown as 3-galloylquinic acid IUPAC except that the orientation of the carboxyl is not explicitly shown.[25] A structure described as 5-*O*-galloylquinic acid is actually 3-galloylquinic acid, but confusingly it is given the synonym '3,4,5-Trihydroxybenzoic acid (1R,2S,3R,5R)-5-carboxy-2,3,5-trihydroxycyclohexyl ester',[26] i.e. with priority given to the ester rather than the free carboxyl. A compound described as 4-galloylquinic acid is shown with the correct IUPAC structure except that the orientation of the carboxyl is not explicitly shown, but is given confusingly the synonym '[1S-(1alpha,2alpha,4alpha,6beta)]-3,4,5-Trihydroxybenzoic acid 4-carboxy-2,4,6-trihydroxycyclohexyl ester',[27] i.e. with priority given to the ester rather than the free carboxyl.

There are two structures for cynarin in this database. One presents this molecule incorrectly as 1,4-dicaffeoylquinic acid as viewed from behind and without the orientation of the C1 ester explicitly shown,[28] when it should be 1,3-dicaffeoylquinic acid IUPAC. The other is described as 1,3-

[19] http://www.chemblink.com/products/1241-87-8.htm
[20] http://www.chemblink.com/products/123372-74-7.htm
[21] http://www.chemblink.com/products/123483-19-2.htm
[22] http://www.chemblink.com/products/1899-29-2.htm
[23] http://www.chemblink.com/products/2613-86-7.htm
[24] http://www.chemblink.com/moreProducts/more1899-30-5.htm
[25] http://www.chemblink.com/asp/searching.asp
[26] http://www.chemblink.com/products/53584-43-3.htm
[27] http://www.chemblink.com/asp/searching.asp
[28] http://www.chemblink.com/products/1182-34-9.htm

dicaffeoylquinic acid [29] but is actually 1,5-dicaffeoyl-quinic acid IUPAC without he orientation of the carboxyl explicitly shown. However, the CIP description (1*R*,3*R*,4*S*,5*R*) is correct for a (–)-quinic acid IUPAC derivative. A structure described as 1,3-dicaffeoylquinic acid, but not as cynarin,[30] is actually correct for 1,5-dicaffeoylquinic acid IUPAC.

A compound described as 'Isochlorogenic acid A' has the correct structure for 3,5-dicaffeoylquinic acid IUPAC except that the carboxyl orientation is not explicitly indicated.[31] The compound described as both '(–)-3,5-dicaffeoylquinic acid' and as '(E,E)-3,5-dicaffeoylquinic acid' is actually 3,5-dicaffeoylquinic acid IUPAC without the orientation of the carboxyl being indicated.[32]

Two compounds are described as 'Isochlorogenic acid c = 4,5-dicaffeoylquinic acid'. Both are correct for 3,4-dicaffeoylquinic acid IUPAC,[33] but viewed from different perspectives,[34] and both have substituents for which the orientation is not explicitly shown.

A compound described as 3,4,5-trigalloylquinic acid fails to define the orientation of either substituent at C1.[35] Compounds described as 1,3,5-tricaffeoylquinic acid and given the confusing synonym '(1alpha,3R,4alpha,5R)-1,3,5-Tris[[3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]-4-hydroxy cyclohexanecarboxylic acid' [36] and 3,4,5-tricaffeoylquinic acid which is given the confusing synonym '3,4,5-Tri-O-caffeoylquinic acid; (1alpha,3R,4alpha,5R)-3,4,5-Tris[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]-1-hydroxycyclohexanecarboxylic acid' [37] are correct for IUPAC numbering except that the latter does not explicitly define the orientation of the carboxyl.

[29] http://www.chemblink.com/products/19870-46-3.htm
[30] http://www.chemblink.com/asp/searching.asp
[31] http://www.chemblink.com/products/2450-53-5.htm
[32] http://www.chemblink.com/products/89919-62-0.htm
[33] http://www.chemblink.com/products/57378-72-0.htm
[34] http://www.chemblink.com/products/32451-88-0.htm
[35] http://www.chemblink.com/asp/searching.asp
[36] http://www.chemblink.com/products/1073897-80-9.htm
[37] http://www.chemblink.com/products/86632-03-3.htm

The search term 'shikimic' returns six entries,[38] but only three relate to natural products relevant to this review, i.e. (–)-3-dehydroshikimic acid,[39] (–)-shikimic acid (3*R*,4*S*,5*R*) [40] and ethyl shikimate,[41] all three are correct IUPAC structures.

Chemical Book database returns 24 substances in response to a search for 'quinic', including the unrelated quinicine and quinicardine.[42] Structures are shown for only 11 of the remaining 22 chlorogenic acids.

Quinic acid is shown correctly although the orientation of the carboxyl is not explicitly shown.
Chlorogenic acid is shown correctly as 5-caffeoylquinic acid IUPAC in three entries albeit one is viewed from behind.
Cryptochlorogenic acid is shown correctly as 4-caffeoylquinic acid IUPAC, albeit it viewed from behind and without the orientation of the carboxyl explicitly shown.

3,4-Dicaffeoylquinic acid is shown as 4,5-dicaffeoylquinic acid IUPAC. Cynarin is shown correctly as 1,3-dicaffeoylquinic acid IUPAC. Isochlorogenic acid A is shown as 3,5-dicaffeoyl-(–)-quinic acid IUPAC although the carboxyl orientation is not explicitly shown

Neochlorogenic acid is shown incorrectly as 3-caffeoylquinic acid.

A search for 'shikimic' returns 15 entries.[43] Two show the correct structure for (–)-shikimic acid IUPAC, one of which is viewed from behind.

[38] http://www.chemblink.com/asp/searching.asp
[39] http://www.chemblink.com/moreProducts/more2922-42-1.htm
[40] http://www.chemblink.com/products/138-59-0.htm
[41] http://www.chemblink.com/products/101769-63-5.htm
[42] http://www.chemicalbook.com/Search_EN.aspx?keyword=quinic
[43] http://www.chemicalbook.com/Search_EN.aspx?keyword=shikimic&start=0

RSC's Chemspider uses the IUPAC numbering for chlorogenic acid = 5-CQA.[44] Two structures are offered for cryptochlorogenic acid, one designated (+)-cryptochlorogenic acid,[45] and the other (–)-cryptochlorogenic acid,[46] the first of which is 4-caffeoyl-(+)-quinic acid incorrectly described as 1*R*,3*S*,4*R*,5*S*, and the second 4-caffeoyl-(–)-quinic acid incorrectly described as *1S*,*3R*,4*S*,5*R*. The logic behind this is unclear. Naturally occurring cryptochlorogenic acid = 4-CQA IUPAC is an ester of (–)-quinic acid and the ester has a specific rotation reported as [–53.6°] 2% in H_2O at 25°C,*(50)* or [–60.3°] 0.1% in MeOH at 20°C.*(51)* Data for 4-caffeoyl-(+)-quinic acid have not been located.

Neochlorogenic acid = 3-CQA is shown correctly and correctly described as 1*R*,3*R*,4*S*,5*R*,[47] but Chemspider for Cynarin shows both IUPAC, i.e. 1,3-diCQA correctly described as 1*R*,3*R*,4*S*,5*R*,[48] and non-IUPAC, i.e. 1,5-diCQA incorrectly described as1*S*,3*R*,4*R*,5*R*.[49] It also shows the IUPAC numbering for 3,5-dicaffeoylquinic acid (but for this isomer it is also the non-IUPAC numbering) describing it acceptably as *3R,5R* but then erroneously gives 3,5-dicaffeoyl-*epi*-quinic acid as a synonym.[50]

PubChem offers three entries for quinic acid, using 3*R*,5*R* to describe both L-quinic acid and D-quinic acid, this latter incorrect, followed by D-quinic acid presented correctly as 3*S*,5*S*.[51]

The search term 'caffeoylquinic acid' returns 39 entries, including chlorogenic acid, cryptochlorogenic acid, isochlorogenic acid, neochlorogenic acid and several dicaffeoylquinic acids, tricaffeoylquinic acids, caffeoyl-feruloylquinic acids and alkyl esters.[52] There is a mix of IUPAC and non-IUPAC numbering, non-standard use of trivial names, e.g. 'isochlorogemic acid' is shown with the synonym 5-caffeoylquinic acid

[44] http://www.chemspider.com/Chemical-Structure.1405788.html?rid=d857a37b-8dfe-4c60-93bc-a10f93fa8c78
[45] http://www.chemspider.com/Chemical-Structure.23359985.html?rid=2294f429-f4a2-42b3-8062-7f998c51ea51&page_num=0
[46] http://www.chemspider.com/Chemical-Structure.22912773.html?rid=2294f429-f4a2-42b3-8062-7f998c51ea51&page_num=0
[47] http://www.chemspider.com/Chemical-Structure.4444237.html?rid=9f5db48e-7175-4ff6-8ca4-04d61f807f61
[48] http://www.chemspider.com/Chemical-Structure.4445082.html?rid=f08b6a3f-3d24-49d0-8160-ce98113b5dd7&page_num=0
[49] http://www.chemspider.com/Chemical-Structure.4976555.html?rid=f08b6a3f-3d24-49d0-8160-ce98113b5dd7&page_num=0
[50] http://www.chemspider.com/Chemical-Structure.22912767.html?rid=44d4b315-a438-40a6-9951-65c03544d816
[51] https://www.ncbi.nlm.nih.gov/pccompound?term=quinic%20acid
[52] https://www.ncbi.nlm.nih.gov/pccompound

and the IUPAC name 3-caffeoylquinic acid. CIP descriptors include (3*R*,5*R*), (3*S*,5*S*), (1*S*,3*R*,4*R*,5*R*), (1*R*,3*R*,4*S*,5*R*) and (1*R*,3*S*,4*S*,5*S*).

The search term 'cynarin' returns eight entries with various combinations of 1,3-dicaffeoylquinic acid, 1,4-dicaffeoylquinic acid, 1,5-dicaffeoylquinic acid, and 'artichoke extract', two structures with one *cis* and one *trans* caffeic acid residue, and another shown bizarrely as the 1,4-dicaffeoyl derivative of 1α,2β,3α,4α-tetrahydroxycyclohexane carboxylic acid.[53]

The correct configuration is shown for 3,5-dicaffeoyl-*muco*-quinic acid, but this optically inactive meso compound is described as (–).[54]

Chemexper lists 139 suppliers of quinic acid, the vast majority of whom describe their product as either quinic acid, D-quinic acid or D-(–)-quinic acid, with a further substantial proportion using 1,3,4,5-tetrahydroxycyclohexane carboxylic acid, or some combination thereof. Other descriptions are:

a. one supplier (biomolekula) uses the correct prefix 1*R*,3*R*,4*S*,5*R*
b. one supplier (Molepedia) uses the acceptable prefix 1α,3*R*,4α,5*R*
c. two suppliers (scbt and manchester organics) use the acceptable prefix 3*R*,5*R*
d. two suppliers (azrsci and amadischem) use the prefix 3*R*
e. one supplier (chemicalpoint) incorrectly uses 1*R*,3*R*,4*R*,5*R*-(–)-quinic acid
f. three suppliers (zerenxmolecular, ibscreenBB and vitasmlabSTK) use the prefix 1S,3R,4S,5R which corresponds to *neo*-quinic acid
g. one supplier (vitasmlabBBL) uses the prefix 3R,5R racemate, and
h. one supplier (raise-chem) describes their product as cis/muco-(1α,3α/β,4α,5α/β)-quinic acid

Descriptions 'g' and 'h' are puzzling.

Chemexper also lists:

82 suppliers for what is apparently 1*S*,3*R*,4*S*,5*R* *trans* 5-CQA IUPAC,[55] which corresponds with a *neo*-quinic acid derivative;

[53] https://pubchem.ncbi.nlm.nih.gov/compound/6537500#section=Top
[54] https://pubchem.ncbi.nlm.nih.gov/compound/6475855#section=Top
[55] http://www.chemexper.com/search/cas/906332.html

259 suppliers for chlorogenic acid that is apparently 1*S*,3*R*,4*R*,5*R trans* 5-CQA IUPAC:[56]

66 suppliers for cryptochlorogenic acid or 4-CQA IUPAC: and

39 suppliers for 1-CQA IUPAC of unknown chirality.

Bizarrely, the search term 'caffeoylquinic acid' also returns 129 suppliers of the terpene l-carvone, but fails to find neochlorogenic acid. A specific search using neochlorogenic acid returns 82 suppliers, displays the correct IUPAC regio-isomer (3-CQA) with 1*R*,3*R*,4*S*,5*R* configuration,[57] but subsequently lists 12 of the offerings as 5-CQA, one as chlorogenic acid, and bizarrely six offerings of ethyl 2-(4-hydroxy-phenoxy)acetate.

The search term 'dicaffeoylquinic acid' returns 86 entries and displays, correctly, the structure of 1,3-diCQA IUPAC.[58] Further inspection reveals that 32 offerings are described only as cynarin(e), 25 as 1,5-diCQA, 17 as 1,3-diCQA, four as 'artichoke extract' and one as 'isochlorogenic acid A 3',5'' apparently identifying it as 3,5-diCQA.

The search term 'isochlorogenic acid' returns the structure of 5-CQA IUPAC with the incorrect configuration 1*S*,3*R*,4*S*,5*R*.[59] The 16 entries include six for isochlorogenic acid, three for isochlorogenic acid A. The trivial name 'isochlorogenic acid' was originally applied to a dicaffeoylquinic acid — see Table 1.

The search term 'tricaffeoylquinic acid' returns structures for 3,4,5-triCQA IUPAC (24 suppliers)[60] and 1,3,5-triCQA IUPAC (five suppliers),[61] and isochlorogenic acid C (65 suppliers)[62] many of whose offerings are described as either 4,5-diCQA or 3,4-diCQA possibly, but not certainly, depending on which numbering

[56] http://www.chemexper.com/search/cas/327979.html
[57] http://www.chemexper.com/search/cas/906332.html
[58] http://www.chemexper.com/search/cas/30964137.html
[59] http://www.chemexper.com/search/cas/534612.html
[60] http://www.chemexper.com/search/cas/86632033.html
[61] https://www.chemexper.com/searchResult.shtml?format=ccd2013%2Cccd&target=structure&options=brandqtyoffercrm&i=ee2f0c&country=GB&searchTemplate=rn.value%3D%22%3F%22+elsor+iupac.value%3D%22%3F%22+elsor+mol.value%3D%22%3F%22+elsor+mol.value%3D~%22%3F%22+elsor+uniqueMolInfo.inchi%3D%22%3F%22+elsor+uniqueMolInfo.inchikey%3D%22%3F%22+elsor+mf.value%3D%22%3F%22+elsor+entry.catalogID%3D%22%3F%22+elsor+%28iupac.value%3D~%22%3F%22+or+catalog.description%3D~%22%3F%22%29&searchValue=tricaffeoylquinic+acid&Search=
[62] http://www.chemexper.com/search/cas/32451880.html

system they favour. The trivial name 'isochlorogenic acid C' was originally introduced to describe a dicaffeoylquinic acid — see Table 1.

The Merck Index Online shows (–)-quinic acid, cynarin(e) = 1,3-diCQA and Chlorogenic acid = 5-CQA correctly.[63]

Spresiweb describes (–)-quinic acid correctly as 3*R*,5*R* but incorrectly as D-(–)-quinic acid.[64] Cynarin(e) is described merely as 1,4-dicaffeoylquinic acid,[65] i.e. using the incorrect assignment given in 1954 *(6)* to what is now recognised as 1,3-diCQA IUPAC.

ADC Labs purport to give structures and IUPAC names. In this database quinic acid is described incorrectly as (1*S*,3*R*,4s)-1,3,4,5-tetrahydroxycyclohexane carboxylic acid (not sure whether their use of the lower case 's' is intentional or accidental),[66] and chlorogenic acid as 3-CQA with the quinic acid moiety incorrectly as 1*S*,3*R*,4*R*,5*R*,[67] and cynarin(e) as 1,3-diCQA with the quinic acid moiety described correctly as 1*R*,3*R*,4*S*,5*R*.[68] The structure for cynarin is correct but the orientation of the C1 ester is not explicitly shown. Unfortunately, the same structure is shown for 1,5-dicaffeoylquinic acid.

Sigma–Aldrich describe the quinic acid moiety of cynarin (IUPAC 1,3-diCQA) correctly as 1*R*,3*R*,4*S*,5*R*.[69] They show a correct structure for 1,5-diCQA but describe it incorrectly as 1*S*,3*R*,4*R*,5*R* and confusingly list 1,3-diCQA as a synonym.[70] Cynarin is correctly described as 1*R*,3*R*,4*S*,5*R*, but they give 1,3-diCQA (correct)

---

[63] https://www.rsc.org/Merck-Index/searchresults?searchterm=quinic%20acid
[64] http://spresi.cds.rsc.org/cgi-bin/spdisp?dbtype=0001002&username=ipdefault&password=ipdefault&LOGINTYPE=ip
[65] http://spresi.cds.rsc.org/cgi-bin/spdisp?dbtype=0001002&username=ipdefault&password=ipdefault&LOGINTYPE=ip
[66] http://ilab.cds.rsc.org/?cdsrdr=1
[67] http://ilab.cds.rsc.org/?cdsrdr=1
[68] http://ilab.cds.rsc.org/?cdsrdr=1
[69] http://www.sigmaaldrich.com/catalog/search?term=Cynarin&interface=Product%20Name&N=0+&mode=mode%20matchpartialmax&lang=en&region=GB&focus=productN=0%20220003048%20219853286%20219853121
[70] http://www.sigmaaldrich.com/catalog/substance/15dicaffeoylquinicacid516451987046311?lang=en&region=GB

and 1,5-diCQA (incorrect) as synonyms.[71] The structure shown for 3,4-diCQA is actually 4,5-diCQA IUPAC.[72] Unsurprisingly, 3,5-diCQA has the correct structure, but then this is the same for both IUPAC and non-IUPAC numbering.[73]

Four products listed as Chlorogenic acid are shown with the correct 5-CQA IUPAC structure, but are described as 3-CQA. Similarly, two products listed as neochlorogenic acid have the 3-CQA IUPAC structure but are listed as 5-CQA, but cryptochlorogenic acid diCQA has the correct structure and regio-isomer description, but then this is the same for both IUPAC and non-IUPAC numbering. [74]

[71] http://www.sigmaaldrich.com/catalog/substance/cynarin516453096413711?lang=en&region=GB
[72] http://www.sigmaaldrich.com/catalog/product/sigma/smb00224?lang=en&region=GB
[73] http://www.sigmaaldrich.com/catalog/product/sigma/smb00131?lang=en&region=GB
[74] http://www.sigmaaldrich.com/catalog/search?term=Quinic+acid&interface=Product%20Name&N=0&mode=mode%20matchpartialmax&lang=en&region=GB&focus=productN=0%20220003048%20219853286%20219853121

6. Examples from the published literature of confusion regarding numbering and configuration

An inspection of nearly 1100 publications concerned with the botanical distribution of chlorogenic acids has located *ca* 40 that clearly do not use the IUPAC numbering system, and another 30 or so where it was impossible to judge which numbering system was used, making the information therein of limited value, and confusing to the uninitiated. Some publications use both.

