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First total synthesis and biological evaluation of halolitoralin A

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Abstract: A new potent bioactive alanine-rich cyclic hexapeptide halolitoralin A (**8**), which was previously isolated from the marine sediment-derived bacterial strain *Halobacillus litoralis* YS3016, has been synthesized by the solution phase technique. All the coupling reactions were performed at room temperature utilizing dicyclohexylcarbodiimide (DCC) as the coupling reagent and *N*-methylmorpholine (NMM) as the base. The structure of the peptide was characterized by IR, ^{1}H-NMR, ^{13}C-NMR, FAB MS spectral data, as well as elemental analysis and DSC. The synthesized cyclopeptide was also screened for its antimicrobial and anthelmintic activities and found to exhibit potent antifungal activity against the pathogenic fungi *Candida albicans* and *Trichophyton mentagrophytes* along with potent antibacterial activity against the gram negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli*. Gram negative bacteria were found to be more sensitive than gram positive bacteria towards the newly synthesized peptide. In addition, the peptide was also found to exhibit moderate anthelmintic activity against the earthworms *Megascoplex konkanensis* and *Eudrilus* sp.

Keywords: halolitoralin A, cyclic hexapeptide, alanine-rich peptide, antimicrobial activity, anthelmintic activity.

INTRODUCTION

Antimicrobial peptides[1–3] have played a crucial role in pharmaceutical research as biomedically useful agents or as lead compounds for drug development. Halolitoralins are natural cyclic peptides isolated from the bacterial strain *Halobacillus litoralis* YS3106 of marine origin.[4] These cyclic congeners are associated with diverse biological activities, such as antifungal and antitumor activities. Only the minute quantities of cyclopeptides, ranging from di to hexapeptides, obtained from natural resources[5] restricted researchers from investigating their biological profiles in detail. Considering the wide spectrum of bioactivities associated with these natural congeners and in order to obtain a potent bioactive compound in good yield, an attempt was made to synthesize the cyclic hexapeptide halolitoralin A (**8**) by a solution phase technique in a convenient and economic manner.

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CHEMISTRY

In order to carry out the synthesis of halolitoralin A (**8**), two dipeptide units Boc–Leu–Ala–OMe (**1**) and Boc–Ala–Ile–OMe (**3**) and two amino acid units Leu–OMe·HCl (**2**) and Ala-OMe·HCl (**4**) were coupled. The ester group of the dipeptide Boc-Leu-Ala-OMe (**1**) was removed with LiOH and the deprotected unit was coupled with the amino acid methyl ester hydrochloride Leu–OMe·HCl (**2**) using DCC to obtain the first tripeptide unit Boc–Leu–Ala–Leu–OMe (**5**). Similarly, the dipeptide unit **3**, after deprotection at the carboxyl end, was coupled with **4** to obtain another tripeptide unit Boc–Ala–Ile–Ala–OMe (**6**). Then, the ester group of **5** was removed using LiOH and Boc group of **6** was removed using CF_3COOH. Both the deprotected units were then coupled using DCC and NMM to obtain the linear hexapeptide Boc–Leu–Ala–Leu–Ala–Ile–Ala–OMe (**7**), which was finally cyclized by keeping the whole contents at 0 °C for 7 days under alkaline conditions, whereby halolitoralin A (**8**) was obtained (Scheme 1).

The structure of the newly synthesized cyclopeptide as well as the intermediate di/tri/hexapeptides were confirmed by IR, ^{1}H-NMR as well as elemental analysis. ^{13}C-NMR and mass spectra as well as DSC curves were recorded for the cyclic peptide only.

PHARMACOLOGY

The newly synthesized cyclic hexapeptide halolitoralin A was screened for *in vitro* antibacterial and antifungal activity against the gram positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*, the gram negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli*, the cutaneous fungi *Microsporum audouinii* and *Trichophyton mentagrophytes*, the diamorphic fungi *Candida albicans* and the plant pathogenic fungi *Ganoderma* sp. using a modified Kirby–Bauer disk diffusion method[6] and anthelmintic activity against earthworms *Megascoplex konkanensis* and *Eudrilus* sp. using the Garg method.[7] The results are tabulated in Tables I and II.

