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새로운 펩티드 유사체인 5-aminobenzimidazoles의 합성

Humaira Y. Gondal*, Mashooda H†, and Muhammad Ali
Department of Chemistry, University of Sargodha, 40100, Sargodha, Pakistan
†*Department of Chemistry, Quaid-i-Azam University, Islamabad Pakistan*
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New Antibacterial Peptide Analogs of 5-Aminobenzimidazoles

Humaira Y. Gondal*, Mashooda H†, and Muhammad Ali
Department of Chemistry, University of Sargodha, 40100, Sargodha, Pakistan
†*Department of Chemistry, Quaid-i-Azam University, Islamabad Pakistan. *E-mail: hygondal@yahoo.com*
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요 약. 새로운 펩티드 유사체인 **5a-c**를 5-amino benzimidazoles **2a-c**과 *L*-phenylalanine과의 커플링반응에 의해 합성하였다. Phenylalanine의 amine 부분을 phthalic anhydride로 보호하고, 나머지 작용기인 carboxylic acid를 염소화시켜서 hthaloyl-*L*-phenylalanyl chloride **4**를 합성한 다음에, 화합물 **2a-c**와 반응시켜서 화합물 **5a-c**를 합성하였다. 얻어진 화합물 **5a-c**를 hydrazine으로 반응시켜서 새로운 펩티드 유사체인 **6a-c** 를 합성하였으며, 얻어진 화합물에 대한 항균성을 측정하였다.

주제어: benzimidazoles, *L*-phenylalanine, peptide, 항균성

ABSTRACT. Three new peptide analogs **5a-c** were obtained through coupling of 5-Amino benzimidazoles **2a-c** with *L*-phenylalanine. For the purpose α-amino group was blocked with phthalic anhydride and activation of α-carboxy group of phenylalanine was carried out by preparing phthaloyl-*L*-phenylalanyl chloride **4.** After developing a successful peptide linkage, the phthaloyl group was removed by treating **5a-c** with hydrazine hydrate to get free peptides **6a-c**, purified through a column of Amberlite (IR-4B). All of these compounds **2a-c** and **5**,**6a-c** have been characterized on the basis of their IR, ^{1}H NMR and EIMS analyses. Antibacterial activity of these compounds is also been reported.

Keywords: benzimidazoles, *L*-phenylalanine, peptide, antibacterial

INTRODUCTION

Benzimidazoles are known to exhibit wide range of biological activities such as antiulcer,[1] antifungal,[2] antipyretic,[3] antihypertensive,[4] anticancer,[5-7] antiviral,[8-10] antiallergic,[11] antihistaminic[12] and antibacterial activity.[13] Moreover, short peptide sequences are known to have variety of biological activities[14] particularly metabolically stable peptide analogs of heterocycles are considered to be strong candidates for various pharmacological activities.[15] This fact motivated us to synthesise new peptide analogs of benzimidazoles. Although pharmacological importance of benzimidazoles is well established, but there are very few reports available on the synthesis of their peptide analogs. Synthesis of 3-(1*H*-benzimidazol-5-yl)alanine derivatives is reported by condensation in solution,[16,17] another approach is by alkylation of glycinate,[18] while Wittig reaction of aldehyde and protected phosphonoglycine for the same purpose is also attempted.[19] Recently solid phase synthesis has also been exploited to prepare derivatives of 3-(1*H*-benzimidazol-5-yl)alanylglycine.[20] We have already reported the synthesis of 2-ethyl-1-methyl-5-(phthaloyl-*L*-phenylalanyl) amino benzimidazole by condensation of protected phenyl alanine with 5-aminobenzimidazole.[21] Now we report here three new peptide analogs of benzimidazole **5a-c**, deprotection of amino group is also achieved successfully to obtain free peptides **6a-c**, ready for further extension of peptide linkage. Compounds **2a-c** and **5**,**6a-c** have been characterized satisfactorily on the basis of their IR, ^{1}H NMR and EIMS spectral analyses. Antibacterial activities of these compounds have also been studied.

