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Original article

Synthetic studies on novel benzimidazolopeptides with antimicrobial, cytotoxic and anthelmintic potential

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Abstract

Four substituted benzimidazolyl-benzoic/salicylic acids **5–8** were synthesized by interaction of 5,6-dimethyl-/6-nitrobenzimidazoles with diazotized substituted/unsubstituted aminobenzoic acids in the presence of cupric chloride. The coupling of compounds **5–8** with different amino acid ester hydrochlorides/dipeptide/tripeptide/tetrapeptide methyl esters afforded novel benzimidazolopeptide derivatives **5a–f**, **6a–h**, **7a–g** and **8a–g**. The structures of all newly synthesized compounds were established on the basis of analytical, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Selected peptide ester derivatives were further hydrolyzed by using lithium hydroxide (LiOH) to yield corresponding acid derivatives **5b$_a$–d$_a$**, **6e$_a$–g$_a$**, **7c$_a$–e$_a$** and **8e$_a$–g$_a$**. All peptide derivatives were screened for their antimicrobial, anthelmintic and cytotoxic activities. Almost all newly synthesized benzimidazolopeptides have shown moderate to good anthelmintic activity against all three earthworm species and good antimicrobial activity against pathogenic fungal strains *Candida albicans* and *Aspergillus niger*, gram negative bacterial strains *Pseudomonas aeruginosa* and *Escherichia coli*. Compounds **8g** and **8g$_a$** possessed significant cytotoxic activity against Dalton's lymphoma ascites (DLA) and Ehrlich's ascites carcinoma (EAC) cell lines.

Keywords: Benzimidazoles; 5-Aminosalicylic acid; *p*-Aminobenzoic acid; Peptides; Antimicrobial activity; Anthelmintic activity; Cytotoxicity

1. Introduction

In past decades, benzimidazole and its derivatives have received much attention due to their chemotherapeutic value in the development of novel anthelmintics and antimicrobial agents [1–3]. Benzimidazole analogs also possessed other pharmacological activities such as antiallergic [4], antimycobacterial [5], inhibitory activity of human blood platelet aggregation [6], antiviral [7], antiprotozoal and antimalarial [8], anti-inflammatory, analgesic and kinase, DHFR inhibitory activity [9,10], antitumoral and tracheal relaxant activity [11]. Moreover, the literature is enriched with several reports indicating antimicrobial and molluscicidal [12], cytotoxicity [13], prooxidant and antioxidant [14], anti-inflammatory and analgesic [15] potential of substituted benzoic acid analogs, in addition to inhibitory activity against aldose reductase, influenza neuraminidase, 3α-hydroxysteroid dehydrogenase, phosphodiesterase (4D), steroid 5α-reductase isozymes 1 and 2, homomeric kainate receptor, histamine H_1 receptor and estrone sulfatase [16–23].

Prompted from the chemotherapeutic importance of benzimidazoles and benzoic acid derivatives, these two vital moieties were combined together into single nucleus by varying the substitution pattern on both the moieties to yield 4-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)-benzoic acid **5** and 4-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)-3,5-diiodobenzoic acid **6**, 2-hydroxy-5-(6-nitro-1*H*-benzo[*d*]imidazol-2-yl)-benzoic acid **7** and 5-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)-2-hydroxybenzoic acid **8**.

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In view of the reported activity of amino acid/peptide derivatives of heterocyclic aromatic compounds [24–27] and in continuation of our earlier work on synthesis of benzimidazole derivatives of amino acids and peptides [28,29], an attempt was made towards the synthesis of four novel series of benzimidazolopeptides, 4-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)-benzoyl amino acid/peptides **5a–f** and 4-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)-3,5-diiodobenzoyl amino acid/peptides **6a–h**, 2-hydroxy-5-(6-nitro-1*H*-benzo[*d*]imidazol-2-yl)-benzoyl amino acid/peptides **7a–g** and 5-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)-2-hydroxybenzoyl amino acid/peptides **8a–g**, respectively. Selected peptide derivatives were further hydrolyzed to get corresponding acid derivatives $\mathbf{5b_a–d_a}$, $\mathbf{6e_a–g_a}$, $\mathbf{7c_a–e_a}$ and $\mathbf{8e_a–g_a}$. Antimicrobial, anthelmintic and cytotoxic activity results of such novel heterocyclic peptide derivatives are also discussed.

