CHAPTER II

HISTORICAL

Taxa and description of tunicates of the genus *Didemnum*
(Abbott and Newberry, 1980; Barnes, 1987; Millar, 1970)

Kingdom : Animal
Phylum : Chordata
Subphylum : Urochordata (Tunicata)
Class : Ascidiacea
Order : Enterogona
Suborder : Aplousobranchia
Family : Didemnidae
Genus : Didemnum

Ascidians or sea squirts are sessile tunicates. The majority are found in shallow water. They attach to rocks, shells, pilings, and ship bottoms or sometimes fixed in mud and sand by filaments or a stalk. The bodies range from spherical to cylindrical in shape. One end is attached to the substratum, and the opposite end contains two openings, the buccal and atrial siphons. The body ranges in size from that of a seed, a millimeter or so in diameter, to that of the large potato.

Colonial ascidians of the genus *Didemnum* have gonads nestle in loop of gut, enterogonous, and simple pharyngeal baskets. Some species have postabdomen. They are very small zooids with short bodies and have four rows of branchial stigmata. Many produce calcareous spicules. Atrail opening often small or of moderate size.

Chemistry of the compounds from tunicates (genus *Didemnum*)

Marine ascidians have proven to be a rich source of unique secondary metabolites that often possess potent and important bioactivities. Colonial ascidians within the genus *Didemnum* have been particularly prolific, generally containing nitrogenous, amino acid-derived metabolites that have been extensively studied for their medical potential (Davidson, 1993).

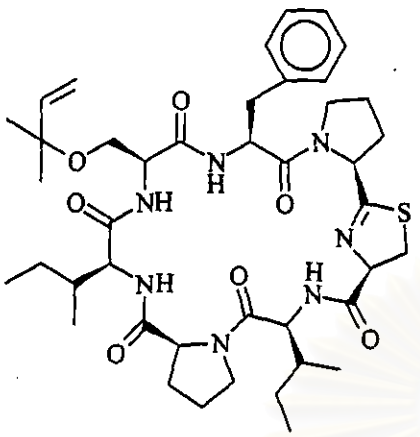
1. Nitrogenous compounds

1.1 Cyclic peptides

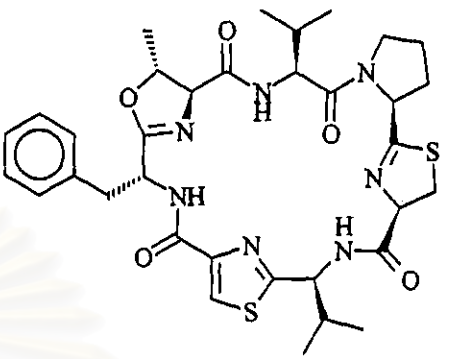
Cyclic peptides have been isolated from a number of marine taxa, and many show remarkably high levels of cytotoxicity. They have continued to be one of the major structural classes isolated from ascidians.

Mollamide [1], a cytotoxic cyclic heptapeptide, was first isolated from Great Barrier Reef ascidian *Didemnum molle*. It was shown to be cytotoxic against P388 murine leukemia (IC_{50} 1 μg/ml), A549 human lung carcinoma (IC_{50} 2.5 μg/ml), HT29 human colon carcinoma (IC_{50} 2.5 μg/ml), and CV1 monkey kidney fibroblast (IC_{50} 2.5 μg/ml). It inhibited RNA synthesis with an IC_{50} of approximately 1 μg/ml (Carroll *et al.*, 1994).

Cyclodidemnamide [2], a cyclic heptapeptide, was isolated from ascidian *D. molle* (Boden, Norley and Pattensen, 1996).



[1]

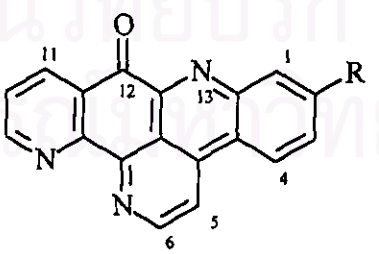


[2]

1.2 Polycyclic aromatic alkaloids

2-bromoleptoclinidinone [3], a pentacyclic aromatic alkaloid, was isolated from an Okinawan ascidian *Didemnum sp.* (De Guzman and Schmitz, 1989).

Ascididemin [4], another pentacyclic aromatic alkaloid, was first isolated from the Okinawan ascidian *Didemnum sp.* It was cytotoxic *in vitro* against L1210 with IC_{50} of 0.39 μg/ml, and was also shown to be seven times more potent than caffeine, a well-known Ca^{2+}-releaser, in the Ca^{2+}-releasing activity in sarcoplasmic reticulum (Kobayashi *et al.*, 1988).



[3] R = Br

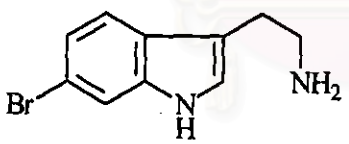
[4] R = H

1.3 Tryptophan-derived metabolites

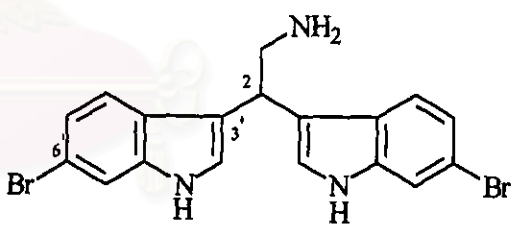
In addition to cyclic peptides, ascidians have yielded many heteroaromatic alkaloids, including pyridoacridines (Molinski, 1993) and β-carbolines (Davidson, 1993).

6-Bromotryptamine [5], a brominated indole derivative, was first isolated from a thin off-white encrusting ascidian *D. candidum*, collected from Isla San Jose in the Gulf of California (Fahy *et al.*, 1991).

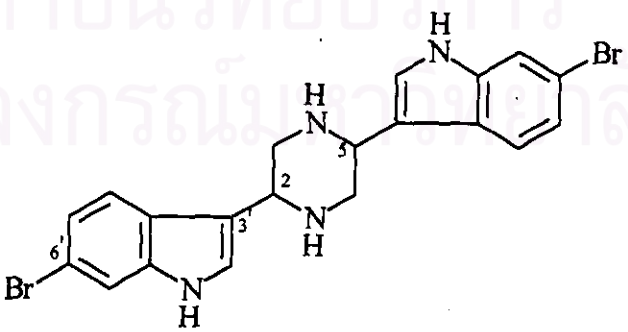
Two 6-bromotryptamine derivatives: 2,2-bis(6′-bromo-3′-indolyl) ethylamine [6] and 2,5-bis(6′-bromo-3′-indolyl)piperazine [7], were first isolated from a thin blue-gray encrusting ascidian *D. candidum*, collected from Isla Camen in the Gulf of California (Fahy *et al.*, 1991).



[5]

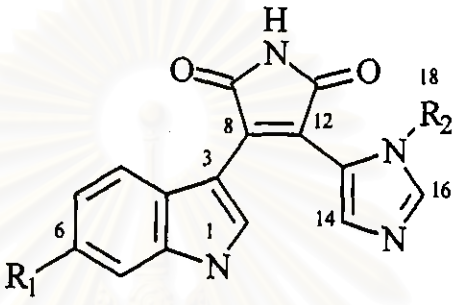


[6]



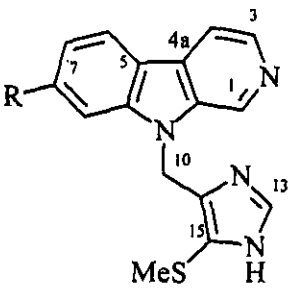
[7]

Didemnimides A [8], B [9], C [10], and D [11], four alkaloids possessing a novel indole-maleimide-imidazole carbon skeleton, were identified as the major predator deterrents found in the chemically-defended Caribbean mangrove ascidian *Didemnum conchyliatum* (Vervoort *et al.*, 1997).