EXPERIMENTAL

All the chemicals and solvents used are of analytical grade. All the reactions were monitored by thin layer chromatography using precoated (silica gel 60F_{254}) alu-

minium sheets (0.2 mm layer thickness). Melting points of the synthesized compounds were recorded at IA-9100 Electrothermal Digital Melting Point Apparatus and uncorrected. ^{1}H NMR spectra were recorded on Bruker Avance at 400MHz. Infrared spectra of the synthesized compounds were recorded at Shimadzo IR Spectrophotometer. ORD of optically active compounds were recorded at JASCO J-20A Automatic Recording Spectropolarimeter. Mass spectra were recorded on a double-focusing mass spectrometer (Varian MAT 311 A).

General procedure for the synthesis of 5-Amino benzimidazoles (2a-c)

A mixture of 5-nitro benzimidazole (0.1 mol) and zinc dust (0.3 mol) was refluxed in 6N HCl (16 ml) for 1 hour. The contents were poured in water after cooling and neutralized with sodium carbonate. The precipitate were collected, washed, dried and recrystallized from water.

5-Amino-1,2-dimethyl benzimidazole (2a): Yield: 82%; m.p. 254 ºC; R_f = 0.21 (Acetone: Pet. ether 4:1); IR (KBr, cm^{-1}): 3490 (NH of 1º amine), 2920 (CH_3), 1687 (C=N), 1041 (C-N); ^{1}H NMR (400 MHz, DMSO, δ/ppm): 7.87 (d, J=3.9 Hz, 1H, H_a), 7.56 (dd, 1H, J=6.8, 3.9 Hz, $H_{a''}$), 7.74 (d, J=6.8Hz, 1H, , $H_{a''}$), 3.81 (s, 3H, N-CH_3), 2.89 (s, 3H, C-CH_3). MS (m/z, %): $M^{+\bullet}$=161 (14), 160 (13), 146 (38), 132 (7), 105 (12).

5-Amino-2-ethyl benzimidazole (2b): Yield=74%; m.p. 145 ºC; R_f= 0.24 (Ethyl acetate: Hexane 4:1); IR (KBr, cm^{-1}): 3325, 3150 (-NH of 1º & 2º amine), 1575 (C=N), 1094 (C-N); ^{1}H NMR (400 MHz, DMSO, δ/ppm): 7.49-7.79 (m, 3H, H_a $H_{a'}$ $H_{a''}$), 2.34 (m, 2H), 1.28 (t, 3H, -CH_3); MS (m/z, %): $M^{+\bullet}$=161 (34), 160 (17), 146 (27), 133 (6), 132 (4), 106 (4), 105 (8).

5-Amino-2-propyl benzimidazole (2c): Yield=72%; m.p. 198ºC; R_f = 0.28 (Acetone: Pet. ether 4:1); IR (KBr, cm^{-1}): 3220, 3070 (-NH of 1º & 2º amine), 1633 (C=N), 1046 (C-N); ^{1}H NMR (400 MHz, DMSO, δ/ppm): 7.81 (d, J=4.1 Hz, 1H, H_a), 7.68 (dd, 1H, J=7.2, 4.1 Hz, $H_{a''}$), 7.47 (d, J=7.2Hz, 1H, , $H_{a''}$), 1.98 (m, 2H), 1.75 (m, 2H), 1.09 (t, 3H, -CH_3); MS (m/z, %): $M^{+\bullet}$=175 (82), 146 (97), 119 (100).

General procedure for coupling of 5-Amino benzimidazoles with phthaloyl-L-phenylalanyl chloride

A solution of phthaloyl-*L*-phenylalanyl chloride in dioxane (10 mmol in 5ml) was added dropwise during 15 minutes to an ice cooled solution of 5-amino benzimidazole (10 mmol) in water (20 ml) in the presence of sodium bicarbonate (5 mmol). The reaction mixture was stirred further for 10 minutes. The suspension was acidified with 2N HCl and resulting precipitates formed were filtered, dried and recrystallized.