2. Chemistry

4-Amino-3,5-diiodobenzoic acid **1a** was prepared according to the literature procedure [30] in good yields by iodination of *p*-aminobenzoic acid (PABA) using iodine monochloride. Benzimidazole was nitrated using nitrating mixture by standard procedure [31] to afford 6-nitrobenzimidazole **1b**. Dipeptides Boc-Leu-Gly-OMe **2a**, Boc-His-Tyr-OMe **2b**, Boc-Pro-nitro (Arg)-OMe **2c**, Boc-His-Pro-OMe **2d**, Boc-Gly-Gly-OMe **2e**, Boc-Pro-Ala-OMe **2f**, Boc-nitro(Arg)-Ala-OMe **2g**, Boc-His-His-OMe **2h** and Boc-Leu-Ile-OMe **2i** were prepared by coupling Boc-amino acids with the respective amino acid methyl ester hydrochlorides using dicyclohexylcarbodiimide (DCC) as coupling agent and *N*-methylmorpholine (NMM) as base according to Bodanzsky and Bodanzsky procedure [32] with suitable modifications [33]. The Boc group of all dipeptides was removed by using trifluoroacetic acid (TFA) to obtain dipeptide derivatives deprotected at the amino terminal **2a′–i′**. Similarly, tripeptides Boc-Pro-Pro-Phe-OMe **3a**, Boc-Ala-Tyr-Gly-OMe **3b**, Boc-Phe-Val-Pro-OMe **3c**, Boc-Pro-Pro-Pro-OMe **3d**, Boc-Val-Phe-His-OMe **3e**, Boc-Trp-Ala-Tyr-OMe **3f**, Boc-Ala-Val-Ala-OMe **3g** and tetrapeptides Boc-Trp-Gly-Ile-Ala-OMe **4a**, Boc-Gly-Ile-Gly-Thr-OMe **4b**, Boc-His-Pro-Leu-Gly-OMe **4c**, Boc-Gly-Trp-Gly-His-OMe **4d** were synthesized by coupling Boc-dipeptides with respective amino acid methyl ester hydrochlorides/dipeptide methyl esters in alkaline conditions. On treatment with TFA, all tri and tetrapeptides afforded tripeptide **3a′–g′** and tetrapeptide **4a′–d′** derivatives with free amino group. Compound **5** and its diiododerivative **6** were prepared by interaction of diazotized solution of PABA/**1a** with 5,6-dimethylbenzimidazole in the presence of aqueous cupric chloride. Similarly, compounds **7** and **8** were synthesized by stirring diazotized solution of 5-aminosalicylic acid with **1b** and 5,6-dimethylbenzimidazole, respectively. Finally, compounds **5** and **6** were coupled with different amino acid methyl ester hydrochlorides and dipeptide/tripeptide/tetrapeptide methyl esters by using DCC/triethylamine (TEA) in THF to get peptide derivatives **5a–f** and **6a–h**, respectively. Similarly, coupling of compounds **7** and **8** with different peptide methyl esters in the presence of DCC/NMM in DMF afforded amino acid/peptide conjugates **7a–g** and **8a–g**, respectively. Furthermore, amino acid/peptide derivatives **5b–d**, **6e–g**, **7c–e** and **8e–g** were hydrolyzed by stirring with LiOH to yield corresponding acid derivatives $\mathbf{5b_a–d_a}$, $\mathbf{6e_a–g_a}$, $\mathbf{7c_a–e_a}$ and $\mathbf{8e_a–g_a}$ (Fig. 1). All the newly synthesized peptide derivatives were characterized by spectral and elemental analyses (Table 1).

