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Biological Activities of Cyclic Peptides: An Overview

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ABSTRACT

Cyclic peptides have emerged as an important class of organic compounds with potent biological activities like antifungal, antibacterial, anthelmintic, antineoplastic, insecticidal, anti-inflammatory, melanin production inhibitory activities. The inherent medicinal properties of cyclic peptides promoted scientists to isolate these compounds from natural sources. Since only minute quantities are obtained from natural sources, attempts have been made for the synthesis of these compounds in laboratories and biological screening of these compounds gave good results. Number of modifications has been done in the structure of basic cyclic peptides in order to increase their biological activities. Thus there is wide scope for synthesis of these peptides and their derivatives to explore more potent biodynamic molecules. The present review encompasses the idea about the various peptide molecules and their derivatives which have been synthesized in the laboratory and had shown potent biological activity.

Keywords: cyclic peptides, solution phase synthesis, solid phase synthesis, gram positive and gram negative, anticancer, antitubercular

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INTRODUCTION

Peptides are the molecules containing –CO-NH linkage. Unfortunately, the linear peptides for clinical application have been limited by the intrinsic properties of peptides which include rapid degradation of peptides by peptidase enzymes, leading to metabolic instability which complicates oral delivery of peptides. Passage through blood brain barrier is an additional problem for peptides which acts on CNS. In order to counteract these undesirable properties, numerous modifications of peptide structure have been considered. One of the most significant modifications is the cyclisation of the linear peptides, which reduces the flexibility of linear molecule and stabilizes secondary structure of peptides and increases its activity [1]. Cyclization of the peptide molecule leads to the development number of medicinal compounds with potent biological activities [2-4]. Most of these peptides have been isolated from natural sources like plants and marine sources but as only minute quantities are obtained from these sources, attempts have been made towrods the synthesis of these cyclic peptides and their derivatives by various methods. These peptides have shown potent biological activities like antifungal, antibacterial, anthelmintic, antineoplastic, insecticidal, anti-inflammatory, antitumour, melanin production inhibitory activities.

History of Peptides

Emil Fischer (1852-1919) is a founding father of the field of peptide chemistry and originator of the term Peptide. He awarded the Nobel Prize in chemistry in 1902. He reported the preparation of the first dipeptide, glycylglycine. The name peptide was derived from pepsis means digestion or peptones means digestion products of proteins [5].
Dr Frederik Paulsen, Ferring's founder chosse to develop Ferring's first medicines using peptide hormones. Initially, production was done through extracting peptides from animal organs and then modifying those using natural hormones and/or ligands. Development of production techniques allowed the chemical synthesis of peptides. In the 1960s Ferring became one of the first pharmaceutical companies in the world to synthesise oxytocin and vasopressin thus establishing Ferring as a peptide company.

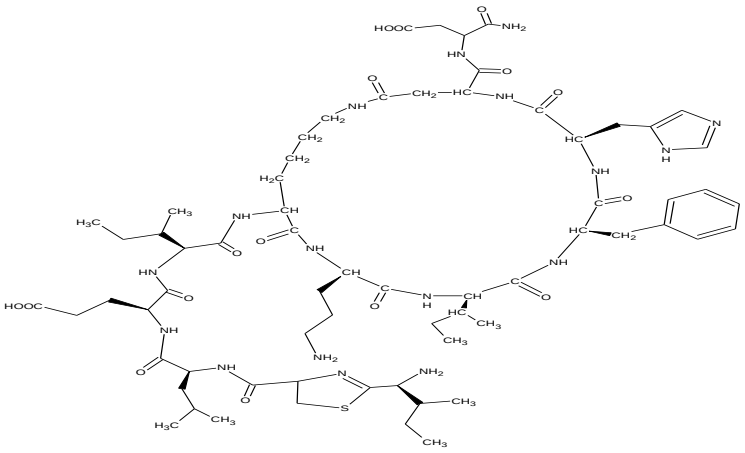
Biologically Important Cyclic Peptides

Antibactrial cyclic peptides

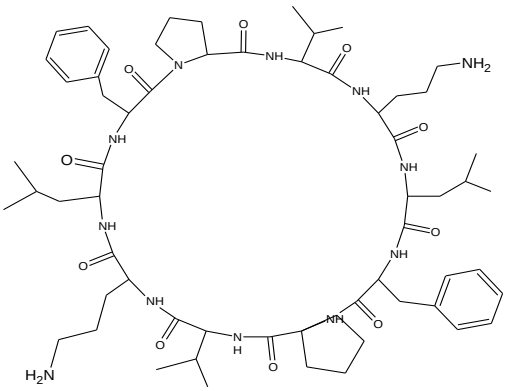
The cyclic peptide antibiotic bacitracin (1) was isolated by B. A. Johnson et al. [6] in 1945 from *Bacillus subtilis*. This is found to possess broad spectrum of antibacterial activity and used clinically as topical agent. The Chemical structure of the compound was later on assigned by Craig.

A cyclic decapeptide antibiotic Gramicidin S (2) was isolated from a culture of *Bacillus brevis*. Its structure was established in 1945 by A.H. Gordon et al. [7]. Total synthesis was

assigned in 1970 by G. Losse et al [8]. This drug showed good antibacterial activity against Gram positive and Gram-negative bacteria and is used clinically in topical applications.

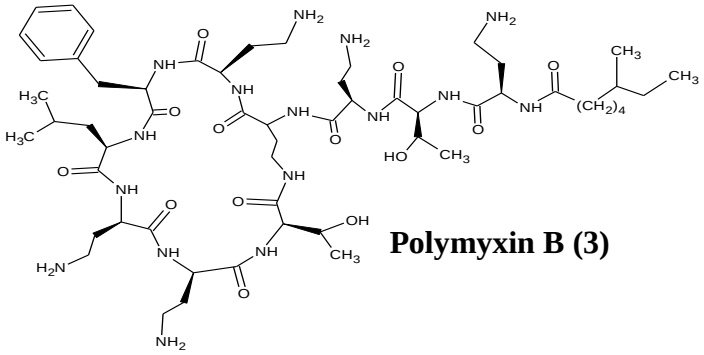


Bacitracin (1)



Gramicidin S (2)

In 1953, Schulman et al. [9] isolated Polymyxin B (3) from *Bacillus polymyxa* followed by its resolution into polymyxins B_1 and B_2 by Hausmann et al. [10] in 1954. The structural formula for polymyxin B was proved by its synthesis, accomplished by Vogler in 1994. Polymyxin B is used mainly against Gram negative organisms such as in the treatment of intestinal infection due to *P. enteritis* or those due to *Shigella* and for local infections in wounds and burns.