1,2-Dimethyl-5-(phthaloyl-L-phenylalanyl)-amino benzimidazole (5a): Yield: 78%; m.p. 312 ºC; R_f = 0.76 (Acetone: Pet. ether 1:1); IR (KBr, cm^{-1}): 3465-3275 (-NH), 1771 (C=O amide), 1788 (C=O of five membered ring anhydride), 1539 (C=N), 1382 (C-C(Ph)), 1227 (C-N of 2º amide). ^{1}H NMR (400 MHz, DMSO, δ/ppm): 10.18 (bds, 1H, NH), 7.98 (d, 4.3Hz, 1H, $H_{a''}$), 7.81-7.85 (m, 4H, H_c, $H_{c'}$), 7.61 (d 6.8 Hz, 1H, $H_{a'}$), 7.33 (dd, 1H, J 6.8, 4.3 Hz, H_a), 7.18-7.21 (m, 5H, H_b, $H_{b'}$, $H_{b''}$), 5.24 (dd, 1H, J_{de}=4.6 Hz, $J_{de'}$=12 Hz, H_d), 3.80 (s, 3H, N-CH_3), 3.24-3.50 (m, 2H, H_e, $H_{e'}$), 2.64 (s, 3H, C-CH_3). MS (m/z, %): $M^{+\bullet}$=438 (85), 229 (100), 250 (51), 188 (61.5), 169 (46), 161 (95), 160 (25), 103 (29), 91 (24). 260, 291; $[\alpha]_D^{28}$ (MeOH): -166.06º.

2-Ethyl-5-(phthaloyl-L-phenylalanyl)-amino benzimidazole (5b): Yield: 75%; m.p. 178 ºC; R_f = 0.81 (Acetone: Pet. ether 1:1); IR (KBr, cm^{-1}): 3270 (NH), 1767 (C=O amide), 1744 (C=O of five membered ring anhydride), 1577 (C=N), 1394 (C-C(Ph)), 1343 (C-N of 2º amide). ^{1}H NMR (400 MHz, DMSO, d/ppm): 7.81 (s, 1H, $H_{a''}$), 7.41 (d 7.1 Hz, 1H, $H_{a'}$), 7.61 (d, 1H, J 7.1 Hz, H_a), 7.78 (dd, 2H, J_{meta}=3 Hz, J_{ortho}=7.7 Hz, H_c, $H_{c¢}$), 7.67 (dd, 2H, J_{meta}=3.1 Hz, J_{ortho}=5.4 Hz, $H_{c''}$, $H_{c'''}$), 7.17 (m, 8H, H_a, $H_{a'}$, $H_{a''}$, H_b, $H_{b'}$, $H_{b''}$), 6.21 (bds, 1H, NH), 5.21 (dd, 1H, J_{de}= 6.7, $J_{de'}$=8.9 Hz, H_d), 3.21-3.53 (m, 2H, H_e, $H_{e'}$), 2.41 (m, 2H, f-CH_2), 1.25 (t, 3H, g-CH_3). MS (m/z, %): $M^{+\bullet}$-40 = 398 (4), 250 (7), 194 (2), 188 (74), 169 (6.5), 160 (3.3), 148 (100), 145 (2), 120 (3), 91 (22).). UV (CH_3OH) (λ_{max}/nm): 251, 291; $[\alpha]_D^{28}$ (MeOH): -184.68º.

