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Research Article

Synthesis and Biological Evaluation of Gallic acid Peptide Derivatives

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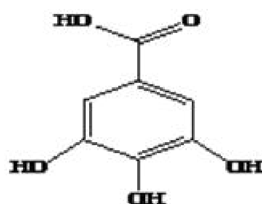
ABSTRACT

The present study deals with the synthesis of substituted gallic acid (3,4,5- triacetoxybenzoic acid & 3,4,5-trimethoxybenzoic acid) peptide derivatives and comparative evaluation of biological activities, such as antibacterial, antifungal and plant growth. Among phenolic compounds, Gallic acid nucleus is found in many bioactive products and incorporation of amino acids and peptides into the phenolic congeners have resulted in compounds with potent activities. All the compounds were synthesized by coupling of substituted gallic acids with amino acid methyl esters/dipeptides/tripeptides in presence of DCC as coupling agent and NMM as base under continuous stirring for 36 hrs. All synthesized peptide derivatives were identified on the basis of melting point range, Rf values, solubility studies, IR and ^{1}H NMR spectral data. The antimicrobial activity of synthesized compounds was determined against bacterial strains viz. *E. Coli* and *S. Aureus* and fungal strains viz. *C. albicans* and *A. Niger* using ciprofloxacin and fluconazole as standard respectively. All the synthesized compounds showed good to moderate antimicrobial activity at 40, 80 and 160 µg/ml. The comparative studies showed the following order of activity profile: 3,4,5-triacetoxybenzoic acid methyl esters <dipeptide <tripeptide and 3,4,5-trimethoxybenzoic acid methyl esters>dipeptide>tripeptide. The comparative studies showed that 3,4,5-triacetoxybenzoic acid peptide derivatives possess more potent antimicrobial activity profile than 3,4,5-trimethoxybenzoic acid peptide derivatives.

Keywords: Antibacterial activity, Antifungal activity, Gallic acid, Peptide.

INTRODUCTION

Gallic acid (GA or 3,4,5-trihydroxybenzoic acid) [1] is a polyhydroxy phenolic compound and Found in various natural products, like gallnuts, sumac, tea leaves, oak bark, green tea, apple-peels, grapes, strawberries, pineapples, bananas, lemons, and in red and white wine. Tea is an important source of gallic acid and contain about 45 g/kg fresh weight gallic acid, while red fruit, black radish and onions have relatively less concentration of gallic acid. It is in a group of chemicals called phenolics. Phenolics[2] are chemicals based on the structure of phenol which is a molecule with a ring structure containing 6 carbons with a –OH (hydroxyl group) attached to one of the carbons. Gallic acid has 3 –OH groups and one –COOH (carboxylic acid) group attached to the ring.



Peptides[3] are made of amino acids linked into linear chain with overall length up to 100 amino acids. Peptides are short polymers of amino acid monomers linked by peptide bonds. Every peptide has N-terminus and C-terminus residue on the ends of peptide. Peptides are synthesized by coupling the carboxyl group or C-terminus of one amino acid to the amino group or N-terminus of another.[4] Thus, keeping in mind the pharmacological potential of gallic acid and its derivatives as well as taking advantage of biodegradability and biocompatibility of peptides, peptide derivatives of gallic acid derivatives were prepared to increase therapeutic efficacy and to decrease adverse effect. In present research, compound or moiety coupled with different peptide methyl ester using DCC[5] and NMM in THF to afford peptide derivatives. Peptide derivatives of gallic acid show good antibacterial activity[6], antifungal activity.[7] The newly synthesized gallic-peptide derivatives were characterized by TLC, IR and NMR analysis.

MATERIALS AND METHODS

The chemicals used were obtained from Spectrochem Pvt. Ltd, Mumbai and Sd fine-chem Limited, Mumbai. All the melting points were determined by open capillary method and uncorrected. The reactions were monitored by TLC on silica gel G plates using Chloroform: Methanol as developing solvent system in the ratio of 9: 1 and brown spots was detected on exposure to iodine vapors in tightly closed chamber. Final peptide derivatives were purified by recrystallization from mixture of chloroform: methanol (1:1). IR spectrum of compounds in KBr pellet was recorded on a FTIR-RXI spectrophotometer (PERKIN ELMER). ^{1}H-NMR Spectra of compounds was recorded on Bruker NMR spectrometer in deuterium-substituted chloroform using TMS as internal standard (Chemical Shift in δ ppm). The biological activity of 3,4,5-trihydroxybenzoic acid derivatives and its methylester/ dipeptide/ tripeptide/ tetrapeptide on different bacterial and fungal strains were tested using Ciprofloxacin (MIC:

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40 µg/ml) as antibacterial standards and Fluconazole (MIC: 40 µg/ml) as antifungal standard.[8]

Synthesis of BOC-amino acids

L-amino acid (20mmol) was dissolved in 1 mmol/litre sodium hydroxide (20ml) and isopropanol (20ml). Ditert-butylpyrocarbonate (Boc) (26mmol) in isopropanol (10ml) was added followed by 1 mmol/litre sodium hydroxide (20ml) to the resulting solution. The solution was stirred at room temperature for 2 hrs, washed with light petroleum ether (b.p 40-60°C) (20ml), acidified to pH 3.0 with 1 mmol/litre H_2SO_4 and finally extracted with chloroform (3x20ml). The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to give the crude product, which was crystallized from chloroform and petroleum ether (b.p 40-60°C).

Synthesis of L-amino acid methyl ester hydrochlorides

Thionyl chloride (1.4ml, 20mmol) was slowly added to methanol (100ml) at 0°C and L-amino acid (20mmol) was added to above solution. The resulting mixture was refluxed for 12 hrs at 70°C. Methanol was evaporated and the residue was triturated with ether at 0°C, until excess dimethyl sulphate was removed. The crude solid was crystallized from methanol and ether at 0°C to give pure amino acid methyl ester.

Synthesis of linear peptide fragments

Amino acid methyl ester hydrochloride/peptide methyl ester (10mmol) was dissolved in chloroform (20mL). To this, N-methyl morpholine (21mmol) was added at 0 °C and the reaction mixture was stirred for 15 minutes. Boc-amino acid/peptide (10mmol) in chloroform (20mL) and N, N-dicyclohexyl carbodiimide (10 mmol) were added with stirring. After 36hrs, the reaction mixture was filtered and the residue was washed with chloroform (30mL) and added to the filtrate. The filtrate was washed with 5% sodium bicarbonate and saturated sodium chloride solutions. The organic layer was dried over anhydrous sodium sulphate, filtered and evaporated in vacuum. The crude product was crystallized from a mixture of chloroform and petroleum ether followed by cooling at 0°C. Deprotection at carboxyl terminal was done by adding lithium hydroxide (0.36 g, 15mmol) to a solution of Boc-di/tripeptide methyl ester (10mmol) in tetrahydrofuran: Water (1:1, 36ml) at 0 °C. Resulting mixture was stirred at RT for 1 hr and then acidified to pH 3.5 with 1N H_2SO_4. The aqueous layer was extracted with diethyl ether (3 × 25mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was crystallized from methanol and ether to get pure Boc-di/tripeptides. Deprotection at amino terminal was accomplished by treatment of Boc di/ tripeptides (10 mmol) dissolved in chloroform (15mL) with trifluoroacetic acid (2.28g, 20mmol). The resulting solution was stirred at RT for 1 hr, washed with saturated sodium bicarbonate solution (25mL). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by crystallization from chloroform and petroleum ether (B.p. 40-60°C) to get pure di/tripeptide methyl esters.

Synthesis of 3,4,5-trihydroxy benzoic acid derivatives

Synthesis of 3,4,5-triacetoxy benzoic acid (1)

3,4,5 trihydroxybenzoic acid (5.0 g, 0.02mol) and 7.5g (0.07mol) of redistilled acetic anhydride were placed in RBF and 4-6 drops of conc.H_2SO_4 were added, the contents of the flask were swirled in order to ensure thorough mixing. It was warmed on a water bath to about 50-60^{0}C for 20-25 mins. The reaction mixture was allowed to cool and stirred occasionally during cooling. Then 30-40 ml of water was added and product obtained was filtered at pump. The triacetoxybenzoic acid (TABA) was recrystallized from ethanol. (Melting point-167^{0}C)

Synthesis of 3,4,5-triacetoxybenzoic acid peptide derivatives (2-4)

To a mixture and compound Di/tri/-peptide methyl ester (10 mmol) in THF (75 ml), 2.3 ml of NMM was added at 0°C with stirring of 3,4,5-triacetoxybenzoic acid (10 mmol) in THF (75 ml) and DCC (2.1 g, 10 mmol) were added to the above mixture and stirring was done for 36 h. After 36 h, the reaction mixture was filtered and residue was washed with THF (50 ml). Then, filtrate was washed with 5% sodium hydrogen carbonate and saturated sodium chloride solution (30 ml) and dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The crude product obtained was crystallized from a mixture of chloroform and n-hexane followed by cooling at 0 ^{0}C to give pure compound **(2-4).**