Polymyxin B (3)

Evolidine, a cyclic heptapeptide (4), was isolated from the leaves of *Evodia xonthoxyloids* and was characterised by Eastwood et al [11] in 1955. The structure was elucidated by Kopple in 1971 and its crystal structure and computational studies were reported by Drake in 1991. Synthesis and evaluation of biological activities of evolidine were carried out by Boja. It showed good antibacterial and antifungal activity.

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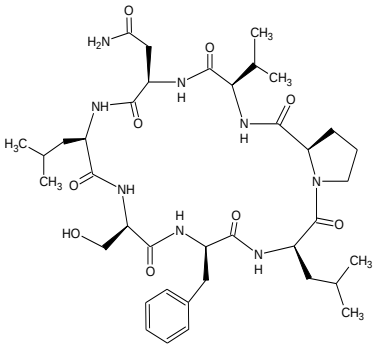
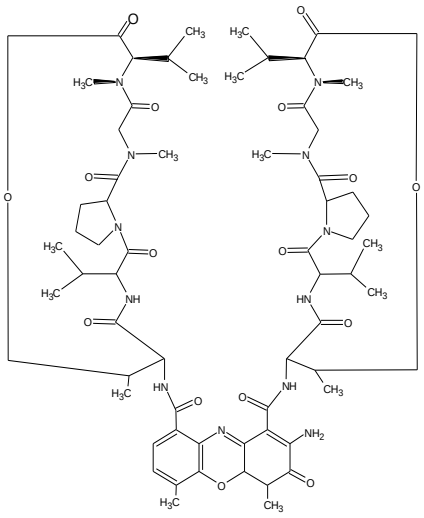


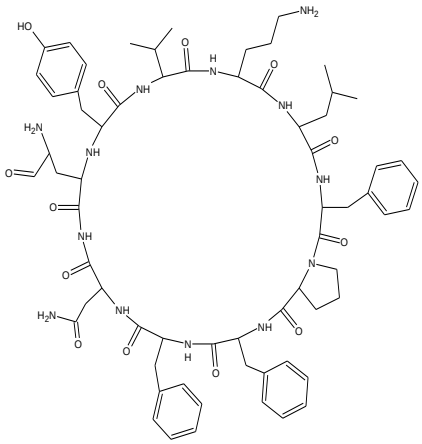
Evolidine (4)



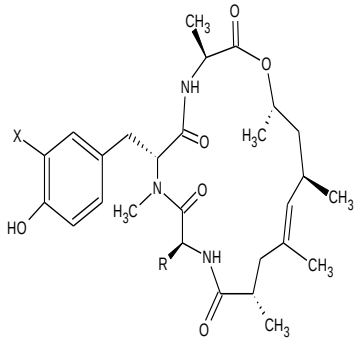
Actinomycin D (5)

Actinomycins (5) were discovered by S.A Waksman et al [12] in 1940 from *Actinomyces antibioticus.* Major investigation of the structure establishment and total synthesis was done in 1960 by W. Brockmann. Actinomycin D or Dactinomycin showed good activity against gram-positive bacteria and tumours.

Tyrocidine-A (6), a cyclic decapeptide antibiotic, constituent of tyrothricin was isolated from *Bacillus brevis*. Its structure has been confirmed by synthesis by Ruttenburg et al. [13] in 1965 and Ohno and Izumiya [14] in 1966. This showed broad spectrum activity and clinically used as topical agent.



Tyrocidine A (6)



Geodiamolides (7)

7a: R=Me, X=I, **7b**: R=Me, X=Br

7c: R=Me,X=Cl, 7d: R=H, X=I

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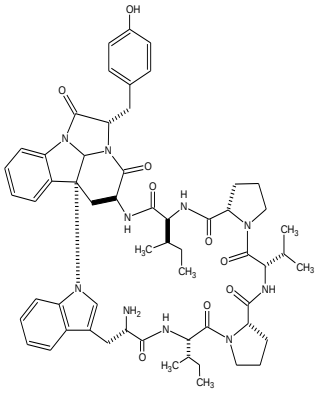
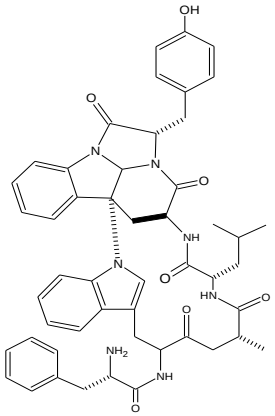
In 1987, Chan W. R. et al. [15] reported the isolation of Geodiamolides A and B (7a, b) from caribbean sponge *Geodia sp.* followed by isolation of other geodiamolides C-F (7c-f) by DeSilva E. D. from Papua new Guinean sponge *Pseudoaxinyssa sp.* Total synthesis of geodiamolides was reported by Grieco P. A. in 1994. All the six cyclic depsipeptides showed cytotoxic activity as well as antimicrobial activity against *yeast*.

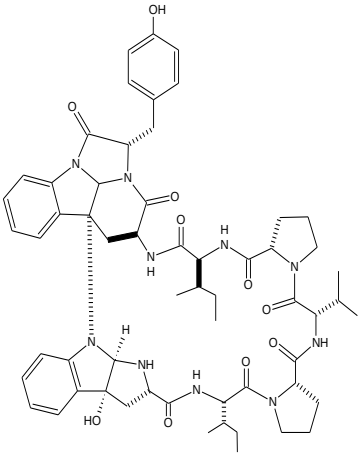
In 1996, Bryan K.S Yeung et al [17], reported four cyclic peptides kapakahines A-D (9a-9d), isolated from the marine sponge, *Cribrochalina olemda*. The unique structural feature of these peptides is the lack of an amide linkage between two tryptophan residues. Instead the ring is closed by a bond from the indole nitrogen of Trp-1 to the ß carbon of Trp-2.