6.1. Demirkiran *et al* present a structure for chlorogenic acid with non-IUPAC numbering but then refer to chlorogenic acid as 5-caffeoylquinic acid, which is correct only if the IUPAC numbering is used.*(52)*

6.2. Ling *et al* use non-IUPAC numbering for chlorogenic acid, i.e. shown as 3-CQA, but IUPAC numbering for 4,5-diCQA and 3,4-diCQA.*(53)*

6.3. Although Plazonic *et al.* clearly use the IUPAC numbering system, the authors describe the only commercial chlorogenic acid used as 3-CQA,*(54)* and with IUPAC numbering this should be 5-CQA.

6.4. Pavlovic *et al.* extracted the aerial flowering parts of *Anthemis triumfetti* L. DC and characterised the chlorogenic acids by NMR, which data were compared with previously published data. They reported 5-CQA, 3,5-diCQA and 3,4-diCQA.*(55)* The identity of the putative 3,4-diCQA is uncertain because the authors compare their data with data from Morishita *et al., (56)* who did not use IUPAC numbering, and Iwai *et al., (57)* who used IUPAC numbering, and Pavlovic *et al*. do not appear to be aware of these differences.

6.5. Yan *et al*. reported 4,5-dicaffeoyl-*iso*-quinic acid in *Artemisia iwayomogi*,*(58)* but did not provide any physical data for this unusual compound. The structures shown in the original paper have the IUPAC structure but in the text the latter is inconsistently described as 3,4-dicaffeoyl-*iso*-quinic acid.

6.6. Farag *et al*. using LC–QTOF-MS reported 3-CQA, 5-CQA, 1,3-diCQA and 3,5-diCQA in *Chrysanthemum pacificum* Nakai.*(59)* The authors appear to use IUPAC numbering in the text (chlorogenic acid is described as 5-CQA) but show structures using non-IUPAC numbering.

6.7. Jang *et al*. reported the isolation of several chlorogenic acids including the unusual 3,5-dicaffeoyl-*epi*-quinic acid from the leaves of *Erigeron annuus*, but they show the structure as 3,5-dicaffeoylquinic acid, and do not use IUPAC numbering.

6.8. De Souza *et al*. reported several chlorogenic acids, including 4,5-dicaffeoylquinic acid, in the flowers of *Senecio brasiliensis* (Spreng) Less,*(60)* but show this compound as having the C1 and C5 hydroxyls axial and the C3 and C4 hydroxyls equatorial suggesting that they have used non-IUPAC numbering, and that this component should be 3,4-diCQA IUPAC.

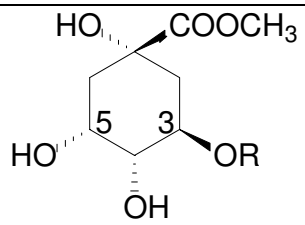
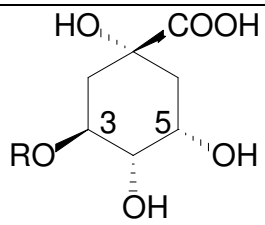
6.9. Becerra-Herrera *et* al. using positive ion LC–MS reported that 3-CQA exceeded 5-CQA in the fruits of *Lonicera oblongifolia*.*(61)* Although the structures shown follow IUPAC numbering, the chromatograms presented have the putative 5-CQA eluting before the putative 3-CQA suggesting that either the chromatogram has been wrongly annotated, or annotated using non-IUPAC numbering.

6.10. Yingngam *et al*. report the isolation from the leaves of *Cratoxylum formosum* ssp. *formosum* of 5-CQA and its characterisation using LC–MS and comparison with a commercial standard.*(62)* However, the structure shown corresponds to 3-CQA IUPAC but the mass fragmentation presented corresponds to 5-CQA IUPAC and it is not clear which is correct.

6.11. Truong *et al*. reported 5-CQA, 3,4-diCQA, 3,5-diCQA and 4,5-diCQA in the leaves, peel and roots of sweet potatoes *(63)* Although the structures used by Truong *et al.* clearly follow the IUPAC numbering, the sequence of elution of the diCQA suggests that the assignments of the diCQA standards used for identification have been described using non-IUPAC numbering.

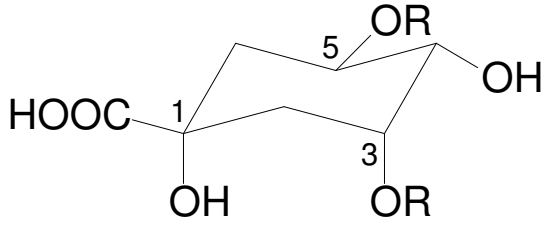
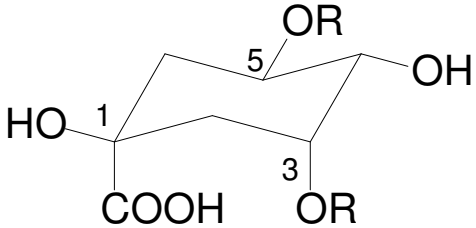
6.12. Chen *et al*. reported methyl 3-caffeoylquinate and 'chlorogenic acid' in the calyces of *Physalis alkekengi*.*(64)* However, the structure of the putative methyl 3-caffeoylquinate has the configuration 1α,3β,4α,5α — i.e. C3 hydroxyl *cis* to the carboxyl if the cyclohexane ring is numbered clockwise (see below). This is correct for (–)-quinic acid if non-IUPAC numbering is used, making it methyl 5-caffeoylquinate IUPAC.

The structure shown for 'chlorogenic acid' can only have the same configuration if the cyclohexane ring as presented in their paper is numbered anti-clockwise. It appears that the authors have either allocated the lowest possible number to the carbon bearing the acylated hydroxyl, or used the system where *cis* precedes *trans*, but either way resulting in two very different compounds (leaving aside whether or not one is a methyl ester) having the same notation applied to different carbons.

	
Methyl-3-caffeoylquinate as shown. The configuration 1α,3β,4α,5α shown is only correct if clockwise non-IUPAC numbering is used	Chlorogenic acid as shown. The configuration 1α,3β,4α,5α is only correct if anti-clockwise IUPAC numbering is used

6.13. Ko *et al.* isolated 3,5-diCQA and 3,5-dicaffeoyl-*epi*-quinic acid from extracts of *A. subulatus* Michx. and characterised them by NMR but did not report their spectral data.*(65)* The authors stated, '*Both the epimers differ in their structures only at C-1 configuration*'. Their structures are presented below with R substituted for the caffeoyl residue. The structure described as 3,5-dicaffeoylquinic acid is correct for IUPAC numbering with the quinic acid configuration 1α,3α,4α,5β where α specifies a substituent *trans* to the carboxyl.

The structure presented by Ko *et* al. for the putative 3,5-dicaffeoyl-*epi*-quinic acid has the configuration 1α,3β,4β,5β for its quinic acid moiety which corresponds to *neo*-quinic acid. The quinic acid moiety of 3,5-dicaffeoyl-*epi*-quinic acid would have the configuration 1α,3α,4β,5β. For the authors' statement, '*Both the epimers differ in their structures only at C-1 configuration*' to be true would require the structure for the *epi*-quinic acid derivative to be numbered using the non-IUPAC system.

	
3,5-dicaffeoylquinic acid IUPAC 1α,3α,4α,5β	Putative 3,5-dicaffeoyl-*epi*-quinic acid 1α,3β,4β,5β = 3,5-dicaffeoyl-*neo*-quinic acid

6.14. Lai *et al*. reported 5-CQA, 3,5-diCQA and 3,5-dicaffeoyl-4-succinoylquinic acid**,** 1,3-diCQA and 4,5-diCQA in *Chrysanthemum coronarium*,*(66)* presenting the structures with some cinnamic acid residues in the *cis* configuration. Additionally, they show the quinic acid moiety with the configuration 1α,3β,4α,5β which is not correct for (–)-quinic acid whichever numbering system is used. The quinic acid commonly encountered has the configuration 1α,3α,4α,5β IUPAC — 1α,3β,4α,5β as used by Lai *et al* corresponds to *muco*-quinic acid.

6.15. In what is otherwise an excellent review, Lin and Harnly *(67)* inexplicably present (–)-quinic acid in its carboxy-equatorial conformer using IUPAC numbering but alongside it appear to present *epi*-quinic acid in its carboxy-axial conformer using non-IUPAC numbering. However, later in the text they refer to this as '1-*epi*-quinic acid, (i.e 1 D-OH)', presumably meaning D-quinic acid or (+)-quinic acid IUPAC. They comment that this is very rare, citing two papers.(Clifford *et al*., 2007 and Kim and Lee, 2005)*(68, 69)* The paper by Clifford *et al*. reports that derivatives of *epi*-quinic acid (meaning the C4 epimer) were not detected in *Chrysanthemum* extracts whereas Kim and Lee had reported 3,5-dicaffeoyl-*epi*-quinic acid and 1,3-dicaffeoyl-*epi* quinic acid in such extracts. The structure presented by Lin and Harnly is a faithful reproduction of the structure presented by Kim and Lee, but it cannot be the carboxy-axial conformer of D-quinic acid (or L-quinic acid) because in both of those diastereomers the C4-OH must be axial in the carboxy-axial conformer — see Table 5. The NMR data presented by Kim and Lee, and from which they deduce this structure, is discussed in Part 2 of these notes, where it is found not to be convincing.

6.16. Ping *et al*. isolated three methyl dicaffeoylquinates from *Bidens* and clearly use the IUPAC numbering system for the structures of methyl 3,5-dicaffeoylquinate and methyl 4,5-dicaffeoylquinate. The structure presented for the third isomer is quite different with the configuration 1α,3α,4β,5β corresponding to methyl 3,4-*epi*-quinate.*(70)* This feature is not discussed by the authors. Although the NMR data are incomplete, with some ^{3}J values not available, the data for H4 are typical of (–)-quinic acid and not consistent with *epi*-quinic acid.

The failure to define which system of numbering is used in a publication, or worse, to use both indiscriminately in the same publication, or to use inconsistent structures, can only lead to greater confusion, but in view of the confusion and conflict in on-line databases and suppliers' catalogues, such a situation is almost inevitable. We hope that our notes above and the associated recommendations will help to resolve these problems

7. The extended Chlorogenic Acids Family

The plural term 'chlorogenic acids' (CGA) is increasingly used to embrace an extended family of structurally and biosynthetically related naturally-occurring compounds.

7.1. The acyl moiety

While the majority of reports currently refer to those acyl quinic acids synthesised *in planta* by esterification of a *trans*-hydroxycinnamic acid such as caffeic, ferulic, *p*-hydroxycinnamic acid (**1–3**) with (–)-quinic acid **29**, *cis* isomers are increasingly reported, as are the less common cinnamic acids (**4–10**),*(71-75)* and the saturated dihydrocinnamic acid derivatives (**11–12**)*(34, 76, 77)* which may have a side chain hydroxyl (**13**)*(78)* or methoxyl (**14**)*(79)* substituent. For structures see Table 2.

There are also C_6–C_2 (phenylacetyl) (**29**) *(80)* and C_6–C_1 (benzoyl) (**20–28**) analogues *(29, 81-86)* and aromatic acyl residues might be accompanied by an aliphatic or hydroxy-aliphatic acyl residue (**30, 31, 33, 34, 36–38**),*(87-89)* or a hydroxy aliphatic acid methyl ester,(**32, 35**)*(90-92)*. On rare occasions an aliphatic acyl substituent of both (–)-quinic acid and (–)-shikimic acid has been observed without an aromatic acyl residue,*(75, 93, 94)* but such compounds lack the characteristic UV absorbance such compounds might easily have been overlooked. For structures see Tables 3 and 4.

Depsides also are known. Those in which the primary C_6–C_1 acyl residue is acylated by one or more further C_6–C_1 residues are quite widespread.*(95)* Those in which a hydroxy-aliphatic acyl residue is esterified with a hydroxycinnamoyl residue are less common.*(92)*

It is almost certain that many of the less common members of the extended family have been overlooked.

7.2. The quinic acid moiety

Quinic acid, apparently first reported in 1790,*(45)*, is not a single compound — it is now recognised that this term encompasses two pairs of optically active enantiomers ((±)-quinic acid (**40–41**) and (±)-*epi*-quinic acid (**42–43**)) and four diastereo-isomers, optically inactive *meso* forms (*muco*-quinic **44**, *cis*-quinic **45**, *neo*-quinic **46** and *scyllo*-quinic **47**).

Enantiomers are chiral molecules, each pair being mirror images of one another that are non-superimposable on one another. Each pair has identical physical properties. Diastereo-isomers have different physical properties. See Table 5 for structures.

Enantiomers differ only by their absolute stereochemistry (*R* or *S*, etc.). In contrast, diastero-isomers differ by their relative stereochemistry. Relative stereochemistry defines the configuration of one stereogenic centre with respect to any other stereogenic centre in the molecule.

(–)-Quinic acid **40** is the form most commonly encountered, and the only form commercially available, but often described in catalogues as D-quinic acid rather than L-quinic acid. Very rarely has the quinic acid moiety of an acyl-quinic acid been released by hydrolysis or saponification and fully characterised, e.g see *(96-99)* — accordingly, the occurrence of chlorogenic acids containing other quinic acids could have been overlooked. Cookman and Sondheimer demonstrated that the commonly encountered 3-caffeoylquinic acid, 5-caffeoylquinic acid and 5-feruloylquinic acid contained a (–)-quinic acid (L-quinic acid) IUPAC moiety,*(100)* and this is usually assumed to be the case. It has not been possible to locate any definitive reports of the natural occurrence of (+)-quinic acid (D-quinic acid) IUPAC or its derivatives, but there are some reports of its chemical synthesis.*(101)* Note that a positive specific rotation for an acyl-quinic acid refers to the behaviour of the full molecule and is not a guide to the optical activity of the quinic acid moiety.

There is unequivocal evidence for the natural occurrence in unprocessed plant material of (±)-*epi*-quinic acid (**41–42**)*(98)* derivatives in *Psiadia trinerva* where the quinic acid released by saponification did not co-chromatograph with (–)-quinic acid **40**. This apparently rare form of quinic acid has also been found by the same research group in *Scorzonera radiata,(102)* and by others in *Tessaria integrifolia*.*(103)* Although Wang *et al.* named this substance *iso*-quinic acid the deduced structure corresponds to the previously described *epi*-quinic acid.

However, note that the prefix '*epi*' applied to either quinic or shikimic acid has sometimes been used to indicate any epimer, rather than one of these specific compounds, and it is clear that such incompletely defined epimers of quinic acid occur in acylated form in *Ilex paraguariensis* (Aquifoliaceae),*(104)* *Rudbeckia hirta*, *Carlina acaulis* and *Helianthus tuberosus* (Asteraceae),*(105)* and some *Galium* spp. (Rubiaceae).*(106)* On other occasions the prefix '*epi*' is accompanied by a number identifying the carbon

atom associated with the epimer,*(107)* thus 4-*epi*-quinic acid is indeed *epi*-quinic acid as reported by Wang *et al*,*(98)* but 3-*epi*-quinic acid is *muco*-quinic acid and 5-*epi*-quinic acid is *cis*-quinic acid.

Muco-quinic acid **44** is thermodynamically the most stable quinic acid isomer. It is therefore not surprising that 3-caffeoyl-*muco*-quinic acid and 3-feruloyl-*muco*-quinic acid have been detected in roasted coffee but are not detectable in green coffee beans.*(43, 108)* A report of an acyl *muco*-quinic acid in *Asimina triloba* (Annonaceae),*(109)* should be treated as tentative because of incomplete NMR data, fully discussed in Part 2, and the observation by Haribal *et al*. that this novel compound could be produced from 5-CQA IUPAC by acyl migration.

There are some other reports of CGA containing unusual forms of quinic acid, but these must be treated as tentative at best and possibly incorrect assignments.*(58, 65, 69, 110-121)* The arguments surrounding these reports will be discussed in full in Part 2.

There are reports also of acyl derivatives of 2-hydroxy-quinic acid (1α,2α,3α,4α,5β-pentahydroxy-cyclohexanecarboxylic acid) **60** *(122-125)* and an acyl derivative of 4-deoxyquinic acid for which the configuration has not been fully assigned, but which is thought to be 1α,3α,5β-trihydroxy-cyclohexanecarboxylic acid **61**.*(126)*

In addition, an investigation of an extract from *Piper guineense* Schum and Thonn (Piperaceae) has detected 4-*O*-caffeoyl-2-*C*-methoxycarbonyl-1-*C*-methyl-2,3,6-trihydroxy-cyclohexane-carboxylic acid. *(127)* If this compound is described so as better to show its similarity to (–)-quinic acid IUPAC, then the methoxycarbonyl is attached at C1 rather than C2, and it becomes the methyl ester of 1,2,3,5-tetra-hydroxy-6-methyl-cyclohexane-1,6-dicarboxylic acid **62**. This resembles both 2-hydroxy-quinic acid (an extra hydroxyl at C2) and 4-deoxyquinic acid, (lacking a C4-hydroxyl) but with the additional carboxyl and a methyl substituent on C6.*(127)* The conformation deduced by the authors is tentative, with the C5-OH alpha rather than beta as in (–)-quinic acid. The difficulty of NMR assignment when peaks are not fully resolved is further discussed in Part 2 of these notes, and this reported configuration must be viewed as tentative.

4-*O*-caffeoyl-5-*O*-methylquinic acid has been reported in *Pteris multifidi* and the 5-*O*-methylquinic acid released as its methyl ester **63** after saponification.*(128)*

There is also a report of a derivative in which quinic acid C5 is connected to the lactic acid side chain hydroxyl of 3,4-dihydroxyphenyl-lactic acid as an ether,*(129)* rather than as an ester with the lactic acid carboxyl.