2-Propyl-5-(phthaloyl-L-phenylalanyl)-amino benzimidazole (5c): Yield: 68%; m.p. 216 ºC; R_f = 0.67 (Chloroform: Methanol 9:1); IR (KBr, cm^{-1}): 3267 (NH), 1758 (C=O amide), 1741 (C=O of five membered ring anhydride), 1576 (C=N), 1397 (C-C(Ph)), 1334 (C-N of 2º amide). ^{1}H NMR (400 MHz, DMSO, d/ppm): 7.86 (d, 3.9Hz, 1H, $H_{a''}$), 7.29 (dd 3.9,7.2 Hz, 1H, $H_{a'}$), 7.58 (d, 1H, J 7.2 Hz, H_a), 7.77 (dd, 2H, J_{meta}=3.1 Hz, J_{ortho}=6.7 Hz, H_c, $H_{c'}$), 7.69 (dd, 2H, J_{meta}=3.1 Hz, J_{ortho}=6.4 Hz, $H_{c''}$, $H_{c'''}$), 7.18 (m, 5H, H_b, $H_{b'}$, $H_{b''}$), 5.30 (m, 1H, H_d), 3.38-3.54 (m, 2H, H_e, $H_{e'}$), 2.02 (m, 2H, f-CH_2), 1.73 (m, 2H, g-CH_2), 1.10 (t, 3H, h-CH_3); MS (m/z, %): $M^{+\bullet}$=452 (8), 398 (4), 229 (78), 250 (51), 188 (21.5), 169 (46), 161 (95), 160 (25), 148 (100), 103 (29), 91 (24).), UV (CH_3OH) (λ_{max}/nm): 254, 293; $[\alpha]_D^{28}$ (MeOH): -213.21º.

General procedure for synthesis of 5-(L-phenylalanyl)-amino benzimidazoles 6a-c

A suspension of (1.1 mmole) of coupled product (**15**) in

ethanol (3ml) was treated with 1M alcoholic hydrazine hydrate (1ml) and the mixture was heated under reflux for 1 hour. The mixture was dried under reduced pressure. The residue was warmed to 50 ºC for 10 minutes with 1.5 ml of 2 N HCl. The mixture was then cooled to room temperature, phthaloyl hydrazine was removed by filtration and the filtrate was dried under reduced pressure. The solid residue was dissolved in 10 ml of water and converted to free peptide by passage through a column of Amberlite (IR-4B). The effluent was dried under reduced pressure and the residue was recrystallized from methanol and dichloromethane.

1,2-Dimethyl-5-(L-phenylalanyl)-amino benzimidazole (6a): Yield: 65%; m.p. 219 ºC; R_f = 0.74 (Ethyl acetate: Hexane 2:1); IR (KBr, cm^{-1}): 3367 (-NH), 1776 (C=O amide), 1569 (C=N), 1377 (C-C(Ph)), 1210 (C-N of 2º amide); ^{1}H NMR (400 MHz, DMSO, δ/ppm): 9.67 (bds, 1H, NH), 7.89 (s, 1H, $H_{a''}$), 7.68-7.73 (m 2H, H_a $H_{a'}$), 7.05-7.13 (m, 5H, H_b, $H_{b'}$, $H_{b''}$), 4.87 (m, 1H, H_d), 3.49 (s, 3H, N-CH_3), 2.94-3.01 (m, 2H, H_e, $H_{e'}$), 2.67 (s, 3H, C-CH_3). MS (m/z, %): $M^{+\bullet}$=308 (85), 229 (100), 250 (51), 188 (61.5), 169 (46), 161 (95), 160 (25), 103 (29), 91 (24). UV (CH_3OH) (λ_{max}/nm): 260, 291; $[\alpha]_D^{28}$ (MeOH): -211.37º.

2-Ethyl-5-(L-phenylalanyl)-amino benzimidazole (6b): Yield: 68%; m.p. 209 ºC; R_f = 0.69 (Ethyl acetate: Hexane 2:1). IR (cm^{-1}): 3412 (NH), 1781 (C=O amide), 1547 (C=N), 1342 (C-C(Ph)), 1210 (C-N of 2º amide). ^{1}H NMR (400 MHz, DMSO, δ/ppm): 7.93 (d, 4.2 1H, $H_{a''}$), 7.80 (d 6.9 Hz, 1H, $H_{a'}$), 7.54 (dd, 1H, 4.2 6.9 Hz, H_a), 7.01-7.09 (m, 5H, H_b, $H_{b'}$, $H_{b''}$), 6.19 (bds, 1H, NH), 4.65 (m H_d), 2.89-2.94 (m, 2H, H_e, $H_{e'}$), 2.51 (m, 2H, f-CH_2), 1.27 (t, 3H, g-CH_3); MS (m/z, %): $M^{+\bullet}$=308 (4), 250 (7), 194 (2), 188 (74), 169 (6.5), 160 (3.3), 148 (100), 145 (2), 120 (3), 91 (22); UV (CH_3OH) (λ_{max}/nm): 251, 291; $[\alpha]_D^{28}$ (MeOH): -197.85º.