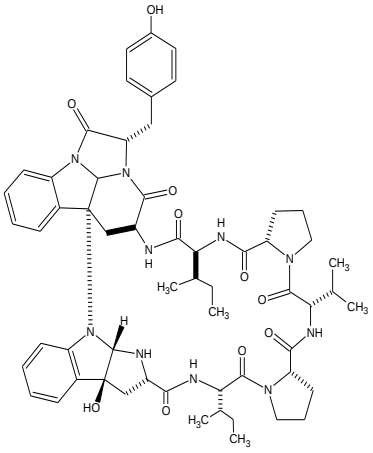


Kapakahine A (9a)



Kapakahine B (9b)





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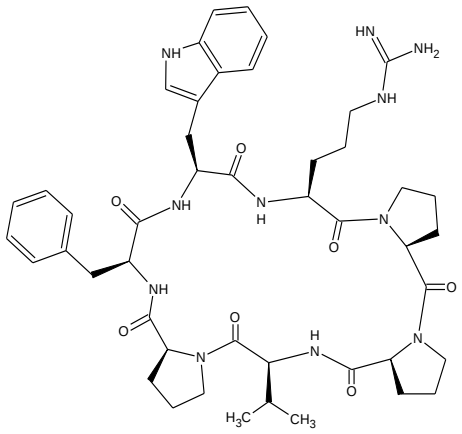
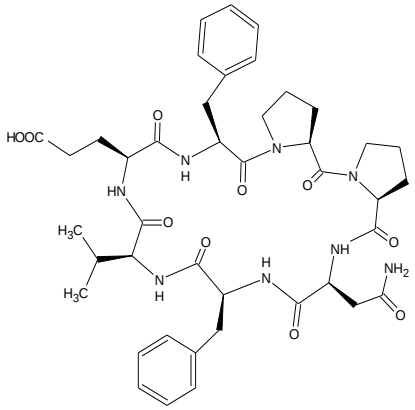
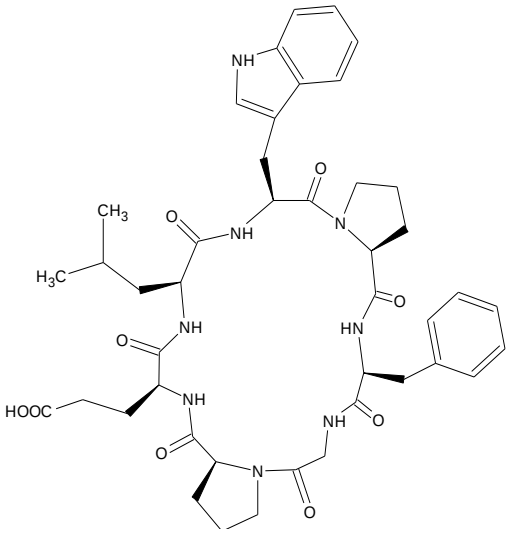
Kapakahine C (9c)



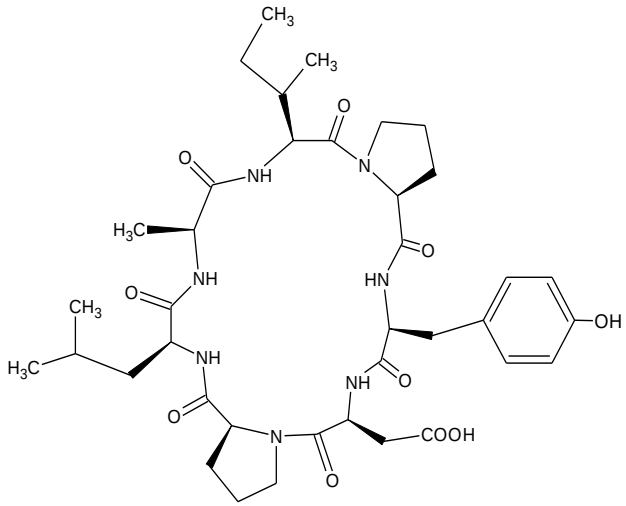
Kapakahine D (9d)



Hymenamide A (8a)

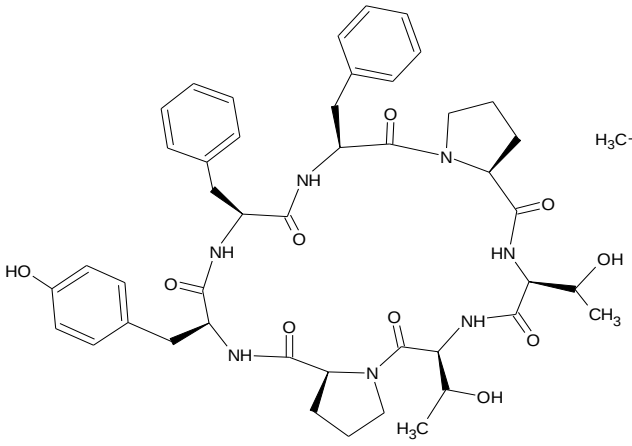


Hymenamide B (8b)

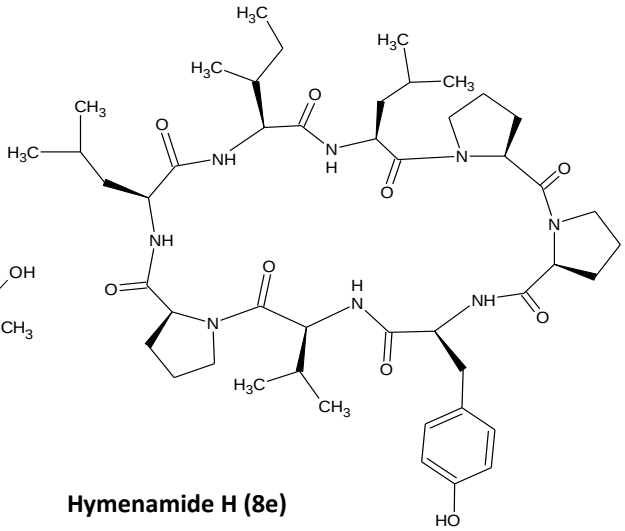


Hymenamide(8c)