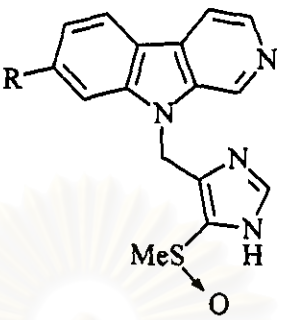


	R_1	R_2
[8]	H	H
[9]	Br	H
[10]	H	CH_3
[11]	Br	CH_3

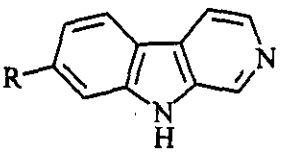
Didemnolines A [12], B [13], C [14], and D [15], four new *β*-carboline based metabolites, were isolated along with the two known compounds, eudistomin O [16], and *β*-carboline [17], from an ascidian *Didemnum sp.*, collected near the island of Rota, Northern Mariana Island. The didemnolines differ from most other marine derived *β*-carboline compounds in that they are substituted at the N9 position, rather than at the C1 position. Didemnolines A-C ([12]-[14]) were moderately cytotoxic toward human epidermoid carcinoma KB cells, with sulfoxide-containing [14] exhibiting the greatest activity. Didemnolines A [12] and C [14] also exhibited antimicrobial activity toward *B. subtilis*, *S. aureus*, *E. coli*, and two strains of the yeast *Saccharomyces cerevisiae* (Schumacher and Davidson, 1995).



[12] R = Br
[13] R = H

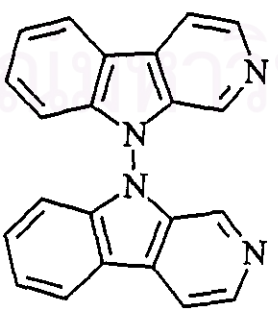


[14] R = Br
[15] R = H



[16] R = Br
[17] R = H

The first naturally occurring *β*-carboline dimer, 9H-pyrido[3,4-*b*] indole dimer with N,N-dimerization [18], previously known as a synthetic compound, was isolated from an ascidian, *Didemnum sp.*, collected from Sykes Reef in the Capricorn Bunker Group of the southern Great Barrier Reef (Kearns, Coll and Rideout, 1995).



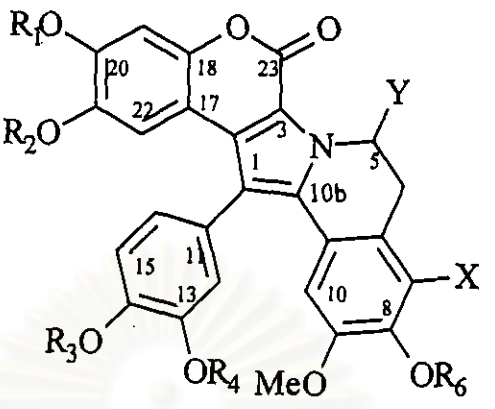
[18]

1.4 Tyrosine and phenylalanine-derived metabolites

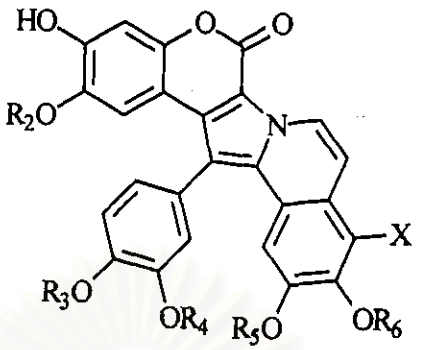
Four lamellarin class alkaloids, lamellarins E [23], F [24], G[25] and H [26], were isolated from the ascidian *D. chartaceum* collected in the Indian Ocean on the atoll of Aldabra, Republic of the Seychelles (Lindquist *et al.*, 1988b).

Six lamellarin class alkaloids, lamellarins I [27], J [28], K [29], L [30], and M [31] and lamellarin N triacetate [32], and four known alkaloids, lamellarins A-C [19]-[21] and triacetate of lamellarin D [22], were isolated from an ascidian, *Didemnum sp.*, collected at South West Cay, Lihou Reef, off the North Queenland coast. Lamellarins I [27], K [29], and L [30] all showed comparable and significant cytotoxicity against P388 and A549 cell lines in culture, with IC_{50} of about 0.25 μg/ml. Lamellarins K [29] and L [30] also exhibited moderate immunomodulatory activity (Carroll, Bowden, and Coll, 1993).

Two alkaloids, lamellarin S [33] and K [29] were isolated from an Australian ascidian *Didemnum sp.* collected near Durras, New South Wales (Urban and Capon, 1996).

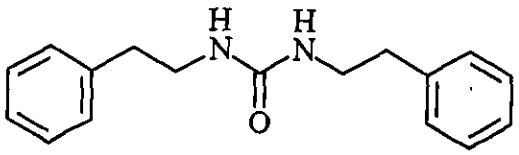


	R_1	R_2	R_3	R_4	R_6	X	Y
Lamellarin A [19]	H	CH_3	H	CH_3	CH_3	OCH_3	OH
Lamellarin C [21]	H	CH_3	H	CH_3	CH_3	OCH_3	H
Lamellarin E [23]	H	CH_3	CH_3	H	CH_3	OH	H
Lamellarin F [24]	H	CH_3	CH_3	CH_3	CH_3	OH	H
Lamellarin G [25]	CH_3	H	CH_3	H	H	H	H
Lamellarin I [27]	H	CH_3	CH_3	CH_3	CH_3	OCH_3	H
Lamellarin J [28]	H	CH_3	CH_3	CH_3	H	H	H
Lamellarin K [29]	H	CH_3	H	CH_3	CH_3	OH	H
Lamellarin L [30]	H	CH_3	CH_3	H	H	H	H
Lamellarin S [33]	H	H	H	H	H	H	H



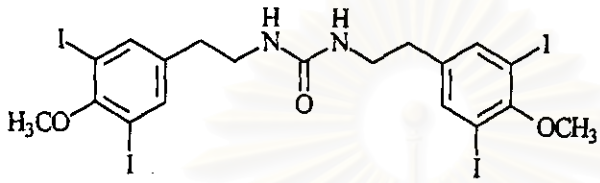
	R_2	R_3	R_4	R_6	R_5	X
Lamellarin B [20]	CH_3	H	CH_3	CH_3	CH_3	OCH_3
Lamellarin D [22]	CH_3	H	CH_3	CH_3	CH_3	H
Lamellarin H [26]	H	H	H	H	H	H
Lamellarin M [31]	CH_3	H	CH_3	CH_3	CH_3	OH
Lamellarin N triacetate [32]	CH_3	CH_3	Ac	CH_3	Ac	Ac

N,N′-Diphenethylurea [34], a known phenylalanine derivative first reported from a *Streptomyces sp.*, was isolated from the ascidian *D. ternatanum* collected at Urukthapal Island, Western Carolines (Ireland, Durso and Scheuer, 1981).

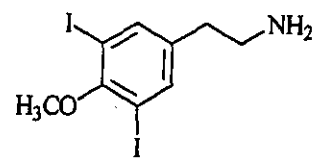


[34]

3,5-Diiodo-4-methoxyphenethylamine [35], a known synthetic compound, and an iodinated tyramine derivative [36] were isolated from an ascidian, *Didemnum sp.*. Compound [35] showed *in vitro* activity against *C. albicans* and was mildly cytotoxic to L1210 with IC_{50} of 20 μg/ml (Sesin and Ireland, 1984).



[35]

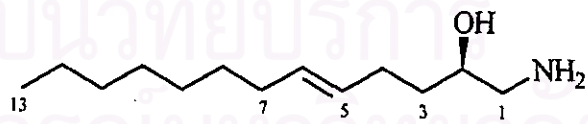


[36]

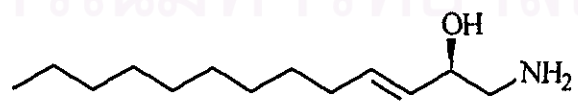
1.5 Amino alcohol derivatives

Three amino alcohol derivatives: (*R*)-(*E*)-1-aminotridec-5-en-2-ol [37], (*R*)-(*E*)-1-aminotridec-3-en-2-ol [38], and (*R*)-(*E*)-1-aminotridec-4-en-2-ol [39], were isolated from an ascidian *Didemnum sp.*. In the agar plate disk diffusion assay, amino alcohol [37] trifluoroacetate showed moderate activity against *C. albican*, producing 9 mm zone of inhibition at 50 μg/disk. Both amino alcohols [38] and [39] as TFA salts showed activity comparable to that of [37], whereas the free base of [37], formed upon treatment of the TFA salt with K_2CO_3, showed slightly enhanced activity *C. albican*, producing 11 mm zone of inhibition at 50 μg/disk (Searle and Molinski, 1993).

