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Review Article

A REVIEW ON PHARMACOLOGICAL ACTIVITIES OF DIFFERENT CLASSES OF CYCLIC PEPTIDES

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ABSTRACT

Peptides play a crucial role in fundamental physiological and biochemical functions of life. Cyclic Peptides are abundantly found in nature and isolated by various methods. The inherent medicinal properties of cyclic peptides promoted scientists to isolate these compounds from natural sources. Cyclic peptides possess various biological activities like antifungal, antibacterial, anthelmintic, antineoplastic, insecticidal, antiinflammatory. This review particularly deals with the various classes of cyclic peptides, their isolation and biological activities.

INTRODUCTION

Peptides are a group of compounds consisting of two or more amino acids linked by peptide bond, and are mostly present in living organisms. Many peptides have been isolated from animals, plants and microorganisms. (Craik, 2006). Based on their chemical structure, peptides can be divided into linear and cyclic types. Cyclic peptides are polypeptide chains in which the amino termini and carboxyl termini; amino termini and side chain; carboxyl termini and side chain; or side chain and side chain are linked with a covalent bond that generates the ring (Borthwick, 2012). Cyclic peptides as compared with linear peptides, exhibit more potent biological activities, due to increased potency and selectivity of cyclic peptides (Jenssen *et al*, 2006). Cyclic peptides played a crucial role in the pharmaceutical research as biomedical useful agents or as lead compounds for drug development. They have originated as an important class of organic compounds with potent biological activities like antimicrobial, antiHIV, anticancer, insecticidal, tyrosinase inhibitors (Shinde *et al*, 2013). Interesting properties of cyclic peptides that are responsible for bioactivity are reduced degree of freedom, reduced flexibility of parent linear molecules, stabilize specific secondary structure and stable conformation. This trait makes cyclic peptides attractive to designers to develop potent and selective peptide drugs (Tapeinou *et al*, 2015).The de novo design of peptide mimetics for the synthesis of linear or cyclic peptides has enhanced the progress of therapeutics and diverse areas of science and technology. In the case of metabolically unstable peptide ligands, the rational design and synthesis of cyclic peptide analogues has turned into an alternative approach for improved biological activity (Mojsoska and Jenssen, 2015).

Some examples of cyclic peptides with biological activities.

Antimicrobial activity

Sclerotiotides A-K were isolated from the broth of the halotolerant Aspergillus sclerotiorum PT06-1.Structures were identified by spectroscopic analysis and were evaluated for their antimicrobial and cytotoxic effects. Sclerotiotides A (1), B (2), F (6), and I (9) showed selective antifungal activity against *Candida albicans* (Zheng *et al*, 2010).

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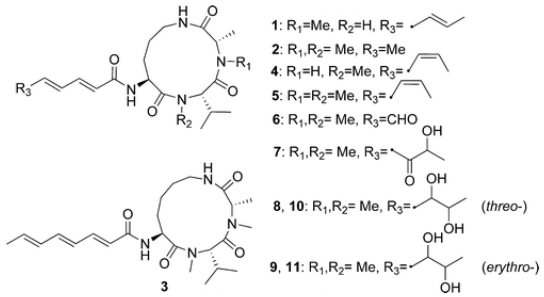
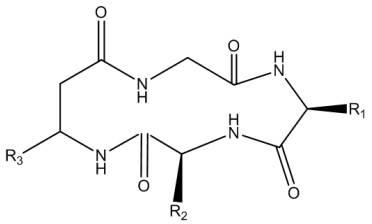


Figure 1 Sclerotiotides A−K

Rhodopeptins: Five novel rhodopeptins Cl (a), C2(b), C3(c), C4(d) and B5(e) were isolated from a strain named Rhodococcus sp. Rhodopeptins showed high antifungal activity against *Candida albicans* and *Cryptococcus neoformans in vitro* and have no antibacterial activity (Chiba *et al*, 1999).