Hymenamide(8d)



Hymenamide E (8e)



Hymenamide H (8e)

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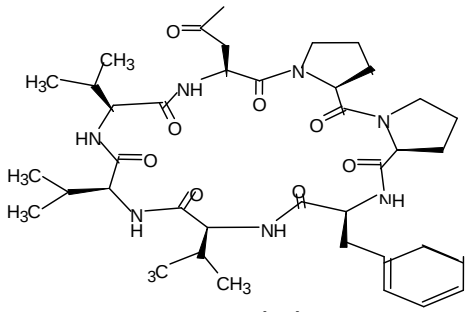
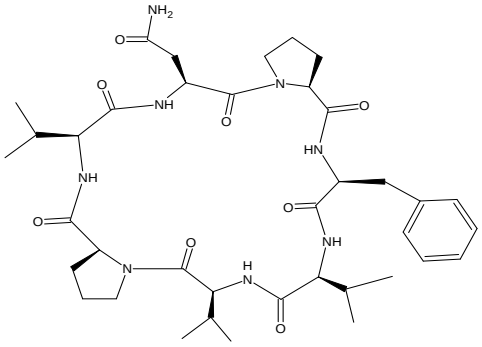
Hymenamides (8a–i) were isolated by Kobayashi et al [16] from the marine sponge *Hymeniacidon* species. Synthesis of hymenamide A, G & H was successfully attempted by Himaja. Hymenamide A showed good antibacterial activity. The cyclic heptapeptide Malaysiatin (10) was isolated and structural elucidation was carried out by Fernandez et al. [18] in 1998. The synthesis was carried out by Boja. The synthetic compound showed good antibacterial activity.

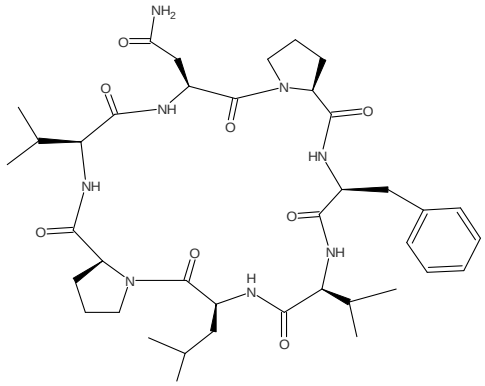


Malaysiatin (10)

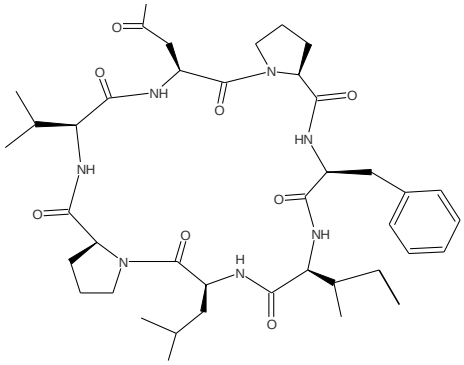
The cyclic heptapeptide Axinastatin 1, 2 and 3 (11a, b, c) were isolated by Pettit G. R. et al [19] from the marine sponge *Axinella* species and were reported to possess cytotoxic activity. Synthesis of Axinastatin 1, 2 and 3 were successfully attempted by Himaja and axinastatin 3 was found to possess potent antibacterial activity.



Axinastatin 1 (11a)



Axinastatin 2 (11b)



Axinastatin 3 (11c)

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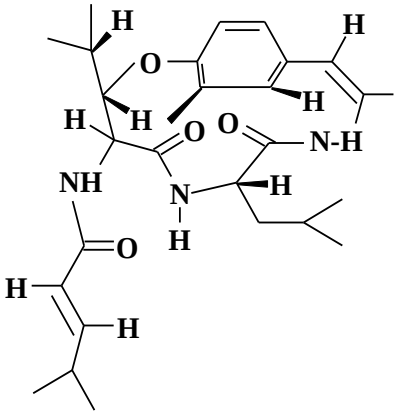
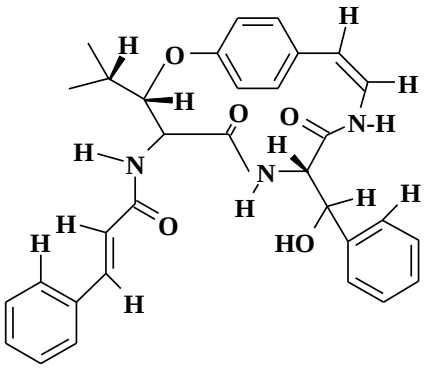
The isolation and structure determination of cyclic peptide alkaloids discarine- M (12a) and discarine -N (12b) along with other seven known cyclic peptide alkaloids has been carried out by Sandro R. Giacomelli et al [20] in 2003. It showed good activity against gram positive and gram negative bacteria.

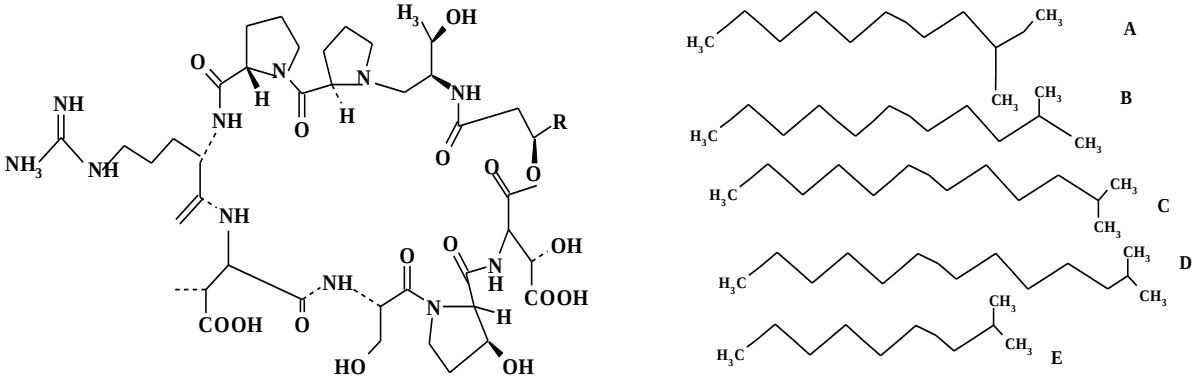


Discarine -M (12a)



Discarine -N (12b)

Hideki Hashizume et al [21] in 2004 isolated Tropropetin A, B, C, D and Z (13) from cells and broth of Lysobacter species. Tropropetin was reported as a novel antimicrobial agent.
Kahalalide A (14), a cyclic depsipeptide was prepared by total synthesis on solid phase by Bourel Bonnet L et al [22] in 2005. Several analogues were synthesized and rested for anti-mycobacterial activity. The results indicate that the alcohol functional group in serine and theronine residues was important, while the methyl butyrate side chain could be replaced by an achiral hexanoate with an increase in activity.