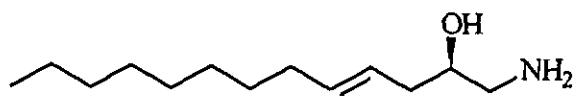
[37]



[38]

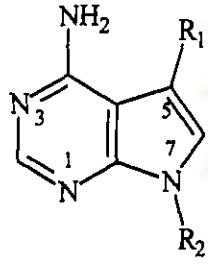


[39]

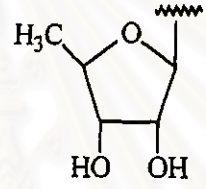


1.6 Nucleosides

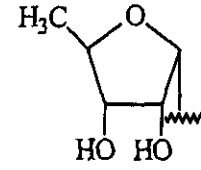
Two 5′-deoxypyrrolo[2,3-*d*]pyrimidine (7-deazapurine) nucleosides, 5′-deoxytubercidin [40] and 5′-deoxy-5-bromotubercidin [41], and two anomers of 5′-deoxy-5-iodotubercidin [42]-[43] were isolated from the ascidian *D. voeltzkowi* collected from Apo Reef, Philippines (Mitchell *et al.*, 1996).



X =



Y =

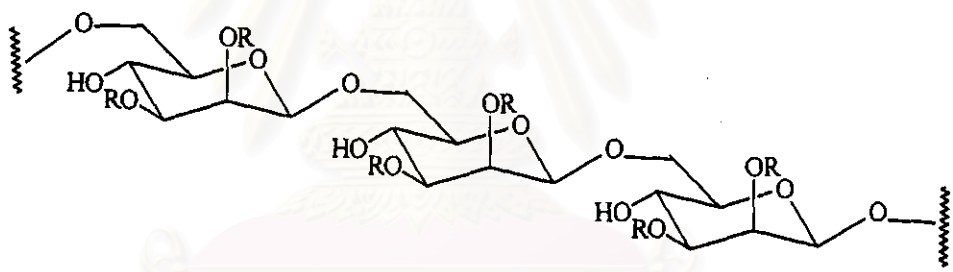


	R_1	R_2
[40]	H	X
[41]	Br	X
[42]	I	X
[43]	I	Y

2. Non-nitrogenous compounds

2.1 Polysaccharide

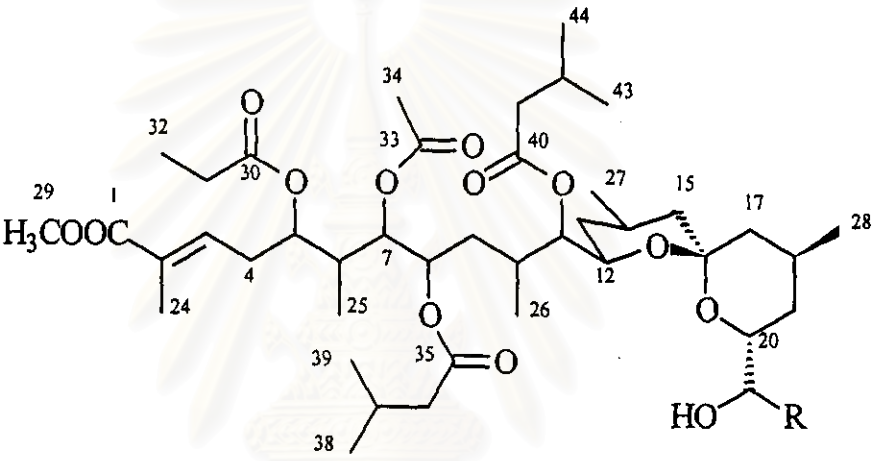
Kakelokelose [44], an unusual sulfated mannose homopolysaccharide, was isolated from the Pacific ascidian *D. molle* collected in Pohnpei, Micronesia. In the HIV cytotoxicity assay with HIV strain RF, CEM cells, and XTT, [44] showed 100% antiviral inhibition down to 0.3 μg/ml but produced no cytotoxicity at 15 μg/ml (Ricio *et al.*, 1996).



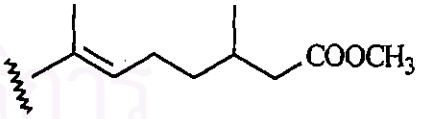
[44] R= $-SO_3^- Na^+$

2.2 Terpenoids

Didemnaketals A [45] and B [46] were isolated from the magenta ascidian *Didemnum sp.* collected at Auluptagel Island, Palau. Inhibition of HIV-1 protease by didemnaketals A [45] (IC_{50} 2 μM) and B [46] (IC_{50} 10 μM) was measured by peptidolysis assay (Potts *et al.*, 1991).

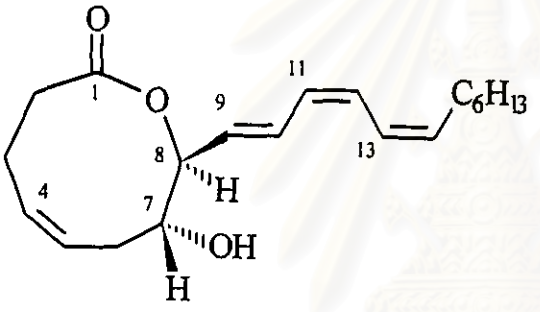


[45] R = $COCH_3$ (23)

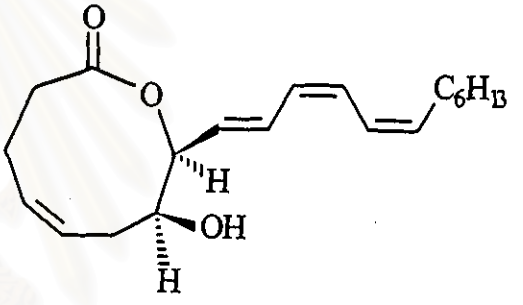
[46] R = 

2.3 Polyketides

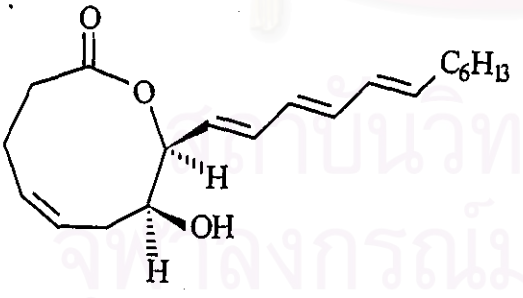
Three nine-membered ring lactones, ascidiatrienolides A [47], B [48], and C [49], were first isolated from the ascidian *D. candidum* collected near Big Pine Key, Florida (Lindquist and Fenical, 1989). The structure of ascidiatrienolide A [47] was revised to the ten-membered ring lactone [50] by Congreve and his co-workers (1993).



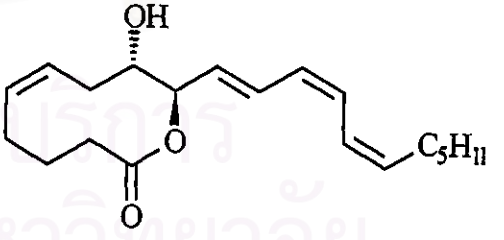
[47]



[48]



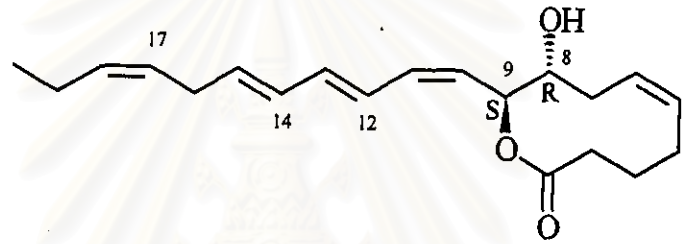
[49]



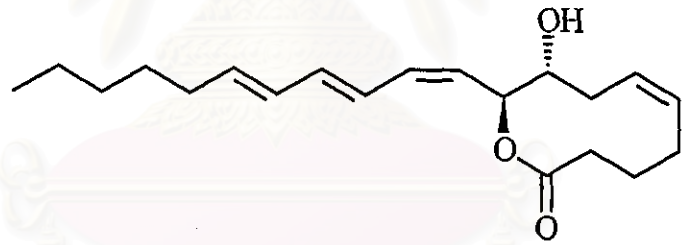
[50]

Didemnilactone [51] and neodidemnilactone [52], two ten-membered lactones, were isolated from the ascidian *D. moseleyi*. Both compounds and the corresponding diol acids obtained by hydrolysis of [51] and [52] exhibited weak binding activity(IC_{50} 50~100 μM) to leukotriene B4 receptors of human polymorphonuclear leukocyte membrane fractions (Niwa, Inagaki and Yamada, 1991).