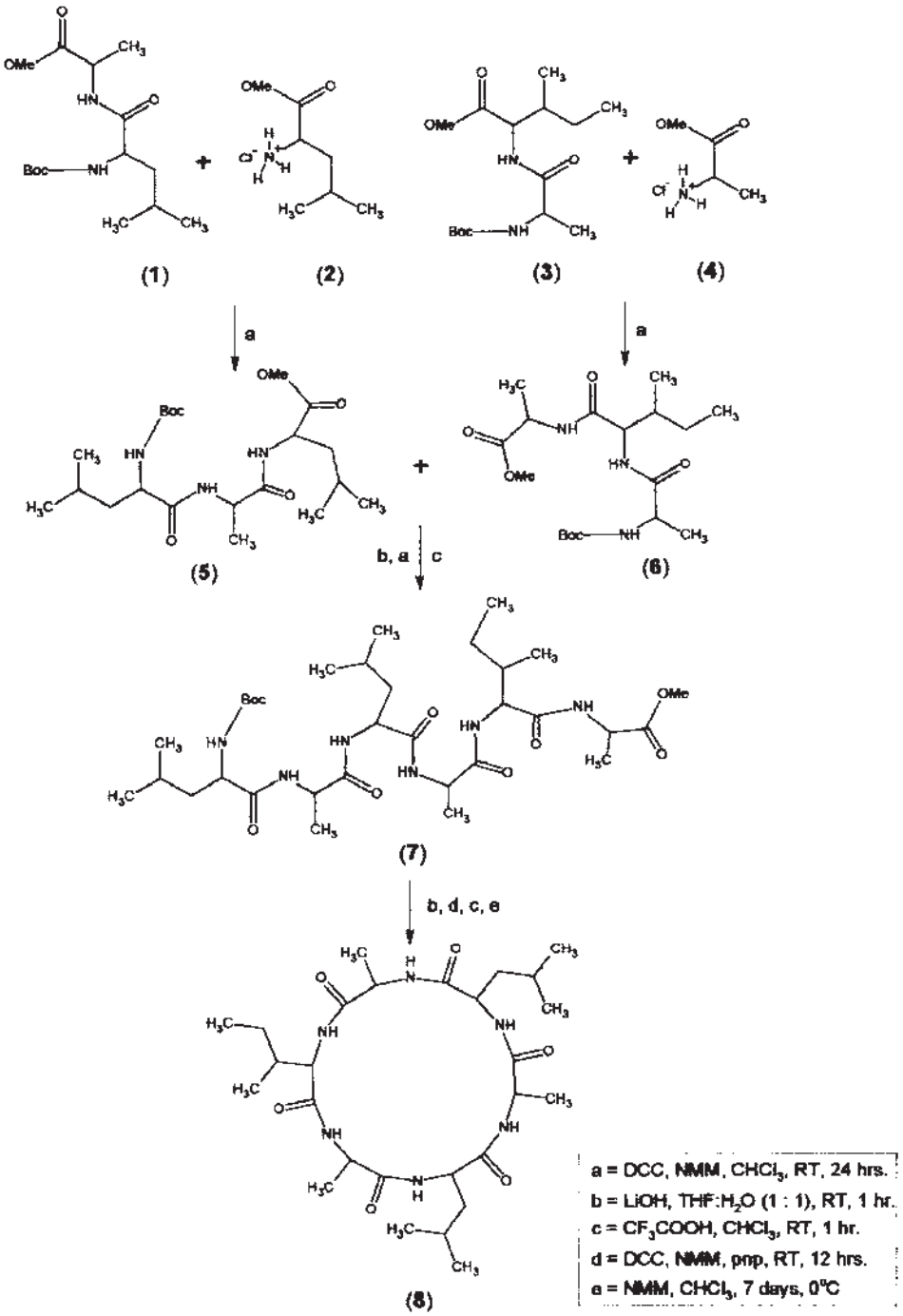
TABLE I. Antimicrobial activity data

Compd. No.	Zone of inhibition (in mm) at 50 μg/ml concentration							
	B. sub.	*E. coli*	*S. aur.*	*P. aeru.*	*C. alb.*	*Gano.* sp.	*M. audo.*	*T. menta.*
8	8	22	7	24	28	9	7	25
Clotrimazole	–	–	–	–	21	14	13	18
Ciprofloxacin	12	16	15	17	–	–	–	–