Synthesis of 3,4,5-trimethoxybenzoic acid (5)

8 g of sodium hydroxide in 50 ml of water was placed in RBF along with 5 g of gallic acid. The flask was immediately stoperred, and then reaction mixture was shaken occasionally until all the acid was dissolved; 6.7 ml of dimethyl sulfate was then added and the flask was stirred for 1hr, during this temperature was maintained below 30–35°C. The flask was then fitted with a reflux condenser and refluxed for 2 hrs. The ester thus produced was saponified by addition of 2g of sodium hydroxide dissolved in 3 ml of water and refluxing for 2 hrs. The reaction mixture was then cooled and acidified with dilute HCl, the precipitated **(5)** was filtered and washed with cold water. The compound **5** was recrystallized from boiling water using decolorizing carbon.

The yield was 60% with m.p.168^{0}C

Synthesis of 3,4,5-trimethoxybenzoic acid peptide derivatives (6-8)

To a mixture of compound Di/tri/-peptide methyl ester (10 mmol) in THF (75 ml), 2.3 ml of NMM was added at 0°C with stirring and 3,4,5-trimethoxybenzoic acid (10 mmol) in THF (75 ml) and DCC (2.1 g, 10 mmol) were added to the above mixture and stirring was done for 36

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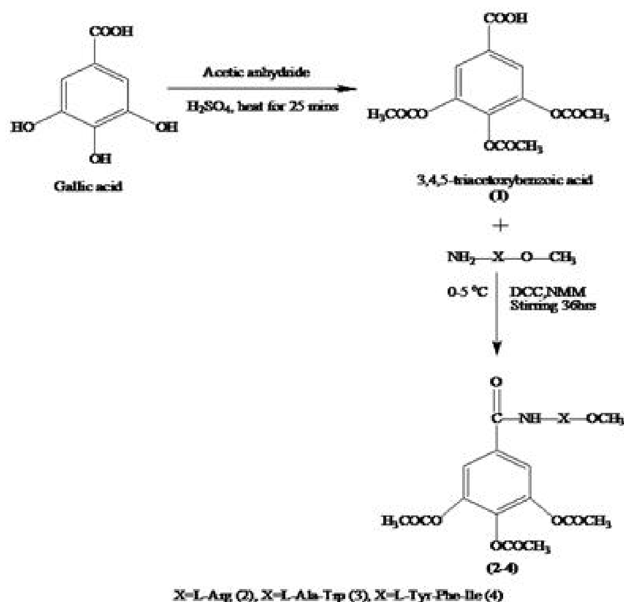
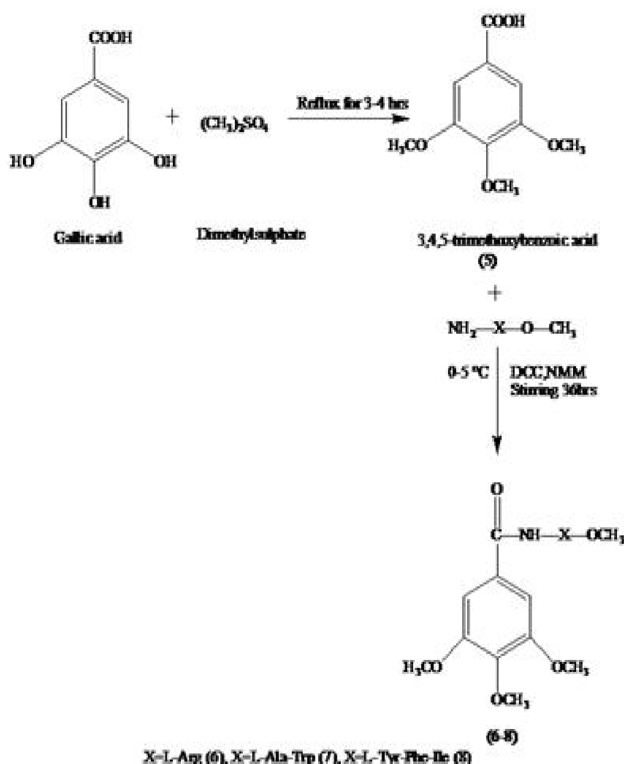
h. After 36 h, the reaction mixture was filtered and residue was washed with THF (50 ml). Then, filtrate was washed with 5% sodium hydrogen carbonate and saturated sodium chloride solution (30 ml) and dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The crude product obtained was crystallized from a mixture of chloroform and n-hexane followed by cooling at 0°C to give pure compound **(6-8).**

Characterizations of synthesized compounds were done by TLC, IR and NMR techniques and corresponding values of synthesized compounds are listed in table 1.