	R_1	R_2	R_3
1.	$-(CH_2)_3NH_2$	i-Pr	$-(CH_2)_6CH$-(Me)Et
2.	$-(CH_2)_3NH_2$	-CH(Me)Et	$-(CH_2)_6CH$-(Me)Et
3.	$-(CH_2)_3NH_2$	i-Pr	$-(CH2)_8$-i-Pr
4.	$-(CH_2)_3NH_2$	i-Pr	$-(CH2)_8CH$(Me)Et
5.	$-(CH_2)_4NH_2$	i-Pr	$-(CH_2)_9$-i-Pr

Figure 2 Rhodopeptins

YIM67005: Cyclo (Tyr-Pro-Phe-*trans*-4-hydroxy--Pro) isolated from the fermentation broth of Streptomyces sp. The isolated compound was investigated for cytotoxicity and antimicrobial activity (Zhou *et al*, 2014).

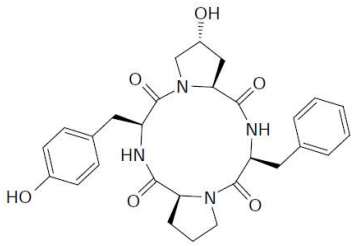


Figure 3 YIM67005

Evolidine: Evolidine was isolated from the leaves of *Evodia xonthoxyloids*. Synthesis and evaluation of biological activities were carried out and showed good antibacterial and antifungal activity (Eggleston *et al*, 1991)

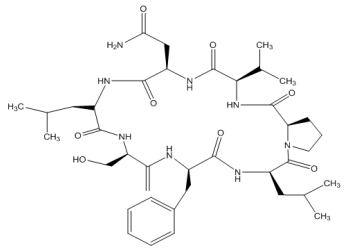


Figure 4 Evolidine

Malastatin A: Malastatin was isolated and structural elucidation was carried out. The synthetic compound showed good antibacterial activity (Fernandez *et al*, 1992).

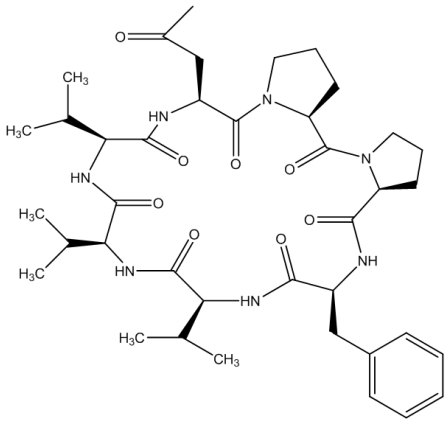


Figure 5 Malastatin

Delavayin-C: A naturally occurring delavayin-C cyclo(gly-tyr-tyr-tyr-pro-val-pro) isolated from the roots of *Stellaria delavayi*. The structure was established on the basis of analytical IR, ^{1}H NMR and FAB mass spectral data. The antibacterial and antifungal activities of this peptide are also described (Shinde *et al*, 2010).

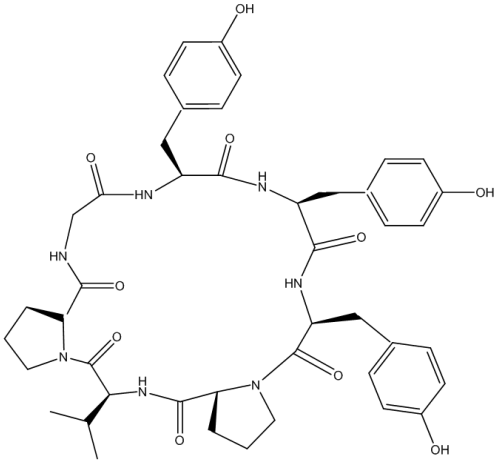
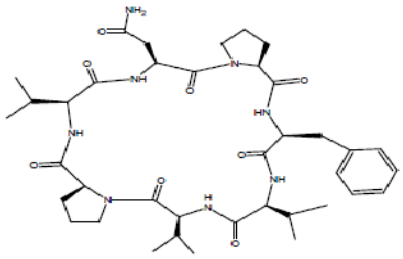
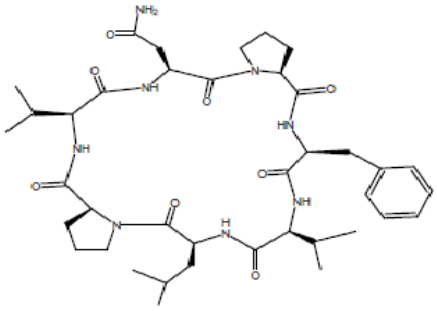