TABLE II. Anthelmintic activity data

Compd. No.	*Eudrilus* sp.		*M. konkanensis*	
	Mean paralyzing time (min) ± S.E.*	Mean death time (min) ± S.E.*	Mean paralyzing time (min) ± S.E.*	Mean death time (min) ± S.E.*
8	12.53 ± 0.92	13.58 ± 0.96	12.52 ± 0.71	13.59 ± 0.38
Piperazine citrate	12.48 ± 0.18	13.53 ± 0.21	12.48 ± 0.37	13.56 ± 0.22
Mebendazole	11.57 ± 0.39	13.46 ± 0.72	12.19 ± 0.93	14.05 ± 0.84

*S.E. = Standard error


(1)
(2)
(3)
(4)
a
a
(5)
(6)
b, a
c
(7)
b, d, c, e
(8)
a = DCC, NMM, CHCl3, RT, 24 hrs.
b = LiOH, THF:H2O (1 : 1), RT, 1 hr.
c = CF3COOH, CHCl3, RT, 1 hr.
d = DCC, NMM, pnp, RT, 12 hrs.
e = NMM, CHCl3, 7 days, 0°C

Scheme 1.

DETERMINATION OF PHYSICOCHEMICAL FACTORS

Different steric and lipophilicity parameters of the cyclopeptide (**8**) were calculated. These parameters are required to describe the intermolecular forces of drug–receptor interactions, as well as the transport and distribution of drugs in a quantitative manner (Table III). As per IUPAC rules, halolitoralin A was named as 3-*sec*-butyl-9,15-diisobutyl-6,12,18-trimethyl-1,4,7,10,13,16-hexaazacyclooctadecane-2,5,8,11,14,17- hexaone.

TABLE III. Various steric and lipophilicity parameters for **8**

Parameter	Calculated value
Molar refractivity (MR^{20})	145.93 ± 0.3 cm^3
Molar volume (MV^{20})	545.0 ± 3.0 cm^3
Parachor (P_r)	1264.3 ± 6.0 cm^3
Index of refraction (n^{20})	1.448 ± 0.02
Surface tension (γ^{20})	(28.9 ± 3.0) × 10^{-5} N/cm
Density (d^{20})	1.014 ± 0.06 g/cm^3
Polarizability (α)	(57.85 ± 0.5) × 10^{-24} cm^3
Logarithm of partition coefficient (log *P*)	3.22±0.64

EXPERIMENTAL

Materials and methods

All the reactions requiring anhydrous conditions were conducted in a flame dried apparatus. Melting points were determined by the open capillary method and are uncorrected. The melting point of **8** was confirmed by DSC analysis using a DSC Q10 TA instrument. The amino acids, di-*tert*-butyl pyrocarbonate (Boc), *p*-nitrophenol (pnp), DCC and NMM were obtained from Spectrochem Limited, Mumbai, India. The IR spectra were recorded on a Shimadzu 8700 Fourier transform infrared spectrophotometer using a thin film supported on KBr pellets for the cyclic hexapeptide halolitoralin A and $CHCl_3$ as solvent for the intermediate semisolids. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC NMR spectrometer (300 MHz) using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. The mass spectra were recorded on a Jeol JMS DX 303 Mass spectrometer operating at 70 eV. Elemental analyses of all compounds were performed on an Elementar vario EL III. The purity of all the compounds was controlled by TLC on precoated silica gel G plates.

Preparation of the peptides

The amino acid/peptide methyl ester hydrochloride (10 mmol) was dissolved in $CHCl_3$ (20 ml). To this, NMM (21 mmol) was added at 0 °C and the reaction mixture was stirred for 15 min. The Boc-amino acid/peptide (10 mmol) in $CHCl_3$ (20 ml) and DCC (10 mmol) were added with stirring. After 24 h, the reaction mixture was filtered and the residue was washed with $CHCl_3$ (30 ml) and added to the filtrate. The filtrate was washed with 5 % $NaHCO_3$ and saturated NaCl solutions. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The crude product was recrystallized from a mixture of chloroform and petroleum ether followed by cooling at 0 °C. For protecting the amino group of the L-amino acids, Boc was used. The carboxyl group of the L-amino acids was protected by esterification with methanol using $SOCl_2$. The peptides were prepared by the Bodanszky method with certain modifications, and cyclization of the linear segment was done

by the *p*-nitrophenyl ester method.[8] Furthermore, trifluoroacetic acid was used for the removal of the Boc group and the ester group was removed by alkaline hydrolysis with lithium hydroxide.

t-*Butoxycarbonyl-leucyl-alanine methyl ester* (**1**)

Semi-solid mass, yield 72.8 %.

