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Review Article

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Chitwin Compounds: A New Revelation of Chemistry and Biology

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Abstract Forms of matter showing themselves in the same relationship as objects and their mirror images were called enantiomeric, and this relationship was discovered at the level of crystals: quartz, sodium wolframate, etc. Separation of tartaric acid enantiomers, as well as the discovery of tetrahedral model of C atom, disclosed the enantiomorphous relationship at molecular level. Then the concept of chirality (kheir, hand, Gr.) partially replaced the concept of enantiomorphism. At first sight at least, the idea of chirality showed a higher mobility in physical-chemical applications. However, both points of view see their running elements – enantiomorphous or chiral forms – as separate, distinct entities. If one consider the two sides of enantiomorphism or chirality as a whole unit, one arrives at interesting and important conclusions. If a molecule contains both sides, i. e., it is formed of two enantiomeric halves (as two gloves of different handedness), the result is a symmetric or *meso* compound. Instead, if a molecule is formed of two identical sides of enantiomorphous objects (as of two gloves of the same handedness), a compound of a two-fold homochirality is obtained, since the molecules of such a compound are homochiral with one another and they are internally homochiral, at the same time. We have called the members of this subgroup *chitwin* compounds (from *chi*, chiral, and *twin*). A tentative discussion of the properties and natural distribution of *chitwin* compounds is made.

Keywords chitwin, internally homochiral, internally heterochiral, symmetry, doubling, dimerization

Introduction

When Pasteur crystalized the salts of paratartaric acid (a racemic mixture), he noticed that he had obtained two types of crystals that were enantiomeric with one another, and separated them according to their form. (At that time the enantiomeric relationship of some crystalline compounds was relatively familiar to chemists). Then he solved them in water, and a polarimeter analysis indicated that one solution was dextrorotary and the other levorotary, with the same numerical value [1,2]. The theory of van't Hoff [3] and Le Bel [4], based on asymmetric C, as well as on spacial distribution of its bonds along the axis of a regular tetrahedron, disclosed the enantiomeric relationship at molecular level. Van't Hoff elaborated molecular models for optical isomers, however a scientific and philosophical dilemma appeared, concerning the correspondence between models and samples of different isomers [5]. This dilemma was solved with some uncertainty by E. Fischer [6-9]. Half a century after Fischer, the group of Bijvoet [10] eliminated every doubt and found out that Fischer had given the correct solution. The cornerstone of many experiments, including those of Pasteur, Fischer, Bijvoet, was tartaric acid, discovered by Scheele (1770) at the dawn of chemical sciences [11,12]. Due to these scholars, and many others, every chemistry graduate of today can state: "on this stone (tartre, Fr.) is built (stereo)chemistry". The isomers of tartaric acid were structurally correlated with the isomers of glyceraldehyde and other monosaccharides as well as with many other chiral compounds [13,14].

Kelvin [15] replaced the relationship of enantiomorphism with the relationship of chirality (kheir, hand, Gr.). It seems quite plausible that Kelvin included in this relationship other objects possessing this quality, equally familiar to the previous scholars who invented the term enantiomorphism: gloves, shoes, augers, screwdrivers, shells of some molluscs (gastropods), etc. (It's a less macabre alternative!). Kelvin also defined homochirality and heterochirality: "…two equal and similar right hands are homochirally similar. Equal and similar right and left hands are heterochirally…". Eight decades later, Prelog adopted Kelvin's chirality and other congeneric terms, however returned to the mirror and included also a reassuring mathematical term: "an object is chiral if it cannot be brought into congruence with its mirror image by translation or rotation" [16,17]. Now, armed with Kelvin's chirality and Prelog's mirror, plus a suitable amount of congruence, we may arrive at unique and important conclusions. Both Kelvin and Prelog regarded the two hands (or chiral objects) of the same handedness as separate, distinct entities. However, every couple of the same hands may be considered as a whole unit, or in chemical terms, molecules containing two (or more, but an even number of) asymmetric carbons of the same chirality, and a double set of chemical functions. Such molecules possess a twofold degree of *homochirality*: they are homochiral with one another and they are also characterized by an *internal homochirality* i. e., they are superhomochiral. Of this reason we have called them *chitwin* molecules (*chi* from *chiral*, plus *twin*).

Chitwin molecules constitute a distinct subgroup of the whole group of chiral ones. Their distinct character is conferred by their physical-chemical and biochemical properties. They have a unique, exceptional quality: once constructed, either of their half suffer a chemical reaction, or a series of reactions, the result is the same. Hence, they are highly versatile molecules and this versatility could have played an important role in molecular evolution, in the process of homeostasis of living things and in other fundamental natural phenomena. Every chiral compound that is not yet *chitwin* is a *chitwin* precursor. In exactly defined conditions, its doubling produces a *chitwin* derivative. As shown in this paper, *chitwin* molecules present a remarkable structural variety and they are well represented among the main classes of natural compounds: monosaccharides, amino acids, proteins, lipids, lignans and neolignans (phenolic derivatives), heterocyclic compounds, polyprenyls (isoprenoids), special natural reagents (coenzymes) and even polynucleotidic structures of palindrome type. *Chitwin* compounds constitute a real, essential, unique and trustworthy network in living matter. Moreover, *chitwin* molecules are isomers and metabolically interchangeable with two other subgroups, *meso* compounds and chiral compounds characterized by an *irregular distribution of their asymmetric centers*.

Kelvin defined heterochiral objects as a couple of chiral ones with opposed handedness, as are right hand and left hand, the two objects being seen as separate entities. If the two entities are considered as parts of the same molecular unit, *meso* substances are obtained. They are identical with one another, however they are *internally heterochiral*. Moreover, their two halves have different priorities (ranks).