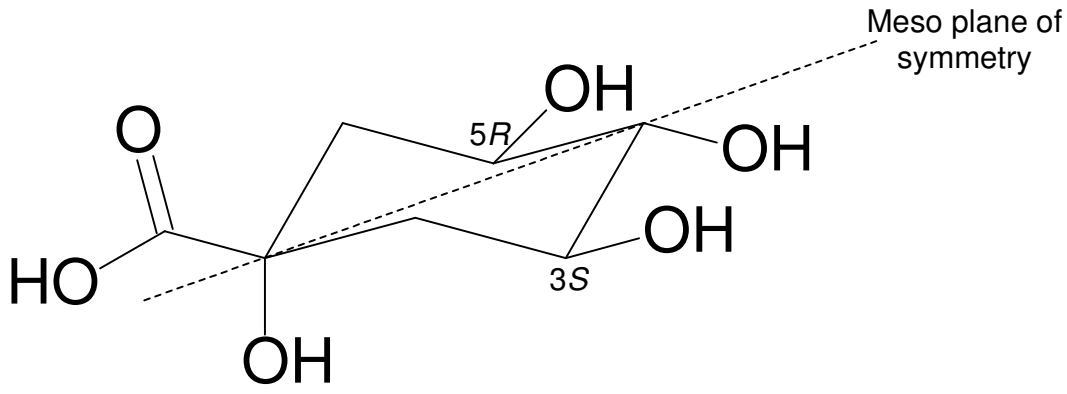
The natural occurrence of CGA incorporating various alkyl-quinates (for example methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl)*(72, 130-134)* is also well established although there is always a risk of artefacts when an alcoholic solvent is used to extract chlorogenic acids. In contrast, reports of CGA incorporating a quinic acid methyl ether are doubtful.*(135)*

The widespread occurrence of analogous acyl-shikimic acids, first reported in 1964, *(20, 72, 104)* is also well established, and acyl derivatives of a shikimic acid epimer also are known.*(105)*

7.3. ***Some notes on the meso quinic acids***

Meso quinic acids are not optically active. A single acylation, however, destroys the inherent symmetry and induces optical activity, but symmetrical di-acylation restores the meso structure. Accordingly, 3,5-dicaffeoyl-*muco*-quinic acid would be expected not to be optically active. As a consequence the report of a (–)-3,5-dicaffeoyl-*muco*-quinic acid by Kwon *et al*.*(136)* with $[\alpha]^D = -153.8°$ must be viewed as extremely doubtful. *Conceivably* hydrogen bonding might induce a small loss of symmetry, but the large specific rotation claimed is untenable.

Because of the meso plane of symmetry present in these quinic acid isomers,*(137)* see below for *muco*-quinic acid, 3-caffeoyl-*muco*-quinic acid and 5-caffeoyl-*muco*-quinic acid are a pair of enantiomers that will not resolve on typical reverse phase column packings. Likewise, 3,4-dicaffeoyl-muco-quinic acid and the 4,5-isomer, and the 1,3- and 1,5-isomers, and strictly should be referred to as 3*R* and 3*S*-caffeoyl-*muco*-quinic acid.



The analogous situation occurs with the relevant acyl derivatives of *cis*-quinic acid, *scyllo*-quinic acid and *neo*-quinic acid.

7.4. ***Some notes on the quinic lactones (quinides) and their acyl derivatives***

There are eight quinic-γ-lactones (four pairs of enantiomers) **50–53** and four quinic-δ-lactones (two meso forms (**54–55**) and one pair of enantiomers **56**). Certain of these quinides are useful intermediates in the chemical synthesis of chlorogenic acids,*(41, 50, 138)* and some have been found in roasted coffee,*(139, 140)* and roasted maté.*(44)* For structures see Table 7.

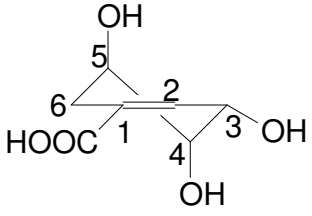
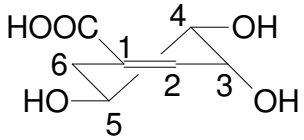
(±)-γ-Quinide dominates this fraction in roasted coffee. This is probably the (–)-enantiomer formed from the carboxy-equatorial conformer of (–)-quinic acid, but epimerization at C1 during roasting cannot be discounted. The origin of the other quinides is less clear, but probably follows epimerization of the (–)-quinic acid and ring closure of a conformer with the relevant substituents in axial conformation. If the relevant quinic acid diastereomer exists preformed then the initial epimerization is not required.*(139-141)*

Acyl γ-quinides, acyl γ-*muco*-quinides and acyl γ-*epi*-quinides have been found in roasted coffee.*(142-147)* and acyl γ-quinides have been reported in roasted maté.*(44)*

The novel 3,4-epoxy-1,5-γ-quinide **57** has been isolated from *Winchia* and characterised by NMR. *(148)*

7.5. ***Acyl-shikimic acids***

Under the IUPAC numbering system (–)-shikimic acid (L-shikimic acid) has the double bond between C1 and C2 whereas in the non-IUPAC system it was shown between C1 and C6. The presence of the double bond markedly alters the conformation relative to the quinic acids, and forces (–)-shikimic acid, the commonest natural enantiomer, to adopt two half-chair conformations as illustrated below.*(149)* There is a modest preference for the conformer in which the C4–OH and C5–OH are equatorial and the C3–OH is quasi-axial.*(150)*

The half-chair conformations of (–)-shikimic acid (L-shikimic acid) IUPAC	
	
	favoured

The full set of half chair conformations for the shikimic acid enantiomers are presented in Table 9. See Table 10 for the structures of the shikimic acid enantiomers presented so as to facilitate comparison with quinic acids.

The shikimic acid epimers seem not to have trivial names and are known as 3-*epi*-, 4-*epi*- and 5-*epi*-shikimic acids (**72–77**). These are the analogues of *muco*-, *epi*- and *cis*-quinic acid respectively.

The commonly encountered shikimic acid is (–)-3*R*,4*S*,5*R*, trihydroxy-1-cyclohexene carboxylic acid **70** and it is generally assumed that this is the form encountered in the acyl-shikimic acids that are quite widespread in nature, but less reported than the acyl-quinic acids. It is known to form galloyl-, *p*-coumaroyl- and caffeoyl-shikimates, including some di- and tri-acyl derivatives. For some isolates the shikimic acid enantiomer has been confirmed by comparison with the authentic material after release by the action of tannase,*(96, 151)* or a hydroxycinnamoylquinate esterase.*(152)*

The occurrence of a shikimic acid epimer, described as 3*S*,4*S*,5*R*-trihydroxy-1-cyclohexene carboxylic acid has been reported in *Sequoiadendron*.*(153)* While it is clear that this is an epimer, the basis of the assignment as 3*S*,4*S*,5*R*-is unclear and it does not correspond to any of the shikimic acids illustrated in Tables 9 and 10. We believe that it should be described as 3*S*,4*R*,5*R*. So far there are no known acyl derivatives thereof although a caffeoyl-*epi*-shikimic acid has been reported in *Rudbeckia hirta*,*(105)* but not fully characterised.

The three mono-acyl-*epi*-shikimic acids reported in roasted coffee have not been fully characterised.*(43)* In view of the expected greater thermodynamic stability of the 3-*epi*-shikimic acid enantiomer this might well be the form that is present in roasted coffee having formed through epimerization of existing acyl-shikimic acids, or epimerisation and dehydration of existing acyl-quinic acids, during roasting. Note, however, it is also possible that the double bond is at a different position, possibly giving rise to a (+)-enantiomer.

7.6. *Brief notes on other acyl-cyclitols*

There are limited reports of acyl-*proto*-quercitols **80** and acyl-*myo*-inositols (acyl-*meso*-inositols) **81**, penta-hydroxy- and hexa-hydroxy-cyclitols, respectively, and although these lack the carboxyl group and

arise through a different biosynthetic route, it seems appropriate to mention them briefly. These cyclitol structures are shown in Table 11.

Trans-1L-4-*p*-coumaroyl-*myo*-inositol, *trans*-1L-2-*p*-coumaroyl-*myo*-inositol and a related but incompletely characterised *cis* isomer have been reported in the genus *Taxus*.*(154-156)*

In the genus *Quercus* a series of one monogalloyl, two digalloyl-, four trigalloyl-, two tetragalloyl- and a single pentagalloyl-*proto*-quercitol plus one digalloyl-ellagoyl- and one galloyl-ellagoyl-*proto*-quercitol has been reported.*(96, 157, 158)*

Three compounds, origanine A–C, have been isolated from *Origanum vulgare* L. (Apiaceae) and characterised by extensive NMR studies. These have a core unit of 3*S*, 4*R*, 5*S*, 6*S*-1,3,4,5-tetra-carboxy-shikimic acid or 3*S*, 4*S*, 5*S*, 6*R*-1,3,5,6-tetra-carboxy-shikimic acid esterified to a variable extent with 3,4-dihydroxy-phenyl-lactic acid and / or 4-hydroxyphenylethanol.*(32)* It is not known whether or not these are related biosynthetically to (–)-quinic and (–)-shikimic acid.

Table 2. Structures of C_6–C_3 acids associated with chlorogenic acids

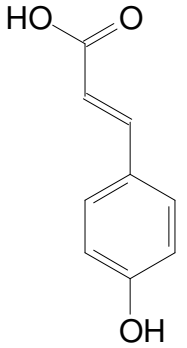
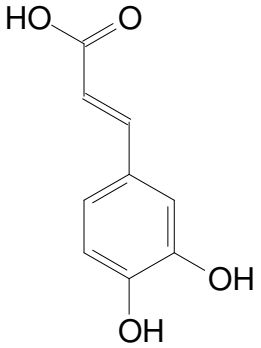
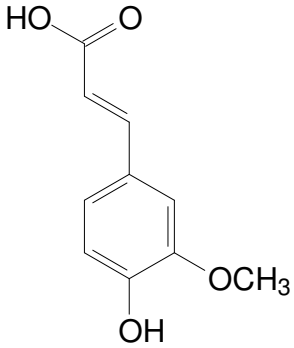
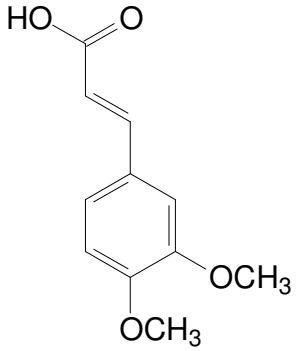
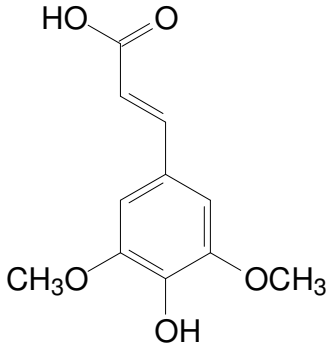
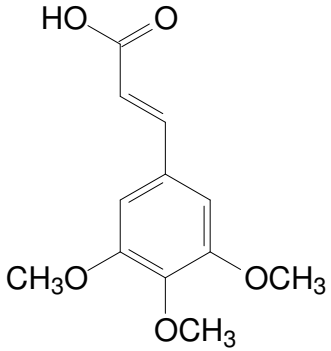
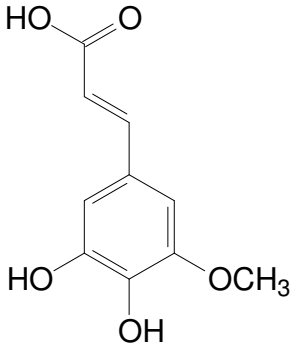
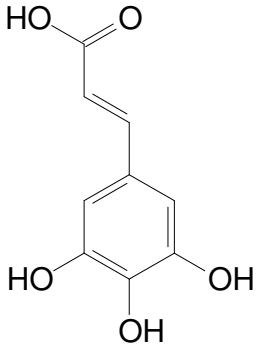
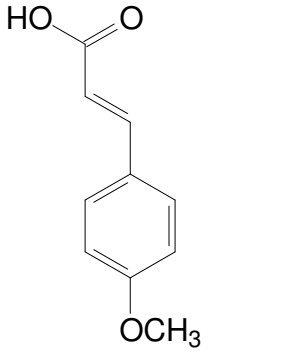
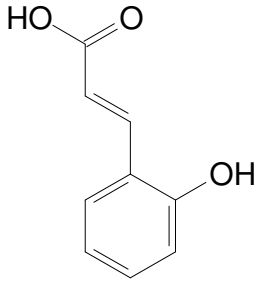
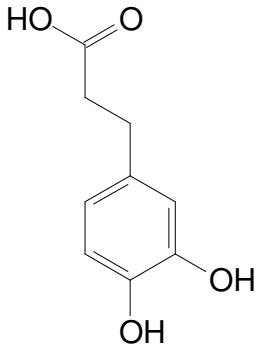
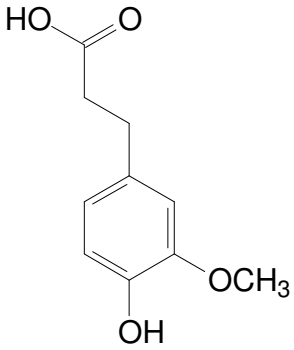
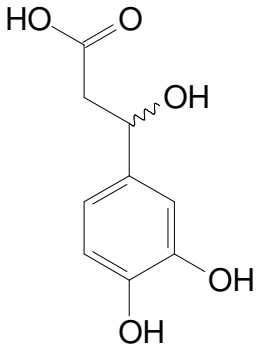
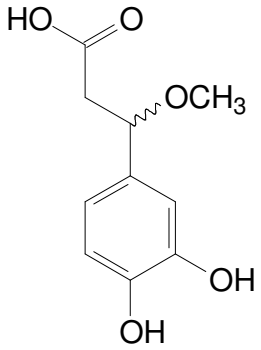
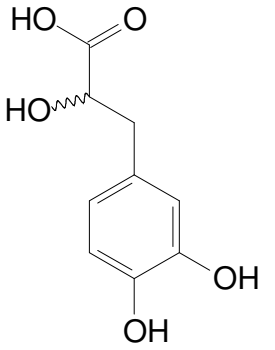
				
1. *p*-Coumaric acid	**2. Caffeic acid**	**3. Ferulic acid**	**4. 3,4-Dimethoxy-cinnamic acid**	**5. Sinapic acid**
				
6. 3,4,5-Trimethoxy-cinnamic acid	**7. 5-Hydroxyferulic acid**	**8. 3,4,5-Trihydroxycinnamic acid**	**9. 4-Methoxycinnamic acid**	**10. *o*-Coumaric acid**
				
11. Dihydrocaffeic acid	**12. Dihydroferulic acid**	**13. 3-Hydroxy-dihydrocaffeic acid**	**14. 3-Methoxy-dihydrocaffeic acid**	**15. 3,4-Dihydroxyphenyl-lactic acid *(30)***

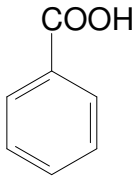
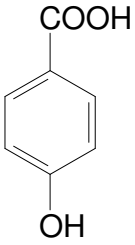
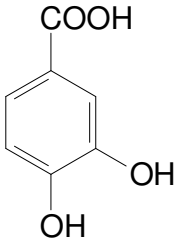
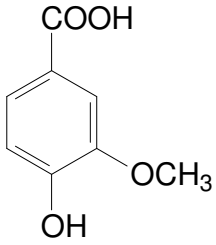
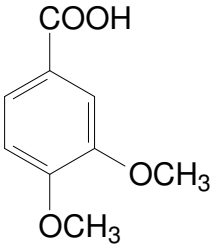
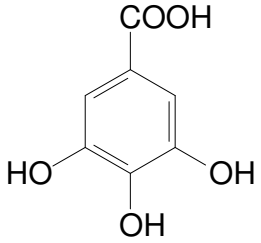
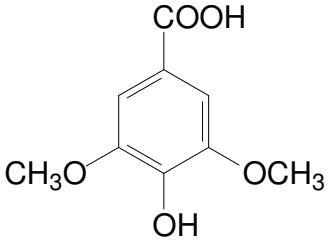
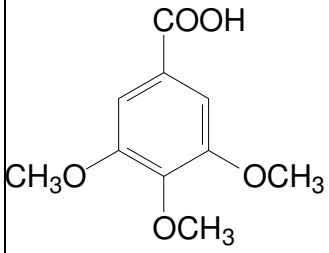
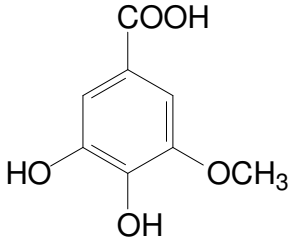
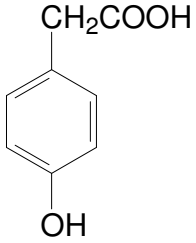
Table 3. Structures of C_6–C_1 and C_6–C_2 acids associated with chlorogenic acids				
				
20. Benzoic acid	**21. 4-Hydroxy-benzoic acid**	**22. Protocatechuic acid**	**23. Vanillic acid**	**24. Veratric acid**
				
25. Gallic acid	**26. Syringic acid**	**27. Eudesmic acid**	**28. 3-Methyl-gallic acid**	**29. 4-Hydroxyphenylacetic acid**

Table 4. Structures of aliphatic acids associated with chlorogenic acids

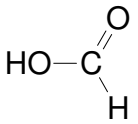
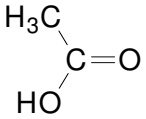
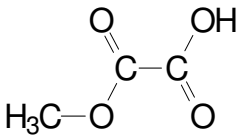
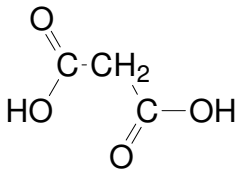
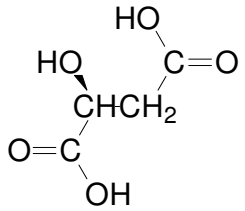
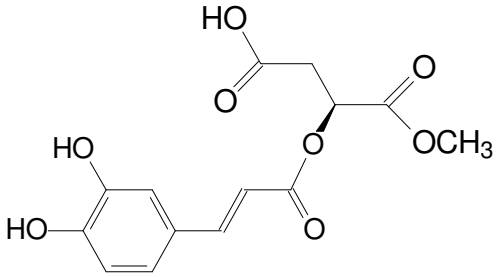
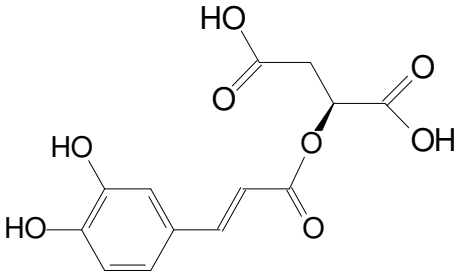
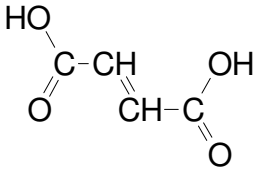
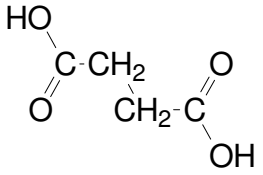
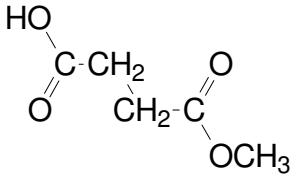
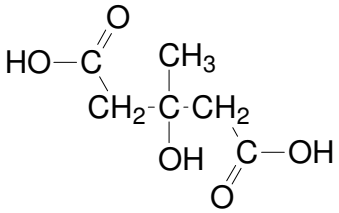
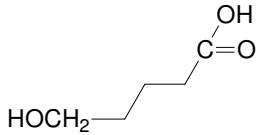
				