IR (**$CHCl_3$**): 3318, 3241 (*s*, –NH str, amide), 2960, 2928 (*m*, –CH str, asym, aliph. CH_3 & CH_2), 2897, 2894 (*m*, –CH str, >CH–), 2873, 2854 (*m*, –CH str, sym, aliph, CH_3 & CH_2),2822 (*m*, –CH str, OCH_3), 1749 (*s*, –C=O str, ester), 1643, 1639 (*s*, –C=O str, 2° amide), 1540, 1534 (*m*, –NH bend, 2° amide), 1389, 1370 (*m*, –CH bend, *t*-butyl group), 1206 (*s*, C–O str, ester), 489 (*m*, C–C bend, aliph.) cm^{-1}.

^{1}H-NMR (**$CDCl_3$** 300 MHz): δ 6.72 (1H, *br. s*, – NH), 6.04 (1H, *br. s*, –NH), 4.45–4.35 (1H, *q*, α-H of Ala), 4.30–4.24 (1H, *m*, α-H of Leu), 3.63 (3H, *s*, OCH_3), 2.05–1.87 (2H, *m*, β-protons of Leu), 1.65–1.48 (1H, *m*, γ-H of Leu), 1.55 (9H, *s*, *t*-butyl group), 1.29–1.27 (3H, *d*, *J* = 4.2 Hz, α-CH_3 of Ala), 1.03–1.01 (6H, *d*, *J* = 6.2 Hz, γ-CH_3 of Leu) ppm.

Found: C, 56.80; H, 9.16; N, 8.89; $C_{15}H_{29}N_2O_5$ requires C, 56.76; H, 9.21; N, 8.83.

t-*Butoxycarbonyl-alanyl-isoleucine methyl ester* (**3**)

Semi-solid mass, yield 68.6 %.

IR (**$CHCl_3$**): 3320, 3240 (*s*, –NH str, amide), 2962, 2927 (*m*, –CH str, asym, aliph. CH_3 & CH_2), 2895 (*m*, –CH str, >CH–), 2875 (*m*, –CH str, sym, aliph. CH_3), 2825 (*m*, –CH str, OCH_3), 1753 (*s*, –C=O str, ester), 1640 (*s*, –C=O str, 2° amide), 1540, 1535 (*m*, –NH bend, 2° amide), 1390, 1369 (*m*, –CH bend, *t*-butyl group), 1210 (*s*, C–O str, ester) cm^{-1}.

^{1}H-NMR (**$CDCl_3$**, 300 MHz): δ 6.7 (1H, *br. s*, –NH), 6.52 (1H, *br. s*, –NH), 4.58–4.46 (1H, *q*, α-H of Ala), 4.24–4.19 (1H, α-H of Ile), 3.5 (3H, *s*, OCH_3), 2.10–1.97 (1H, *m*, β-H of Ile), 1.75–1.40 (2H, *m*, γ-protons of Ile), 1.60–1.58 (3H, *d, J* = 4.2 Hz, α–CH_3 of Ala), 1.56 (9H, *s*, *t*-butyl group), 0.95–0.88 (6H, triplet overlapped over doublet, β-CH_3 & δ-CH_3 of Ile) ppm.

Found: C, 56.72; H, 9.26; N, 8.79; $C_{15}H_{29}N_2O_5$ requires C, 56.76; H, 9.21; N, 8.83.

t-*Butoxycarbonyl-leucyl-alanyl-leucine methyl ester* (**5**)

Semi-solid mass, yield 65.4 %.