Scheme of Work: 1a



Scheme-1b



Antimicrobial activity

The synthesized peptide derivatives were screened for antibacterial activity[9] against *Escherichia coli* (Gram-negative bacteria) and *Staphylococcus aureus* (Gram-positive bacteria) and antifungal activity[9] against fungal strain *Aspergillus niger* and *Candida albicans.* using modified Kirby-Bauer disc diffusion method. All synthesized compounds were dissolved separately to prepare stock solution of 1mg ml^{-1} using dimethyl sulphoxide (DMSO) and chloroform as solvent. From this stock solution, further dilutions of concentration 40, 80 and 160 µg/ml were made respectively. Three discs of test samples 40,80,160µg ml^{-1} were placed on three portions together and one disc with standard drug ciprofloxacin (40µg ml^{-1}) and a disc impregnated with the solvent (DMSO and Chloroform) as negative control. The test samples tested at the concentration 40, 80, 160µg ml^{-1} were checked, incubated and then the diameters obtained for the test samples were compared with the diameter obtained with standard drug ciprofloxacin (40µg ml^{-1}) and fluconazole (40µg ml^{-1}).[9]

MIC values of synthesized compounds are listed in table 2 and in table 3. The results of antibacterial activity are shown in figure 1 & 2 and antifungal activity is shown in figure 3 & 4.

RESULTS AND DISCUSSION

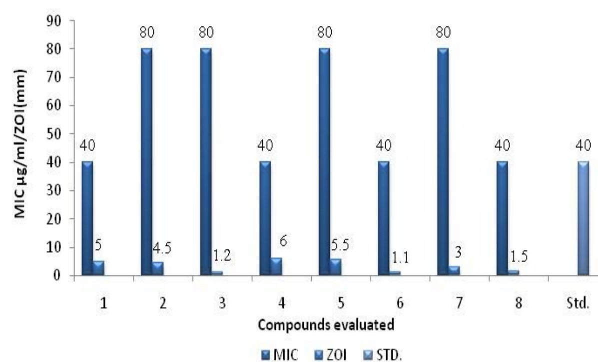


Figure 1: Comparison of minimum inhibitory concentration (µg/ml)/ZOI of standard Ciprofloxacin and Gallic acid- peptide derivatives in case of *S.aureus.*

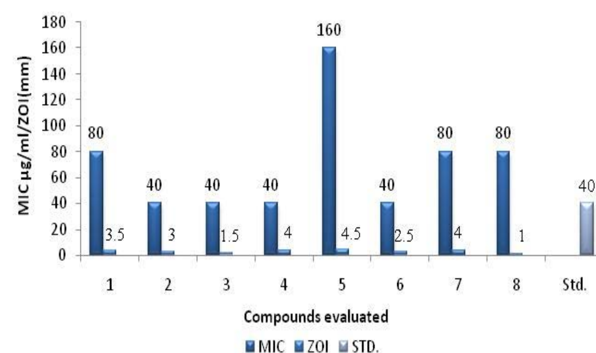


Figure 2: Comparison of minimum inhibitory concentration (µg/ml) /ZOI of standard Ciprofloxacin and Gallic acid- peptide derivatives in case of *E coli.*

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Table 1: TLC, IR, NMR ranges of compounds