Tropropetin A,B,C,D and Z (13)

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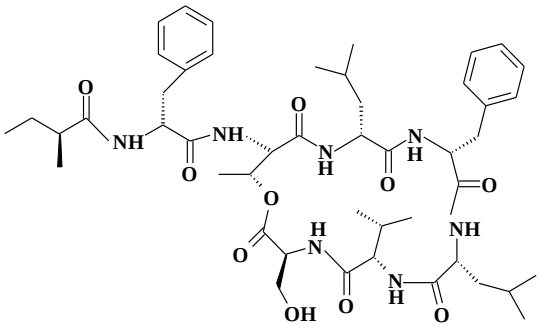
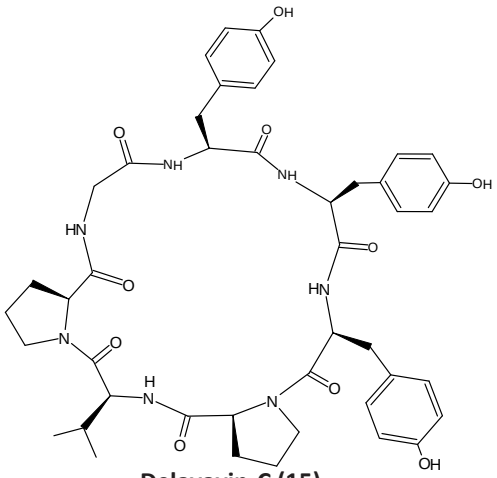
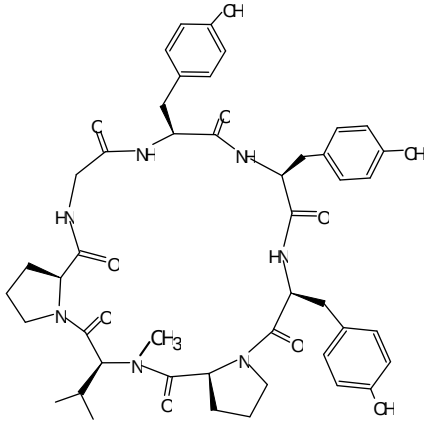


Kahalalide (14)

In 2008, Nirmala V.S. [23] carried out the total synthesis of cyclic heptapeptide, Delavayin-C, (15) a naturally occuring heptapeptide isolated from the roots of '*Stellaria delavayi*'.The synthesis was carried out by using solution phase technique. The molecule was shown to possess good antimicrobial activity.



Delavayin-C (15)

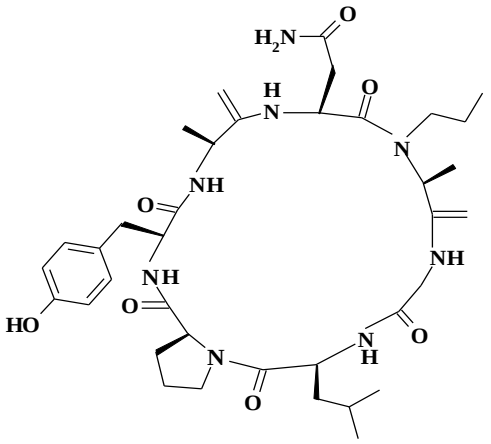


N-Me Analog of Delavayin-C (16)

In 2010, Nirmala V.S., M. Himaja et. al [24] carried out the total synthesis of N-methylated analog of Delavayin-C (16). The synthesis was carried out by solution phase technique using DIPC as a coupling agent. The compound has shown good Antimicrobial and Anthelmintic activity.

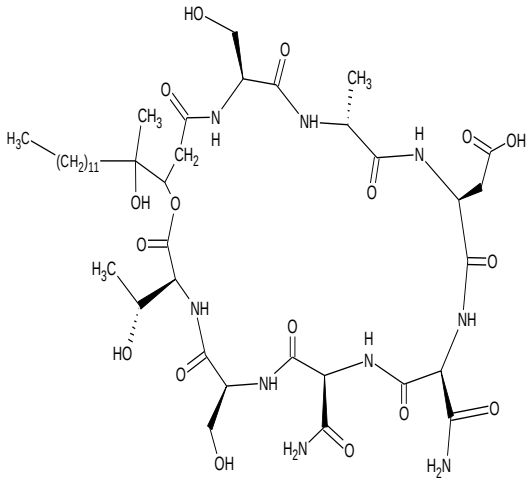
Synthesis a natural proline-rich cyclooligopeptide Cyclomontanin D (17) was carried out by Dahiya et. al [25]. It was done by coupling of tripeptide Boc-L-Asn (bzh)-L-Pro-Gly-OH and tetrapeptide L-Leu-LPro-L-Tyr-L-Ala-OMe followed by cyclization of linear polypeptide fragment. The newly synthesized cyclooligopeptide possessed good bioactivity against Gram-negative bacteria *Klebsiella pneumonia*, *Pseudomonas aeruginosa* as well as potent antidermatophyte

activity against *Microsporum audouinii* and *Trichophyton mentagrophytes*, in comparison to reference drugs ciprofloxacin and griseofulvin. Moreover, exhibited moderate antifungal activity against pathogenic *Candida albicans* with minimum inhibitory concentration (MIC) value of 60 µg/ml.