30. Formic acid	**31. Acetic acid**	**32. Methyl oxalate (Methoxyoxalyl)**	**33. Malonic acid**	**34. (*S*)-Malic acid OR L-(–)-Malic acid**
 		 		
35. 2-Caffeoyl-methyl-malate *(92)* and 2-Caffeoyl-malic acid *(159-161)*	**36. Fumaric acid**	**37. Succinic acid and methyl succinate *(160)***	**38. 3-Hydroxy-3-methylglutaric acid**	**39. 5-hydroxy-pentanoic acid**

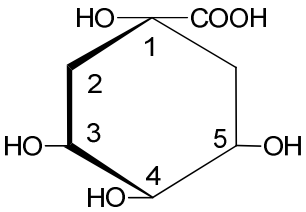
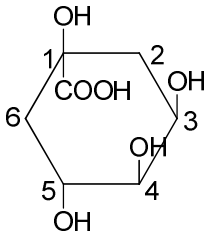
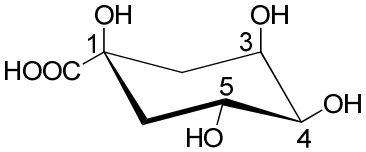
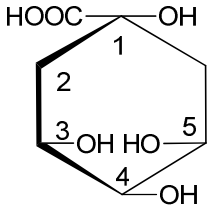
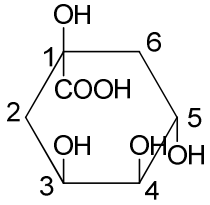
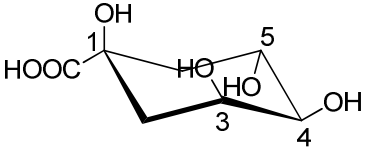
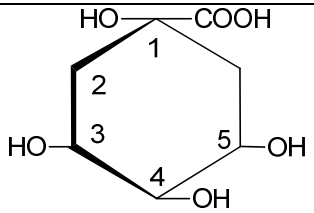
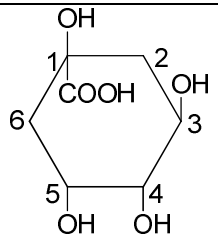
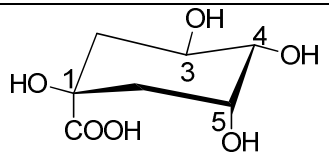
Table 5. Structures of Quinic Acid Enantiomers and Meso Forms						
Name	**CIP name**	**Structure (F-T)**	**2D structure**	**Conformational structure(s)**	**Description (*Orientation of OH groups relative to C1-COOH*)**	**Remarks**
40. 1L-quinic acid	1*R*, 3*R*, 4*S*, 5*R*				4C-OH: *cis* meta-OH groups: *cis*: *R* = C3 *trans*: *R* = C5 *Chem. Abs.* 1α,3α,4α,5β	IUPAC 1976: "…when the formula is drawn in a way that the substituent (i.e. OH group) on the lowest numbered asymmetric carbon atom is above the plane of the ring, and the numbering is clockwise, the compound is L; if anti-clockwise, it is D". Proposed carboxy-equatorial conformation is identical to the one shown in Corse and Lundin 1970,*(41)* and in Pauli *et al* 1999.*(48)*
41. 1D-quinic acid	1*S*, 3*S*, 4*R*, 5*S*				4C-OH: *cis* meta-OH groups: *cis*: *S* = C3 *trans*: *S* = C5 *Chem. Abs.* 1α,3α,4α,5β	CIP symbols are opposite in enantiomers. Proposed carboxy-equatorial conformation is identical to the one shown in Corse and Lundin 1970,*(41)* and in Pauli *et al* 1999.*(48)*
42. 1L-*epi*-quinic acid (derived from 1L-quinic acid by 4-OH inversion)	1*R*, 3*R*, 4*S*, 5*R*				4C-OH: *trans* meta-OH groups: *cis*: *R* = C3 *trans*: *R* = C5 *Chem. Abs.* 1α,3α,4β,5β	flipped chair conformation compared to 1L-quinic acid in order to set COOH and C4-H axial as suggested in Corse and Lundin 1970.*(41)* Carboxy-axial conformation favoured.*(41)*

Table 5. Structures of Quinic Acid Enantiomers and Meso Forms

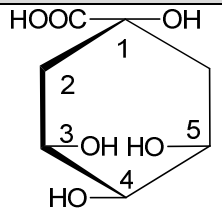
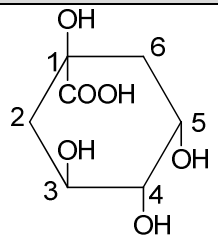
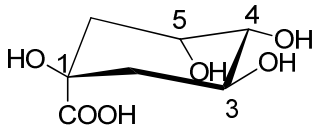
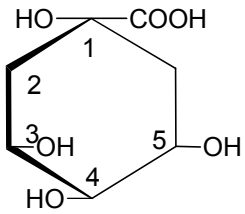
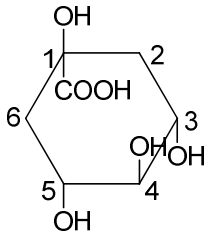
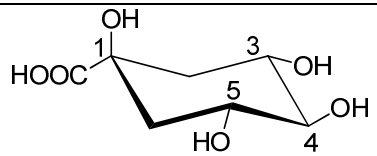
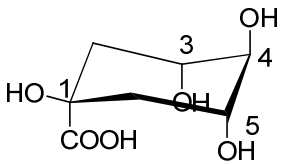
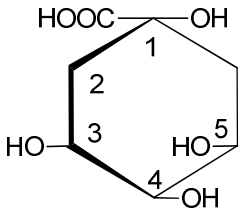
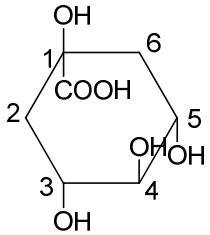
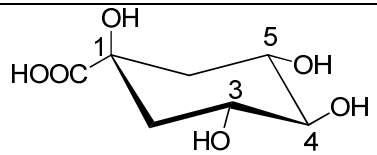
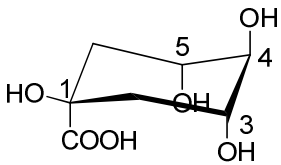
Name	CIP name	Structure (F-T)	2D structure	Conformational structure(s)	Description (*Orientation of OH groups relative to C1-COOH*)	Remarks
43. 1D-*epi*-quinic acid (derived from 1D-quinic acid by 4-OH inversion)	1*S*, 3*S*, 4*R*, 5*S*				4C-OH: *trans* meta-OH groups: *cis*: *S* = C3 *trans*: *S* = C5 *Chem Abs.* 1α,3α,4β,5β	flipped chair conformation compared to 1D-quinic acid in order to set COOH and C4-H axial as suggested in Corse and Lundin 1970.*(41)* Carboxy-axial conformation favoured.*(41)*
44. *Muco*-quinic acid (derived from 1L-quinic acid by 3-OH inversion) **meso form**	1*S*, 3*S*, 4*R*, 5*R*			 **or** 	4C-OH: *cis* meta-OH groups: *trans: S* = C3 and *R* = C5 *Chem. Abs.* 1α,3β,4α,5β	3-OH-inversion of 1L-quinic acid. **C5 is R and C3 is S.** Consequently, C4 is R and C1 is S, since **R>S sub-rule (5)** is needed to distinguish between the priorities regarding C1 and C4. Carboxy-equatorial conformation favoured.*(41)*
44. *Muco*-quinic acid (derived from 1D-quinic acid by 3-OH inversion) **meso form**	1*S*, 3*R*, 4*R*, 5*S*			 **or** 	4C-OH: *cis* meta-OH groups: *trans*: *R* = C3 and *S* = C5 *Chem. Abs.* 1α,3β,4α,5β	3-OH-inversion of 1D-quinic acid. **C5 is S and C3 is R.** Consequently, C4 is R and C1 is S, since **R>S sub-rule (5)** is needed to distinguish between the priorities regarding C1 and C4. Carboxy-equatorial conformation favoured.*(41)*

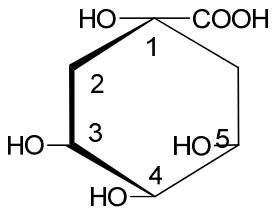
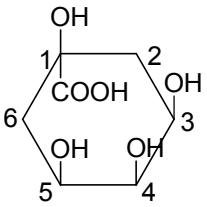
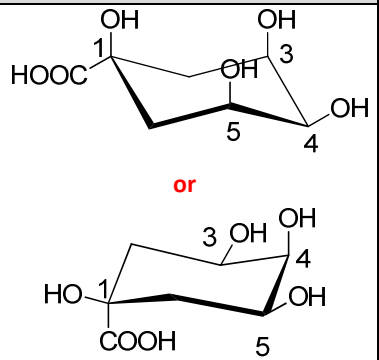
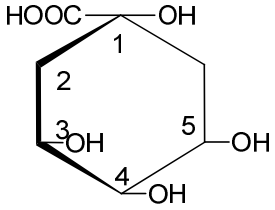
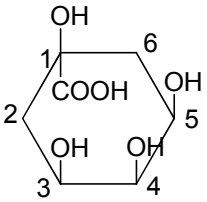
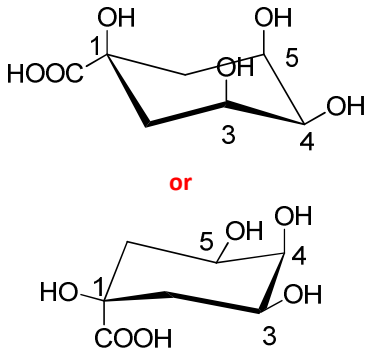
Table 5. Structures of Quinic Acid Enantiomers and Meso Forms						
Name	**CIP name**	**Structure (F-T)**	**2D structure**	**Conformational structure(s)**	**Description (*Orientation of OH groups relative to C1-COOH*)**	**Remarks**
45. *Cis*-quinic acid (derived from 1L-quinic acid by 5-OH inversion) **meso form**	1*R*, 3*R*, 4*S*, 5*S*				4C-OH: *cis* meta-OH groups: *cis*: *R* = C3 and *S*= C5 *Chem. Abstracts* 1α,3α,4α,5α	5-OH-inversion of 1L-quinic acid. **C5 is S and C3 is R.** Consequently, C4 is S and C1 is R, since **R>S sub-rule (5)** is needed to distinguish between the priorities regarding C1 and C4. Carboxy-axial conformation favoured.*(41)*
45. *Cis*-quinic acid (derived from 1D-quinic acid by 5-OH inversion) **meso form**	1*R*, 3*S*, 4*S*, 5*R*				4C-OH: *cis* meta-OH groups: *cis*: *S* = C3 and *R* = C5 *Chem. Abstracts* 1α,3α,4α,5α	5-OH-inversion of 1D-quinic acid. **C5 is R and C3 is S.** Consequently, C4 is S and C1 is R, since **R>S sub-rule (5)** is needed to distinguish between the priorities regarding C1 and C4. Carboxy-axial conformation favoured.*(41)*

Table 5. Structures of Quinic Acid Enantiomers and Meso Forms

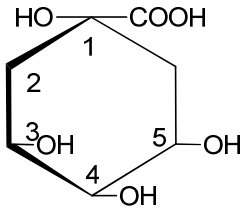
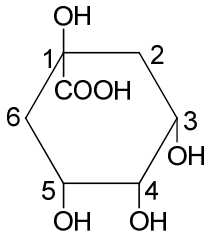
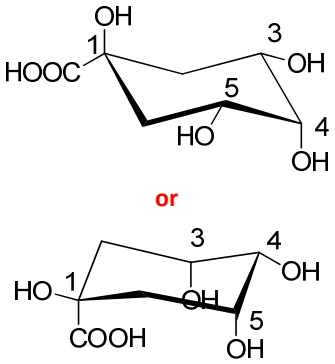
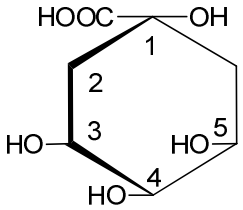
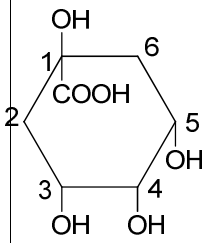
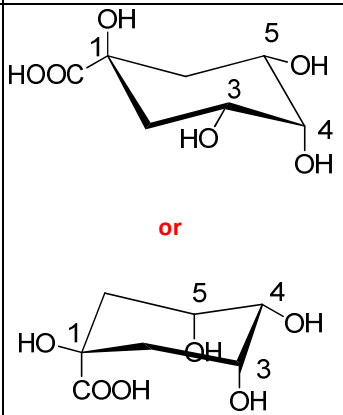
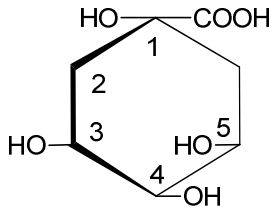
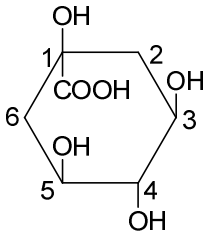
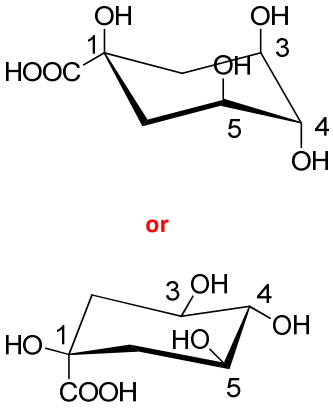
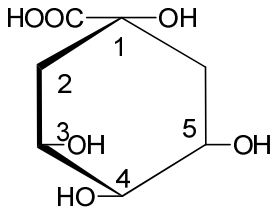
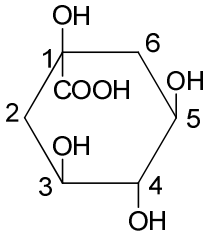
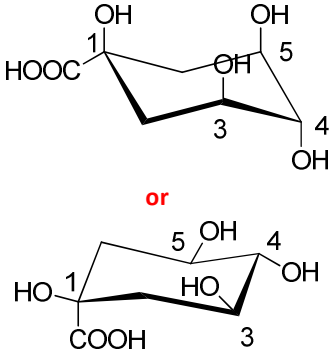
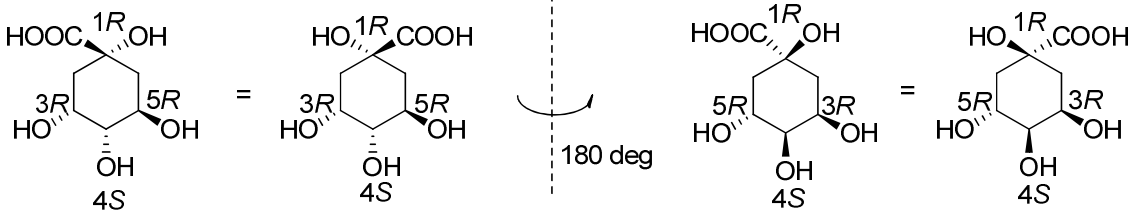
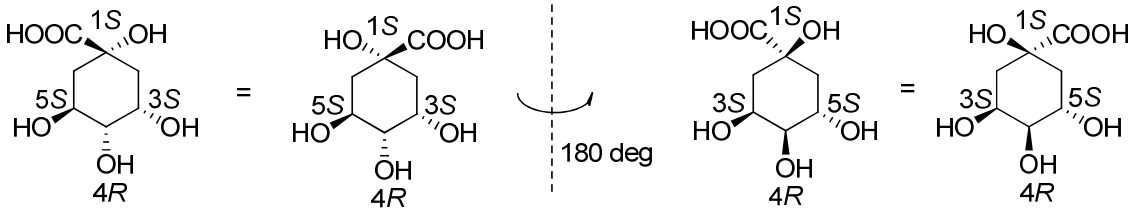
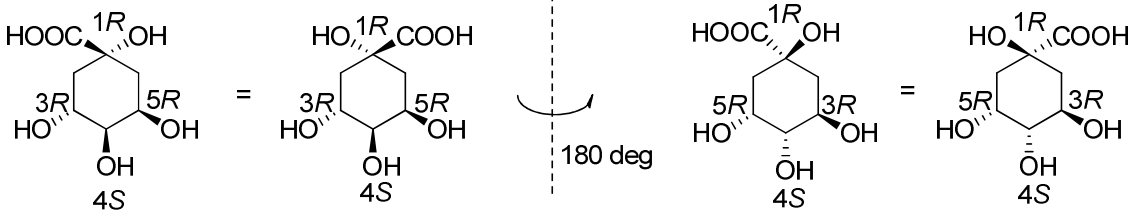
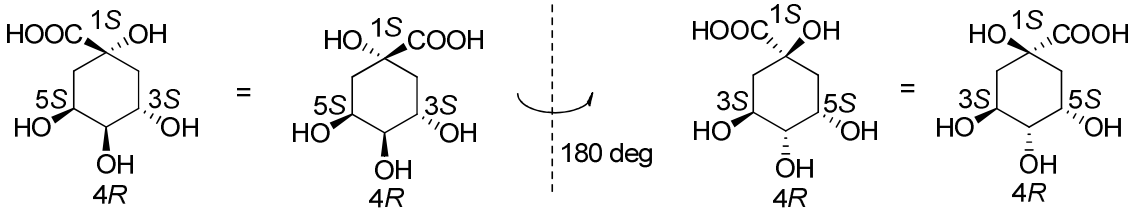
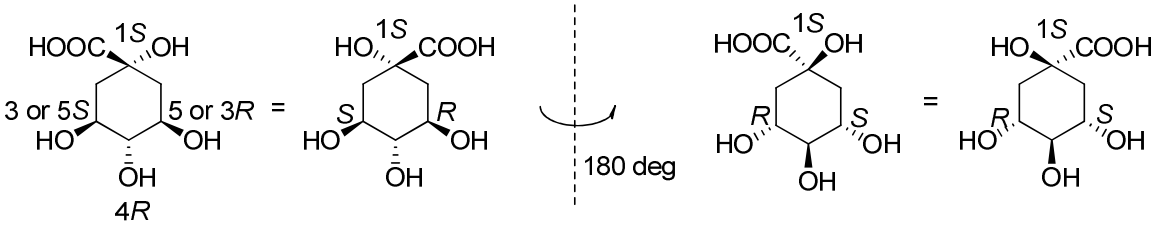
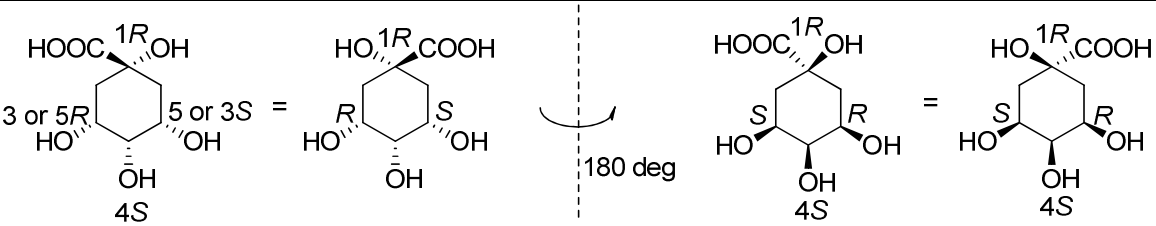
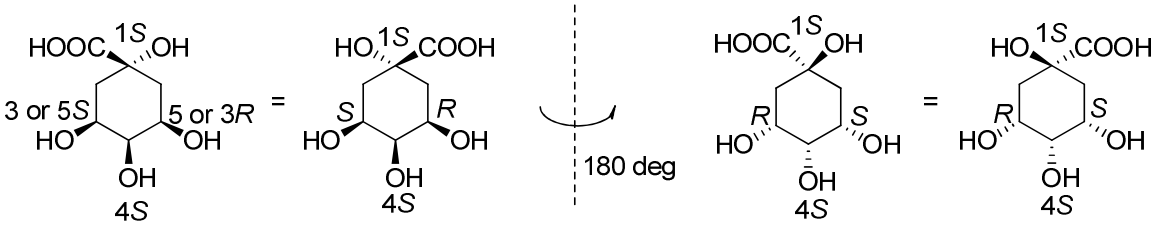
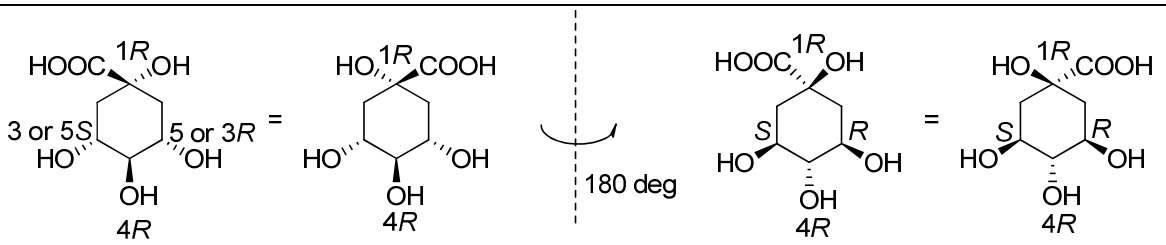
Name	CIP name	Structure (F-T)	2D structure	Conformational structure(s)	Description (*Orientation of OH groups relative to C1-COOH*)	Remarks
46. *Neo*-quinic acid (derived from 1L-quinic acid by 3-OH and 4-OH inversion) **meso form**	1*S*, 3*S*, 4*S*, 5*R*				4C-OH: *trans* meta-OH groups: *trans*: *S* = C3 and *R* = C5 *Chem. Abstracts* 1α,3β,4β,5β	3-OH and 4-OH inversion of 1L-quinic acid. **C5 is R and C3 is S.** Consequently, C4 is S and C1 is S, since **R>S sub-rule (5)** is needed to distinguish between the priorities regarding C1 and C4. Carboxy-axial conformation favoured.*(41)*
46. *Neo*-quinic acid (derived from 1D-quinic acid by 3-OH and 4-OH inversion) **meso form**	1*S*, 3*R*, 4*S*, 5*S*				4C-OH: *trans* meta-OH groups: *trans*: *R* = C3 and *S* = C5 *Chem. Abstracts* 1α,3β,4β,5β	3-OH and 4-OH inversion of 1D-quinic acid. **C5 is S and C3 is R.** Consequently, C4 is S and C1 is S, since **R>S sub-rule (5)** is needed to distinguish between the priorities regarding C1 and C4. Carboxy axial favoured.*(41)*