In macrocosmic world, Kelvin-Prelog theory discloses us the existence of three types of objects: (i) symmetric, (ii) chiral, and (iii) *chitwin* ones. Every object that isn't symmetric is chiral and all we need is to confront it with Prelog's mirror and construct a replica as mirror shows it. The couple will constitute a *symmetric* system, and its two halves have different ranks (priorities). Otherwise, if we build a copy of the chiral object, their couple will constitute a *chitwin* or a homochiral system. Let's remember Pasteur's experiment: a couple of crystals of the same group constitute a homochiral (or *chitwin*) system, while a couple of enantiomeric crystals make a heterochiral (or symmetric) system. Living things also illustrate this point of view. Moreover, contrary to dead chiral objects (except hands!) that we associate just mentally – of the same, or of opposed handedness – living things of the same species are linked by the transfer of genetic material in view of species preservation – pollination by plants, and mating by animals. Symmetrical systems are illustrated by a vast number and diversity of vertebrate species. On the other hand, some species of plants (flowers) and animals (gastropods) manifest all three possibilities. A phenomenon characteristic to plants, enantiostyly, was defined as a plant sexual polymorphism in which female sex organs are deflected to the left or right, resulting in symmetrical pairs (mirror-image) of flowers [18]. It was proved that this form of sexual asymmetry has the role to promote cross-pollination in bee-pollinated plants [19,20]. The vast majority of snail species are almost exclusively of one handedness and the individuals of minority are unable to

mate with individuals of normal coil, so directionality is maintained by frequency dependent selection [21]. One can assert that these snail species are in a biological race for *chitwin* phenomenon. An exception to this rule are the snails of subgenus *Amphidromus*, because dextral (D) and sinistral (S) individuals occur in about equal proportions (so-called 'antisymmetry') in most species. It was shown that the species of this subgenus accomplish a sexual selection for dimorphism, rather than for monomorphism. Moreover, the transfer of genetic material between D and S individuals occurs more frequently than expected by chance. Physiology and biochemistry of these snails are arguments for symmetrical systems [21].

In this paper, the representation of *chitwin* molecules by the members of the main classes of natural compounds is presented in an exemplifying manner.

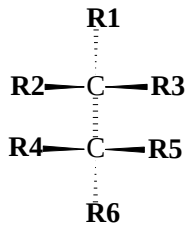
1. Monosaccharides

Monosaccharides and oligosaccharides are a good illustration of *chitwin* molecules. E. Fischer disclosed *chitwin* compounds as redox homogenous derivatives of aldoses which possessed the exceptional quality that by reversing their ends, the same product was obtained: mannose, idose, threose [6-9].

1.1. Redox homogenous derivatives

The group of C_4 has a number of well-known and characterized *chitwin* representatives (Table 1.1). Every compound of Table 1.1 has two asymmetric carbons with the same chirality [22-25]. On the other hand, all of them have their *meso* (or *internally heterochiral*) counterpart. Of the ten isomers of linear hexitols, four are *chitwin* (D- and L-mannitol, D- and L-iditol) (Table 1.2) two are *meso* (allitol and galactitol) and four are based on an *irregular distribution* of their chiral centers {D-glucitol (L-gulitol) is (2S,3R,4R,5R)-hexahydroxy-hexane}. *Idem* for the ten linear isomers of aldaric acids (Table 1.2). Many other polyols and aldaric acids, especially those with an even number of C atoms and hydroxyl functions, present a similar molecular variety of their isomers. Also, there was a tentative to extend this concept to C_8 and C_9 [26-28].

Table 1.1: Chitwin molecules as represented by C_4 group.



R						Chitwin compound
R1	R2	R3	R4	R5	R6	
-COOH	-H	-OH	-OH	-H	-COOH	(2R,3R)-Tartaric acid (chitwin 1.1)
-COOH	-OH	-H	-H	-OH	-COOH	(2S,3S)-Tartaric acid (chitwin 1.2)
$-H_2C-OH$	-H	-OH	-OH	-H	$-H_2C-OH$	(2S,3S)-Threitol (chitwin 1.3)
$-H_2C-OH$	-OH	-H	-H	-OH	$-H_2C-OH$	(2R,3R)-Threitol (chitwin 1.4)
$-CH_3$	-H	-OH	-OH	-H	$-CH_3$	(2S,3S)-2,3-Butanediol (chitwin 1.5)
$-CH_3$	-OH	-H	-H	-OH	$-CH_3$	(2R,3R)-2,3-Butanediol (chitwin 1.6)
$-H_2C-C_6H_5$	-OH	-H	-H	-OH	$-H_2C-C_6H_5$	(2R,3R)-1,4-Diphenyl-2,3-butanediol (chitwin 1.7)
$-H_2C-C_6H_5$	-H	-OH	-OH	-H	$-H_2C-C_6H_5$	(2S,3S)-1,4-Diphenyl-2,3-butanediol (chitwin 1.8)
$-C(C_6H_5)_2-OCH_3$	-H	-OH	-OH	-H	$-C(C_6H_5)_2-OCH_3$	(2R,3R)-1,1,4,4,-Tetraphenyl-1,4-dimethoxy-2,3-butanediol (chitwin 1.9)

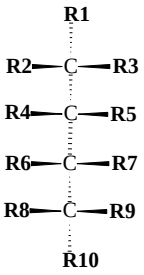
1.2. 5-Ketohexoses of some ketohexoses (fructose, sorbose) and their 1,ω-diphosphates (5-ketofructose-1,6-diphosphate) are *chitwin* molecules [29-32].

1.3. Dimeric saccharides

Fischer prepared other *chitwin* compounds by a doubling reaction of glycosyl bromides: trehalose, isotrehalose, β,β-dicellobiose, β,β-dilactose [33-36]. Hence, all homogenous unreducing disaccharides having the same ring and

glycosidic configuration are *chitwin* representatives. Trehalose (α-D-glucopyranosyl-1,1'-α-D-glucopyranose) was found *per se* and as a 6,6'-diester of mycolic acid (cord factor) [37] (Fig. 1.1). Isotrehalose (β-D-glucopyranosyl-1,1'-β-D-glucopyranose), with the two sugar residues linked by a spacer, was found in carotenoid glycosides (see polyprenyl lipids), lignans and cyclobutane alkaloids (see below). An isomer of *chitwin* tetrasaccharides synthesized by Fischer, based on gentiobiose, was found in crocin [38]. On the other hand, all the ether dimers of reducing saccharides linked to the same carbon, belong to this subgroup (Fig. 1.1). Till now, some representatives of 2,2'-dimer ether of β-D-glucopyranose, linked directly, in cinnacasolide C [39], or of 6,6'-dimer ether, linked by a spacer in monochaetin [40], sagerinic acid [41] and stachysetin [42] (see below).