Cpds	IR ranges (KBr) υ cm-1	NMR ranges(DMSO) δ ppm	TLC Rf value
1.	IR(KBr)υ : 3059 (OH stretching, COOH), 3025 (C-H stretching, aromatic ring), 1735 (C=O, COOH), 1641 (C=C stretching, aromatic ring), 1194 (C-O stretching, COOH) cm^{-1}.	^{1}HNMR ($CDCl_3$) δ: 7.84 (s, 2H, aromatic ring), 2.279 (s, 6H, at meta position of $OCOCH_3$, acetoxy), 2.284 (s, 3H, at para position of $OCOCH_3$, acetoxy), 11.1 (s, 1H, COOH) ppm.	R_f-0.47
2.	IR(KBR)υ : 3062 (N-H stretching, amide), 3027 (C-H stretching, aromatic ring), 2933 (C-H stretching, CH_3), 2856 (C-H stretching, CH_2), 1734 (C=O stretching, ester), 1579(C=C, aromatic ring), 1563 (N-H bending, amide), 1497 (N-H bending, amine), 1217 (C-O stretching, ester), 1244(C-N stretching amines) cm^{-1} .	^{1}HNMR ($CDCl_3$) δ: 8.93(s ,1H, NH, amide), 7.86 (s, 2H, arom), 4.58 (m, 1H, CH, arg), 2.27(s,6H, at meta position of $OCOCH_3$, acetoxy), 3.78 (s, 3H, OCH_3 ester), 2.29 (s, 3H, at para position of $OCOCH_3$, acetoxy), 2.55 (m, 2H, CH_2, arg), 1.93 (s, 4H, NH, arg), 1.78 (m, 2H, CH_2, arg), 1.54 (m, 2H, CH_2, arg) ppm.	R_f-0.52
3.	IR(KBR)υ : 3312 (N-H stretching, amine), 3062 (N-H stretching, amide), 3009 (C-H stretching ,aromatic ring), 2957 (C-H stretching, CH_2), 1737 (C=O stretching, ester), 1664 (C=O stretching, amide), 1434 (C=C stretching, aromatic ring), 1564 (N-H bending, amine), 1347 (C-N stretching amide), 1202 (C-O stretching, ester) cm^{-1}.	^{1}HNMR ($CDCl_3$) δ: 8.96 (s, 2H, NH, amide), 7.86 (s, 2H, arom), 7.71 (s, 1H, NH, Indole ring) , 7.62 (s, 4H, arom), 4.05 (s, 1H, CH, ala), 6.43 (s, 1H, Indole ring), 2.27(s, 6H, at meta position of $OCOCH_3$, acetoxy), 3.71 (s, 3H, OCH_3, ester), 2.29 (s, 3H, at para position of $OCOCH_3$, acetoxy), 3.91 (s, 1H CH, trp), 1.46 (d, 3H, CH_3, ala), 3.69 (s, 2H, CH_2, trp) ppm.	R_f-0.80.
4.	IR(KBR)υ : 3443 (OH stretching, tyrosine), 3321 (N-H stretching, amine), 3226 (N-H stretching, amide), 3011 (C-H stretching, aromatic ring), 2930 (C-H stretching, CH_3), 2856 (C-H stretching, CH_2), 1730 (C=O stretching, ester), 1669 (C=O, amide), 1455 (C=C stretching, aromatic ring), 1459 (N-H bending, amide), 1742 (C-N stretching, amide) 1216 (C-O stretching, ester) cm^{-1}	^{1}HNMR ($CDCl_3$) δ: 7.88 (s, 3H, NH, amide), 7.20-7.23 (m, 5H, aromatic ring of Pheala), 7.84 (s, 2H, aromatic ring), 7.12 (m, 4H, aromatic ring of Tyr), 4.56 (s, 1H, OH, Tyr), 4.39 (m, 1H, CH, Ileu), 2.27 (s, 6H, at meta position of $OCOCH_3$, acetoxy), 3.77 (s, 3H, OCH3, ester), 2.5 (m, 1H, CH, Ileu), 3.06 (d, 2H, CH_2, Pheala), 2.38-2.39 (d, 2H, CH_2, Tyr), 2.29 (s, 3H, at para position of $OCOCH_3$, acetoxy), 2.65-2.67 (m, 1H, CH, Tyr), 2.60-2.62 (m, 1H, CH, Pheala), 1.26 (m, 2H, CH_2, Ileu), 1.0 (m, 6H, CH_3, Ileu),) ppm.	R_f-0.87