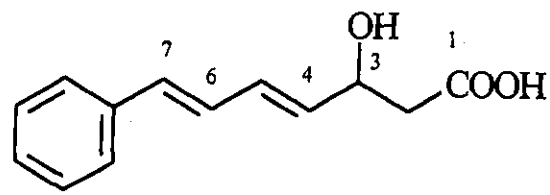
[51]



[52]

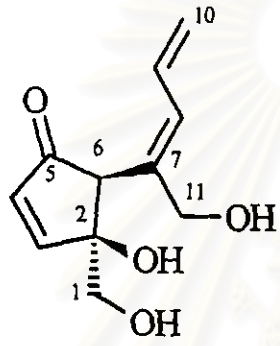


A hydroxy phenyldienoic acid, 3-hydroxy-7-phenyl-4*E*,6*E*-heptadienoic acid [53], were isolated from the pale pink ascidian *D. granulatum* (Isaacs, Kashman and Benayahu, 1994).



[53]

Didemnenones C [54] and D [55], isolated from the ascidian *D. voeltzkowi* collected from Fiji, exhibited cytotoxicity *in vitro* to L1210 cell lines with IC_{50} of 5.6 μg/ml (Lindquist *et al.*, 1988a)



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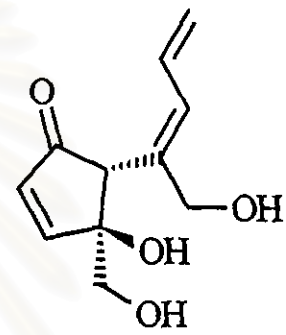
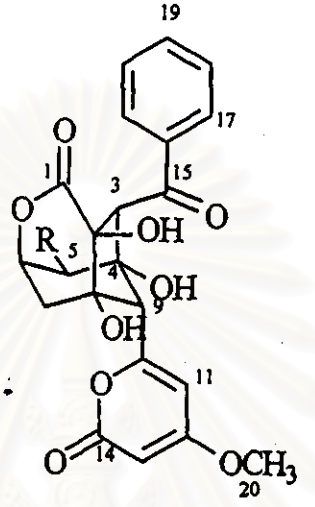
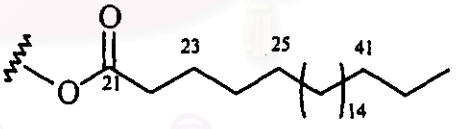
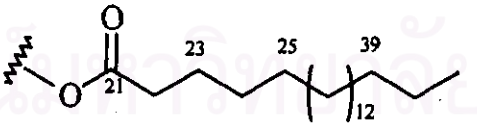


[55]

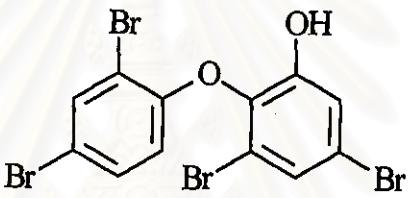
Enterocin [56] or vulgamycin, 5-deoxyenterocin [57], enterocin-5-behenate [58], and enterocin-5-arachidate [59] were isolated from a Western Australian ascidian, *Didemnum sp.*. Enterocin [56] and 5-deoxyenterocin [57] were first isolated from three strains of soil-derived *Streptomyces* species (Kang, Jensen and Fenical, 1996).



	R
[56]	OH
[57]	H
[58]	
[59]	

2.4 Phenolic derivative

2-(2′,4′-Dibromophenoxy)-3,5-dibromophenol [60], was isolated from the ascidian *Didemnum sp.*, collected near the island of Rota, Northern Mariana Island (Schumacher and Davidson, 1995).



[60]

Chemistry of nucleosides (Ross, 1981; Rodwell, 1988)

A nucleoside is composed of a purine or a pyrimidine base to which a sugar, usually either D-ribose or 2-deoxyribose, is attached in β-linkage at N_9 or N_1, respectively. The sugar component of ribonucleic acid (RNA), D-ribose, occurs in the furanose form. In deoxyribonucleic acid (DNA) this sugar is replaced by 2-deoxyribose, also in the D-furanose form. This apparently small difference between the two types of nucleic acid has wide-ranging effects on both their chemistry and structure since the presence of the bulky hydroxyl group on the 2-position of the sugar not only limits the range of possible secondary structures available to the RNA molecule but also makes it more susceptible to chemical and enzymic degradation.

1. Pyrimidine bases (Figure 2)

The pyrimidine bases are derivatives of the parent compound pyrimidine, and the bases found in the nucleic acids are cytosine found in both DNA and RNA, uracil found in RNA and thymine and 5-methylcytosine found in DNA. In certain colifages cytosine is replaced by 5-hydroxymethylcytosine or glucosylated.

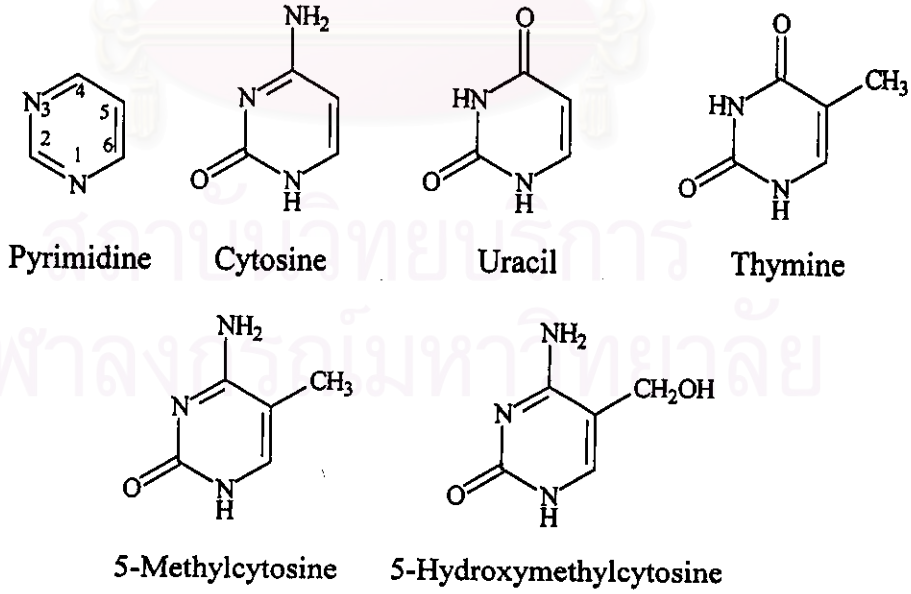
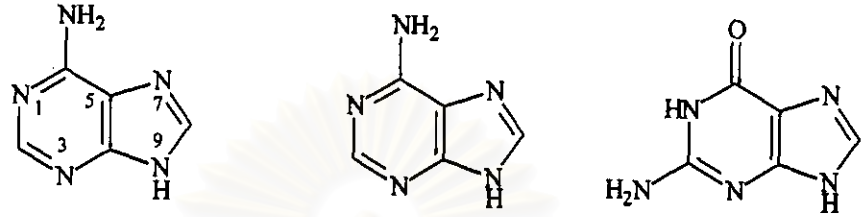


Figure 2. Structures of pyrimidine bases

2. Purine bases (Figure 3)

They are derivatives of purine which is form by the fusion of a pyrimidine and an imidazole ring. The bases found in the nucleic acids are adenine and guanine.



Purine Adenine Guanine

Figure 3. Structures of purine bases

Biosynthesis of these compounds are not known, but nucleoside may be hydrolyzed product of nucleotides and nucleic acids. Nucleic acids and nucleotides are constantly being degraded to nucleosides and free bases, the bases are to some extent degraded further to carbon dioxide and ammonia. Plants and other organisms can reconvert the nucleosides, deoxynucleosides, and bases to nucleotides and deoxynucleotides by so called salvage reaction.