Table 5. Structures of Quinic Acid Enantiomers and Meso Forms

Name	CIP name	Structure (F-T)	2D structure	Conformational structure(s)	Description (*Orientation of OH groups relative to C1-COOH*)	Remarks
47. *scyllo*-quinic acid (derived from 1L-quinic acid by 4-OH and 5-OH inversion) **meso form**	1*R*, 3*R*, 4*R*, 5*S*				4C-OH: *trans* meta-OH groups: *cis*: *R* = C3 and *S* = C5 *Chem. Abstracts* 1α,3α,4β,5α	4-OH and 5-OH inversion of 1L-quinic acid. **C5 is S and C3 is R.** Consequently, C4 is R and C1 is R, since **R>S sub-rule (5)** is needed to distinguish between the priorities regarding C1 and C4. Carboxy axial conformation favoured.*(41)*
47. *scyllo*-quinic acid (derived from 1D-quinic acid by 4-OH and 5-OH inversion) **meso form**	1*R*, 3*S*, 4*R*, 5*R*				4C-OH: *trans* meta-OH groups: *cis*: *S* = C3 and *R*= C5 *Chem. Abstracts* 1α,3α,4β,5α	4-OH and 5-OH inversion of 1L-quinic acid. **C5 is R and C3 is S.** Consequently, C4 is R and C1 is R, since **R>S sub-rule (5)** is needed to distinguish between the priorities regarding C1 and C4. Carboxy axial conformation favoured.*(41)*

Note that *Chemical Abstracts* use α to define a substituent that is *trans* to the carboxyl. Also note that the favoured conformations as presented by Corse and Lundin apply to free quinic acids, and do not necessarily apply to associated acyl-quinic acids.*(41)* Markovic *et al*. have reported that the preferred conformation of the quinic moiety of 5-CQA in methanol is characterized with directed hydrogen bonds, where the carboxylic hydrogen is not oriented towards the carbonyl oxygen of the carboxylic group, but towards the oxygen of the proximate hydroxyl group.*(162)* D'Amelio *et al*. have investigated the structure of CQA and diCQA complexes with caffeine in aqueous solution.*(163, 164)*

	Table 6. Two dimensional structures for Quinic Acid Enantiomers and Meso Forms	
	View 1	View 2
40. 1L-quinic acid		
41. 1D-quinic acid		
42. 1L-*epi*-quinic acid		
43. 1D-*epi*-quinic acid		
44. *Muco*-quinic acid		
45. *Cis*-quinic acid		
46. *Neo*-quinic acid		

47. *Scyllo*-quinic acid	

The representation and interpretation of three dimensional structures in two dimensions, while very important because of the influence of three dimensional structure on chemical, physical and biological properties, is far from easy. In the structures above the carboxyl and hydroxyl at C1 are projecting at right angles to the plane of the paper on which they are presented — the substituent with the hatched bond is projected into the paper and away from the observer and the substituent with the solid bond is projected out of the paper and towards the observer.

If the observer is looking straight down the C–C bond of the carboxyl, or the C–O of the hydroxyl, as appropriate, then the other substituent projecting into the paper would be masked by the substituent projecting out of it.

Accordingly, the structures have to be presented with the observer looking at an angle either slightly less than 90° or slightly more than 90° in order to see both C1 substituents. Depending on which of these positions is adopted by the observer the carboxyl will either appear to the left and the hydroxyl to the right, or the carboxyl to the right and the hydroxyl to the left, but it is the same compound. This is possibly the most confusing feature associated with presenting three dimensional structures in two dimensions.

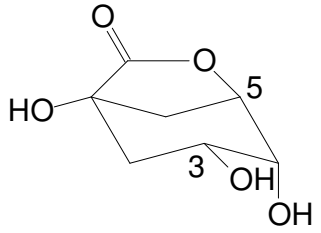
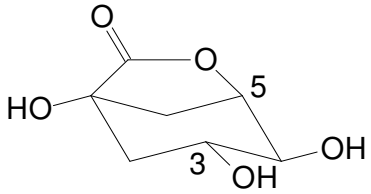
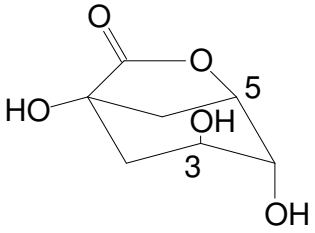
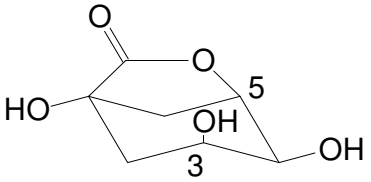
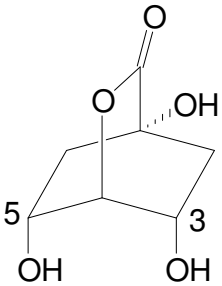
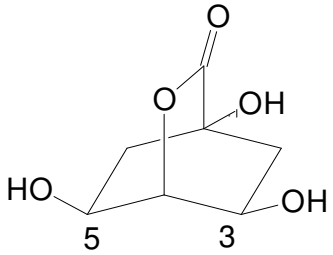
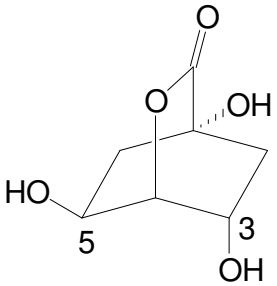
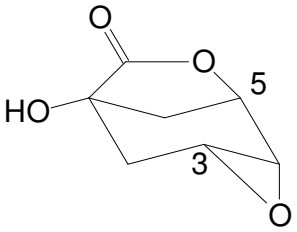
Table 7. Structures of Quinic Lactones (Quinides)			
			
50. (±)-γ-Quinide	**51. (±)-*epi*-γ-Quinide**	**52. (±)-*muco*-γ-Quinide**	**53. (±)-*neo*-γ-Quinide**
Formed from carboxy axial conformer of (±)-quinic acid	Formed from carboxy axial conformer of (±)-*epi*-quinic acid	Formed from carboxy axial conformer of the meso *muco*-quinic acid utilising the axial C3 or axial C5 hydroxyl to produce the two enantiomers	Formed from carboxy axial conformer of the meso *neo*-quinic acid utilising the axial C3 or axial C5 hydroxyl to produce the two enantiomers
			
54. *Scyllo*-δ-quinide	**55. *Neo*-δ-quinide**	**56. (±)-E*pi*-δ-quinide**	**57. 3,4-Epoxy-1,5-γ-quinide**
Route of formation uncertain but possibly from a boat or skewed conformer of *scyllo*-quinic acid. Mono-acylation at C3 and C5 produces a pair of enantiomers	Route of formation uncertain but possibly from a boat or skewed conformer of *neo*-quinic acid. Mono-acylation at C3 and C5 produces a pair of enantiomers	Route of formation uncertain but possibly from a boat or skewed conformer of (±)-*epi*-quinic acid	

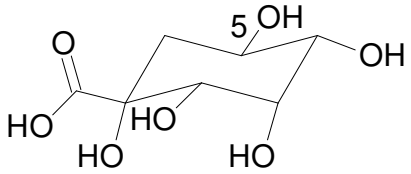
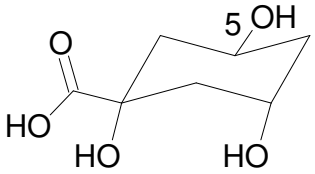
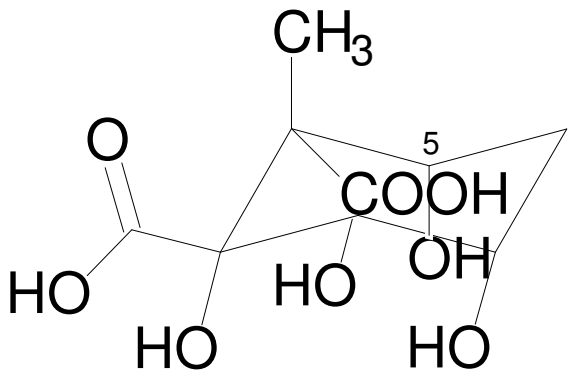
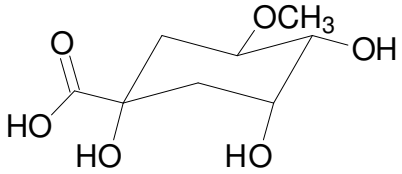
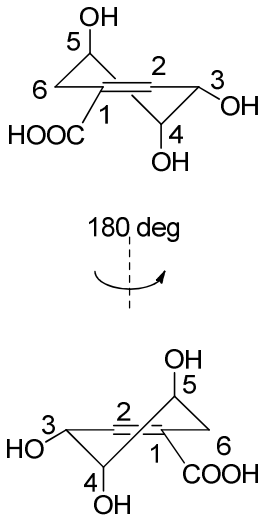
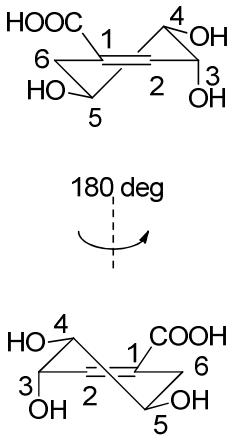
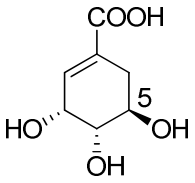
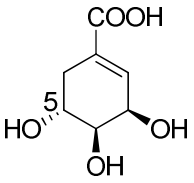
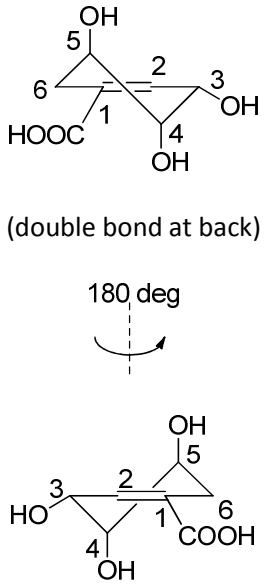
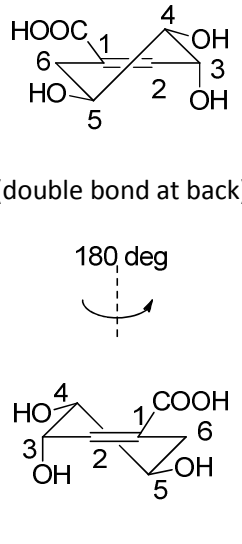
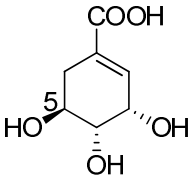
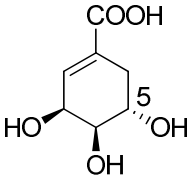
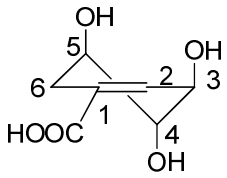
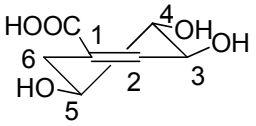
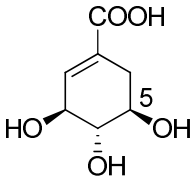
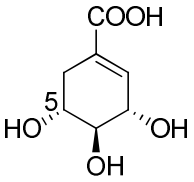
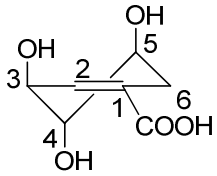
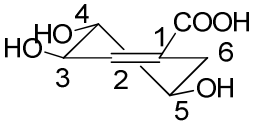
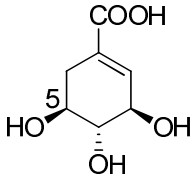
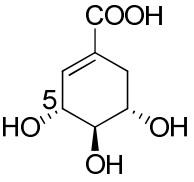
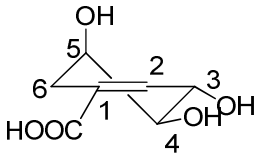
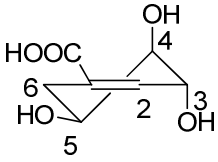
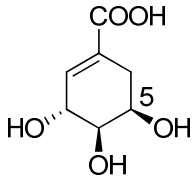
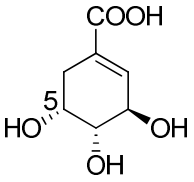
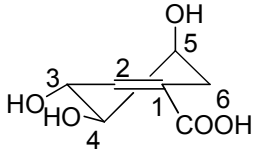
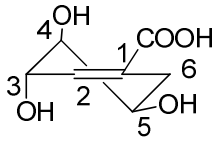
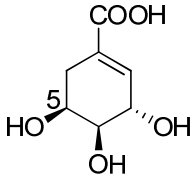
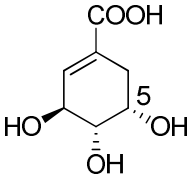
Table 8. Uncommon hydroxycyclohexane carboxylic acid derivatives			
			
60. 2-Hydroxy-quinic Acid with configuration 1α,2α,3α,4α,5β	**61. 4-Deoxy-quinic acid with configuration 1α,3α,5β. Configuration tentative**	**62. Methyl 1,2,3,5-tetrahydroxy-6-methyl-cyclohexane-1,6-dicarboxylic acid. Configuration tentative**	**63. 5-*O*-methylquinic acid Configuration tentative**

Table 9. Half Chair Structures of the Shikimic Acid Enantiomers			
 (double bond at back)	 (double bond at back)		
70. IUPAC L-Shikimic acid or (–)-Shikimic acid			
CIP 1966 3*R*,4*S*,5*R*			
	Favoured (Snyder et al.)*(165)*	Viewed from in front	Viewed from behind
			
71. IUPAC D-Shikimic acid or (+)-Shikimic acid			
CIP 1966 3*S*,4*R*,5*S*			
		Viewed from in front	Viewed from behind

			
72. IUPAC L-3-*epi*-Shikimic acid or (–)-3-*epi*-Shikimic acid			
CIP 1966 3*S*,4*R*,5*R*			
	favoured (Geiger *et al*)*(153)*	Viewed from in front	Viewed from behind
			
73. D-3-*epi*-Shikimic acid or (+)-3-*epi*-Shikimic acid			
CIP 1966 3*R*,4*R*,5*S*			
		Viewed from in front	Viewed from behind
			
74. L-4-*epi*-Shikimic acid or (–)-4-*epi*-Shikimic acid			
CIP 1966 3*R*,4*S*,5*R*			
favoured (Snyder *et al*)		Viewed from in front	Viewed from behind
			