3. Biological activity studies

All the newly synthesized peptide derivatives $\mathbf{5a–8g_a}$ were evaluated for their antibacterial, antifungal, anthelmintic and cytotoxic activity. The antimicrobial activities are carried out against four bacterial strains *Bacillus subtilis* (NCIM 2063), *Staphylococcus aureus* (NCIM 2079), *Pseudomonas aeruginosa* (NCIM 2034), *Escherichia coli* (NCIM 2065) according to modified Kirby–Bauer disc diffusion method [34] and four fungal strains *Candida albicans* (MUCC 29), *Microsporum audouinii* (MUCC 545), *Trichophyton mentagrophytes* (MUCC 665), *Aspergillus niger* (MUCC 177) according to serial plate dilution method [35]. Ciprofloxacin and griseofulvin were used as standard drugs against bacterial and fungal strains at 10 μg mL^{-1} concentration. MIC values of test compounds were determined by tube dilution technique [36]. The results of antimicrobial activity are summarized in Table 2. The anthelmintic activity was carried out against the three earthworm species *Megascoplex konkanensis* (ICARBC 211), *Pontoscotex corethruses* (ICARBC 408) and *Eudrilus* sp. (ICARBC 042) by Garg and Atal method [37] at concentration of 2 mg mL^{-1} using mebendazole as standard drug. The results of anthelmintic activity are tabulated in Table 3. The cytotoxic activity was carried out against Dalton's lymphoma ascites (DLA) cells and Ehrlich's ascites carcinoma (EAC) cells according to the method of Kuttan et al. [38] using 5-fluorouacil (5-FU) as standard drug and the results are presented in Table 4. Moreover, various physicochemical parameters of selected synthesized peptide derivatives were calculated using ACD ChemSketch software and the results of such studies are presented in Table 5.

4. Results and discussion

The newly synthesized compounds were analyzed for C, H and N content and structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Results of elemental analyses revealed the variation by a factor of ±0.04 from calculated values. Coupling reaction was accomplished and confirmed by appearance of bands of medium to strong intensity at 1663–1627 cm^{-1} (amide I band, C=O str.) and 1536–1520 cm^{-1} (amide II band, N–H def.) in IR spectra of all Boc-di/tri/tetrapeptide methyl esters **2a–i**, **3a–g** and **4a–d**. Deprotection at amino terminal was indicated by disappearance of singlets at 1.55–1.50 ppm (for nine protons of ^{t}butyl group) in ^{1}H NMR spectra, peaks at 157.2–152.3, 80.9–79.7 and 27.5–26.8 ppm (for carbonyl carbon of Boc group and α-, β-carbons of ^{t}butyl group of Boc) in ^{13}C NMR spectra of compounds **2a′–i′**, **3a′–g′** and **4a′–d′**.