The ribonucleosides have three positions (2′, 3′ and 4′ hydroxyl) that may be substituted with phosphate. On the other hand, the deoxyribonucleosides have only two positions (3′ and 5′ hydroxyl) that may be substituted with phosphate. The ribonucleoside 5′-phosphate may be further phosphorylated at position 5′ to yield 5′-di and triphosphates. For example, the adenosine 5′-phosphate (AMP) may be phosphorylated to adenosine 5′-diphosphate (ADP) and adenosine 5′-triphosphate (ATP). The phosphate ester of nucleosides is the nucleotides. Nucleotide is the component of nucleic acid. Nucleic acids act as storage and translator of genetic information.

3. Biosynthesis of pyrimidine nucleotides

3.1 Formation of UTP and CTP

The biosynthetic pathway for UTP and CTP in all organisms involves formation of a basic pyrimidine ring, orotic acid, using carbon dioxide, aspartate, and the amide group of glutamine, with ATP as an energy source. The phosphoribosyl moiety of 5-phosphoribosyl-1-pyrophosphate (PRPP) is added to orotic acid, yielding orotidine 5′-phosphate (OMP). Subsequently, the carboxyl group of OMP is removed, forming UMP, and UMP is successively phosphorylated to UDP and UTP. The amino group attached to position 6 of cytosine in CTP is added to UTP from the amide group of another glutamine.

3.2 Formation of thymidine nucleotides *de novo*

Thymidine nucleosides can be formed by two mechanisms. In the first mechanism, deoxyuridine nucleotides are substrate. The second mechnism involves deoxycytidine nucleotides as substrate.

3.2.1 Formation of thymidine from deoxyuridine nucleotides

In animal, deoxy-UDP is reversibly converted to deoxy-UMP by a kinase in the presence of ADP. In *E. coli*, deoxy-UDP is converted to deoxy-UTP by ATP-dependent kinase, and pyrophosphate is removed by a specific pyrophosphatase, forming deoxy-UMP. Deoxy-UMP is then transported to cell. Subsequent methylation of deoxy-UMP to yield TMP is catalyzed by thymidylate synthetase (TMP synthetase). The source of the methyl group transferred to the 5-position of the pyrimidine ring in deoxy-UMP is N^5,N^{10}-methylenetetrahydrofolic acid (N^5,N^{10}-methylene THFA).

3.2.2 Formation of thymidine from deoxycytidine nucleotides

In animals but not in several bacterial species, thymidine nucleotides also arise from deoxycytidine nucleotides. The key enzyme is a

deaminase that removes ammonia from deoxy-CMP, forming deoxy-UMP. The latter is then converted to TMP by TMP synthetase.

4. Biosynthesis of purine nucleotides

4.1 Formation of IMP (Figure 4)

The first step (reaction 1) in the synthesis of purine nucleotides is the formation of 5-phosphoribosyl-1-pyrophosphate (PRPP). The conversion of ribose 5-phosphate and ATP to AMP + PRPP is not, however, unique to the synthesis of purine nucleotides. PRPP also served as a precursor of the pyrimidine nucleotides and is required for the synthesis of NAD and NADP, 2 coenzymes derived from niacin.

PRPP then reacts (reaction 2) with glutamine in a reaction catalyzed by phosphoribosylpyrophosphate gltamyl amidotransferase to form 5-phospho-ribosylamine. The reaction is accompanied by the displacement of pyrophosphate and the formation of glutamate. Although other mechanisms have been proposed for the synthesis of 5-phosphoribosylamine, the physiologically important reaction in mammalian tissues is that catalyzed by the amidotransferase.

5-phosphoribosylamine then reacts (reaction 3) with glycine to produce glycinamide ribosylphosphate (glycinamide ribotide [GAR]). The amido group from glutamine contributes what will become the N_9 of the purine ring, while the glycine contributes carbons 4 and 5 and the N_7. The enzyme catalyzing reaction 3 is glycinamide kinosynthetase.

The N_7 of glycinamide ribosylphosphate is then formylated (reaction 4) by N^5,N^{10}-methenyltetrahydrofolate and the enzyme glycinamide ribosylphosphate formyltransferase. The C_1 moiety becomes the C_8 of the purine base. In reaction 5, again with glutamine as the amide donor, amidation occurs at the

C_4 of the formylglycinamide ribosylphosphate, catalyzed by formylglycinamide ribosyl-phosphate synthetase. The amide N becomes position 3 in the purine.

Closure of the imidazole ring, catalyzed by aminoimidazole ribosylphosphate synthetase, forms aminoimidazole ribosylphosphate (reaction 6). The synthesis progresses (reaction 7) to aminoimidazole carboxylate ribosylphosphate by addition of a carbonyl group, the source of which is respiratory CO_2. The source of the nitrogen in the 1 position is the α-amino group of aspartate (reaction 8), the remaining portion of which is indicated as the succinyl moiety of aminoimidazole succinyl carboxamide ribosylphosphate (SAICAR).

In reaction 9, the succinyl group of SAICAR is removed as fumarate. Aminoimidazole carboxamide ribosylphosphate, which remains, is then formylated (reaction 10) by N^{10}-formyltetrahydrofolate (N^{10} H_4-folate) to form amidoimidazole carboxamide ribosylphosphate in the reaction catalyzed by the appropriate formyltransferase. The newly added carbon, which, like the C_8 of the purine base, is derived from the C_1 pool via the tetrahydrofolate carrier, will be C_2 of the purine nucleus. Ring closure now occurs (reaction 11) via IMP cyclohydrolase, and the first purine nucleotide, inosinic acid (inosine monophosphate, IMP), is thus formed.

4.2 Conversion of IMP to AMP and GMP

The amination of IMP is accomplished through the formation of an intermediate compound in which aspartate is attached to inosinic acid to form adenylosuccinate. The splitting off, as fumarate, of the remaining portion of aspartate from adenylosuccinate produces the final product, adenylic acid (adenosine monophosphate, AMP).