Table 1.2: *Chitwin* molecules as represented by C_6 group.



R										Chitwin compound
R1	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R9**	**R10**	
$-H_2C-OH$	-OH	-H	-OH	-H	-H	-OH	-H	-OH	$-H_2C-OH$	(2R,3R,4R,5R)-Mannitol (chitwin 1.10)
$-H_2C-OH$	-H	-OH	-H	-OH	-OH	-H	-OH	-H	$-H_2C-OH$	(2S,3S,4S,5S)-Mannitol (chitwin 1.11)
$-H_2C-OH$	-OH	-H	-H	-OH	-OH	-H	-H	-OH	$-H_2C-OH$	(2R,3S,4S,5R)-Iditol (chitwin 1.12)
$-H_2C-OH$	-H	-OH	-OH	-H	-H	-OH	-OH	-H	$-H_2C-OH$	(2S,3R,4R,5S)-Iditol (chitwin 1.13)
-COOH	-OH	-H	-OH	-H	-H	-OH	-H	-OH	-COOH	(2S,3S,4S,5S)-Mannaric acid (chitwin 1.14)
-COOH	-H	-OH	-H	-OH	-OH	-H	-OH	-H	-COOH	(2R,3R,4R,5R)-Mannaric acid (chitwin 1.15)
-COOH	-OH	-H	-H	-OH	-OH	-H	-H	-OH	-COOH	(2S,3R,4R,5S)-Idaric acid (chitwin 1.16)
-COOH	-H	-OH	-OH	-H	-H	-OH	-OH	-H	-COOH	(2R,3S,4S,5R)-Idaric acid (chitwin 1.17)

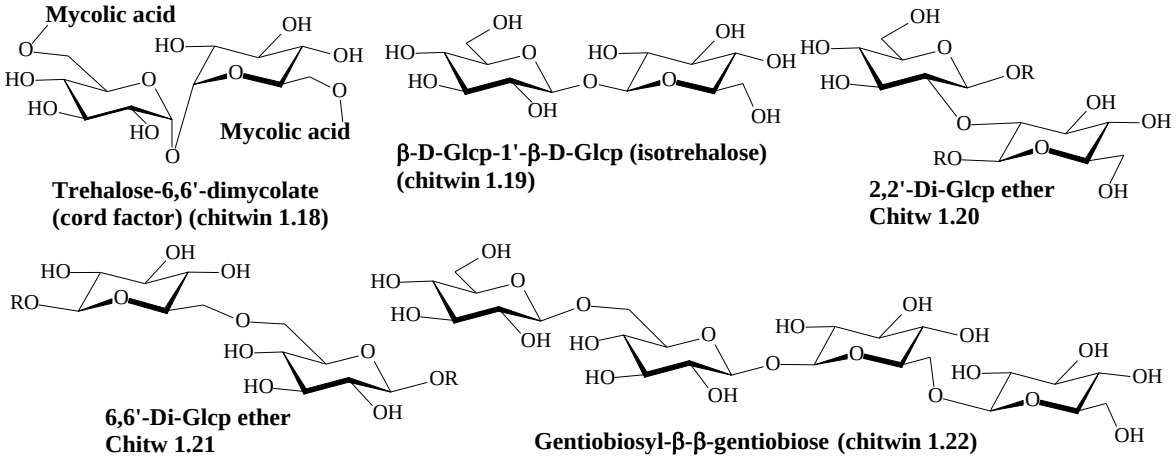


Figure 1.1: Unreducing oligosaccharides and reducing dimer ethers of saccharides as chitwin representatives

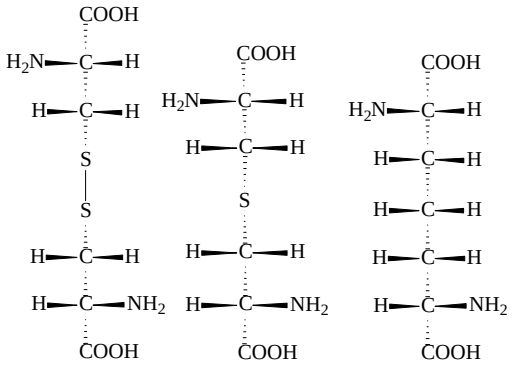
2. Amino Acids

It was Vickery [43] who noticed *chitwin* molecules as a distinct subgroup, and got involved systematically in these compounds, including their chemical nomenclature [44]. He defined them as "symmetrical substances which have identical asymmetric structures at both ends of a chain". Vickery showed that other classes of compounds, especially amino acids, may also submit to this principle.

Amino acids *per se* or as derivatives present three forms, all including representatives of *chitwin* molecules:

2.1. Diamino-dicarboxylic acids

Cystine and its higher homologues, α,ε-diaminopimelic acids and other similar linear diamino-dicarboxylic acids, and lanthionine (Fig. 2.1).

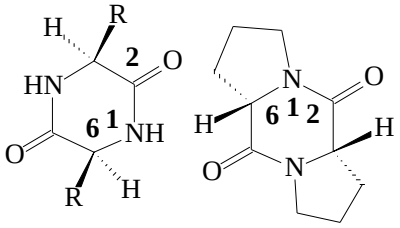


L,L-Cystine (chitwin 2.1) **Lanthionine (chitwin 2.2)** **L,L-Diaminopimelic acid (chitwin 2.3)**

Figure 2.1: Amino acids as chitwin molecules

2.2. Diketopiperazines and derivatives formed of aminoacids with the same configuration. Of the 20 common aminoacids, 19 produce *chitwin* diketopiperazines and derivatives (Tab. 2.1).