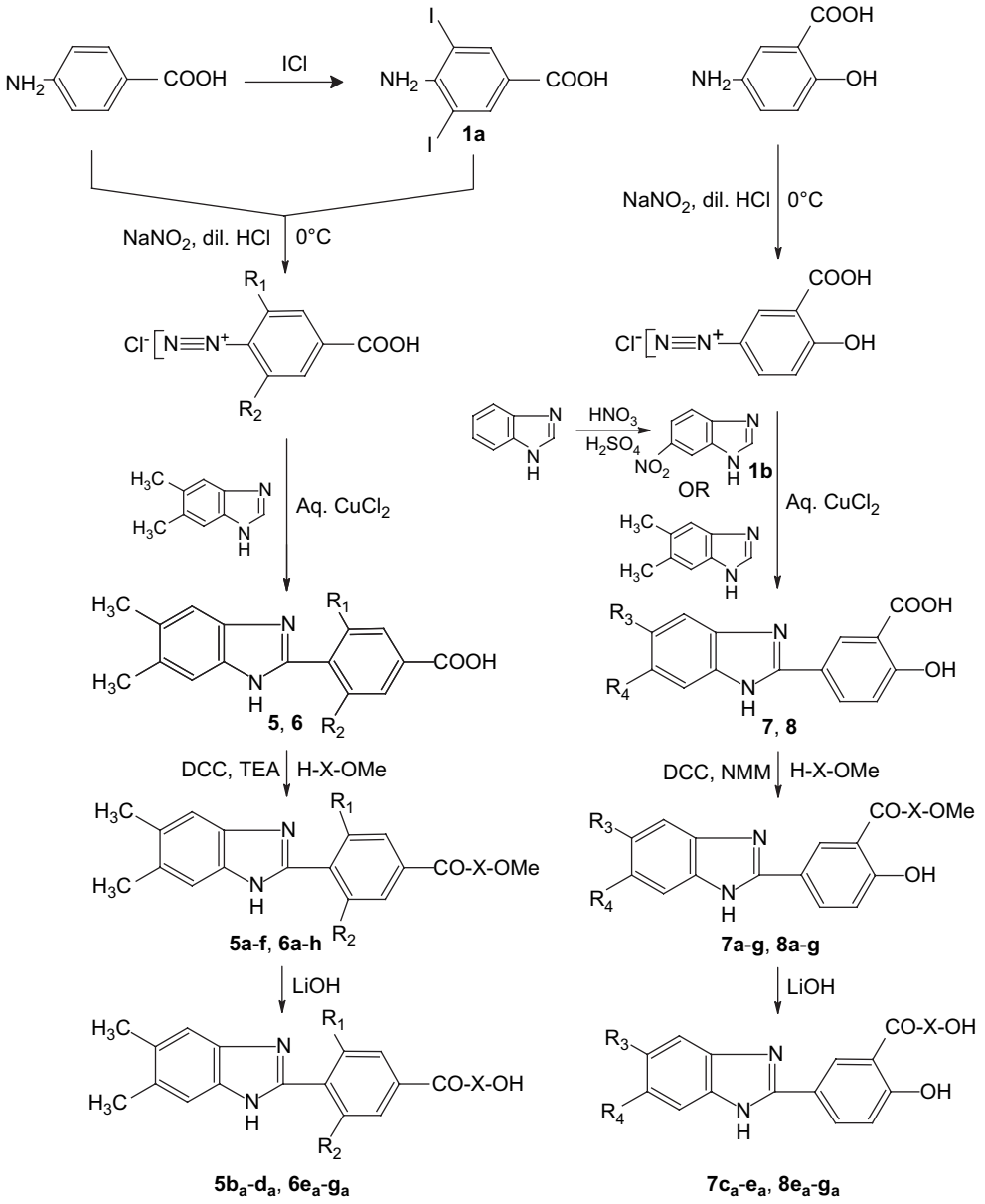

Fig. 1. Synthesis of amino acid and peptide derivatives of 4-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)-benzoic acid **5**, 4-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)-3,5-diiodobenzoic acid **6**, 2-hydroxy-5-(6-nitro-1*H*-benzo[*d*]imidazol-2-yl)-benzoic acid **7** and 5-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)-2-hydroxybenzoic acid **8**.

Presence of two aromatic rings in structures of compounds **5**–**8** was confirmed by strong out-of-plane deformation bands (C–H bending) at 886–820 cm^{-1} in their IR spectra. Moreover, presence of NO_2 group in compound **7** was indicated by appearance of medium bands at 1540 and 1349 cm^{-1} (asymmetric and symmetric NO_2 stretching) in IR spectra whereas presence of iodine atoms in compound **6** and its peptide derivatives was indicated by appearance of bands of medium intensity at 602–588 cm^{-1} (C–I str.) in IR spectra.