2-Propyl-5-(L-phenylalanyl)-amino benzimidazole (6c): Yield: 63%; m.p. 198 ºC; R_f = 0.71 (Ethyl acetate: Hexane 2:1), IR (cm^{-1}): 3334 (NH), 1777 (C=O amide), 1565 (C=N), 1378 (C-C(Ph)), 1217 (C-N of 2º amide). ^{1}H NMR (400 MHz, DMSO, δ/ppm): 7.86 (d, 3.9Hz, 1H, $H_{a''}$), 7.29 (dd 3.9,7.2 Hz, 1H, $H_{a'}$), 7.58 (d, 1H, J 7.2 Hz, H_a), 7.77 (dd, 2H, J_{meta}=3.1 Hz, J_{ortho}=6.7 Hz, H_c, $H_{c'}$), 7.69 (dd, 2H, J_{meta}=3.1 Hz, J_{ortho}=6.4 Hz, $H_{c''}$, $H_{c'''}$), 7.18 (m, 5H, H_b, $H_{b'}$, $H_{b''}$), 5.30 (m, 1H, H_d), 3.38-3.54 (m, 2H, H_e, $H_{e'}$), 2.02 (m, 2H, f-CH_2), 1.73 (m, 2H, g-CH_2), 1.10 (t, 3H, h-CH_3). MS (m/z, %): $M^{+\bullet}$=324 (41), 229 (100), 250 (51), 188 (21.5), 174, 169 (46), 161 (95), 160 (25), 103 (29), 91 (24); UV (CH_3OH) (λ_{max}/nm): 252, 291; $[\alpha]_D^{28}$ (MeOH): -116.09º.