Table 2.1: 2,5-Diketopiperazines of natural aminoacids, as *chitwin* molecules



2,5-Diketo-pyperazines **Cyclo-L-Pro-L-Pro (chitwin 2.4)**

R	2,5-Diketopiperazine	R	2,5-Diketopiperazine
$-CH_3$	Ala (chitwin 2.5)	$-CH_2-CH_2-CONH_2$	Gln (chitwin 2.14)
$-CH(CH_3)_2$	Val (chitwin 2.6)	$-CH_2-COOH$	Asp (chitwin 2.15)
$-CH_2-CH(CH_3)_2$	Leu (chitwin 2.7)	$-CH_2-CONH_2$	Asn (chitwin 2.16)
$-CH(CH_3)-CH_2-CH_3$ (3S)	Ile (chitwin 2.8)	$-CH_2$-(4-OH)Phenyl	Tyr (chitwin 2.17)
$-CH(OH)-CH_3$ (3S)	Thr (chitwin 2.9)	$-CH_2$-Phenyl	Phe (chitwin 2.18)
$-CH_2-OH$	Ser (chitwin 2.10)	$-CH_2$-Imidazolyl	His (chitwin 2.19)
$-CH_2-SH$	Cys (chitwin 2.11)	$-CH_2$-Indolyl	Trp (chitwin 2.20)
$-CH_2-CH_2-S-CH_3$	Met (chitwin 2.12)	$-(CH_2)_2$-guanidyl	Arg (chitwin 2.21)
$-CH_2-CH_2-COOH$	Glu (chitwin 2.13)	$-(CH_2)_3-NH_2$	Lys (chitwin 2.22)

2.3. Homogenous diesters of amino acids, their prototype being amino acid peroxydes and anhydrides. (For lysine diester with a spacer see carotenoid esters).

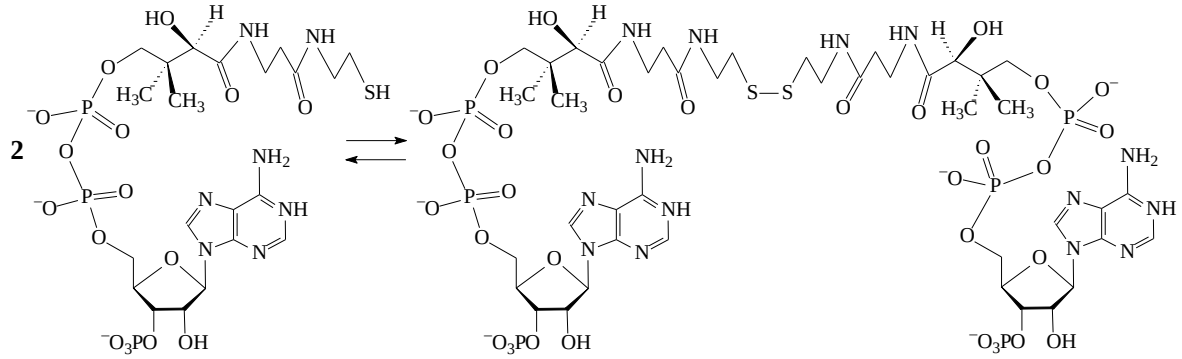
Cystine and diaminopimelic acid have been introduced in this group by Vickery [43] and lanthionine was introduced by us on the same biochemical basis. Cystine (Cys-Cys) may suffer a reducing reaction, cysteine (Cys) being the

reduced form. All three amino acids – cysteine, diaminopimelic acid, lanthionine, fully exemplify the type of indirect biosynthesis, every dimerization reaction being omitted [45], except conversion of Cys to Cys-Cys. This reaction is characteristic to all oligo- and polypeptides containing Cys (see 3. Coenzymes and 4. Homomeric Proteins).

2,5-Diketopiperazines were discovered by E. Fischer [46]. All possible forms of homogenous (LL, DD) and mixed (D and L) as well as of different amino acids, were synthesized and discovered in natural materials [47-52]. 2,5-Diketopiperazines formed of different amino acids are important since their doubling as chiral molecules leads to *chitwin* ones (see 6. Heterocyclic derivatives of 2,5-diketopiperazines). Cyclo(L-Val-L-Val) and cyclo(L-Val-D-Val) were synthesized in view of their comparative oxidation with dioxiranes [53]. Cyclodipeptide synthases were discovered as a novel enzyme family that employs aminoacyl-tRNAs as substrates for 2,5-diketopiperazine synthesis. A cyclodipeptide synthase of *Streptomyces noursei*, AlbC, uses aminoacyl-tRNAs as substrates to catalyze the formation of cyclo-L-Phe-L-Leu [54]. A number of 51 cyclodipeptide synthases were analyzed concerning their substrate specificity, and the conclusion was that they use 17 proteinogenic amino acids [55]. Two such enzymes of *Nocardiopsis* sp., NozA and NcdA, catalyze cyclo-L-Trp-L-Trp biosynthesis from tryptophanyl-tRNA, being outstandingly specific [56].

3. Coenzymes

Coenzymes included in the subgroup of *chitwin* molecules are coenzyme A, 4-phosphopantetheine and glutathione, all in oxidized state (Fig. 3.1) [45]. Multiple biochemical and physiological reasons determined vast and detailed research about all three compounds. Coenzyme A is involved in the metabolism of organic acids and can serve also as a hydrogen carrier (Fig. 3.1). Phosphopantetheine, a fragment of coenzyme A, similarly with the latter, possesses a thiol group in its molecule. Of this reason, it may function as a redox system and bind to cellular proteins. A well studied tripeptide undergoing this transformation is glutathione; in oxidized form glutathione is a chitwin molecule (Fig. 3.1). Glutathione was studied especially due to its implications in redox reactions, detoxification processes and glutathione cycle. The amino acid Cys suffers decarboxylation and becomes cysteamine. This amino thiol is a biochemical constituent of phosphopantetheine and coenzyme A.