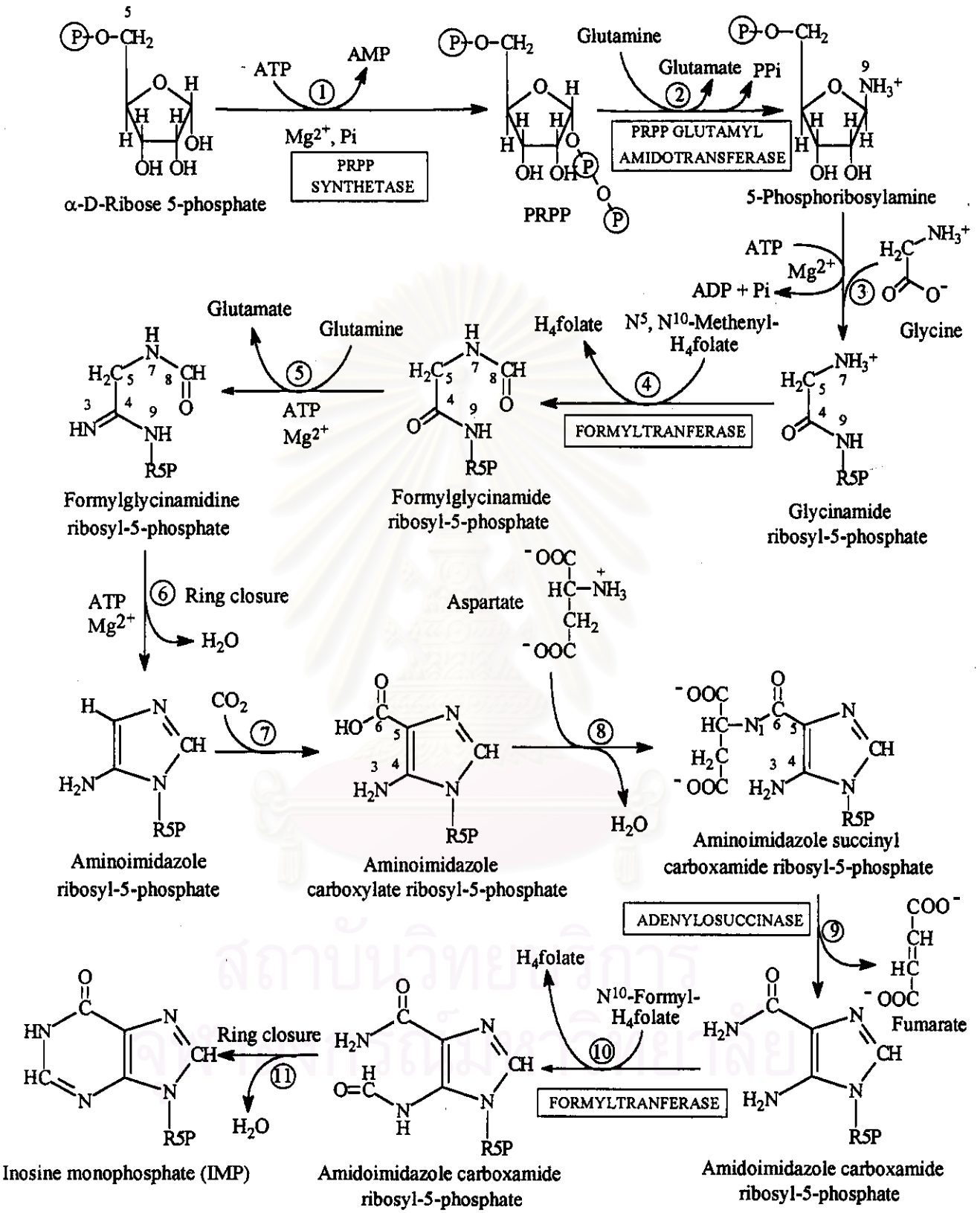


Figure 4. Pathway of *de novo* purine biosynthesis from ribose-5-phosphate and ATP (Rodwell, 1988)

The first reaction of the conversion of IMP to GMP is an oxidation utilizing NAD and water to form xanthosine monophosphate (XMP). XMP is then aminated by the amido group of glutamine to form guanosine monophosphate (GMP).

5. Formation of deoxyribonucleotides

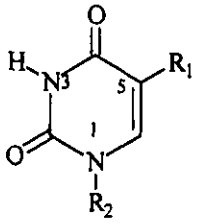
The ribonucleotides are reduced to deoxyribonucleotides by two distinct reduction mechanisms exist in nature. In most *E. coli* strains and in animals, nucleoside diphosphates (UDP, CDP, ADP) are substrate, an NADPH is indirect reductant. Thioredoxin-S-S is reduced by NADPH to thioredoxin-$(SH)_2$. Thioredoxin-$(SH)_2$ provides a hydride that displaces the 2′-hydroxyl group from ribose moiety of the nucleoside diphosphate . A second mechanism occurs in several bacteria species, euglenoid flagellate and some fresh water blue green algae. Nucleoside triphosphate are reduced to deoxynucleoside triphosphate, and a coenzyme deoxyadenosylcobalamin donates the hydride ion that replaces the 2′-hydroxy group of deoxyribose. NADPH and thioredoxin are still necessary, and electron transport occurs from NADPH to thioredoxin to 5′-deoxyadenosylcobalamin to the nucleoside triphosphate.

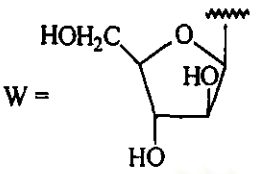
Distribution of pyrimidine and purine nucleosides

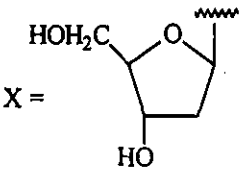
Table 1. Sources of pyrimidine nucleosides and derivatives

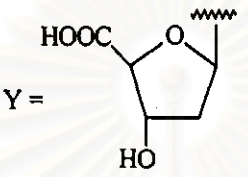
Compound	Source	Reference
[61] Thymine	*Cryptotethia crypta*	Bergmann and Burke, 1955
[62] Uracil	*Cryptotethia crypta*	Bergmann and Burke, 1955
	Trididemnum cereum	Dematté *et al.*, 1985
	Didemnum voeltzkowi	Mitchell *et al.*, 1996
[63] Spongothymidine	*Cryptotethia crypta*	Bergmann and Feeney, 1951
[64] Spongouridine	*Cryptotethia crypta*	Bergmann and Burke, 1955
	Eunicella cavolini	Cimino, De Rosa, and De Stefano, 1984
[65] 2′-Deoxythymidine	*Trididemnum cereum*	Dematté *et al.*, 1985
	Didemnum voeltzkowi	Mitchell *et al.*, 1996
[66] 2′-Deoxyuridine	*Trididemnum cereum*	Dematté *et al.*, 1985
[67] Thymidine-5′-carboxylic acid	*Aplidium fuscum*	Dematté *et al.*, 1986
[68] 2′-Deoxyuridine-5′-carboxylic acid		
[69] 2′,3′-Didehydro-2′,3′-dideoxyuridine	*Aplysina sp.*	Kondo *et al.*, 1992
[70] Cytidine	*Cryptotethia crypta*	Cohen, 1963
[71] 2′-Deoxycytidine	*Trididemnum cereum*	Dematté *et al.*, 1985

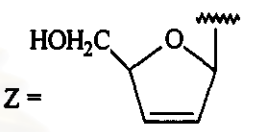
Table 2. Chemical structures of pyrimidine nucleosides and derivatives



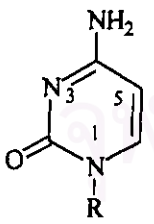


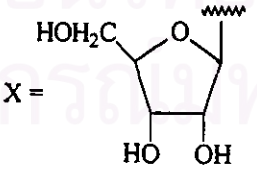


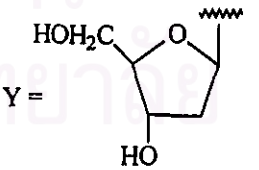




Compound	R_1	R_2
[61] Thymine	CH_3	H
[62] Uracil	H	H
[63] Spongothymidine	CH_3	W
[64] Spongouridine	H	W
[65] 2′-Deoxythymidine	CH_3	X
[66] 2′-Deoxyuridine	H	X
[67] Thymidine-5′-carboxylic acid	CH_3	Y
[68] 2′-Deoxyuridine-5′-carboxylic acid	H	Y
[69] 2′,3′-Didehydro-2′,3′-dideoxyuridine	H	Z







Compound	R
[70] Cytidine	X
[71] 2′-Deoxycytidine	Y

Table 3. Sources of purine nucleosides and derivatives

Compound	Source	Reference
[72] Spongosine	*Cryptotethia crypta*	Bergmann *et al.*, 1951
[73] Spongoadenosine (9-β-D-Arabinofuranosyl-adenine)	*Eunicella cavolini*	Cimino *et al.*, 1984
[74] 3′-Acetate-9-β-D-arabino-furanosyl adenine		
[75] Adenosine	*Cryptotethia crypta*	Cohen, 1963
[76] 5′-Deoxy-5′-dimethyl-arsinyl adenosine	*Tridacna maxima*	Francesconi, Stick and Edmonds, 1991
[77] 9-[5′-Deoxy-5′-(methylthio)-β-D-xylofuranosyl]-adenosine	*Doris verrucosa*	Cimino *et al.*, 1986
[78] Trachycladine A	*Trachycladus laevispirulifer*	Searle and Molinski, 1995
[79] Inosine	*Tapes japonica* *Trididemnum cereum*	Baker and Murphy, 1981 Dematté *et al.*, 1985
[80] 2-Deoxyinosine	*Trididemnum cereum*	Dematté *et al.*, 1985
[81] Hypoxanthine		
[82] Trachycladine B	*Trachycladus laevispirulifer*	Searle and Molinski, 1995