Antibaceterial Actvity

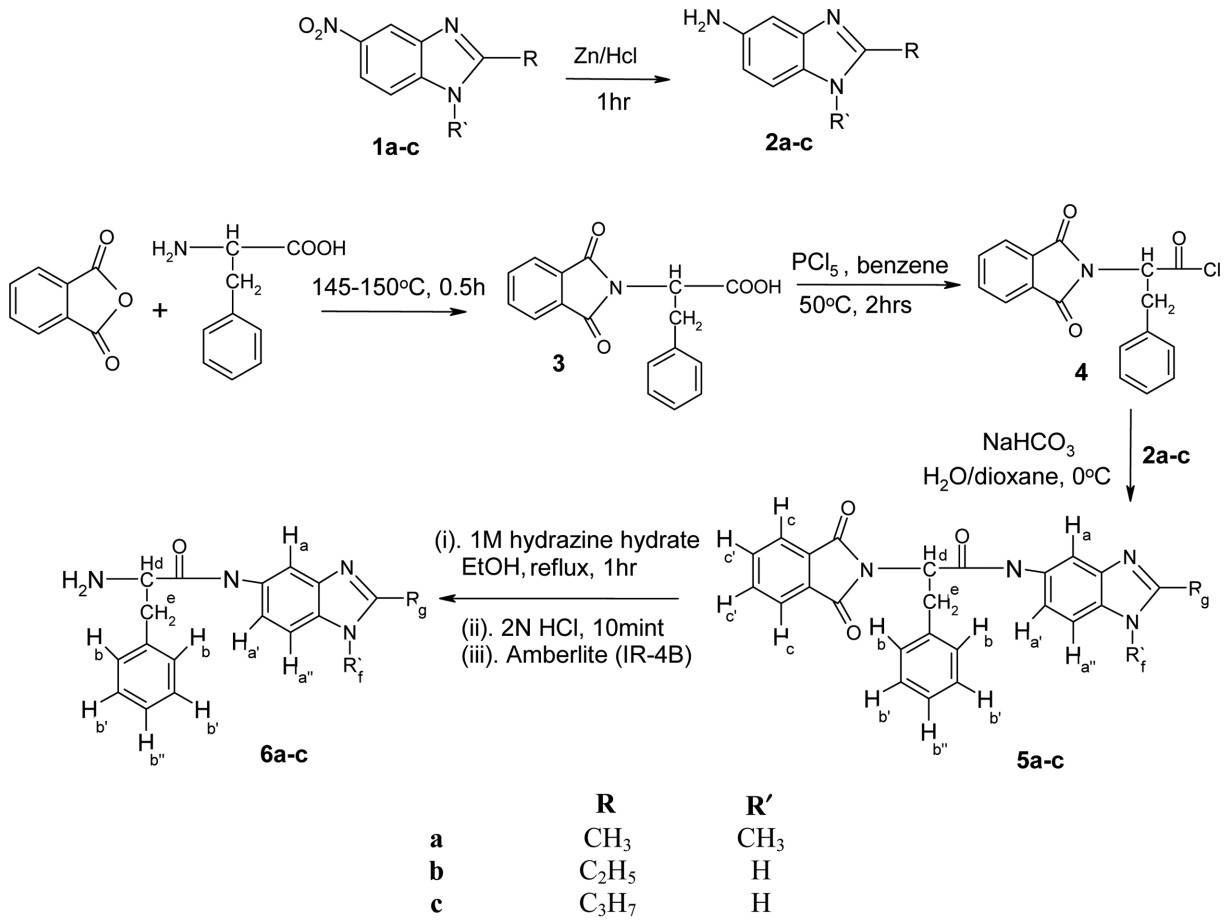
Antibaceterial activity of synthesized compounds was carried out against gram positive bacteria (*Staphylococcus aureus*, *Echerichia coli, Bacillus subtilus*) in nutrient agar medium at concentration of 100 μg/ml of DMSO by Agar Well Diffusion Method. Zone of inhibition was measured after 24 hr of incubation at 37 ºC. Compounds inhibiting growth of these microorganisms were further tested for MIC (minimum inhibitory concentration). Imipenem, a broad-spectrum β-lactam antibiotic, was used as a positive control, and DMSO as a negative control.

RESULTS AND DISCUSSION

5-Nitro benzimidazoles **1a-c** were synthesized by reported method[22] and reduced to corresponding amino benzimidazoles **2a-c**, using Zn/HCl. The next step was coupling of **2a-c** to naturally occurring amino acid *L*-phenylalanine. However, prior to coupling, α-amino group of *L*-phenylalanine was blocked with phthalic anhydride to form phthaloyl-*L*-phenylalanine **3** and α-carboxy group was activated by reacting it with phosphorous pentachloride to form phthaloyl-*L*-phenylalanyl chloride **4** as reported earlier.[21] Coupling of this protected and activated *L*-phenylalanine **4** with 5-amino benzimidazoles **2a-c** was accomplished under alkaline conditions in dioxane at 0 ºC to obtain **5a-c** (*Fig*. 1). Finally the pthaloyl group was removed to obtain free amine in peptide analogs of benzimidazoles **6a-c**. All these coupling products exhibited negative optical rotation as of the substrate *L*-phenylalanine, since racemization free procedures are adopted for the protection and deprotection.