Coenzyme A (reduced) **Coenzyme A (oxidized) (chitwin 3.1)**

Glutathion (reduced) **Glutathion (oxidized) (chitwin 3.2)**

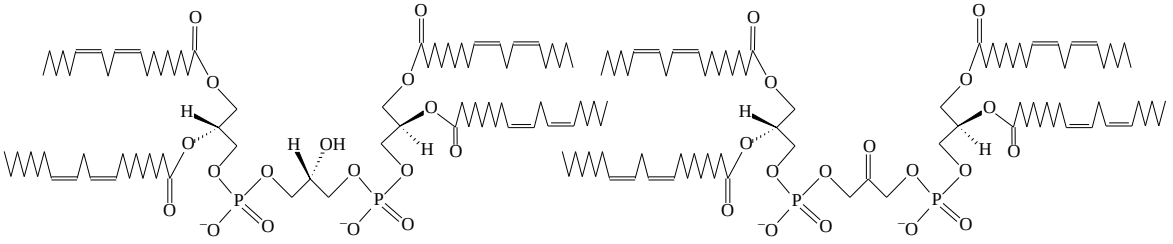
Figure 3.1: Oxidized coenzyme A and glutathione as chitwin molecules

4. Homomeric Proteins

When amino acids are integrated in protein chains, their amino and carboxyl groups of C-α constitute the peptide backbone, and manifest themselves in a totally different manner, in comparison with free state. Physical-chemical character of amino acids in this new state is predominantly expressed by their side chains (tails). They allow a variety of linkages, some of them relatively weak but significant in number (Van der Waals, hydrogen bonds), others strong, and of this reason easily approached: covalent (disulfuric), ionic, etc. Disulfuric bonds are due exclusively to Cys, a relatively widespread natural constituent of proteins. Hence this amino acid is an important agent for the association of proteins in oligomeric constructions, by disulfide bridges. Being formed of amino acids that are chiral, proteins are also chiral. And the association of two (or more) chiral structures of the same handedness can produce only a *chitwin* system and not a symmetrical one [57-60]. Consequently, homooligomeric structures or homomeric complexes are *chitwin*, rather than symmetric. The homomeric complexes are *chitwin* rather than symmetric of two reasons: (1) the constituent amino acids of proteins have L-configuration; (2) the sense of monomeric protein helices is of the same handedness. And the answer to a question raised by Metzler and Metzler [45] is this one: two chromatids coiled with opposite handedness form a *symmetric* system and snail shells or flowers [18,19] with both right and left handedness are also *symmetric*.

5. Lipids

Lipids are represented as *chitwin* molecules (Fig. 5.1) by cardiolipin [61], bis-phosphatidyl-dihydroxy acetone and other similar compounds. However, a doubling reaction of every lipidic chiral molecule would produce a *chitwin* structure. It was shown that when cholesterol, a chiral molecule with eight asymmetric C atoms, is put in the presence of concentrated sulfuric acid, a dimer, *bicholestadiene, is formed, in which cholesterol kept seven* asymmetric C atoms *[62]*. *Bicholestadiene is a veritable* chitwin *compound. On the other hand, enantiomeric cholesterol has been synthesized [*63*]. It might be supposed that if racemic cholesterol is mixed with sulfuric acid, three types of bicholestadiene* are formed, two *chitwin* and one symmetric.



Cardiolipin (bis-phosphatidyl-glycerol) (chitwin 5.1) **Bis-phosphatidyl-dihydroxyacetone (chitwin 5.2)**

Figure 5.1: Chitwin molecules represented by lipids

6. Heterocyclic Derivatives of 2,5-Diketopiperazines

Compounds of this group manifest a variety of biological activities. The relatively loose diketopiperazine is closed to a tighter structure, both *chitwin* molecules [52]. Moreover, their lipophilic character is increased by methylation or prenylation (Fig. 6.1). Their meso isomers follow a similar metabolic path. Some of them have antibiotic activity, i. e., they are interspecies mediators. They are especially derivatives of substituted diketopiperazines, and are implicitly biosynthesized of amino acids. Only those that belong to *chitwin* molecules will be discussed here.

Diketopiperazines of two different amino acids are just chiral. Their doubling make them *chitwin*. The following *chitwin* dimers of mixed 2,5-diketopiperazines are known: cyclo-L-Phe-L-Trp: ditryptophenaline, WIN 64821 and *ent*-WIN 64821; cyclo-L-Trp-L-Ala and -S-S- bridges: (+)-11,11'-Dideoxyverticillin A; cyclo-L-Trp-L-Ser and -S-S- bridges: epidithiodiketopiperazine-1, epidithiodiketopiperazine-2; cyclo-L-Phe-L-Ser: vertihemiptellide A [52]. Producing of *chitwin* molecules by dimerization and a series of trimming reactions is very plausible for the following heterocyclic derivatives: cyclo-L-Phe-L-Phe and -S-S- bridges: scabrosin ester; cyclo-L-Glu-L-Glu: epicoccin C, epicoccin D; hematocin; mycoedyketopiperazine; epicoccin G; epicoccin H; alternarosin A [52].