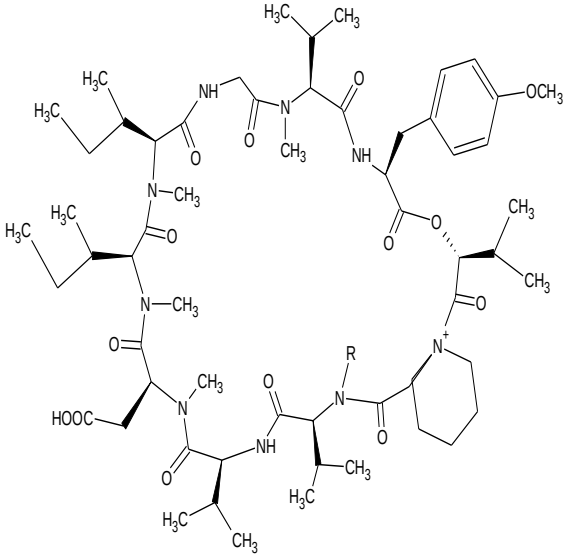


Cyclomontanin D(17)

Tsutomu Sato et al [26] isolated a novel antifungal cyclic depsipeptide termed Glomosporin (18) from a barley solid culture of *Glomospora sp.* BAUA 2825, showed antimicrobial activity against fungi including clinically important *Aspergillus fumigatus*.



Glomosporin (18)

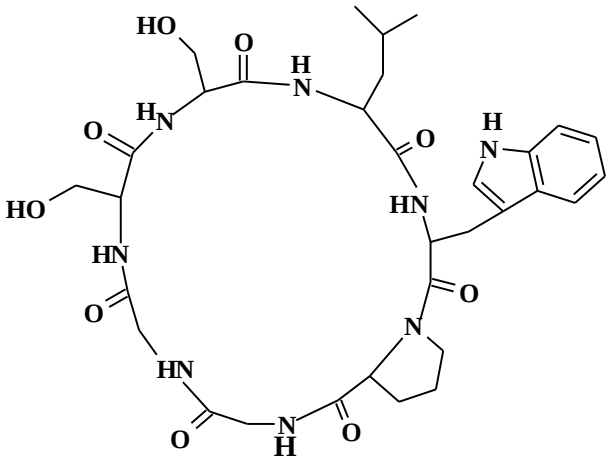


Clavariopsins (19)

The isolated Clavariopsins (19) from the fermentation broth of *Clavariopsis aquatica* AJ 117363 showed in vitro antifungal activity against *Aspergillus fumigatus*, *A.niger* and *Candida albicans* [27].

Rajiv Dahiya [28] et.al.carried out the synthesis of novel séries of 3,5-diiodo-4-(2-methyl-*1H*-imidazol-5-yl) benzoic acid analogs of amino acids, dipeptides and tripeptides was synthesized by using dicyclohexylcarbodiimide and diisopropylcarbodiimide (DIPC) as coupling agents and triethylamine (TEA) as base. The compound has shown potent bioactivity against pathogenic fungi *Candida albicans* and dermatophytes *Trichophyton mentagrophytes* and *Microsporum audouini* compared to the reference drug griseofulvin.

Synthesis of a novel glycine and serine-rich cyclopeptide Gypsin D (20) was carried out by Rajiv Dahiya and Hemendra Gautam [29].The synthesis is carried out by coupling of tripeptide unit Boc-L-Trp-L-Pro-Gly-OH and tetrapeptide unit Gly-L-Ser-L-Ser-L-Leu-OMe utilizing DCC as coupling agent, followed by cyclization of linear heptapeptide fragment. Biological screening of synthesized compound concluded that cyclic heptapeptide exhibited potent antifungal activity against dermatophytes *Microsporum audouinii* and *Trichophyton mentagrophytes*. It has also shown good bioactivity against pathogenic *Candida albicans*



Gypsin D (20)

Anthelmintic acivity:

Synthesis and Biological studies of Cherimolacyclopeptide E (21) and its N-methylated analog was carried out by Himaja M. [30]. The compound has shown potent anthelmintic activity similar to that of the drug mebendazole. A new potent bioactive proline rich cyclic heptapeptide (22) was synthesized using the solution phase technique by cyclization of the linear peptide BOC-Pro-Phe-Tyr-Tryp-Phl-Pro-Tryp-OMe after proper deprotection at carboxyl and amino terminals. The newly synthesized cyclopeptide was screened for its anthelmintic activity against pathogenic earthworm species and showed anthelmintic activity against earthworms *Megascoplex konkanesis* and Eudrilus species in comparision to albendazole [31].

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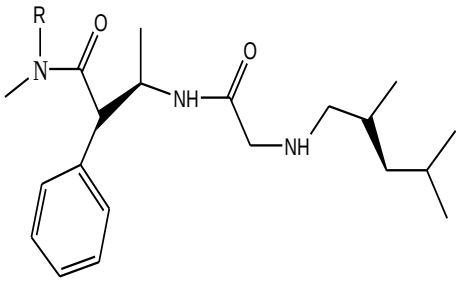
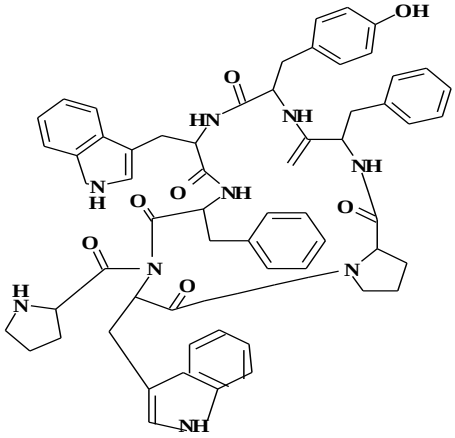


Cherimolacyclopeptide E (21)



Proline rich cyclic heptapeptide (22)

Angiotensin converting enzyme inhibitors

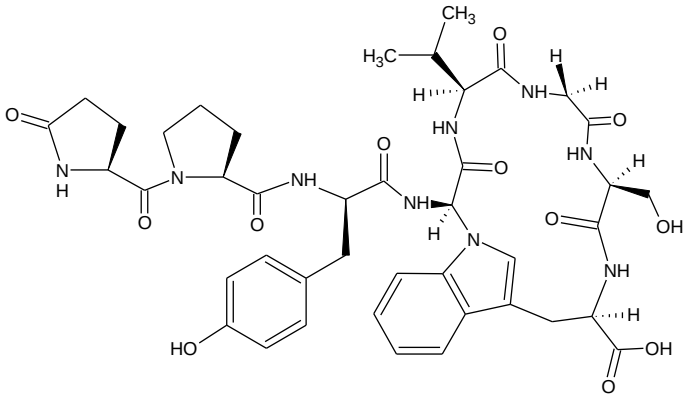
The isolation of monocyclic octapeptides Lyciumins A and B (23) was carried out from roots of *Lycium chinense* MILL [32]. Total synthesis of lyciumins A and B was conducted by Schmidt U. in 1992. Morita H. et al. [33] reported the elucidation of complete stereostructure and conformation analysis of lyciumin A in 1996. These cyclic octapeptides were found to exhibit inhibitory activity on angiotensin converting enzyme.