IR spectrum of compounds **5a-c** revealed absorption at 1744, 1767 and 1759 cm^{-1} for amide carbonyl and at 1771, 1779 and 1788 cm^{-1} for the carbonyl group of five member anhydride ring respectively. Broad signal at 3465-3275 cm^{-1} were observed for -NH. EIMS spectrum of all coupled products **5a-c** exhibited similar fragmentation pattern. Molecular formulae of **5a-c** were confirmed from their molecular ion $M^{+\bullet}$ peaks observed at *m/z*=438, 438 and 454 respectively. The presence of acylium ion peaks at *m/z*=188, 188 and 174 correspondingly, has further confirmed the successful coupling reaction.

In ^{1}H NMR spectrum of compound **5a**, methyl group attached to the nitrogen appeared as a singlet at 3.80 ppm while methyl group attached to carbon appeared as a singlet relatively upfield at 2.64 ppm. Diastereotopic protons of CH_2 group (H_e, $H_{e'}$) adjacent to chiral center showed a broad multiplet (3.24-3.50 ppm) due to vicinal and gem-



	R	R′
a	CH_3	CH_3
b	C_2H_5	H
c	C_3H_7	H

***Fig.* 1.** Synthesis of 5-(*L*-phenylalanyl) amino benzimidazoles **6a-c**.

inal couplings. The proton H_d attached to the chiral center, exhibited a doublet of doublet at 5.24 ppm due to coupling with the diastereotopic H_e, $H_{e'}$ protons. $H_{a''}$ experienced some deshielding because electron donating effect of three nitrogen atoms is minimum at this position so it resonated at 7.98 ppm while $H_{a'}$ appeared as singlet at 7.61 ppm and H_a gave doublet at 7.33 ppm ($J_{a,a'}$=4.3 Hz). A multiplet at 7.18 ppm has been assigned to five protons of the phenyl ring (H_b, $H_{b'}$, $H_{b''}$), while four aromatic protons of phthaloyl moiety appeared as a singlet at 7.84 ppm.

Coupling of 5-amino-2-ethyl benzimidazole with phthaloyl *L*-phenylalanyl chloride led to the coupling product **5b**. Its ^{1}H NMR spectrum exhibited a triplet of 3H at 1.25 and a multiplet of 2H at 2.41 corresponding to 2-ethyl group. H_d proton exhibited a double doublet at 5.21 ppm due to coupling with diastereotopic H_e, $H_{e'}$ protons. These two protons H_e and $H_{e'}$ of the methylene group showed a multiplet at 3.21-3.53 ppm. Two protons H_c appeared as double doublet at 7.78 ppm, while two other protons $H_{c'}$, resonated as double doublet at 7.67 ppm. Other eight aromatic protons (H_a, $H_{a'}$, $H_{a''}$ and H_b, $H_{b'}$, $H_{b''}$) were observed between 7.16-7.81 ppm.

^{1}H NMR spectrum 2-propyl-5-(phthaloyl-*L*-phenylalanyl)-amino benzimidazole **5c** was exactly in accord with **5b**, except an additional multiplet of 2H observed at 1.73 along with 2.02 (m, 2H) and 1.10 (t, 3H) due to the presence of propyl group at C-2 instead of ethyl in **5b**.

After developing a successful peptide linkage, the phthaloyl group was removed by refluxing **5a-c** with alcoholic hydrazine hydrate; reaction mixture was neutralized with 2N HCl, precipitates of phthaloyl hydrazine was removed by filtration. Free peptides **6a-c** were finally purified by passing through a column of acid adsorbing resin Amberlite (IR-4B).[23] A significant feature of IR spectra of **6a-c** is that a prominent band at 1740-1790 cm^{-1} assigned to the carbonyl group of a 5-membered ring anhydride, which was observed in all coupling products **5a-c**, was not observed in this case indicating that phthaloyl group has got removed. Specific optical rotation showed that **6a-c** still remained levorotatory after depro-

tection, exempted chances of racemization. ^{1}H NMR and mass spectral data has further supported the expected structures of free peptides **6a-c**. Molecular ion $M^{+\bullet}$ peaks appeared at *m/z*=308, 308, and 324 in EIMS spectra is exactly in accord with expected molecular formulae of **6a-c**. Loss of M-130 in each case is a clear evidence of the loss of pthaloyl group, while presence of acylium ion peaks confirming successful peptide linkage is similar as **5a-c**. In ^{1}H NMR spectra of **6a-c**, disappearance of four aromatic protons of pthaloyl group (H_c, $H_{c'}$) resonated between 7.65-7.85 have further confirmed loss of pthaloyl group. All other spectral features are in concurrence with compounds **5a-c**, and described in experimental section.