IR (**$CHCl_3$**): 3325, 3238 (*s*, –NH str, amide), 2963, 2960, 2929 (*m*, –CH str, asym, aliph. CH_3 & CH_2), 2898, 2893 (*m*, –CH str, >CH–), 2877, 2874, 2853 (*m*, –CH str, sym, aliph. CH_3 & CH_2), 2823 (*m*, –CH str, OCH_3), 1750 (*s*, –C=O str, ester), 1644, 1640 (*s*, –C=O str, 2° amide), 1542, 1535 (*m*, –NH bend, 2° amide), 1389, 1370 (*m*, –CH bend, *t*-butyl group), 1204 (*s*, C–O str, ester), 932 (*w*, CH_3 rock, *t*-butyl group) cm^{-1}.

^{1}H-NMR (**$CDCl_3$**, 300 MHz): δ 8.12 (1H, *br. s*, –NH), 6.80 (1H, *br. s*, –NH), 6.54 (1H, *br. s*, –NH), 4.48–4.39 (1H, *q*, α-H of Ala), 4.19–4.12 (1H, *q*, α-H of Leu^1), 3.60 (3H, *s*, OCH_3), 3.56–3.49 (1H, *m*, α-H of Leu^2), 2.02–1.84 (2H, *m*, β-protons of Leu^1), 1.63–1.21 (7H, *m*, γ-H of Leu^1 & Leu^2, β-protons of Leu^2, α-CH_3 of Ala), 1.54 (9H, *s*, *t*-butyl group), 1.04–1.02 (6H, *d*, *J* = 6.2 Hz, γ-protons of Leu^1), 0.98–0.96 (6H, *d*, *J* = 6.2 Hz, γ-protons of Leu^2) ppm.

Found: C, 58.63; H, 9.36; N, 9.79; $C_{21}H_{40}N_3O_6$ requires C, 58.58; H, 9.36; N, 9.76.

t-*Butoxycarbonyl-alanyl-isoleucyl-alanine methyl ester* (**6**)

Semi-solid mass, yield 77.8 %.

IR (**$CHCl_3$**): 3324, 3235 (*s*, –NH str, amide), 2966, 2959, 2930 (*m*, –CH str, asym, aliph. CH_3 & CH_2), 2895, 2892 (*m*, –CH str, >CH–), 2875, 2872, 2854 (*m*, –CH str, sym, aliph. CH_3 & CH_2), 2826 (*m*, –CH str, OCH_3), 1745 (*s*, –C=O str, ester), 1647, 1640 (*s*, –C=O str, 2° amide), 1545 (*m*, –NH bend, 2° amide), 1392, 1373 (*m*, –CH bend, *t*-butyl group), 1206 (*s*, C–O str, ester), 929 (*w*, CH_3 rock, *t*-butyl group) cm^{-1}.

^{1}H-NMR (**$CDCl_3$** 300 MHz): δ 7.65 (1H, *br. s,* –NH), 7.10 (1H, *br. s,* –NH), 6.52 (1H, *br. s*, –NH), 4.42–4.27 (2H, *m*, α-H of Ala^1 & Ile), 3.80–3.71 (1H, *q*, α-H of Ala^2), 3.58 (3H, *s*, OCH_3), 2.10–1.97 (1H, *m*, β-H of Ile), 1.69–1.37 (2H, *m*, γ-protons of Ile), 1.60–1.58 (3H, *d*, *J* = 4.3 Hz,

α-CH_3 of Ala^1), 1.54 (9H, *s*, *t*-butyl group), 1.27–1.25 (3H, *d*, *J* = 4.2 Hz, α-CH_3 of Ala^2), 1.02–0.94 (6H, *m*, β-CH_3 & δ-CH_3 of Ile) ppm.

Found: C, 55.64; H, 8.85; N, 10.79; $C_{18}H_{34}N_3O_6$ requires C, 55.65; H, 8.82; N, 10.82.

t-*Butoxycarbonyl-leucyl-alanyl-leucyl-alanyl-isoleucyl-alanine methyl ester* (**7**)

Semi-solid mass, yield 80.6 %.