Figure 6 Delavayin-C

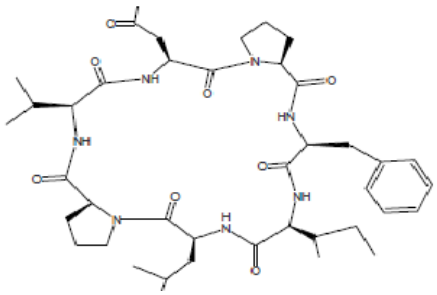
Axinastatins: Axinastatin (a), (b) and (c), were isolated from the marine sponge *Axinella* species and were found to possess cytotoxic activity. Axinastatin c was found to possess potent antibacterial activity (Bates *et al*, 1998).



a



b

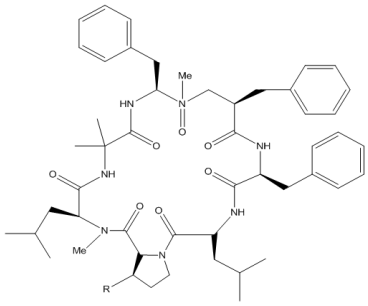


c

Figure 7 Axinastatins

Cytotoxic activity

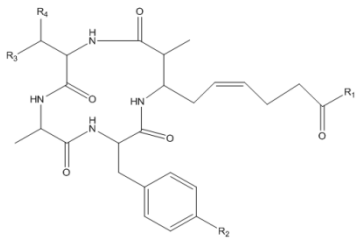
Scytalidamides: Scytalidamides A (a) and B (b) were reported from Scytalidium sp. CNC-310.These showed moderate *in vitro* cytotoxicity towards HCT-116 human adenocarcinoma (Tan *et al*, 2003).



a R=H **b** R=Me

Figure 8 Scytalidamides

Azumamides A–E: Azumamides A–E (a-e) showed potent HDAC inhibitory activity with IC50 values of 0.045 to 1.3 mm in an assay using enzymes prepared from K562 human leukemia cells (Nakao *et al*, 2006).



	R^1	R^2	R^3=R^4
(a)	NH_2	H	Me
(b)	NH_2	OH	Me
(c)	OH	OH	Me
(d)	NH_2	H	H
(e)	OH	H	Me

Figure 9 Azumamides A–E

Asperterrestide A: Asperterrestide A was isolated from the fermentation broth of the marine-derived fungus *Aspergillus terreus.* Structure was elucidated by spectroscopic analysis. It showed cytotoxicity against U937 and MOLT4 human carcinoma cell lines and inhibitory effects on influenza virus strains H1N1 and H3N2 (He *et al*, 2013).

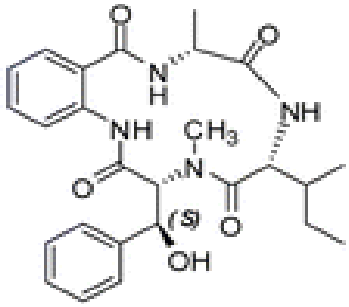


Figure 10 Asperterrestide A

Trapoxin A: Trapoxin is a fungal product. It irreversibly inhibits HDAC activity in crude cell lysates and induces the accumulation of hyperacetylated core histones in a number of mammalian cell lines and tissues and has been suggested as a potential anticancer agent for pre-clinical trials (Kijima *et al*, 1993).

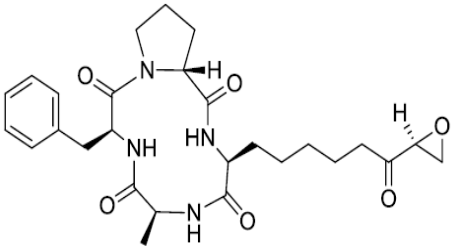


Figure 11 Trapoxin A

Chrysosporide: It was isolated from the mycoparasitic fungus *Sepedonium chrysospermum,* found in *New Zealand.* The structure was deduced by detailed spectroscopic analysis. It exhibited weak cytotoxic activity against the murine P388 murine leukemia cell line (Mitova *et al*, 2006).