75. D-4-*epi*-Shikimic acid or (+)-4-*epi*-Shikimic acid			
CIP 1966 3*S*,4*R*,5*S*			
		Viewed from in front	Viewed from behind

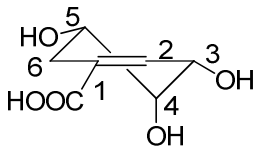
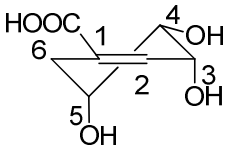
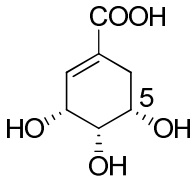
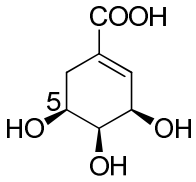
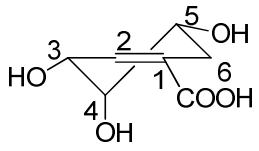
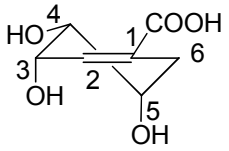
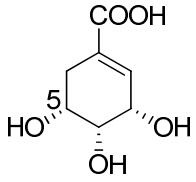
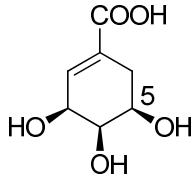
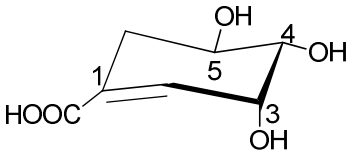
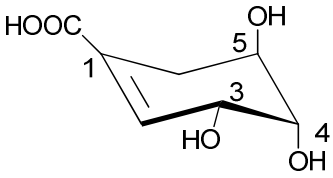
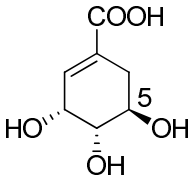
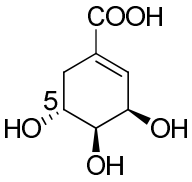
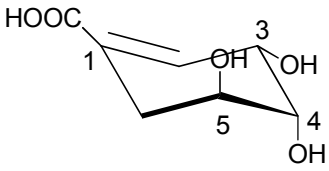
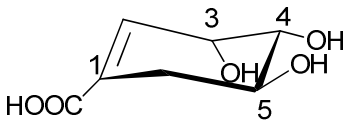
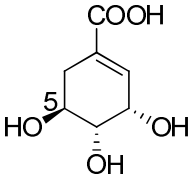
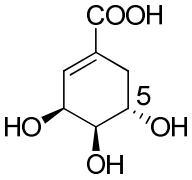
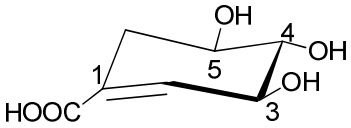
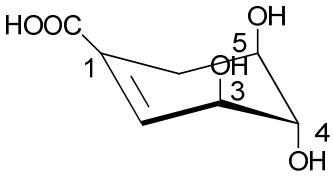
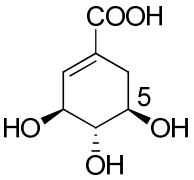
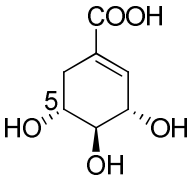
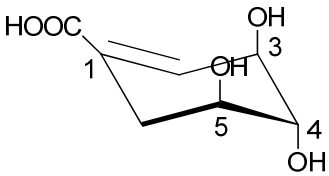
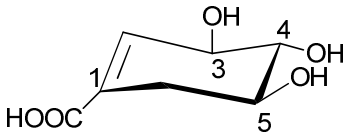
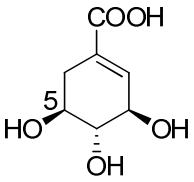
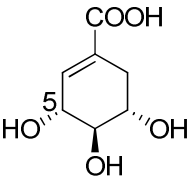
			
76. L-5-*epi*-Shikimic acid or (–)-5-*epi*-Shikimic acid			
CIP 1966 3*R*,4*S*,5*S*			
		Viewed from in front	Viewed from behind
			
77. D-5-*epi*-Shikimic acid or (+)-5-*epi*-Shikimic acid			
CIP 1966 3*S*,4*S*,5*R*			
		Viewed from in front	Viewed from behind

Table 10. Structures of the Shikimic Acid Enantiomers Drawn to facilitate comparison with Quinic Acid Enantiomers			
			
70. IUPAC L-Shikimic acid or (–)-Shikimic acid			
CIP 1966 3*R*,4*S*,5*R*			
Favoured (Snyder *et al.*)*(165)*		Viewed from in front	Viewed from behind
			
71. IUPAC D-Shikimic acid or (+)-Shikimic acid			
CIP 1966 3*S*,4*R*,5*S*			
		Viewed from in front	Viewed from behind
			
72. IUPAC L-3-*epi*-Shikimic acid or (–)-3-*epi*-Shikimic acid			
CIP 1966 3*S*,4*R*,5*R*			
		Viewed from in front	Viewed from behind
			
73. D-3-*epi*-Shikimic acid or (+)-3-*epi*-Shikimic acid			
CIP 1966 3*R*,4*R*,5*S*			
		Viewed from in front	Viewed from behind

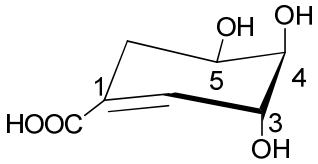
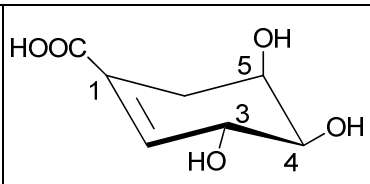
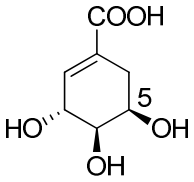
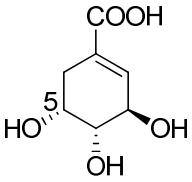
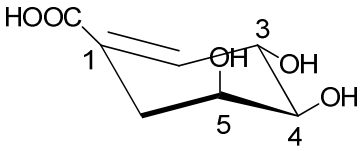
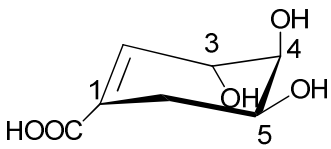
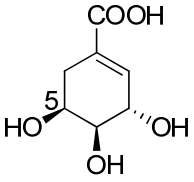
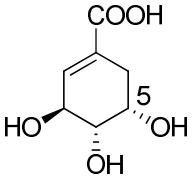
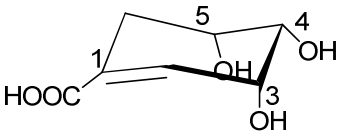
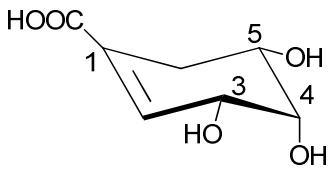
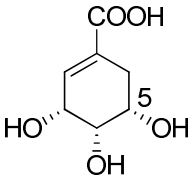
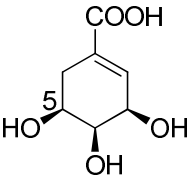
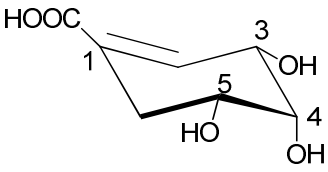
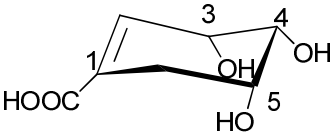
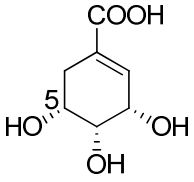
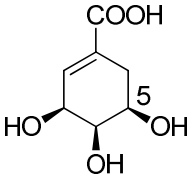
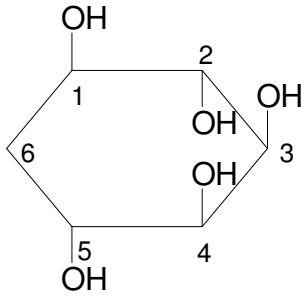
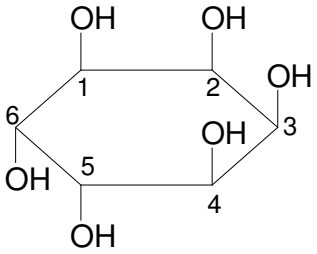
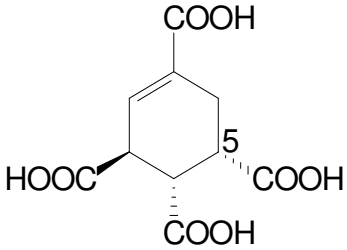
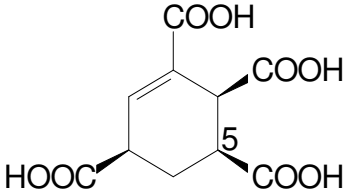
			
74. L-4-*epi*-Shikimic acid or (–)-4-*epi*-Shikimic acid			
CIP 1966 3*R*,4*S*,5*R*			
		Viewed from in front	Viewed from behind
			
75. D-4-*epi*-Shikimic acid or (+)-4-*epi*-Shikimic acid			
CIP 1966 3*S*,4*R*,5*S*			
		Viewed from in front	Viewed from behind
			
76. L-5-*epi*-Shikimic acid or (–)-5-*epi*-Shikimic acid			
CIP 1966 3*R*,4*S*,5*S*			
		Viewed from in front	Viewed from behind
			
77. D-5-*epi*-Shikimic acid or (+)-5-*epi*-Shikimic acid			
CIP 1966 3*S*,4*S*,5*R*			
		Viewed from in front	Viewed from behind

Table 11. Miscellaneous Structures		
		
80. *proto*-Quercitol	**81. *myo*-Inositol**	**82. 1,3,4,5-Tetra-carboxy-shikimic acid**
		
83. 1,3,5,6-Tetra-carboxy-shikimic acid		

9. Reference List

1. Payen Untersuchung des Kaffees. *Annalen* **1846,** *60*, 286-294.
2. Payen Memoire sur le café (3º Part). *Comptes Rendus* **1846,** *23*, 244-251.
3. Fischer, H. O. L.; Dangschat, G. Konstitution der Chlorogensäure (3. Mitteil. über Chinasäure und Derivate). *Berichte* **1932,** *65*, 1037-1040.
4. IUPAC Nomenclature of cyclitols. *Biochem. J.* **1976,** *153*, 23-31.
5. Barnes, H. M.; Feldman, J. R.; White, W. V. Isochlorogenic acid isolation from coffee and structure studies. *J. Am. Chem. Soc.* **1950,** *72*, 4178-4182.
6. Panizzi, L.; Scarpati, M. L. Constitution of cynarine, the active principle of the artichoke. *Nature* **1954,** *174*, 1062-1063.
7. Cartwright, R. A.; Roberts, E. A. H. Theogallin, a polyphenol occurring in tea. *J. Sci. Food Agric.* **1954,** *5*, 593-597.
8. Cartwright, R. A.; Roberts, E. A. H. Theogallin as a galloyl ester of quinic acid. *Chem. Ind.* **1955,** 230-231.
9. Cartwright, R. A.; Roberts, E. A. H.; Flood, E. A. The suspected presence of *p*-coumaroylquinic acids in tea, apple and pear. *Chem. Ind.* **1955,** 1062-1063.
10. Roberts, E. A. H. The chemistry of tea manufacture. *J. Sci. Food Agric.* **1958,** *9*, 381-390.
11. Corse, J.; Lundin, R.; Sondheimer, E. 3-Feruloylquinic acid - a 3'-methyl ether of chlorogenic acid. *Tetrahedron* **1962,** *18*, 2107-2108.
12. Corse, J.; Lundin, R. E.; Waiss, A. C. Identification of several components of isochlorogenic acid. *Phytochem.* **1965,** *4*, 527-529.
13. Tsuchida, T.; Suzuki, M.; Kurogi, M. Evaluation of antioxidant activity of vegetable extracts and determination of some active compounds. *J. Jpn. Soc. Food Sci. Technol.* **1968,** *13*, 199-206.
14. Corse, J.; Patterson, D. C. 3-*O*-sinapoylquinic acid. *Phytochem.* **1969,** *8*, 203-205.
15. Kremr, D.; Bajer, T.; Bajerova, P.; Surmova, S.; Ventura, K. Unremitting problems with chlorogenic acid nomenclature: A review. *Qumica Nova* **2016,** *39*.
16. Sondheimer, E. On the distribution of caffeic acid and the chlorogenic acid isomers in plants. *Arch. Biochem. Biophys.* **1958,** *74*, 131-138.
17. Ouattara, B.; Angenot, L.; Guissou, P.; Fondu, P.; Dubois, J.; Frederich, M.; Jansen, O.; van Heugen, J. C.; Wauters, J. N.; Tits, M. LC/MS/NMR analysis of isomeric divanilloylquinic acids from the root bark of *Fagara zanthoxyloides* Lam. *Phytochem.* **2004,** *65* (8), 1145-1151.
18. Kirmizibekmez, H.; Demir, D. Iridoid glycosides and phenolic compounds from the flowers of *Vitex agnus-castus*. *HCA* **2016,** *99* (7), 518-522.
19. Panizzi, L.; Scarpati, M. L.; Scarpati, R. Sintesi della cinarina, principio attivo del carciofo. *Gazz. Chim. Ital.* **1954,** *84*, 806-815.

20. Maier, V. P.; Metzler, D. M.; Huber, A. F. 3-*O*-caffeoylshikimic acid (dactylifric acid) and its isomers, a new class of enzymic browning substrates. *Biochem. Biophys. Res. Commun.* **1964,** *14*, 124-128.

21. Wada, H.; Tanaka, N.; Murakami, T.; Uchida, T.; Kozawa, K.; Saiki, Y.; Chen, C. M. Chemical and chemotaxonomical studies of *Filices* .76. An unusual flavanone derivative from *Wagneriopteris japonica* Loeve et Loeve. *Yakugaku Zasshi-Journal of the Pharmaceutical Society of Japan* **1988,** *108* (8), 740-744.

22. Hauschild, W. Untersuchung über die Bestandteile des Mate. *Mitteilungen aus dem Gebiete der Lebensmittel Untersuchungen und Hygiene* **1935,** *26*, 329-350.

23. Antognoni, F.; Perellino, N. C.; Crippa, S.; Dal, T. R.; Danieli, B.; Minghetti, A.; Poli, F.; Pressi, G. Irbic acid, a dicaffeoylquinic acid derivative from *Centella asiatica* cell cultures. *Fitoterapia* **2011,** *82* (7), 950-954.

24. Long, H. S.; Stander, M. A.; Van Wyk, B. E. Notes on the occurrence and significance of triterpenoids (asiaticoside and related compounds) and caffeoylquinic acids in *Centella* species. *South African Journal of Botany* **2012,** *82*, 53-59.

25. Maulidiani, A. F.; Khatib, A.; Shaari, K.; Lajis, N. H. Chemical characterization and antioxidant activity of three medicinal Apiaceae species. *Industrial Crops and Products* **2014,** *55* (0), 238-247.

26. Zhang, Y.; Shi, P.; Qu, H.; Cheng, Y. Characterization of phenolic compounds in *Erigeron breviscapus* by liquid chromatography coupled to electrospray ionization mass spectrometry. *Rapid Commun. Mass Spectrom.* **2007,** *21* (18), 2971-2984.

27. Scarpati, M. L.; Guiso, M. Structure of the three dicaffeoylquinic acids of coffee. *Tetrahedron Lett.* **1964,** 2851-2853.

28. Chen, M.; Wu, W. W.; Shen, G. Q.; Luo, S. Q.; Li, H. T. Chemical Constituents of *Lonicera macranthoides* Hand-mazz. Part V. Isolation and Structures of Macranthoin F and G. *Acta Pharmaceutica Sinica* **1994,** *29*, 620.

29. Nakamura, S.; Fujimoto, K.; Matsumoto, T.; Nakashima, S.; Ohta, T.; Ogawa, K.; Matsuda, H.; Yoshikawa, M. Acylated sucroses and acylated quinic acids analogs from the flower buds of *Prunus mume* and their inhibitory effect on melanogenesis. *Phytochem.* **2013,** *92*, 128-136.

30. Maier, H. G.; Grimsehl, A. Die Säure des Kaffees. II. Chlorogensäuren im Rohkaffee. *Kaffee und Tee-Markt* **1982,** *32* (16), 3-5.

31. Corse, J. A new isomer of chlorogenic acid from peaches. *Nature* **1953,** *172*, 771-772.

32. Liu, H.; Zheng, A.; Liu, H.; Yu, H.; Wu, X.; Xiao, C.; Dai, H.; Hao, F.; Zhang, L.; Wang, Yu.; ang, H. Identification of three novel polyphenolic compounds, Origanine A–C, with unique skeleton from *Origanum vulgare* L. using the hyphenated LC-DAD-SPE-NMR/MS methods. *J. Agric. Food Chem.* **2012,** *60* (1), 129-135.

33. Hou, A. J.; Peng, L. Y.; Liu, Y. Z.; Lin, Z. W.; Sun, H. D. Gallotannins and related polyphenols from *Pistacia weinmannifolia*. *Planta Med.* **2000,** *66* (7), 624-626.

34. Zidorn, C.; Petersen, B. O.; Udovicic, V.; Larsen, T. O.; Duus, J. A.; Rollinger, J. M.; Ongania, K. H.; Ellmerer, E. P.; Stuppner, H. Podospermic acid, 1,3,5-tri-O-(7,8-dihydrocaffeoyl)quinic acid from *Podospermum laciniatum* (Asteraceae). *Tetrahedron Lett.* **2005,** *46* (8), 1291-1294.

35. Tsevegsuren, N.; Edrada, R.; Lin, W.; Ebel, R.; Torre, C.; Ortlepp, S.; Wray, V.; Proksch, P. Biologically active natural products from Mongolian medicinal plants *Scorzonera divaricata* and *Scorzonera pseudodivaricata*. *J. Nat. Prod.* **2007,** *70* (6), 962-967.

36. Uritani, I.; Miyano, M. Derivatives of caffeic acid in sweet potato attacked by black rot. *Nature* **1955,** *175*, 812.

37. Kim, J. Y.; Cho, J. Y.; Ma, Y. K.; Park, K. Y.; Lee, S. H.; Ham, K. S.; Lee, H. J.; Park, K. H.; Moon, J. H. Dicaffeoylquinic acid derivatives and flavonoid glucosides from glasswort (*Salicornia herbacea* L.) and their antioxidative activity. *Food Chem.* **2011,** *125* (1), 55-62.

38. Roberts, E. A. H.; Myers, M. Theogallin, a polyphenol, occurring in tea. II. Identification as a galloylquinic acid. *J. Sci. Food Agric.* **1958,** *9*, 701-705.