5.	IR(KBR)υ : 3059 (OH stretching, COOH), 3025 (C-H stretching, aromatic ring), 1735 (C=O, COOH), 1441 (C=C stretching, aromatic ring), 1194 (C-O stretching, COOH) cm^{-1}.	^{1}HNMR ($CDCl_3$) δ: 7.84 (S, 2H, aromatic), 3.94 (s, 6H, at meta position of OCH_3, methoxy), 11.1(S, 1H, COOH), 3.79 (s, 3H, at para position of OCH_3, methoxy) ppm.	R_f-0.75
6.	IR(KBR)υ :3068 (N-H stretching, amide), 3022 (C-H stretching, aromatic ring), 2958 (C-H stretching, CH_3), 2853 (C-H stretching, CH_2), 1734 (C=O stretching, ester), 1479(C=C, aromatic ring), 1561 (N-H bending, amide), 1497 (N-H bending, amine), 1214 (C-O stretching, ester), 1244 (C-N stretching amines) cm^{-1}	^{1}HNMR ($CDCl_3$) δ: 8.04 (s, 1H, NH, amide), 7.72 (s, 2H, arom), 3.79 (s, 3H, at Para position of OCH_3, methoxy), 4.55 (m, 1H, CH, arg), 3.76 (s, 2H, CH_2, arg), 3.70 (s, 3H, OCH_3, ester), 3.94 (s, 6H, at meta position of OCH_3, methoxy), 2.52 (m, 2H, CH_2, arg), 1.97 (s, 4H, NH, arg), 1.77 (m, 2H, CH_2, arg) ppm.	R_f-0.79
7.	IR(KBR)υ : 3328 (N-H stretching, amine), 3063 (N-H stretching, amide), 3009 (C-H stretching of aromatic ring), 2853 (C-H stretching, CH_2), 1737 (C=O stretching, ester), 1627 (C=O stretching, amide), 1474 (C=C stretching, aromatic ring), 1535 (N-H bending, amine) , 1460 (N-H bending, amide), 1244 (C-N stretching amines), 1203 (C-O stretching, ester) cm^{1}.	^{1}HNMR ($CDCl_3$) δ: 8.96 (s, 2H, NH, amide), 7.84 (S, 2H, aromatic), 7.71 (s, 1H, NH, Indole ring) , 6.87 (s, 1H, Indole ring), 4.05 (m, 1H, CH, ala), 7.62 (s, 4H, arom), 1.46 (d, 3H, CH_3, ala), 3.92 (m, 6H, at meta position of OCH_3, methoxy), 3.98 (s, 1H, CH, try), 3.86 (s, 3H, OCH_3, ester), 3.74 (s, 3H, at para position of OCH_3, methoxy), 3.63 (s, 2H, CH_2, trp) ppm.	R_f-0.85.
8	IR(KBR)υ : 3743 (OH stretching, tyrosine), 3329 (N-H stretching, amine), 3216 (N-H stretching, amide), 3011 (C-H stretching ,aromatic ring), 2936 (C-H stretching, CH_3), 2856 (C-H stretching, CH_2), 1742 (C-N stretching, amide), 1735 (C=O stretching, ester), 1669 (C=O, amide), 1458 (C=C stretching, aromatic ring), 1462 (N-H bending, amide), 1216(C-O stretching, ester) cm^{-1}.	^{1}HNMR ($CDCl_3$) δ: 7.98 (s, 3H, NH, amide), 7.25-7.27(m, 5H, aromatic ring of Pheala), 1.0 (m, 6H, CH_3, Ileu), 7.16 (m, 4H, Aromatic ring of Tyr), 7.72 (s, 2H, arom), 3.96 (s, 6H, at meta position of OCH_3, methoxy), 2.5 (m, 1H, CH, Ileu) 4.56 (s, 1H, OH, Tyr), 4.49 (m, 1H, CH, Ileu), 3.79 (s, 3H, OCH_3, ester), 3.06 (d, 2H CH_2, Pheala), 3.82 (s, 3H, at para position of OCH_3, methoxy), 2.38-2.39 (d, 2H, CH_2, Tyr), 2.65-2.67 (m, 1H, CH, Tyr), 2.60-2.62 (m, 1H, CH, Pheala), 1.26 (m, 2H, CH_2, Ileu) ppm.	R_f-0.84