IR (**$CHCl_3$**): 3270–3126 (*s,* –NH str, amide), 2965–2957, 2930–2923 (*m*, –CH str, asym, aliph. CH_3 & CH_2), 2877–2870, 2853 (*m*, –CH str, sym, aliph. CH_3 & CH_2), 2894, 2890 (*m*, –CH str, >CH-), 2828 (*m*, –CH str, OCH_3), 1748 (*s*, –C=O str, ester), 1645–1637 (*s*, –C=O str, 2° amide), 1560–1528 (*m*, –NH bend, 2° amide), 1455, 1452 (*m*, –CH bend, aliph. CH_3), 1392, 1372 (*m*, –CH bend, *t*-butyl group), 1204 (*s*, C–O str, ester), 930 (*w*, CH_3 rock, *t*-butyl group), 490–485 (*m*, C–C bend, aliph.) cm^{-1}.

^{1}H-NMR (**$CDCl_3$**, 300 MHz**):** δ 8.22 (1H, *br. s*, –NH), 8.10 (1H, *br. s*, –NH), 7.84 (1H, *br. s*, –NH), 7.11 (1H, *br. s*, –NH), 6.59 (1H, *br. s,* –NH), 6.05 (1H, *br. s*, –NH), 4.50–4.41 (1H, *q*, α-H of Ala^1), 4.25–4.16 (3H, *m*, α-H of Ala^2, Leu^1 & Ile), 3.95–3.89 (1H, *q*, α-H of Leu^2), 3.80–3.71 (1H, *q*, α-H of Ala^3), 3.62 (3H, *s*, OCH_3), 2.10–1.38 (15H, *m*, β-H of Ile, β-CH_2 of Leu^1 & Leu^2, γ-CH_2 of Ile, γ-H of Leu^1 & Leu^2, α-CH_3 of Ala^1 & Ala^2), 1.59 (9H, *s*, *t*-butyl group), 1.29–1.27 (3H, *d, J* = 4.2 Hz, α-CH_3 of Ala^3), 1.04–0.96 (18H, *m*, γ-protons of Leu^1 & Leu^2 & β- and δ-protons of Ile) ppm.

Found: C, 57.73; H, 8.97; N, 12.28; $C_{33}H_{61}N_6O_9$ requires C, 57.79; H, 8.96; N, 12.25.

Cyclo(alanyl-leucyl-alanyl-leucyl-alanyl-isoleucyl) (**8**)

White solid, m.p. 169–170 °C, yield 78.3 %.

IR (KBr**):** 3140–3065 (*s*, –NH str, amide), 2970–2955, 2930–2922 (*m*, –CH str, asym, aliph. CH_3 & CH_2), 2895–2889 (*m*, –CH str, >CH-), 2877–2867 (*m*, –CH str, sym, aliph. CH_3 & CH_2), 1645–1634 (*s*, –C=O str, 2° amide), 1575–1538 (*m*, –NH bend, 2° amide), 1456, 1449 (*m*, –CH bend, aliph. CH_3), 1379, 1368 (*s*, C–H bend, isopropyl group), 920 (*w*, CH_3 rock, isopropyl group), 498–493 (*m*, C–C bend, aliph.) cm^{-1}.

^{1}H-NMR (**$CDCl_3$**, 300 MHz): δ 9.50 (1H, *br. s,* –NH), 8.35 (1H, *br. s*, –NH), 7.78 (1H, *br. s*, –NH), 7.71 (1H, *br. s*, –NH), 7.50 (1H, *br. s*, –NH), 7.45 (1H, *br. s*, –NH), 7.33–7.25 (2H, *m*, α-H of Leu^1 & Leu^2), 5.98–5.90 (3H, *m*, α-H of Ala^1, Ala^2 & Ala^3), 5.30–5.25 (1H, *t*, α-H of Ile), 1.92–1.65 (4H, *m*, β-CH_2 of Leu^1 & Leu^2), 1.64–1.30 (3H, *m*, β-H & γ-CH_2 of Ile), 1.45–1.42 (9H, doublet overlapped over doublets, *J* = 4.2 Hz, α-CH_3 of Ala^1, Ala^2 & Ala^3), 1.02–0.93 (18H, *m*, β- & γ-protons of Ile and γ-protons of Leu^1 & Leu^2), 0.90–0.72 (2H, *m*, γ-H of Leu^1 & Leu^2) ppm.