39. Chung, Y. C.; Chun, H. K.; Yang, J. Y.; Kim, J. Y.; Han, E. H.; Kho, Y. H.; Jeong, H. G. Tungtungmadic acid, a novel antioxidant, from *Salicornia herbacea*. *Arch. Pharm. Res.* **2005,** *28* (10), 1122-1126.

40. Wu, S. B.; Meyer, R. S.; Whitaker, B. D.; Litt, A.; Kennelly, E. J. Antioxidant glucosylated caffeoylquinic acid derivatives in the invasive tropical Soda Apple, *Solanum viarum*. *J Nat. Prod.* **2012,** *75* (12), 2246-2250.

41. Corse, J.; Lundin, R. E. Diastereomers of quinic acid. Chemical and nuclear magnetic resonance studies. *J. Org. Chem.* **1970,** *35*, 1904-1909.

42. Eliel, E. L. Infelicitous stereochemical nomenclature. *Chirality* **1997,** *9* (5-6), 428-430.

43. Jaiswal, R.; Matei, M. F.; Golon, A.; Witt, M.; Kuhnert, N. Understanding the fate of chlorogenic acids in coffee roasting using mass spectrometry based targeted and non-targeted analytical strategies. *Food Funct.* **2012,** *3*, 976-984.

44. Lima, J. d. P.; Farah, A.; King, B.; de Paulis, T.; Martin, P. R. Distribution of major chlorogenic acids and related compounds in Brazilian green and toasted *Ilex paraguariensis* (maté) leaves. *J. Agric. Food Chem.* **2016,** *64*, 2361-2370.

45. Eliel, E. L.; Ramirez, M. B. (–)-Quinic acid: configurational (stereochemical) descriptors. *Tetrahedron: Asymmetry* **1997,** *8* (21), 3551-3554.

46. Cahn, R. S. An introduction to the sequence rule: A system for the specification of absolute configuration. *J. Chem. Educ.* **1964,** *41* (3), 116-125.

47. Cahn, R. S.; Ingold, C.; Prelog, V. Specification of molecular chirality. *Angewandte Chemie-International Edition* **1966,** *5* (4), 385-415.

48. Pauli, G. F.; Kuczkowiak, U.; Nahrstedt, A. Solvent effects in the structure dereplication of caffeoyl quinic acids. *Magnetic Resonance in Chemistry* **1999,** *37* (11), 827-836.

49. Clifford, M. N.; Johnston, K. L.; Knight, S.; Kuhnert, N. A hierarchical scheme for LC–MS^n identification of chlorogenic acids. *J. Agric. Food Chem.* **2003,** *51*, 2900-2911.

50. Corse, J.; Lundin, R. E.; Sondheimer, E.; Waiss, A. C. Conformation analysis of D-(–)-quinic acid and some of its derivatives by nuclear magnetic resonance. *Phytochem.* **1966,** *5*, 767-776.

51. Kuczkowiak, U.; Petereit, F.; Nahrstedt, A. Hydroxycinnamic acid derivatives obtained from a commercial *Cratageus* extract and from authentic *Crataegeus* spp. *Scientia Pharmaceutica* **2014,** *82*, 835-846.

52. Demirkiran, O.; Mesaik, M.; Beynek, H.; Abbaskhan, A.; Choudhary, M., I Immunosupressive phenolic constituents from *Hypericum montbretii* Spach. *Records of Natural Products* **2013,** *7* (3), 210-219.

53. Ling, Y.; Liu, K.; Zhang, Q.; Liao, L.; Lu, Y. High performance liquid chromatography coupled to electrospray ionization and quadrupole time-of-flight-mass spectrometry as a powerful analytical strategy for systematic analysis and improved characterization of the major bioactive constituents from Radix Dipsaci. *J. Pharm. Biomed. Anal.* **2014,** *98*, 120-129.

54. Plazonic, A.; Bucar, F.; Males, Z.; Mornar, A.; Nigovic, B.; Kujundzic, N. Identification and quantification of flavonoids and phenolic acids in burr parsley (*Caucalis platycarpos* L.), using high-performance liquid chromatography with diode array detection and electrospray ionization mass spectrometry. *Molecules* **2009,** *14* (7), 2466-2490.

55. Pavlovic, M.; Kovacevic, N.; Couladis, M.; Tzakou, O. Phenolic constituents of *Anthemis triumfetti* (L.) DC. *Biochem. Syst. Ecol.* **2006,** *34*, 449-452.

56. Morishita, H.; Iwahashi, H.; Osaka, N.; Kido, R. Chromatographic separation and identification of naturally occurring chlorogenic acids by ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry. *J. Chromatogr.* **1984,** *315*, 253-260.

57. Iwai, K.; Kishimoto, N.; Kakino, Y.; Mochida, K.; Fujita, T. *In vitro* antioxidative effects and tyrosinase inhibitory activities of seven hydroxycinnamoyl derivatives in green coffee beans. *J. Agric. Food Chem.* **2004,** *52* (15), 4893-4898.

58. Yan, X. T.; Ding, Y.; Li, W.; Sun, Y. N.; Yang, S. Y.; Koh, Y. S.; Kim, Y. H. Two new phenolic compounds from *Artemisia iwayomogi*. *HCA* **2014,** *97* (2), 283-289.

59. Farag, N. F.; Farag, M. A.; Abdelrahman, E. H.; Azzam, S. M.; El-Kashoury, E. S. Metabolites profiling of *Chrysanthemum pacificum* Nakai parts using UPLC-PDA-MS coupled to chemometrics. *Natural Product Research* **2015,** *29*, 1342-1349.

60. de Souza, R. R.; Bretanha, L. C.; Dalmarco, E. M.; Pizzolatti, M. G.; Fröde, T. S. Modulatory effect of *Senecio brasiliensis* (Spreng) Less. in a murine model of inflammation induced by carrageenan into the pleural cavity. *J. Ethnopharmacol.* **2015,** (0).

61. Becerra-Herrera, M.; Lazzoi, M. R.; Sayago, A.; Beltr+ín, R.; Del Sole, R.; Vasapollo, G. Extraction and determination of phenolic compounds in the berries of *Sorbus americana* Marsh and *Lonicera oblongifolia* (Goldie) Hook. *Food Anal. Methods* **2015,** 1-6.

62. Yingngam, B.; Monschein, M.; Brantner, A. Ultrasound-assisted extraction of phenolic compounds from *Cratoxylum formosum* ssp. *formosum* leaves using central composite design and evaluation of its protective ability against H_2O_2-induced cell death. *Asian Pacific journal of tropical medicine* **2014,** *7S1*, S497-S505.

63. Truong, V. D.; McFeeters, R. F.; Thompson, R. T.; Dean, L. L.; Shofran, B. Phenolic acid content and composition in leaves and roots of common commercial sweetpotato (*Ipomea batatas* L.) cultivars in the United States. *J Food Sci.* **2007,** *72* (6), C343-C349.

64. Chen, L. X.; Xia, G. Y.; Liu, Q. Y.; Xie, Y. Y.; Qiu, F. Chemical constituents from the calyces of *Physalis alkekengi* var. *franchetii*. *Biochem. Syst. Ecol.* **2014,** *54* (0), 31-35.

65. Ko, R. K.; Kang, M. C.; Kim, B. S.; Han, J. H.; Kim, G. O.; Lee, N. H. A new phloroglucinol glycoside from *Aster subulatus* Michx. *Bulletin of the Korean Chemical Society* **2009,** *30* (5), 1167-1169.

66. Lai, J. P.; Lim, Y. H.; Su, J.; Shen, H. M.; Ong, C. N. Identification and characterization of major flavonoids and caffeoylquinic acids in three Compositae plants by LC/DAD-APCI/MS. *J Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2007,** *848* (2), 215-225.

67. Lin, L. Z.; Harnly, J. M. Identification of hydroxycinnamoylquinic acids of Arnica flowers and Burdock roots using a standardized LC-DAD-ESI/MS profiling method. *J. Agric. Food Chem.* **2008,** *56* (21), 10105-10114.

68. Clifford, M. N.; Wu, W.; Kirkpatrick, J.; Kuhnert, N. Profiling the chlorogenic acids and other caffeic acid derivatives of herbal Chrysanthemum by LC–MS^n. *J. Agric. Food Chem.* **2007,** *55*, 929-936.

69. Kim, H. J.; Lee, Y. S. Identification of new dicaffeoylquinic acids from *Chrysanthemum morifolium* and their antioxidant activities. *Planta Med.* **2005,** *71* (9), 871-876.

70. Ping, L.; Wang, Y.; Guo, Z.; Wu, S.; Kennelly, E. J.; Wang, J.; Li, T.; Long, C. Separation of three bioactive isomers from *Bidens pilosa* by countercurrent chromatography. *Journal of Liquid Chromatography & Related Technologies* **2014,** *37* (18), 2598-2609.

71. Clifford, M. N.; Knight, S.; Surucu, B.; Kuhnert, N. Characterization by LC-MS^n of four new classes of chlorogenic acids in green coffee beans: dimethoxycinnamoylquinic acids, diferuloylquinic acids, caffeoyl-dimethoxycinnamoylquinic acids, and feruloyl-dimethoxycinnamoylquinic acids. *J. Agric. Food Chem.* **2006,** *54*, 1957-1969.

72. Jaiswal, R.; Karakose, H.; Ruhmann, S.; Goldner, K.; Neumuller, M.; Treutter, D.; Kuhnert, N. Identification of phenolic compounds in plum fruits (*Prunus salicina* L. and *Prunus domestica* L.) by high-performance liquid chromatography/tandem mass spectrometry and characterization of varieties by quantitative phenolic fingerprints. *J. Agric. Food Chem.* **2013,** *61* (49), 12020-12031.

73. Jaiswal, R.; Patras, M. A.; Eravuchira, P. J.; Kuhnert, N. Profile and characterization of the chlorogenic acids in green Robusta coffee beans by LC-MS(n): identification of seven new classes of compounds. *J. Agric. Food Chem.* **2010,** *58* (15), 8722-8737.

74. Harbaum, B.; Hubbermann, E. M.; Wolff, C.; Herges, R.; Zhu, Z.; Schwarz, K. Identification of flavonoids and hydroxycinnamic acids in pak choi varieties (*Brassica campestris* L. ssp. *chinensis* var. *communis*) by HPLC-ESI-MSn and NMR and their quantification by HPLC-DAD. *J. Agric. Food Chem.* **2007,** *55* (20), 8251-8260.

75. Clifford, M. N.; Wu, W.; Kirkpatrick, J.; Jaiswal, R.; Kuhnert, N. Profiling and characterisation by liquid chromatography/multi-stage mass spectrometry of the chlorogenic acids in Gardeniae Fructus. *Rapid Commun. Mass Spectrom.* **2010,** *24* (21), 3109-3120.

76. Zidorn, C.; Ellmerer, E. P.; Sturm, S.; Stuppner, H. Tyrolobibenzyls E and F from *Scorzonera humilis* and distribution of caffeic acid derivatives, lignans and tyrolobibenzyls in European taxa of the subtribe Scorzonerinae (Lactuceae, Asteraceae). *Phytochem.* **2003,** *63* (1), 61-67.

77. Narváez-Cuenca, C. E.; Vincken, J. P.; Zheng, C.; Gruppen, H. Diversity of (dihydro) hydroxycinnamic acid conjugates in Colombian potato tubers. *Food Chem.* **2013**.

78. Jaiswal, R.; Müller, H.; Müller, A.; Karar, M. G. E.; Kuhnert, N. Identification and characterization of chlorogenic acids, chlorogenic acid glycosides and flavonoids from *Lonicera henryi* L. (Caprifoliaceae) leaves by LC--MS^n. *Phytochem.* **2014,** *108* (0), 252-263.

79. Lee, S. Y.; Moon, E.; Kim, S. Y.; Lee, K. R. Quinic acid derivatives from *Pimpinella brachycarpa* exert anti-neuroinflammatory activity in lipopolysaccharide-induced microglia. *Bioorg. Med. Chem. Lett.* **2013,** *23* (7), 2140-2144.

80. Xu, Y. J.; Sun, S. B.; Sun, L. M.; Qiu, D. F.; Liu, X. J.; Jiang, Z. B.; Yuan, C. S. Quinic acid esters and sesquiterpenes from *Sonchus arvensis*. *Food Chem.* **2008,** *111* (1), 92-97.

81. Cao, S.; Ranarivelo, L.; Ratsimbason, M.; Randrianasolo, S.; Ratovoson, F.; Andrianjafy, M.; Kingston, D. G. Antiplasmodial activity of compounds from *Sloanea rhodantha* (Baker) Capuron var. rhodantha from the Madagascar rain forest. *Planta Med.* **2006,** *72* (15), 1438-1440.

82. Liu, J.; Feng, Z.; Xu, J.; Wang, Y.; Zhang, P. Rare biscoumarins and a chlorogenic acid derivative from *Erycibe obtusifolia*. *Phytochem.* **2007,** *68* (13), 1775-1780.

83. McGrath, T. E.; Brown, A. P.; Meruva, N. K.; Chan, W. G. Phenolic compound formation from the low temperature pyrolysis of tobacco. *Journal of Analytical and Applied Pyrolysis* **2009,** *84* (2), 170-178.

84. Fujimoto, K.; Nakamura, S.; Matsumoto, T.; Ohta, T.; Ogawa, K.; Tamura, H.; Matsuda, H.; Yoshikawa, M. Medicinal flowers. XXXVIII. structures of acylated sucroses and inhibitory effects of constituents on aldose reducatase from the flower buds of *Prunus mume*. *Chem. Pharm. Bull. (Tokyo)* **2013,** *61* (4), 445-451.

85. Nogueira, M. S.; Furtado, R. A.; Bastos, J. K. Flavonoids and methoxy-galloyiquinic acid derivatives from the leaf extract of *Copaifera langsdorffii* Desf. *J. Agric. Food Chem.* **2015,** *63* (31), 6939-6945.

86. Armata, A.; Gabrieli, C.; Termentzi, A.; Zervou, M.; Kokkalou, E. Constituents of *Sideritis syriaca*. ssp *syriaca* (Lamiaceae) and their antioxidant activity. *Food Chem.* **2008,** *111* (1), 179-186.

87. Chuda, Y.; Ono, H.; Ohnishi-Kameyama, M.; Nagata, T.; Tsushida, T. Structural identification of two antioxidant quinic acid derivatives from Garland (*Chrysanthemum coronarium.L.*). *J. Agric. Food Chem.* **1996,** *44*, 2037-2039.

88. Meyer, R. S.; Whitaker, B. D.; Little, D. P.; Wu, S. B.; Kennelly, E. J.; Long, C. L.; Litt, A. Parallel reductions in phenolic constituents resulting from the domestication of eggplant. *Phytochem.* **2015,** (0).

89. Gu, W. Y.; Li, N.; Leung, E. L. H.; Zhou, H.; Yao, X. J.; Liu, L.; Wu, J. L. Rapid identification of new minor chemical constituents from Smilacis Glabrae Rhizoma by combined use of UHPLC-Q-TOF-MS, preparative HPLC and UHPLC-SPE-NMR-MS techniques. *Phytochemical Analysis* **2015,** *26* (6), 428-435.

90. Spitaler, R.; Schlorhaufer, P. D.; Ellmerer, E. P.; Merfort, I.; Bortenschlager, S.; Stuppner, H.; Zidorn, C. Altitudinal variation of secondary metabolite profiles in flowering heads of *Arnica montana* cv. ARBO. *Phytochem.* **2006,** *67* (4), 409-417.

91. Wang, S.; Hao, L.-J.; Zhu, J.-J.; Wang, Z.-M.; Zhang, X.; Song, X.-M. Comparative evaluation of Chrysanthemum Flos from different origins by HPLC-DAD-MS^n and relative response factors. *Food Anal. Methods* **2014**.

92. Zou, X.; Liu, D.; Liu, Y.; Xiu, Z.; Xiao, H. A new polyphenol, 1, 3-di-O-caffeoyl-5-O-(1-methoxyl-2-O-caffeoyl-4-maloyl)-quinic acid, isolated from cultured cells of *Saussurea involucrata*. *Chinese Journal of Natural Medicines* **2015,** *13* (4), 295-298.

93. Falsone, G.; Peters, W. Constituents of Euphorbiaceae Part 4 Constitution of the isomeric O-Beta Hydroxy-Gamma-Hydroxycarbonyl-Beta-Methylbutanoyl Shikimic Acids from *Euphorbia biglandulosa*. *Justus Liebigs Annalen der Chemie* **1978,** (12), 1905-1912.

94. Falsone, G. Constituents of Euphorbiaceae .3. Calcium salts of isomeric O-(Beta-Hydroxy-Beta-Methylglutaroyl)Shikimic Acids from *Euphorbia biglandulosa* Desf. *Justus Liebigs Annalen der Chemie* **1977,** (5), 727-731.

95. Clifford, M. N.; Stoupi, S.; Kuhnert, N. Profiling and characterization by LC–MS^n of the galloylquinic acids of green tea, Tara tannin and tannic acid. *J. Agric. Food Chem.* **2007,** *55*, 2797-2807.

96. Ishimaru, K.; Nonaka, G.-I.; Nishioka, I. Gallic acid esters of *proto*quercitol, quinic acid and (–)-shikimic acid from *Quercus mongolica* and *Q. mysinaefolia*. *Phytochem.* **1987,** *26*, 1501-1504.

97. Nishimura, H.; Nonaka, G.-I.; Nishioka, I. Seven quinic acid gallates from *Quercus stenophylla*. *Phytochem.* **1984,** *23*, 2621-2623.

98. Wang, Y.; Hamburger, M.; Gueho, J.; Hostettmann, K. Cyclohexanecarboxylic acid derivatives from *Psiadia trinervia*. *HCA* **1992,** *75*, 269-275.

99. Scholz, E.; Heinrich, M.; Hunkler, D. Caffeoylquinic acids and some biological activities of *Pluchea symphytifolia*. *Planta Med.* **1994,** *60* (4), 360-364.

100. Cookman, G.; Sondheimer, E. The determination of D-quinic and D-shikimic acids by microbiological assay in the characterization of chlorogenic acids and related compounds. *Phytochem.* **1965,** *4* (5), 773-775.

101. Grewe, R.; Lorenzen, W.; Vining, L. Die Totalsynthese der Chinasaure. *Chemische Berichte-Recueil* **1954,** *87* (6), 793-802.

102. Wang, Y.; Wray, V.; Tsevegsuren, N.; Lin, W.; Proksch, P. Phenolic compounds from the Mongolian medicinal plant *Scorzonera radiata*. *Z. Naturforsch. C.* **2012,** *67* (3-4), 135-143.