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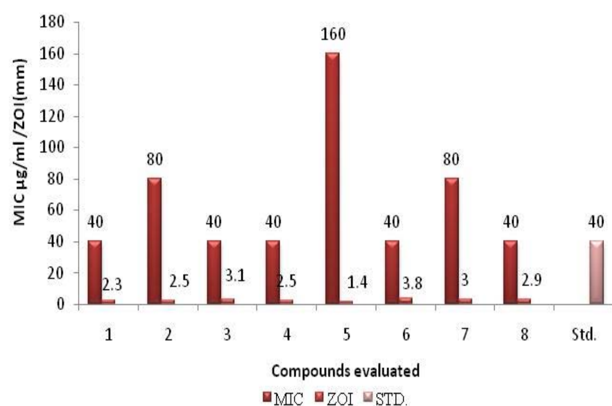

Figure 3: Comparison of minimum inhibitory concentration (µg/ml) /ZOI of standard fluconazole and Gallic acid- peptide derivatives in case of *A.niger*

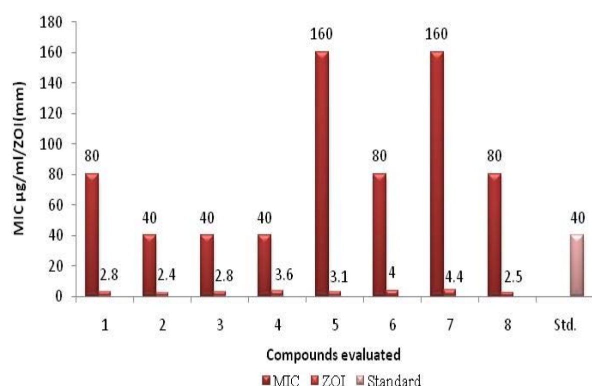

Figure 4: Comparison of minimum inhibitory concentration (µg/ml)/ZOI of standard fluconazole and Gallic acid- peptide derivatives in case of *C. albicans*

Table 2: The results of antibacterial activity of different compounds against *S.aureus* and *E.coli*

Compounds	*Staphylococcus aureus*		*Escherichia coli*	
	MIC µg/ml	Zone of diameter (mm)	MIC µg/ml	Zone of diameter (mm)
1	40	5	80	3.5
2	80	4.5	40	3
3	80	1.2	40	1.5
4	40	**6**	40	4
5	80	5.5	160	**4.5**
6	40	1.1	40	2.5
7	80	3	80	4
8	40	1.5	80	1
Ciprofloxacin (std.)	40	7.5	40	7

From table 2 it is concluded that compounds 1, 4, 6, and 8 are most effective and Compounds 2,3, 5 and 7 are least effective in case of *S.aureus* and compounds 2, 3, 4 and 6 are most effective and 1, 5, 7 are least effective in case *E.coli* fungal strain.

Table 3: Antifungal activity of different compounds against *A. niger* and *candida albicans*

Compounds	*Aspergillus niger*		*Candida albicans*	
	MIC µg/ml	Zone of diameter (mm)	MIC µg/ml	Zone of diameter (mm)
1	40	2.3	80	2.8
2	80	2.5	40	2.4
3	40	3.1	40	2.8
4	40	2.5	40	**3.6**
5	160	1.4	160	3.1
6	40	**3.8**	80	4
7	80	3.0	160	4.4
8	40	2.9	80	2.5
Fluconazole (std.)	40	4.6	40	4

From table it is concluded that compounds 1, 2, 3, 4, 6 and 8 are most effective and Compounds 5 and 7 are least effective in case of *A.niger* and compounds 2, 3, 4 and 6 are most effective and 5, 7 are least effective in case *C. albicans* fungal strain.

CONCLUSION

Synthesis of all peptide derivatives were carried out successfully via coupling reaction with good yields. N, N-dicyclohexyl carbodiimide proved to be a good coupling agent both economically and yield wise. The title compounds were synthesized by coupling of gallic acid derivatives with amino acid methyl esters/dipeptides/ tripeptides/tetrapeptides in the presence of N, N-dicyclohexyl carbodiimide as a coupling agent and N-methyl morpholine as a base under continuous stirring for 36 hrs. All synthesized peptide derivatives were identified on the basis of melting point range, Rf values, and IR and ^{1}H NMR spectral data. Gallic acid derivatives and its peptide derivatives showed the presence of characteristic absorption bands in the region 3409-3363, 1768-1768, 1582-1517 cm-1 respectively. In ^{1}H NMR spectra, the range 8.10-7.31 ppm corresponding to the (CO-NH) proton. Gallic acid derivatives and its methylester /dipeptide/tripeptide all showed mild to moderate antimicrobial activity. From the antibacterial studies, we concluded that newly synthesized peptide derivative **3** exhibits highest activity against *S. aureus;* compound **4** exhibits good activity against *E. coli.* at 40 µg/ml concentration. In case of fungal strains, compound **6** exhibits highest activity against *C. albicans*; compound **1** exhibits potent activity against *A. niger.*

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