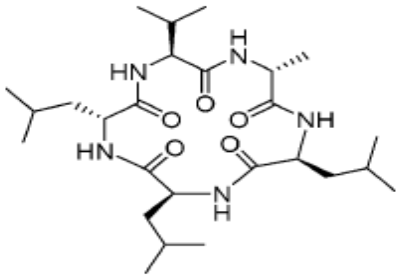
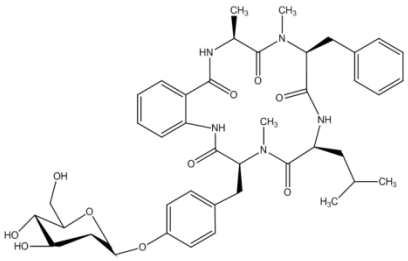
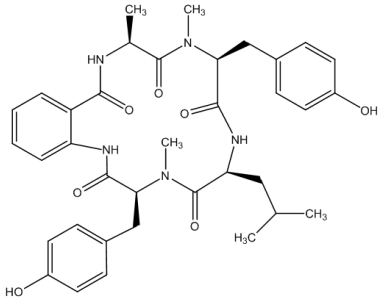


Figure12 Chrysosporide

Cycloaspeptides: Cycloaspeptides F**(a)** and G**(b)** were found to show cytotoxic effects against HeLa and MCF7 cell lines, and the known cycloaspeptides A **(c)** and C **(d)** have been isolated from the crude extract of the fungus *Isaria farinosa* and colonizes *Cordyceps sinensis* (Zhang *et al*, 2009).



a



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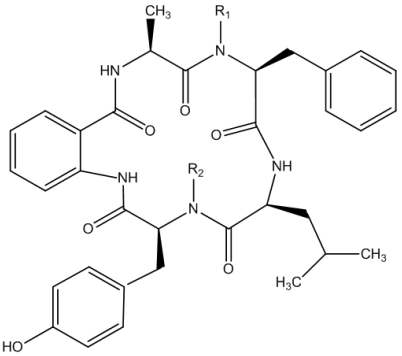

Figure 13 Cycloaspeptides

Nazumazoles: A mixture of nazumazoles (A-C) was purified from the extract of the marine sponge *Theonella swinhoei*. The structures of nazumazoles were interpreted NMR data and chemical degradations. Nazumazoles exhibited cytotoxicity against P388 cells (Fukuhara *et al*, 2015).

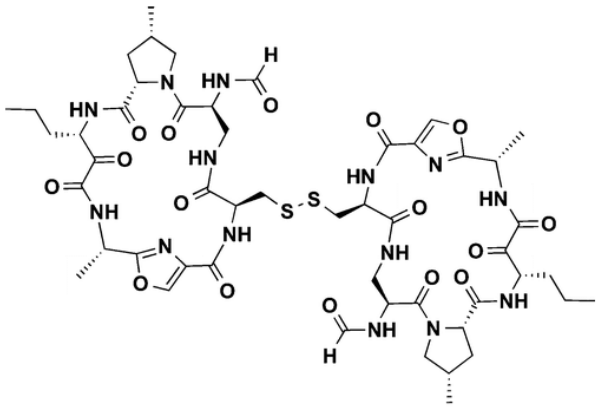

Figure 14 Nazumazole A

Antibiotic

Polymyxin B: Isolated Polymyxin B from *Bacillus polymyxa* followed by its resolution into polymyxins B1 and B2 was reported. The structural formula for polymyxin B was proved by its synthesis. 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 (Orwa *et al*, 2001).

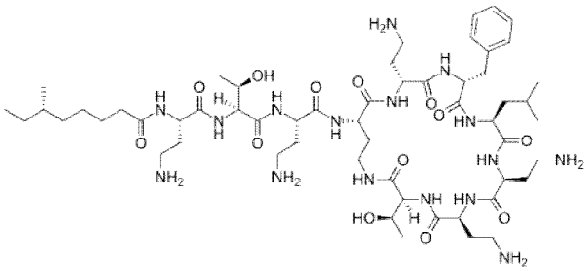

Figure 15 Polymyxin B

Bacitracin: Cyclic peptide antibiotic Bacitracin was isolated from *Bacillus subtilis* and found to possess broad spectrum of antibacterial activity and as topical agent. The Chemical structure of the compound was elucidated by spectral analysis (Johnson, *et al* 1945).