Tyrosinase inhibitors:

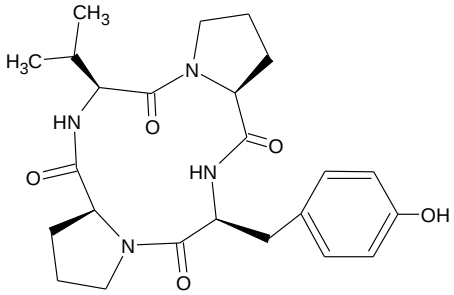
A novel tyrosinase inhibitor cyclotetrapeptide cyclo [L-Pro-L-Tyr-L-Pro-L-Val] (24) was isolated by Kawagishi et al [34] in 1993 from the lactic bacterium *Lactobacillus helveticus*. The synthesis and antibacterial activity was carried out by Harish. et al [35].

Estrogen like activity

Young sook and Hiroshi Morita [35] carried out the study on structures and estrogen like activity of cyclic pentapeptides, Segetalins G (25) and H (26). Both these cyclic peptides were

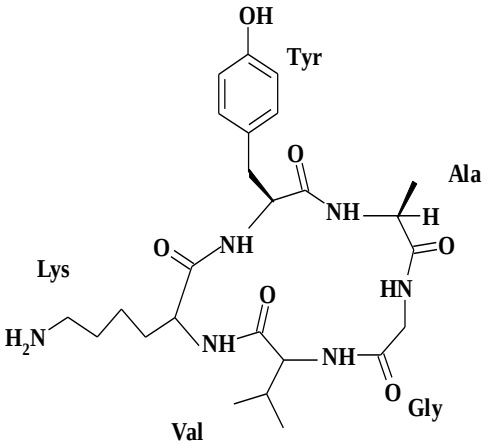


Lyciumin A (23)

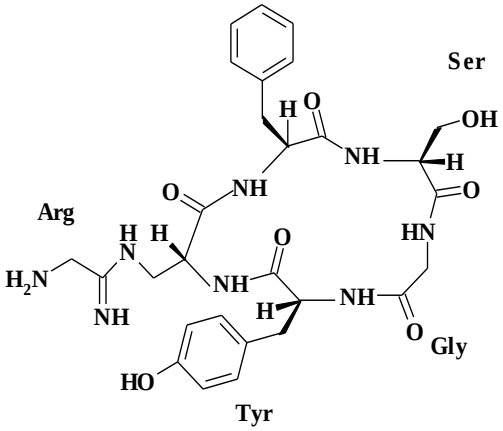


Cyclotetrapeptide (24)

found to possess estrogen like activity which was assayed by the increment of uterus against ovariectomized rats.



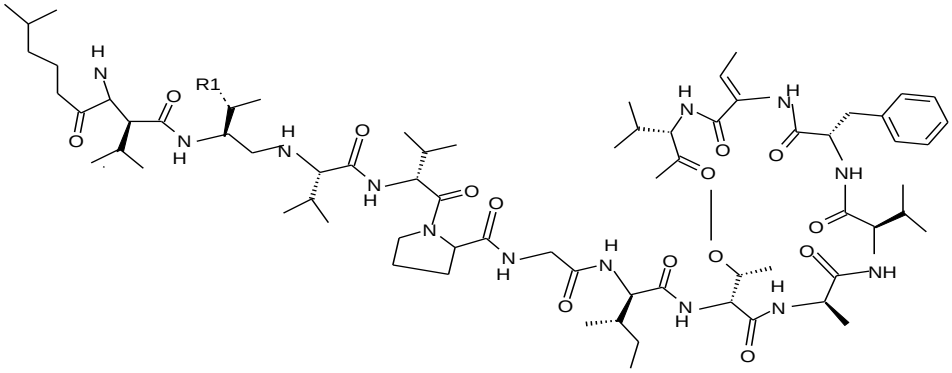
Segetalins G (25)



Segetalins H (26)

Anticancer Activity

Abbas Gholipour Shilabin and Noer Kasanahet et.al[36] found that Kahalalide F (27) which was isolated from marine sources exhibits good anticancer activity and has recently completed Phase I clinical trials and under consideration for Phase II trials.



Kahalalide F (27)

Vladimir V.Ryakhovsky et.al [37] reported the first solution phase of Melanotan II (28), a cyclic heptapeptide used to prevent a sunlight-induced skin cancer by stimulating the skin tanning process. The cyclic heptapeptide melanotan II is obtained in 2.6% overall yield for 12 steps by solution phase technique.