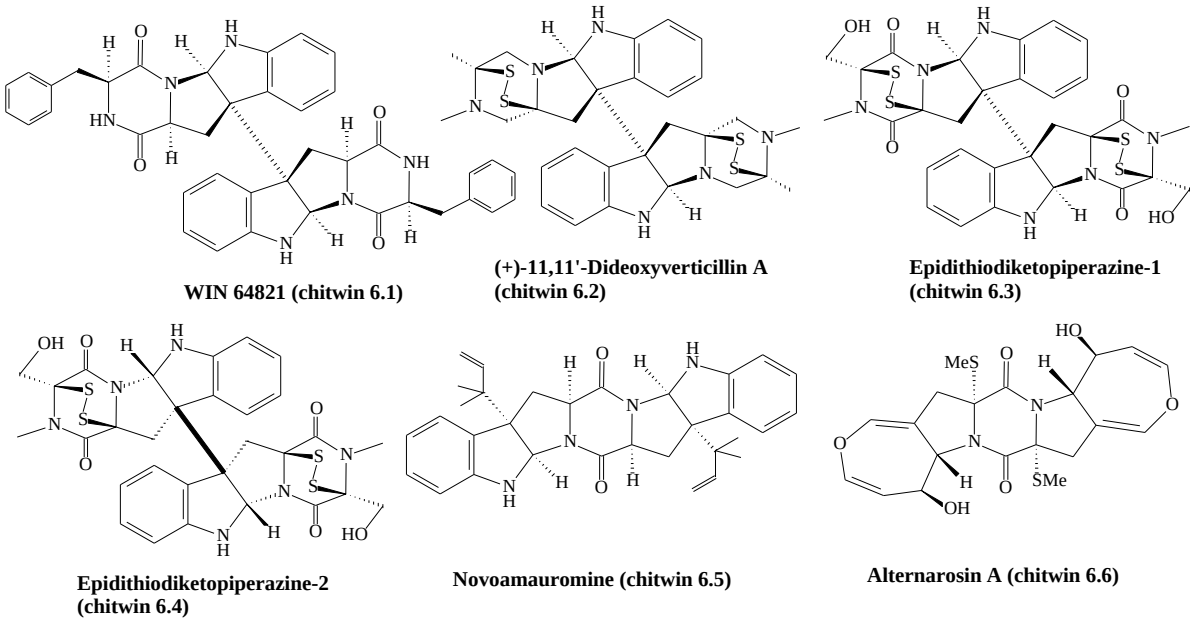


Figure 6.1: Heterocyclic derivatives as chitwin molecules

7. Polyprenyl (Isoprenoid) Compounds

Polyprenyl (isoprenoid) compounds present two facets as representatives of *chitwin* molecules:

7.1. Perhydro optically active hydrocarbons: squalane, perhydrolycopene, perhydrocrocetin, perhydronorbixin, perhydrocarotene, etc., [64].

7.2. Isoprenoid compounds *per se* or glycosylated or esterified with amino acids (Fig. 7.1).

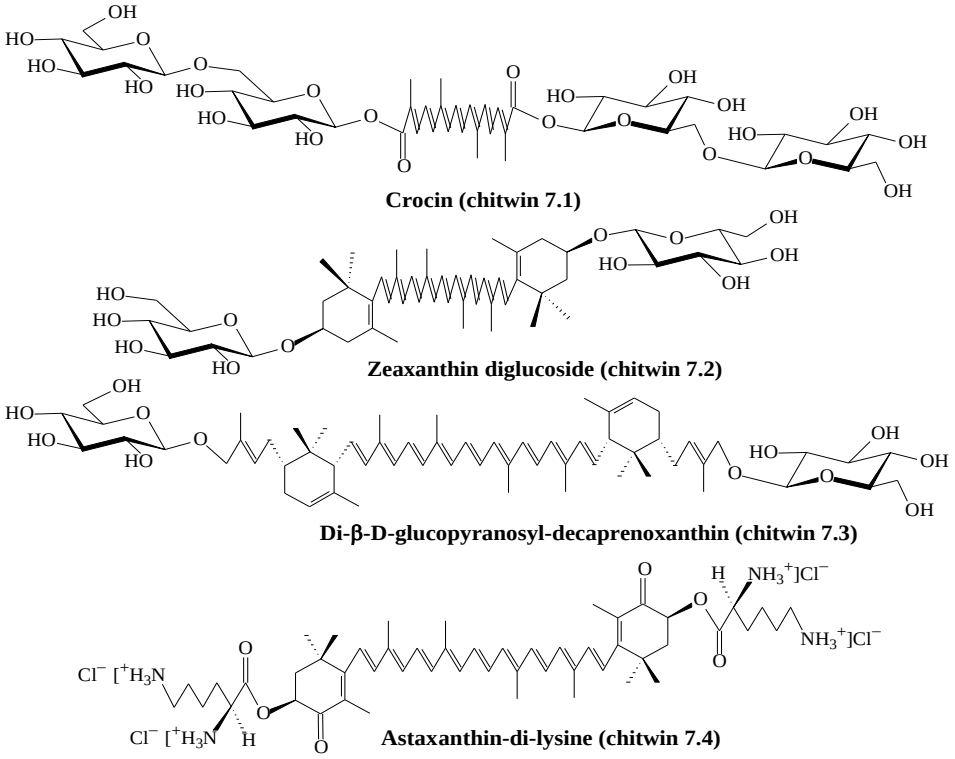


Figure 7.1: Carotenoids and their derivatives as chitwin molecules

Carotenoids play the role of photons modulators in biochemistry and physiology. This biochemical role is shared with relatively few other molecules. Carotenoids are biosynthesized by a dimerization (condensation) reaction of digeranyl diphosphate [65-67]. The unsaturation of produced hydrocarbons (phytoene, β-carotene, lycopene) is stepwise brought to a conjugated system and then submitted to a variety of chemical transformations – hydroxylation, chain lenghthening or oxidative cleavage, epoxidation, glycosylation, amino acylation, etc., [68-70]. Carbohydrates currently used for carotenoids glycosylation are D-glucose [71] and L-rhamnose [**72**]. Many other *chitwin* carotenoids are known: crocin bis-glycosylated with β-(2-β-cellobiosyl)gentiobiose [73], γ,γ-carotene [74], astaxanthin [75], β,β-carotene-2,2'-diol [76], bacterioruberin and bacterioruberin-diglucoside [77], auroxanthin ((8R,8'R)-, (8S,8'S)-) [78], bisanhydrobacyerioruberin [79]. More than 600 different carotenoid structures are known [80] and the question how many of these are *chitwin* will be answered quite soon.