103. Ono, M.; Masuoka, C.; Odake, Y.; Ikegashira, S.; Ito, Y.; Nohara, T. Antioxidative constituents from *Tessaria integrifolia*. *Food Science and Technology Research* **2000,** *6* (2), 106-114.

104. Jaiswal, R.; Sovdat, T.; Vivan, F.; Kuhnert, N. Profiling and characterization by LC-MS^n of the chlorogenic acids and hydroxycinnamoylshikimate esters in maté (*Ilex paraguariensis*). *J. Agric. Food Chem.* **2010,** *58* (9), 5471-5484.

105. Jaiswal, R.; Deshpande, S.; Kuhnert, N. Profiling the chlorogenic acids of R*udbeckia hirta*, *Helianthus tuberosus*, *Carlina acaulis* and *Symphyotrichum novae-angliae* leaves by LC-MS(n). *Phytochem. Anal.* **2011,** *22*, 432-441.

106. Jaiswal, R.; Matei, M. F.; Deshpande, S.; Kuhnert, N. Identification and characterization of hydroxycinnamates of six *Galium* species from the Rubiaceae family. In *Encyclopedia of Analytical Chemistry*, Hostettmann, K.; Stuppner, H.; Marston, H.; Chen, S., Eds.; John Wiley & Sons, Ltd: 2014; pp 505-524.

107. Armesto, N.; Ferrera, S.; Ferrero, M. Influence of intramolecular hydrogen bonds in the enzyme-catalyzed regioselective acylation of quinic and shikimic acid derivatives. *Tetrahedron* **2006,** *62*, 5401-5410.

108. Jaiswal, R.; Dickman, M. H.; Kuhnert, N. First diastereoselective synthesis of methyl caffeoyl- and feruloyl-*muco*-quinates. *Org. Biomol. Chem.* **2012,** *10* (27), 5266-5277.

109. Haribal, M.; Feeny, P.; Lester, C. C. Caffeoylcyclohexane-1-carboxylic acid derivative from *Asimina triloba*. *Phytochem.* **1998,** *49*, 103-108.

110. Lee, J. Y.; Song, D. G.; Lee, E. H.; Jung, S. H.; Nho, C. W.; Cha, K. H.; Pan, C. H. Inhibitory effects of 3,5-*O*-Dicaffeoyl-*epi*-quinic acid from *Gymnaster koraiensis* on AKR1B10. *Journal of the Korean Society for Applied Biological Chemistry* **2009,** *52*, 731-734.

111. Thong, P. T.; Su, N. D.; Ngoc, T. M.; Hung, T. M.; Dang, N. H.; Thuan, N. D.; Bae, K. H.; Oh, W. K. Antioxidant activity and principles of Vietnam bitter tea *Ilex kudingcha*. *Food Chem.* **2009,** *113*, 139-145.

112. Xie, Y. Y.; Yuan, D.; Yang, J. Y.; Wang, L. H.; Wu, C. F. Cytotoxic activity of flavonoids from the flowers of *Chrysanthemum morifolium* on human colon cancer Colon205 cells. *J. Asian Nat. Prod. Res.* **2009,** *11* (9), 771-778.

113. Jang, D. S.; Yoo, N. H.; Kim, N. H.; Lee, Y. M.; Kim, C. S.; Kim, J.; Kim, J. H.; Kim, J. S. 3,5-Di-*O*-caffeoyl-*epi*-quinic acid from the leaves and stems of *Erigeron annuus* inhibits protein glycation, aldose reductase, and cataractogenesis. *Biol. Pharm. Bull.* **2010,** *33* (2), 329-333.

114. Xie, Y. Y.; Qu, J. L.; Wang, Q. L.; Wang, Y.; Yoshikawa, M.; Yuan, D. Comparative evaluation of cultivars of *Chrysanthemum morifolium* flowers by HPLC-DAD-ESI/MS analysis and antiallergic assay. *J Agric. Food Chem.* **2012,** *60* (51), 12574-12583.

115. Zhang, X.; Wu, C.; Wu, H.; Sheng, L.; Su, Y.; Zhang, X.; Luan, H.; Sun, G.; Sun, X.; Tian, Y.; Ji, Y.; Guo, P.; Xu, X. Anti-hyperlipidemic effects and potential mechanisms of action of the caffeoylquinic acid-rich *Pandanus tectorius* fruit extract in hamsters fed a high fat-diet. *PLoS ONE* **2013,** *8* (4), e61922.

116. Wu, C.; Zhang, X.; Zhang, X.; Luan, H.; Sun, G.; Sun, X.; Wang, X.; Guo, P.; Xu, X. The caffeoylquinic acid-rich *Pandanus tectorius* fruit extract increases insulin sensitivity and regulates hepatic glucose and lipid metabolism in diabetic db/db mice. *The Journal of Nutritional Biochemistry* **2014,** *25* (4), 412-419.

117. Forino, M.; Tenore, G. C.; Tartaglione, L.; Carmela, D.; Novellino, E.; Ciminiello, P. (1*S*,3*R*,4*S*,5*R*)5-*O*-Caffeoylquinic acid: Isolation, stereo-structure characterization and biological activity. *Food Chem.* **2015,** *178*, 306-310.

118. Tuerxuntayi, A.; Liu, Y. Q.; Tulake, A.; Kabas, M.; Eblimit, A.; Aisa, H. A. Kaliziri extract upregulates tyrosinase, TRP-1, TRP-2 and MITF expression in murine B16 melanoma cells. *BMC. Complement Altern. Med* **2014,** *14* (1), 166.

119. Wang, Y.; Wang, E.; Shang, J.; Wang, H. [Caffeoylquinic acid derivatives from the seeds of *Vernonia anthelmintica*]. *Zhongguo Zhong. Yao Za Zhi.* **2012,** *37* (11), 1590-1592.

120. Liu, Q.; Zhang, Y. J.; Yang, C. R.; Xu, M. Phenolic antioxidants from green tea produced from *Camellia crassicolumna* Var. *multiplex*. *J Agric. Food Chem.* **2009,** *57* (2), 586-590.

121. Zhou, Z. H.; Yang, C. R. Chemical constituents of crude green tea, the material of Pu-er tea in Yunnan. *Acta Botanica Yunnanica* **2000,** *22*, 343-350.

122. Adlersberg, M.; Bondinell, W. E.; Sprinson, D. B. Synthesis of 2-hydroxyquinic and 2-hydroxyepiquinic acids from shikimic acid. *J. Am. Chem. Soc.* **1973,** *95* (3), 887-896.

123. Sprogoe, K.; Staerk, D.; Jager, A. K.; Adsersen, A.; Hansen, S. H.; Witt, M.; Landbo, A. K.; Meyer, A. S.; Jaroszewski, J. W. Targeted natural product isolation guided by HPLC-SPE-NMR: constituents of *Hubertia* species. *J. Nat Prod.* **2007,** *70* (9), 1472-1477.

124. Wu, Y. P.; Liang, X.; Liu, X. Y.; Zhong, K.; Gao, B.; Huang, Y. N.; Gao, H. *Cedrus deodara* pine needle as a potential source of natural antioxidants: Bioactive constituents and antioxidant activities. *Journal of Functional Foods* **2015,** *14*, 605-612.

125. Liu, M.; Dong, J.; Lin, Z.; Niu, Y.; Zhang, X.; Jiang, H.; Guo, N.; Li, W.; Wang, H.; Chen, S. Rapid screening of transferrin-binders in the flowers of *Bauhinia blakeana* Dunn by on-line high-performance liquid chromatography–diode-array detector–electrospray ionization–ion-trap–time-of-flight–mass spectrometry–transferrin–fluorescence detection system. *J. Chromatogr. A* **2016,** *1450*, 17-28.

126. Stevenson, P. C.; Anderson, J. C.; Blaney, M.; Simmonds, M. S. J. Developmental inhibition of *Spodoptera litura* (Fab.) larvae by a novel caffeoylquinic acid from wild groundnut *Arachis paraguariensis* (Chod et Hassl.). *J. Chem. Ecol.* **1993,** *19*, 2917-2933.

127. Kamto, E. L. D.; Ngono, D. S. B.; Mbing, J. N.; Atchade, A. d. T.; Pegnyemb, D. E.; van der Westhuizen, J. H. An aromatic amide *C*-glycoside and a cyclitol derivative from stem barks of *Piper guineense* Schum and Thonn (Piperaceae). *Phytochemistry Letters* **2014,** *10*, LXXVI-lxxxi.

128. Harinantenaina, L.; Matsunami, K.; Otsuka, H. Chemical and biologically active constituents of *Pteris multifida*. *J Nat. Med* **2008,** *62* (4), 452-455.

129. Gohari, A.; Saeidnia, S.; Moghaddam, M. K.; Yassa, N.; Malmir, M.; Shahverdi, A. Isolation of a new quinic acid derivative and its antibacterial modulating activity. *Daru-Journal of Faculty of Pharmacy* **2010,** *18* (1), 69-73.

130. Jaiswal, R.; Kuhnert, N. How to identify and discriminate between the methyl quinates of chlorogenic acids by liquid chromatography-tandem mass spectrometry. *J. Mass Spectrom.* **2011,** *46* (3), 269-281.

131. Hu, X.; Chen, L.; Shi, S.; Cai, P.; Liang, X.; Zhang, S. Antioxidant capacity and phenolic compounds of Lonicerae macranthoides by HPLCΓÇôDADΓÇôQTOF-MS/MS. *J. Pharm. Biomed. Anal.* **2016,** *124*, 254-260.

132. Akihisa, T.; Kawashima, K.; Orido, M.; Akazawa, H.; Matsumoto, M.; Yamamoto, A.; Ogihara, E.; Fukatsu, M.; Tokuda, H.; Fuji, J. Antioxidative and melanogenesis-inhibitory activities of caffeoylquinic acids and other compounds from moxa. *Chem. Biodivers.* **2013,** *10* (3), 313-327.

133. Kirmizibekmez, H.; Bassarello, C.; Piacente, S.; Celep, E.; Atay, I.; Mercanoglu, G.; Yesilada, E. Phenolic compounds from *Hypericum calycinum* and their antioxidant activity. *Nat. Prod. Commun.* **2009,** *4* (4), 531-534.

134. Song, S.; Li, Y.; Feng, Z.; Jiang, J.; Zhang, P. Hepatoprotective constituents from the roots and stems of *Erycibe hainanesis*. *J Nat. Prod.* **2010,** *73* (2), 177-184.

135. Zeller, W. E. Synthesis of 1-O-methylchlorogenic acid: reassignment of structure for MCGA3 isolated from bamboo (*Phyllostachys edulis*) leaves. *J. Agric. Food Chem.* **2014,** *62* (8), 1860-1865.

136. Kwon, H. C.; Jung, C. M.; Shin, C. G.; Lee, J. K.; Choi, S. U.; Kim, S. Y.; Lee, K. R. A new caffeoyl quinic acid from *Aster scaber* and its inhibitory activity against human immunodeficiency virus-1 (HIV-1) integrase. *Chem. Pharm. Bull.* **2000,** *48* (11), 1796-1798.

137. Stetten, D. Symmetry, asymmetry and meso-symmetry. *The American Journal of Medicine* **1959,** *26* (2), 161-164.

138. Sinisi, V.; Boronova, K.; Colomban, S.; Navarini, L.; Berti, F.; Forzato, C. Synthesis of Mono-, Di-, and Tri-3,4-dimethoxycinnamoyl-1,5-gamma-quinides. *European Journal of Organic Chemistry* **2014,** *2014* (6), 1321-1326.

139. Hucke, J.; Maier, H. G. [Quinic acid lactone in coffee]. *Z. Lebensm. Unters. Forsch.* **1985,** *180* (6), 479-484.

140. Scholz, B. M.; Maier, H. G. Isomers of quinic acid and quinide in roasted coffee. *Z. Lebensm. Unters. -Forsch.* **1990,** *190*, 132-134.

141. Scholz-Böttcher, B. M.; Ludger, E.; Maier, H. G. New stereoisomers of quinic acid and their lactones. *Liebigs Ann. Chim.* **1991,** *1991*, 1029-1036.

142. Farah, A.; dePaulis, T.; Moreira, D. P.; Trugo, L. C.; Martin, P. R. Chlorogenic acids and lactones in regular and water-decaffeinated arabica coffees. *J. Agric. Food Chem.* **2006,** *54* (2), 374-381.

143. Frank, O.; Blumberg, S.; Krumpel, G.; Hofmann, T. Structure determination of 3-O-caffeoyl-epi-gamma-quinide, an orphan bitter lactone in roasted coffee. *J. Agric. Food Chem.* **2008,** *56* (20), 9581-9585.

144. Perrone, D.; Farah, A.; Donangelo, C. M.; de Paulis, T.; Martin, P. R. Comprehensive analysis of major and minor chlorogenic acids and lactones in economically relevant Brazilian coffee cultivars. *Food Chemistry.* **2008,** *106* (2), 859-867.

145. Blumberg, S.; Frank, O.; Hofmann, T. Quantitative studies on the influence of the bean roasting parameters and hot water percolation on the concentrations of bitter compounds in coffee brew. *J. Agric. Food Chem.* **2010,** *58* (6), 3720-3728.

146. Matei, M. F.; Jaiswal, R.; Kuhnert, N. Investigating the chemical changes of chlorogenic acids during coffee brewing - conjugate addition of water to the olefinic moiety of chlorogenic acids and their quinides. *J Agric. Food Chem.* **2012,** *60*, 12105-12115.

147. Kaiser, N.; Birkholz, D.; Colomban, S.; Navarini, L.; Engelhardt, U. H. A new method for the preparative isolation of chlorogenic acid lactones from coffee and model roasts of 5-caffeoylquinic Acid. *J Agric. Food Chem.* **2013,** *61* (28), 6937-6941.

148. Zhu, W. M.; Lu, C. H.; Wang, Y.; Zhou, J.; Hao, X. J. Monoterpenoids and their glycosides from *Winchia calophylla*. *Journal of Asian Natural Products Research* **2004,** *6* (3), 193-198.

149. Talapatra, B.; Das, A. K.; Talapatra, S. K. Defuscin, a new phenolic ester from *Dendrobium fuscescens*: Conformation of shikimic acid. *Phytochem.* **1989,** *28* (1), 290-292.

150. Danieli, B.; Debellis, P.; Barzaghi, L.; Carrea, G.; Ottolina, G.; Riva, S. Studies on the Enzymatic Acylation of Quinic Acid, Shikimic Acid, and Their Derivatives in Organic-Solvents. *HCA* **1992,** *75* (4), 1297-1304.

151. Nonaka, G.-I.; Ageta, M.; Nishioka, I. Tannins and related compounds. XXV. A new class of gallotannins possessing a (–)-shikimic acid core from C*astanopsis cuspidata* var. *sieboldii*. *Chem. Pharm. Bull.* **1985,** *33*, 96-101.

152. Goupy, P. M.; Varoquaux, P. J. A.; Nicolas, J. J.; Macheix, J.-J. Identification and localization of hydroxycinnamoyl and flavonol derivatives from endive (*Cichorium endivia* L. cv. Geante Maraichere) leaves. *J. Agric. Food Chem.* **1990,** *38*, 2116-2121.

153. Geiger, H.; El-Dessouki, S.; Seeger, T. (3S,4S,5R)-3,4,5-trihydroxy-1-cyclohexene-carboxylic acid from *Sequoiadendron giganteum*. *Phytochem.* **1995,** *40* (6), 1705-1707.

154. Dittrich, P.; Danböck, T. Isolation and characterisation of a novel *p*-coumaric acid ester of *myo*-inositol from needles of *Taxus baccata*. *Plant Physiol.* **1977,** *59*, 279-281.

155. Shen, Y. C.; Chen, C. Y.; Hung, M. C. Taxane diterpenoids from seeds of *Taxus mairei*. *Chem. Pharm. Bull.* **2000,** *48* (9), 1344-1346.

156. Heilemann, J.; Wray, V.; Strack, D. Synthesis of 2-O-(4-coumaroyl)-myo-inositol by a protein preparation from needles of *Taxus baccata*. *Phytochem.* **1990,** *29* (11), 3487-3489.

157. Nishimura, H.; Nonaka, G.; Nishioka, I. Tannins and Related Compounds .19. 8 New gallotannins containing a proto-quercitol core from *Quercus stenophylla* Makino .3. *Chem. Pharm. Bull.* **1984,** *32* (5), 1741-1749.

158. Nishimura, H.; Nonaka, G.; Nishioka, I. Tannins and Related Compounds .20. 2 New ellagitannins containing a proto-quercitol core from *Quercus stenophylla* Makino .4. *Chem. Pharm. Bull.* **1984,** *32* (5), 1750-1753.

159. Zou, X.; Liu, D.; Liu, Y.; Fu, Y.; Zhang, X.; Xiu, Z.; Xiao, H. Isolation and characterization of two new phenolic acids from cultured cells of *Saussurea involucrata*. *Phytochemistry Letters* **2014,** *7* (0), 133-136.

160. Jiang, X. W.; Bai, J. P.; Zhang, Q.; Hu, X. L.; Tian, X.; Zhu, J.; Liu, J.; Meng, W. H.; Zhao, Q. C. Caffeoylquinic acid derivatives from the roots of *Arctium lappa* L. (burdock) and their structure-activity relationships (SARs) of free radical scavenging activities. *Phytochemistry Letters* **2016,** *15*, 159-163.

161. Bai, J. P.; Hu, X. L.; Jiang, X. W.; Tian, X.; Zhao, Q. C. Caffeic acids from roots of *Arctium lappa* and their neuroprotective activity. *Chinese Traditional and Herbal Drugs* **2015,** *2015*, 163-168.

162. Markovic, S.; Tosovic, J.; Markovic, J. M. Synergic application of spectroscopic and theoretical methods to the chlorogenic acid structure elucidation. *Spectrochimica Acta Part A-Molecular and Biomolecular Spectroscopy* **2016,** *164*, 67-75.

163. D'Amelio, N.; Fontanive, L.; Uggeri, F.; Suggi-Liverani, F.; Navarini, L. NMR reinvestigation of the caffeine–chlorogenate complex in aqueous solution and in coffee brews. *Food Biophysics* **2009,** *4*, 321-330.

164. D'Amelio, N.; Papamokos, G.; Dreyer, J.; Carloni, P.; Navarini, L. NMR studies of hetero-association of caffeine with di-*O*-caffeoylquinic acid isomers in aqueous solution. *Food Biophysics* **2015,** *10*, 235-243.

165. Snyder, C. D.; Rapoport, H. Stereochemistry of quinate-shikimate conversions. Synthesis of (–)-4-epi-shikimic acid. *J. Am. Chem. Soc.* **1973,** *95* (23), 7821-7828.