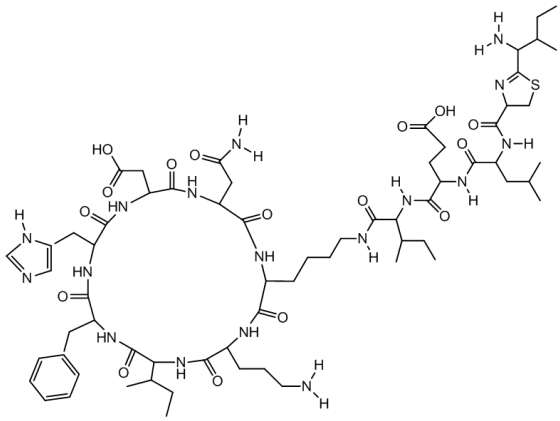

Figure16 Bacitracin

Gramicidin S: Cyclic decapeptide antibiotic Gramicidin S was isolated from a culture of *Bacillus brevis.* Total synthesis was carried out and showed good antibacterial activity against Gram positive and Gram-negative bacteria and also clinically proven in topical applications (Consden *et al* 1947).

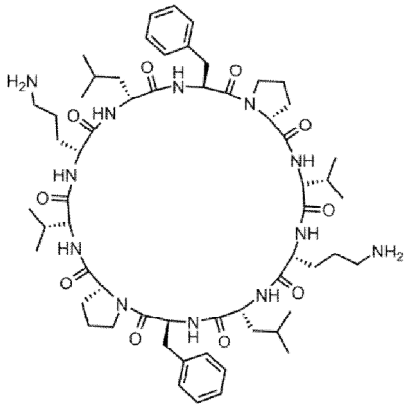

Figure 17 Gramicidin S

Anthelmintic activity

Segetalin D: A natural Segetalin D have been isolated from the seeds of Vaccaria segetalis, were elucidated by computational

and NMR methods. The synthesized cyclopeptide was tested for its antibacterial, antifungal, anthelmintic and cytotoxic activities. Compound showed high cytotoxicity against DLA and EAC cell lines (Dahiya *et al*, 2007).

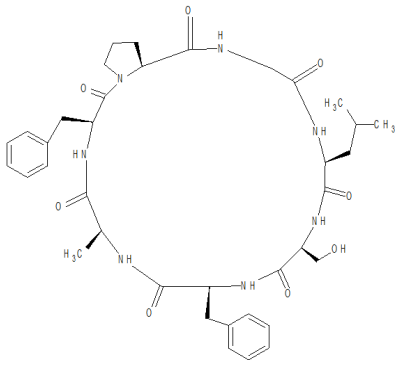

Figure 18 Segetalin D

Immunosuppressant activity

FR235222: A novel immunosuppressant has been isolated from the fermentation broth of a fungus, Acremonium. FR235222 showed potent and selective inhibitory effects on both T cell proliferation and lymphokine production. The structure was assigned cyclo(-(2S,9R)-2-amino-9-hydroxy-8-oxodecanoic acid-trans-4-(Me-Pro-Phe-Iva-) (Mori *et al*, 2003).

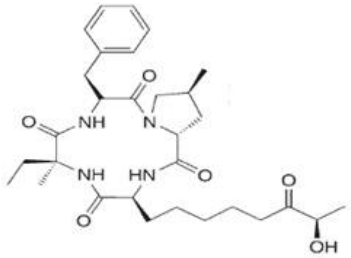

Figure 19 FR235222

CONCLUSION

Cyclic Peptides emerges as an important class of organic compounds with an array of a variety of biological activities. There are several naturally occurring cyclic peptides used clinically. Cyclic peptides have numerous structural features that consider as a good drug leads. Various biologically active cyclic peptides have been developed with genetic and synthetic approaches and they are useful as therapeutic and biochemical agents.

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