8. Lignans and Neolignans

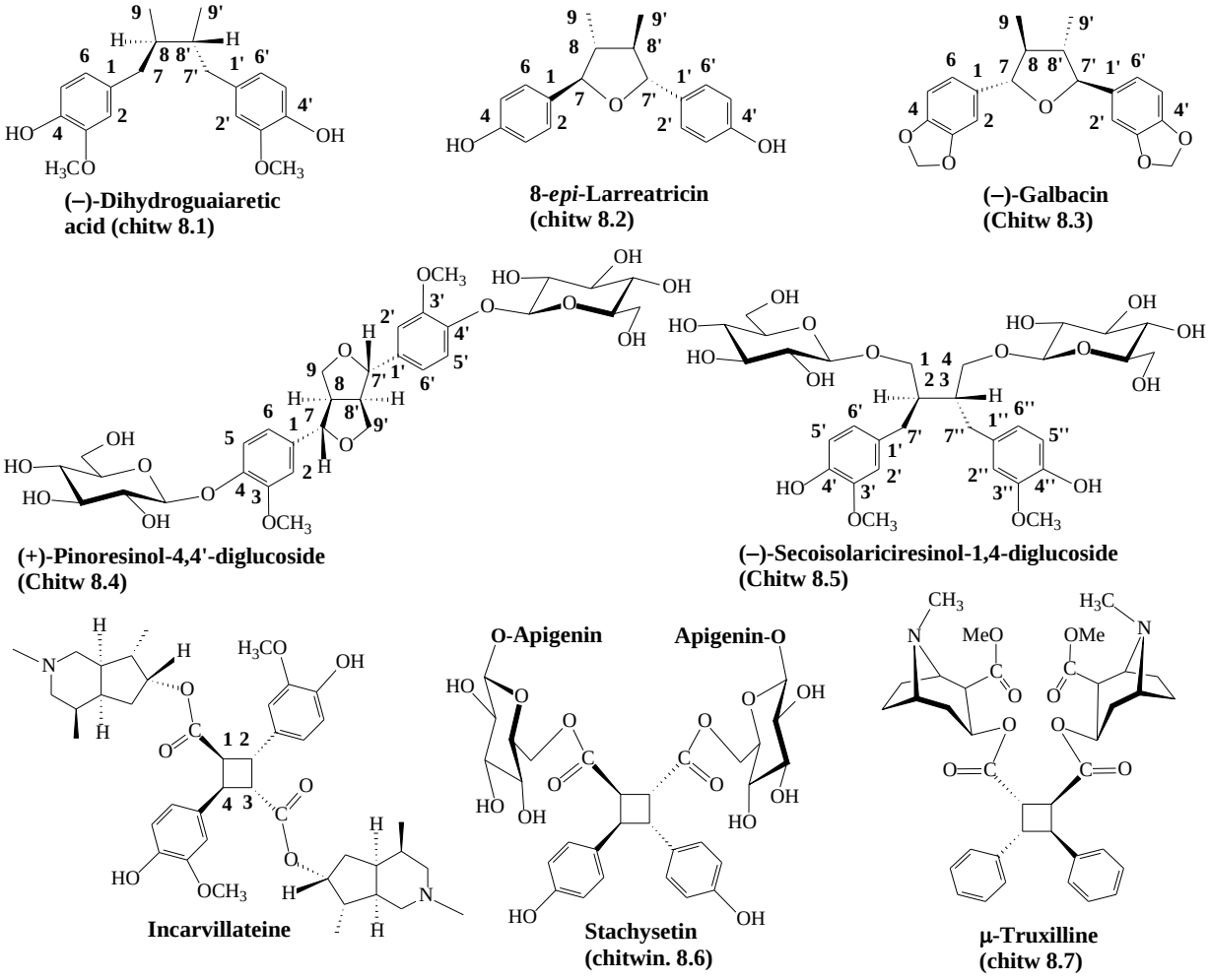


Figure 8.1: Lignans and neolignans as kitwin molecules

The word lignan was coined by Haworth [81] as an unequivocal term concerning the vegetable origin of these compounds. Lignans and neolignans are typically dimerization products of monolignols, with a wide distribution in higher plants. Dimerization of monolignols is a remarkably versatile reaction: both head to head and head to tail linkages lead to lignans, the atoms involved being in both cases C-8 and C-8'. When linkages other than 8-8' are formed, e. g., 3-3′ (or 5-5′), 8-*O*-4′, and 8-3′ (8-5′), neolignans are produced (Fig. 8.1). Most of the lignans and neolignans are optically active, some of them are even *chitwin* and others are *meso*. Metabolic interchangeability of

the three categories – *meso*, *chitwin* and based on *irregular distribution of chiral centers* – is well illustrated by lignans and neolignans. Structural variety of lignans and neolignans is increased yet by the diversity of structures forming aromatic rings and side chains. Of ten subtypes of classical lignans, six can provide chitwin molecules: dibenzocyclooctadiene, dibenzylbutane, dibenzylbutyrolactol (with the two alcoholic groups blocked by glycosylation, esterification or methylation), furofuran, 2,5-diaryltetrahydrofuran, 3,4-dibenzyl-tetrahydrofuran [82]. Diarylcyclobutane, of neolignan subtypes,provide a diversity of *chitwin* and *meso* derivatives (Fig. 8.1).

The number of biochemical precursors of metabolites produced by dimerization is relatively low in comparison with the number of final products:

1. The major monolignols involved in the production of lignans are: coniferyl alcohol, (*E*)-isoeugenol, (*E*)-5-methoxyisoeugenol, and sinapyl alcohol [83-85]. Anol was converted, in the presence of (+)-larreatricin hydroxylase, a polyphenol oxidase from the creosote bush (*Larrea tridentata*), to the following metabolites: larreatricin, 3-hydroxy-larreatricin, 3,3'-dihydroxy-larreatricin, 3,3'-didemethoxyverrucosin, 3'-hydroxy-larreatricin, nordihydroguaiaretic acid, 3,3'-didemethoxy nectandrin B, 8'-*epi*-larreatricin, 3'-hydroxy-8'-*epi*-larreatricin-; 3-O-Me-nor-dihydroguaiaretic acid, dihydroguaiaretic acid [86].
2. Head to tail dimerization of coniferyl alcohol produces either (+)- or (–)-pinoresinol, the two enantiomers being biosynthesized in a characteristic ratio by different plants organs. The two enantiomers are both *chitwin* molecules and they are either glucosylated or converted to other metabolites, enterodiols being terminal points. Bis-β-D-Glcp glycosides of (+)- and (–)-pinoresinol and of (+)- and (–)-seoisolariciresinols are *chitwin*. The same type of dimerization of sinapyl alcohol leads to syringaresinols and yangambin [39].
3. Dimerization of cinnamic acid presents two alternatives [87]: head to tail and head to head. All isomers produced by head to tail dimerization are achiral: α-truxillic acid due an alternative axis of symmetry, and the others – γ-, epi-, ε-, peri-, due to some planes of symmetry. All are constituent of alkaloids. Doubling of chiral molecules on these acids produces esters that are neither *chitwin* nor meso: incarvillateine [88], nitroxideincarvillateine, α-truxilline [89], santiaguine [90], thesine [91], hoveine, γ-truxilline, epi-truxilline, ε-truxilline, peri-truxilline. Head to head dimerization of cinnamic acid gives three types of acids: *chitwin* (δ- and μ-truxinnic acids), *meso* (β-truxinic and ω-truxillic acids), acids with an *irregular distribution of chiral carbons* (neo- and ζ-truxinic acids). Doubling of chiral compounds on *chitwin* acids produces *chitwin* molecules: nigramide R, sceptrin, stachysetin [42], sagerinic acid [41], monochaetin [40], δ-truxilline, μ-truxilline. Doubling of chiral molecules on symmetrical acids overturns their status without making them chitwin: β-truxilline, ω-truxilline, 4,4'-dimethoxy-β-truxinic acid catalpol diester. Doubling of chiral molecules on acids that are neither chitwin nor meso, keeps their status: neo-truxilline, ζ-truxilline [92].

9. Palindromes

Scholars approaching palindromes in a cultural perspective will be surprised to find them in two completely different, extreme positions: on one hand artistic (literary), and the scientific one, on the other hand. In fact they offered artistic delight before delivering scientific satisfaction, and over two millennia elapsed between the two facets.

A palindrome is a word, verse or sentence that is the same when read forward or backward, letter by letter. The inventor (discoverer) of palindromic writing was Sotades of Maroneea (in Thrace) [93,94], a Greek poet and satirist of the third century B. C. Being read in two directions, palindromes cause a double effect and Sotades had to pay with his life for a palindromic satire directed against the despot of the time [95].

Palindromes as biochemical phenomena were discovered in the second half of the twentieth century. Palindromic sequences occur frequently in DNA and have been often associated with functionally important locations such as replication points or operator sites [45]. They were detected soon after the discovery of DNA structure, due to some cruciform appearances containing intrastrand base pairing of the self-complementary sequence [96,97]. Then the DNA strands were sequenced [97,98] and in this way palindromic messages became quite explicit as *chitwin* structures (Fig. 9.1).

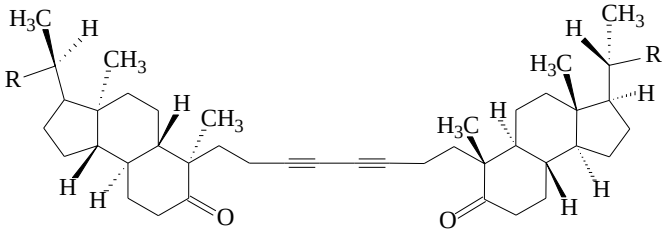
A-C-G-T-A-A-G-C-G-C-T-T-A-C-G-T

T-G-C-A-T-T-C-G-C-G-A-A-T-G-C-A

Figure 9.1: Palindromic sequence as chitwin structure

10. Is There a Chitwin (Bio)chemical Force?

It's a general principle that symmetrical joining of two chiral molecules leads to a *chitwin* chemical system. Steroid dimers have been isolated from living matter. As a result, steroid dimers – *chitwin* molecules – linked by a flexible diyne spacer have been synthesized (Fig. 10.1) [99].



Cholesterol diyne dimer (chitwin 10.1)

Figure 10.1: Cholesterol diyne dimer as a chitwin structure

More independent research groups have undoubtedly established that cholesterol, when mixed with lipids that are common constituents of cellular membrane – phospholipids [100], dipalmitoylphosphatidylcholine [101], phosphatidylcholine or phosphatidylethanolamine [102], – forms dimers, i. e., *chitwin* structures. Moreover, attaching of a series of residues to hydroxyl group [103] or a fluorescent group on lateral chain [104,105] do not affect this behaviour. On the other hand, cholesterol induces dimerization of β2-adrenergic receptor, the result being a *chitwin* construction [106]. Saposin B, the nonenzymatic glycosphingolipid activator protein, is destined to facilitate the hydrolysis of cerebroside sulfates (sulfatides) within the lysosome [107]. Human saposin B behaves as a shell-like dimer consisting of a monolayer of α-helices enclosing a large hydrophobic cavity. The helices of saposin B are repacked into a tertiary arrangement to form the homodimer, and the latter is a *chitwin* structure.

11. Conclusions

Chitwin molecules are chiral structures formed of two identical halves, i. e., two sets of asymmetric C of the same chirality and two identical sets of chemical functions. They are homochiral with one another and are also internally homochiral. *Chitwin* structures have a unique, exceptional quality: no matter which of their half suffer chemical transformations, the result is the same. Doubling of a chiral molecule by its symmetrical joining, either directly by itself (trehalose, isotrehalose, 2,2'-di-β-D-glucopyranosyl ether, cystine, 2,5-diketpiperazines of amino acids, glutathione and coenzyme A, both in oxidized state, lignans) or by an achiral (crocin, di-β-D-glucopyranosyl-dihydroxy lycopene) or chiral spacer (diglucosides of zeaxanthin, decaprenoxanthin, astaxanthin, pinoresinol, secoisolariciresinol, stachysetin, μ-truxilline) leads to a *chitwin* system. When this symmetrical doubling is made on a *meso* frame (α-truxillic acid, meso-lignans), *meso* status is abolished, without becoming *chitwin*; a kind of hybrid product is rather obtained.

Chitwin molecules present a remarkable structural variety, they are well represented among the main classes of natural compounds and they are interchangeable with achiral, meso and chiral compounds. Due to these qualities, they constitute a real, essential, unique and trustworthy network in living matter.

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