Table 3. continued

Compound	Source	Reference
[83] 4-Amino-5-bromo-pyrrolo[2,3-*d*]pyrimidine	*Echinodictyum sp.*	Kazlauskas *et al.*, 1983
[84] Tubercidin	*Streptomyces tubercidicus*	Suhadolnik, 1970
[40] 5′-Deoxytubercidin	*Didemnum voeltzkowi*	Mitchell *et al.*, 1996
[41] 4-Amino-7-(5′-deoxyribos-1′β-yl)-5-bromopyrrolo[2,3-*d*]pyrimidine		
[42] 4-Amino-7-(5′-deoxyribos-1′β-yl)-5-iodopyrrolo[2,3-*d*] pyrimidine	*Hypnea valendiae*	Kazlauskas *et al.*, 1983
[43] 4-Amino-7-(5′-deoxyribos-1′α-yl)-5-iodopyrrolo[2,3-*d*] pyrimidine	*Didemnum voeltzkowi*	Mitchell *et al.*, 1996
[85] Toyocamycin	*Streptomyces sp.* *Jaspis johnstoni*	Suhadolnik, 1970 Schmitz *et al.*, 1993
[86] Sangivamycin	*Streptomyces rimosus*	Suhadolnik, 1970
[87] 5-(Methoxycarbonyl)-tubercidin	*Jaspis johnstoni*	Schmitz *et al.*, 1993
[88] 7-Deazainosine	*Aplidium pantherinum*	Kim *et al.*, 1993
[89] Mycalisine A	*Mycale sp.*	Kato *et al.*, 1985
[90] Mycalisine B		

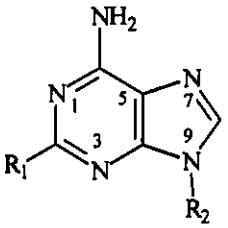
Table 3. continued

Compound	Source	Reference
[91] 1,3,7-Trimethylguanine	*Latrunculia brevis*	Perry, Blunt and Munro, 1987
[92] Aplysidine	*Aplysina sp.*	Kondo *et al.*, 1992
[93] Phidolopin	*Phidolopora pacifica*	Ayer *et al.*, 1984
[94] Desmethylphidolopin	*Phidolopora pacifica*	Tischler, Ayer and Andersen, 1986
[95] 1,3,9-Trimethyl-8-nitrosoisoxanthine	*Cucumaria frondosa*	Yayli and Findlay, 1994
[96] Doridosine (1-Methylisoguanosine)	*Tedania digitata* *Anisodoris nobilis*	Quinn *et al.*, 1980 Fuhrman *et al.*, 1980
[97] 3-Methyladenine	*Topsentia genitris*	Stoller, Braekman and Daloze 1988
[98] Spongopurine (1-Methyladenine)	*Geodia gigas* *Hymeniacidon sanuinea*	Cimino *et al.*, 1985
[99] 1,9-Dimethyl-6-imino-8-oxopurine	*Hymeniacidon sanuinea*	Cimino *et al.*, 1985
[100] Caissarone	*Bunodosoma caissarum*	Zelnik *et al.*, 1986
[101] 2-Iminomethyl-3-methyl-6-aminomethyl-9*H*-purine	*Sagartia troglodytes*	De Rosa *et al.*, 1987

Table 3. continued

Compound	Source	Reference
[102] Herbipoline	*Geodia gigas*	Ackermann and List, 1960
[103] 1-Methylherbipoline	*Jaspis sp.*	Yagi, Matsunaga and Fusetani, 1994
[104] Zeatin	*Valoniopsis pachynema*	Abad Farooqi *et al.*, 1990
[105] Dihydrozeatin	Blue coral	
[106] Isopentenyladenine	*Caulerpa texifolia* *Udotea indica*	
[107] 2-Hydroxy-6-methylamino-purine	Blue coral	
[108] 2-Hydroxy-1′-methylzeatin	Green alga	
[109] Zeatin riboside	*Udotea indica*	
[110] Shimofuridin A	*Aplidium multiplicatum*	Kobayashi, Doi and Ishibashi, 1994
[111] Shimofuridin B	*Aplidium multiplicatum*	Doi, Ishibashi and Kobayashi, 1994
[112] Shimofuridin C		
[113] Shimofuridin D		
[114] Shimofuridin E		
[115] Shimofuridin F		
[116] Shimofuridin G		

Table 4. Chemical structures of purine nucleosides and derivatives



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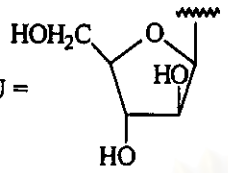

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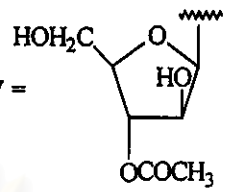

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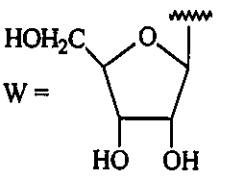

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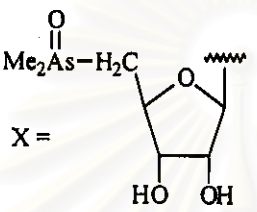

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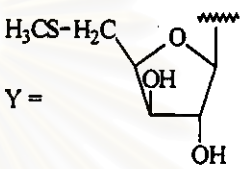

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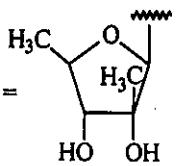
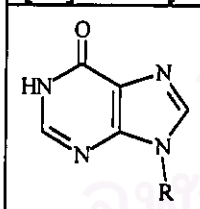
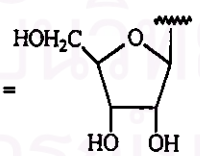


Compound	R_1	R_2
[72] Spongosine	OCH_3	W
[73] Spongoadenosine	H	U
[74] 3′-Acetate-9-β-D-arabinofuranosyl adenine	H	V
[75] Adenosine	H	W
[76] 5′-Deoxy-5′-dimethylarsinyladenosine	H	X
[77] 9-[5′-Deoxy-5′-(methylthio)-β-D-xylo-furanosyl]adenosine	H	Y
[78] Trachycladine A	Cl	Z



X =



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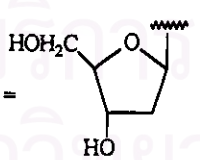

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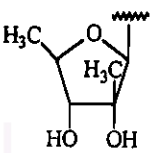
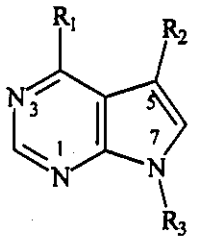
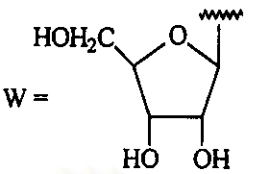
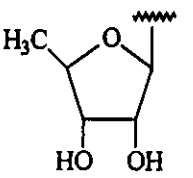


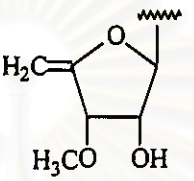
Compound	R
[79] Inosine	X
[80] 2-Deoxyinosine	Y
[81] Hypoxanthine	H
[82] Trachycladine B	Z

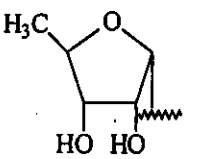
Table 4. continued



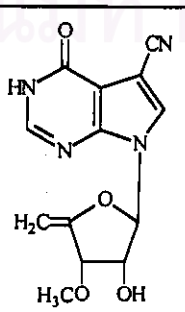
W = 

X = 

Y = 

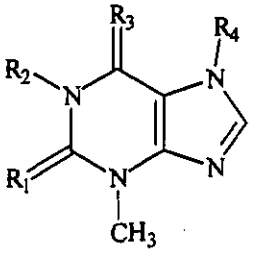
Z = 

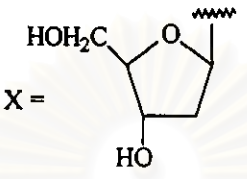
Compound	R_1	R_2	R_3
[83] 4-Amino-5-bromopyrrolo[2,3-d]pyrimidine	NH_2	Br	H
[84] Tubercidin	NH_2	H	W
[40] 5′-Deoxytubercidin	NH_2	H	X
[41] 4-Amino-7-(5′-deoxyribos-1′*β*-yl)-5-bromo-pyrrolo[2,3-*d*]pyrimidine	NH_2	Br	X
[42] 4-Amino-7-(5′-deoxyribos-1′*β*-yl)-5-iodo-pyrrolo[2,3-*d*]pyrimidine	NH_2	I	X
[43] 4-Amino-7-(5′-deoxyribos-1′*α*-yl)-5-iodo-pyrrolo[2,3-*d*]pyrimidine	NH_2	I	Z
[85] Toyocamycin	NH_2	CN	W
[86] Sangivamycin	NH_2	$CONH_2$	W
[87] 5-(methoxycarbonyl)tubercidin	NH_2	$COOCH_3$	W
[88] 7-Deazainosine	OH	H	W
[89] Mycalisine A	NH_2	CN	Y