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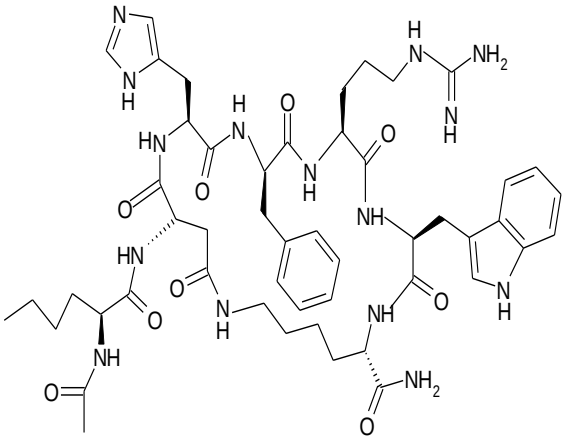
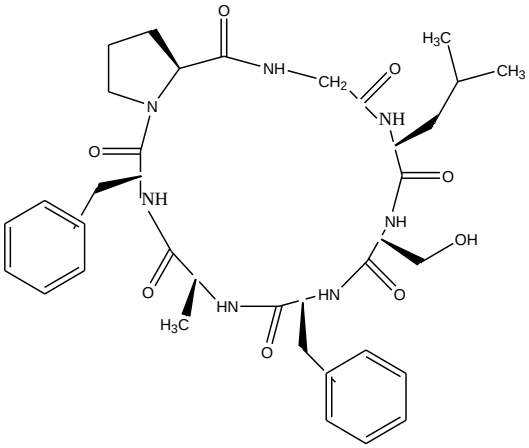


Melanotan II (28)



Segetalin D (29)

A natural cyclic heptapeptide segetalin D (29) was synthesized by coupling of tripeptide unit Boc-Pro-Gly-Leu-OMe [**V**] with tetrapeptide unit Boc-Ser-Phe-Ala-Phe-Ome. The synthesis was carried out by solution phase synthesis technique. The synthesized cyclopeptide was tested for its antibacterial, antifungal, anthelmintic and cytotoxic activities. Compound showed high cytotoxicity against *Daltonís lymphoma ascites* (DLA) and *Ehrlichís ascites carcinoma* (EAC) cell lines with CTC50 values of 7.54 and 13.56 µM. [38]

A natural phenylalanine-rich cyclic peptide - cordyheptapeptide B was synthesized by coupling of N methylated tetrapeptide and tripeptide units after proper deprotection at carboxyl and amino terminals followed by cyclization of linear heptapeptide fragment found to exhibit potent cytotoxicity against Dalton's lymphoma ascites (DLA) and Ehrlich's ascites carcinoma (EAC) cell lines, in addition to good antidermatophyte activity against Trichophyton mentagrophytes and Microsporum audouinii. **[**39]

Buforin IIb is a novel cell-penetrating anticancer peptide derived from histone H2A. Here we analyzed the anticancer activity and cancer cell-killing mechanism of buforin IIb. Buforin IIb displayed selective cytotoxicity against 62 cancer cell lines by specifically targeting cancer cells through interaction with cell surface gangliosides [40].

Antitubercular Activity

Study on docking, and synthesis of some heptapeptide derivatives was carried out. By Kariger Asif, M. Himaja et.al. [41] The docking study was carried out to determine which compounds can show activity and based on this study, Glaucacyclopeptide A (30), a cyclic heptapeptide and its N-methylated analogs were synthesized. The synthesized compounds were screened for antitubercular activity against *M. Tuberculi.* The synthesized compounds have shown good antitubercular activity.

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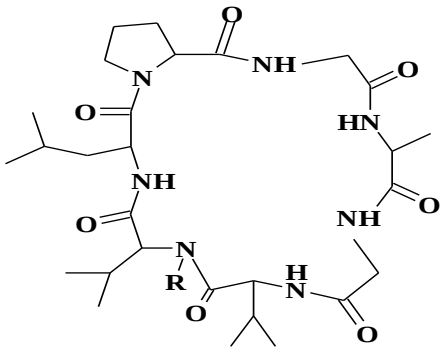
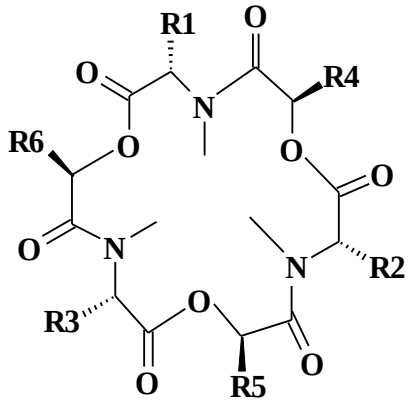
Four cyclic peptides, namely, Enniatins H (31a), I (31b), B (31c), and B4 (31d) which are the components of the pathogenic fungus *Verticillium hemipterigenum*, inhibit growth of *M. tuberculosis* H37Ra (MIC 3.12–6.25µg/mL) [42]. Syringomycin E (32), isolated from *Pseudomonas syringae* pv.*Syringae*, is found to be active against *M. smegmatis* (MIC 1.5 µg/mL) [43].



Glaucacyclopeptide A (30)



Enniatins H (31a), I (31b), B (31c), and B4

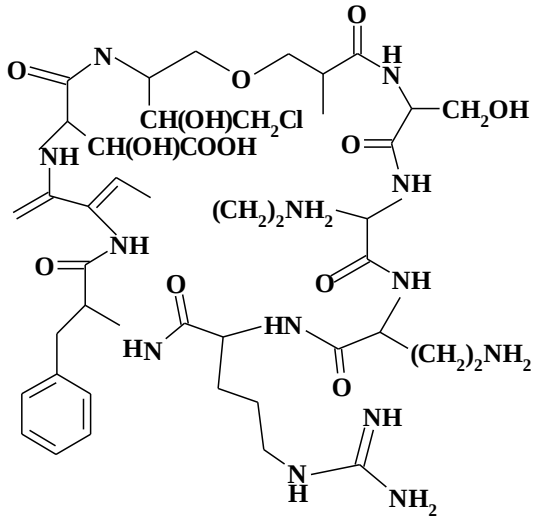
R = NHCOCH2CH(OH)(CH2)8CH3

(31a) R1 = R2 = R3 = R5 = R6 = i-Pr; R4 = s-Bu;

(31b) R1 = R2 = R3 = R6 = i-Pr; R4 = R5 = s-Bu;

(31c) R1 = R2 = R3 = R4 = R5 = R6 = i-Pr;

(31d) R1 = i-Bu; R2 = R3 = R4 = R5 = R6 = i-Pr



Syringomycin E (32)

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CONCLUSION AND FUTURE OUTLOOK

Cyclic Peptides emerges as an important class of organic compounds with an array of a variety of biological activities.With respect to their functionalisation, different modified methods can be used for their synthesis. An introduction of heteroatomic nucleus in the basic structure of molecule is found to increase in the intinsic activity of molecule. As numbers of drugs are already available from this class, there is lot of scope to develop and to synthesize some new cyclic peptides and their derivatives for new biological activities.

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