^{13}C-NMR (**$CDCl_3$**, 300 MHz): 173.78 (C=O, Leu^1 & Leu^2), 170.58 (C=O, Ile), 168.7 (C=O, Ala^2), 168.2 (C=O, Ala^1 & Ala^3), 60.7 (α-C, Ile), 56.65 (α-C, Leu^1 & Leu^2), 50.1 (α-C, Ala^1), 49.3 (α-C, Ala^2), 48.7 (α-C, Ala^3), 43.5 (β-C, Leu^1 & Leu^2), 35.4 (β-C, Ile), 29.6 (γ-C, Leu^1 & Leu^2), 26.47 (γ-C, Ile), 23.3 (δ-C, Leu^1 & Leu^2), 18.25 (β-C, Ala^1), 17.9 (β-C, Ala^2), 17.0 (β-C, Ala^3), 16.2 (β'-C, Ile), 9.95 (δ-C, Ile) ppm.

FAB MS: *m/z* 553 $(M + 1)^+$, 525 $(553–CO)^+$, 440 $(Ala\text{-}Leu\text{-}Ala\text{-}Leu\text{-}Ala)^+$, 412 $(440–CO)^+$, 369 $(Ala\text{-}Leu\text{-}Ala\text{-}Leu)^+$, 341 $(369–CO)^+$, 256 $(Ala\text{-}Leu\text{-}Ala)^+$, 228 $(256–CO)^+$, 185 $(Ala\text{-}Leu)^+$, 157 $(185–CO)^+$, 72 $(Ala)^+$, 44 $(72–CO)^+$.

Found: C, 58.65; H, 8.79; N, 15.19; $C_{27}H_{48}N_6O_6$ requires C, 58.67; H, 8.75; N, 15.21.

RESULTS AND DISCUSSION

Synthesis of the alanine-rich cyclic peptide, halolitoralin A, was carried out successfully with good yields and its structure was confirmed by spectral as well as elemental analysis. The IR spectrum of the synthesized cyclopeptide showed characteristic Amide I and Amide II bands of the –CO–NH– moiety. The ^{1}H-NMR spectrum of the cyclized product clearly indicated the presence of all 7 amino acid moieties and the Mass spectrum showed a $M^+ + 1$ peak at *m/z* 553, which is consis-

tent with the molecular formula $C_{27}H_{48}N_6O_6$. The synthesized peptide was found to exhibit potent antimicrobial activity against pathogenic fungi *C. albicans* and *T. mentagrophytes*, as well as pathogenic bacteria *E. coli* and *P. aeruginosa* at the 50 μg level. However, gram positive bacteria were found to be resistant. In addition, halolitoralin A was found to exhibit moderate anthelmintic activity against earthworms *Eudrilus* sp. and *M. konkanensis* at the 100 mg level. On passing toxicity tests, this compound may prove to be a good candidate for clinical studies and may be a new antimicrobial drug of the future.

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ИЗВОД

ПРВА ТОТАЛНА СИНТЕЗА И ИСПИТИВАЊЕ БИОЛОШКЕ АКТИВНОСТИ ХАЛОЛИТОРАЛИНА А

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Нови потенцијално биоактиван аланински циклични хекскапептид халолиторалин А (**8**), претходно изолован из бактеријског соја *Halobacillus litoralis* YS3106, добијеног из морског седимента, синтетизован је техником растворне фазе. Све куповане реакције изведене су на собној температури коришћењем дициклохексилкарбодиимида (DCC) као куплујућег реагенса и *N*-метилморфолина (NMM) као базе. Структура пептида окарактерисана је на основу података IR, ^{1}H-NMR, ^{13}C-NMR и FAB MS мерења, као и елементалне анализе и DSC. Синтетизовани циклопептиди испитивани су и са аспекта антимикробне и антхелминтичке активности и нађено је да су потенцијално активни према патогеним гљивицама *Candida albicans* и *Trichophyton mentagrophytes*, као и према грам-негативним бактеријама *Pseudomonas aeruginosa* и *Escherichia coli*. Нађено је да су грам-негативне бактерије осетљивије на нови синтетизовани пептид него грам-позитивне. Такође је нађено да пептиди показују умерену антхелминтичку активност према кишним глистама *Megascoplex konkanensis* и *Eudrilus* sp.

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