Antibaceterial Actvity

Since peptide analogs of heterocycles are considered to be strong candidates for various pharmacological activities,[15] we synthesized peptide analogs of pharmacological importance benzimidazoles, to study the influence of peptide linkage on their antibacterial activity. *L*-phenylalanine is selected on the basis of its economical and easy availability.

Compounds **2a-c** and **5-6a-c** were screened for antibacterial activity by Agar Well Diffusion method[24] against three standard bacterial strains, i.e., *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*. Development of peptide linkage showed good activity of compounds **5a-c** against tested microorganisms than the parent benzimidazoles, with MIC value of 22-45 μg/ml. Compounds **6a-c** showed significant activity against *Escherichia coli* and *Staphlococcus aureus* with MIC value of 13.5-8 μg/ml, while moderate activity was observed against *Bacillus subtilis.* (*Table* 1, *Chart* 1) The careful analysis of results revealed that increase in chain length (R) at C-2 is moderately effective to increase in activity. Almost same pattern of activity relationship was observed for peptides **6a-c** against *E. Coli* and *B. Subtilis*, but nearly opposite behavior was observed against *S. Aureus*, where more potency was demonstrated by least number of carbons at C-2. Results are elaborated in *Table* 1 and compared in *Chart* 1, which helped to conclude that antibacterial activity of 5-Amino benzimidazoles **2a-c** was significantly enhanced with the development of peptide linkage in **5a-c**. Moreover, potency was further improved by obtaining free peptides **6a-c**, which showed that peptide linkage play crucial role to enhance the antibacterial activity of parent benzimidazoles. Antibacterial activities of new synthesized peptide series **6a-c** are found comparable with standard drug imipenem, particularly against *E. Coli* and *S. Aureus.*

***Table* 1.** Antibacterial Activity of Compounds **2a-c** and **5-6a-c**

Compounds	MIC/μg/ml		
	Escherichia coli	*Bacillus subtilis*	*Staphylococcus aureus*
2a	38	43	35
2b	38	49	41
2c	37	48	31
5a	32	39	27
5b	26	41	34
5c	29	45	22
6a	14	24.5	8
6b	10.5	21	9.5
6c	11	16.5	12
imipenem	14	16	13

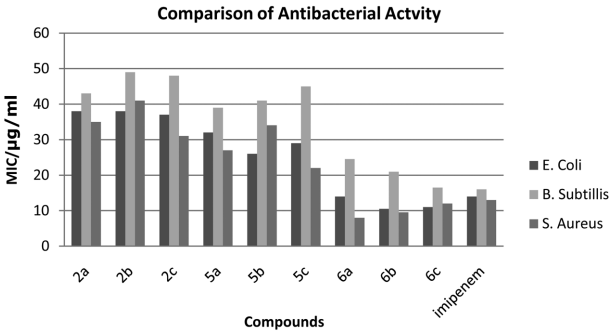


***Chart* 1.** Comparison of Antibacterial Activity of Synthesized Compounds.

CONCLUSION

This study reports the successful synthesis of new 5-(phthaloyl-L-phenylalanyl)-amino benzimidazoles **5a-c** and their corresponding free peptides 5-(L-phenylalanyl)-amino benzimidazoles **6a-c**. Structures of these compounds were determined on the basis of their spectral data. The potential antibacterial effects of these new peptide analogs were investigated and found that antibacterial activity of 5-Amino benzimidazoles **2a-c** was significantly enhanced with the development of peptide linkage in **5a-c** followed by free peptides **6a-c**.

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