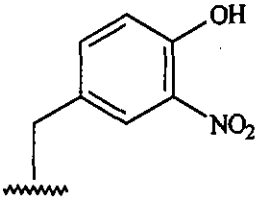


[90] Mycalisine B

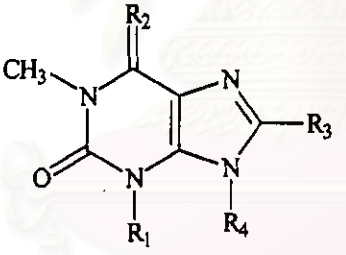
Table 4. continued

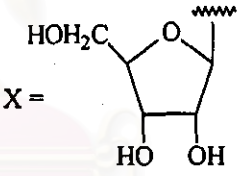


X = 

Y = 

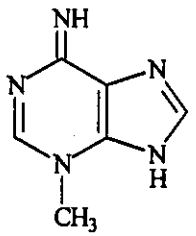
Compound	R_1	R_2	R_3	R_4
[91] 1,3,7-Trimethylguanine	NH	CH_3	O	CH_3
[92] Aplysidine	O	CH_3	O	X
[93] Phidolopin	O	CH_3	O	Y
[94] Desmethylphidolopin	O	H	O	Y



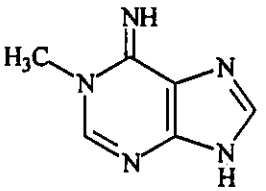
X = 

Compound	R_1	R_2	R_3	R_4
[95] 1,3,9-Trimethyl-8-nitrosoisoxanthine	CH_3	O	NO	CH_3
[96] Doridosine	H	NH	H	X

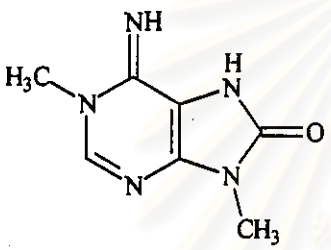
Table 4. continued



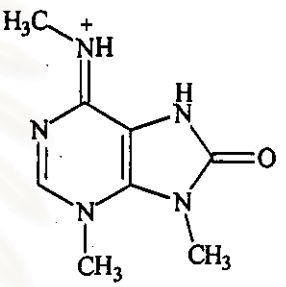
[97] 3-Methyladenine



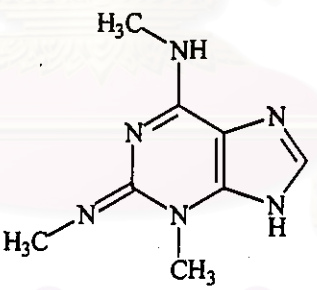
[98] Spongopurine



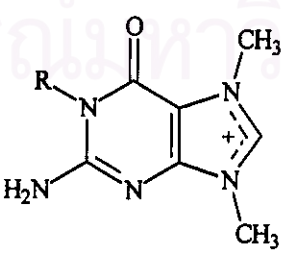
[99] 1,9-Dimethyl-6-imino-8-oxopurine



[100] Caissarone

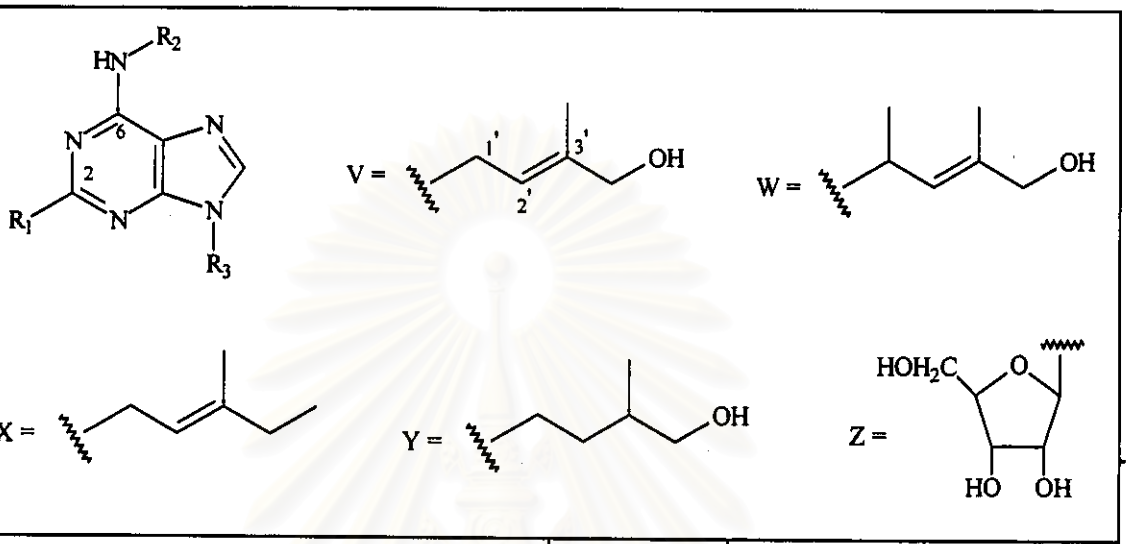


[101] 2-Iminomethyl-3-methyl-6-aminomethyl-9*H*-purine



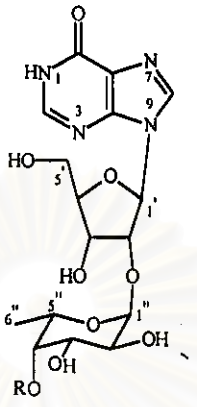
Compound	R
[102] Herbipoline	H
[103] 1-Methylherbipoline	CH_3

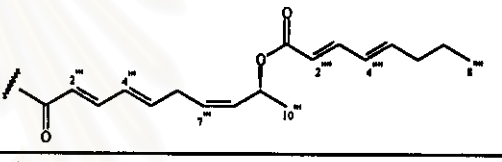
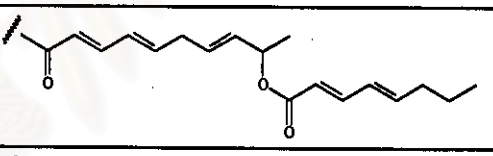
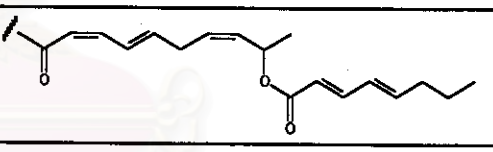
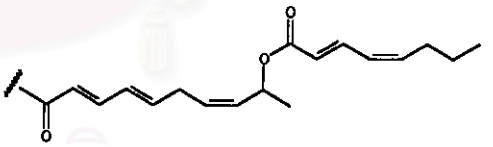
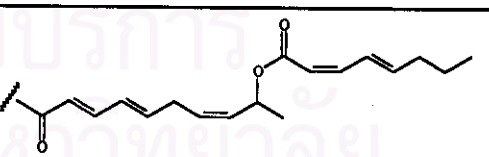
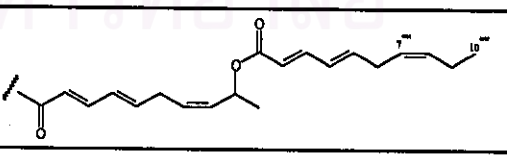
Table 4. continued



Compound	R_1	R_2	R_3
[104] Zeatin	H	V	H
[105] Dihydrozeatin	H	Y	H
[106] Isopentenyladenine	H	X	H
[107] 2-Hydroxy-6-methylaminopurine	OH	CH_3	H
[108] 2-Hydroxy-1′-methylzeatin	OH	W	H
[109] Zeatin riboside	H	V	Z

Table 4. continued



Compound	R
[110] Shimofuridin A	
[111] Shimofuridin B	
[112] Shimofuridin C	
[113] Shimofuridin D	
[114] Shimofuridin E	
[115] Shimofuridin F	
[116] Shimofuridin G