All peptide derivatives **5a**–**8g$_a$** were synthesized in good yields by utilizing DCC as coupling agent, TEA and NMM as bases in THF and DMF, respectively. IR spectra of peptide derivatives **5a**–**8g** showed amide I and amide II bands at 1668–1622 cm^{-1} and 1548–1522 cm^{-1}, indicating formation of peptide bonds and successfulness of coupling reaction. This fact was further confirmed by the appearance of broad singlets at 9.98–6.25 ppm (for imino proton of CO–NH moiety) in ^1H NMR spectra and singlets at 175.3–163.6 ppm (for carbonyl carbon of CO–NH moiety) in ^{13}C NMR spectra of compounds **5a**–**8g**. Mass spectra of peptide ester derivatives showed molecular ion peaks along with isotopic peaks at *m*/*z* values, consistent with their respective molecular formulas. All peptide

Table 1
Characterization data of compounds **5a–6g$_a$**

Compound	R_1	R_2	R_3	R_4	X	Mol. formula (mol. wt.)	M.p. (°C)	Yield (%)	R_M value[a]	Analysis, %found (calcd.)		
										C	H	N
5a	H	H	–	–	Pro	$C_{22}H_{23}N_3O_3$ (377)	144–145	76	−0.7533 ± 0.0207	69.98 (70.01)	6.15 (6.14)	11.09 (11.13)
5b	H	H	–	–	Nitro(Arg)	$C_{23}H_{27}N_7O_5$ (481)	160–161	72	−0.6585 ± 0.0062	57.35 (57.37)	5.68 (5.65)	20.37 (20.36)
5c	H	H	–	–	Leu-Gly	$C_{25}H_{30}N_4O_4$ (450)	128–129	69	−0.8860 ± 0.0113	66.59 (66.65)	6.74 (6.71)	12.40 (12.44)
5d	H	H	–	–	His-Tyr	$C_{32}H_{32}N_6O_5$ (580)	116–117	72	−0.5247 ± 0.0028	66.24 (66.19)	5.56 (5.55)	14.44 (14.47)
5e	H	H	–	–	Pro-Pro-Phe	$C_{36}H_{39}N_5O_5$ (621)	137–138	79	−0.0696 ± 0.0127	69.54 (69.55)	6.30 (6.32)	11.28 (11.26)
5f	H	H	–	–	Trp-Gly-Ile-Ala	$C_{39}H_{45}N_7O_6$ (707)	173–174	73	−0.3075 ± 0.0486	66.17 (66.18)	6.37 (6.41)	13.79 (13.85)
5b$_a$	H	H	–	–	Nitro(Arg)	$C_{22}H_{25}N_7O_5$ (467)	122–123	71	−0.3474 ± 0.0085	56.49 (56.52)	5.42 (5.39)	21.01 (20.97)
5c$_a$	H	H	–	–	Leu-Gly	$C_{24}H_{28}N_4O_4$ (436)	109–110	74	−0.6886 ± 0.0032	66.05 (66.04)	6.55 (6.47)	12.82 (12.84)
5d$_a$	H	H	–	–	His-Tyr	$C_{31}H_{30}N_6O_5$ (566)	99–100	72	−0.3273 ± 0.0118	65.69 (65.71)	5.36 (5.34)	14.88 (14.83)
6a	I	I	–	–	His	$C_{23}H_{21}I_2N_5O_3$ (669)	218–219	80	−0.3888 ± 0.0076	41.28 (41.28)	3.15 (3.16)	10.49 (10.46)
6b	I	I	–	–	Trp	$C_{28}H_{24}I_2N_4O_3$ (718)	262–263	76	−0.3474 ± 0.0110	46.80 (46.82)	3.39 (3.37)	7.79 (7.80)
6c	I	I	–	–	Thr	$C_{21}H_{21}I_2N_3O_4$ (633)	201–202	79	−0.0173 ± 0.0079	39.85 (39.83)	3.31 (3.34)	6.65 (6.64)
6d	I	I	–	–	Pro-(nitro)Arg	$C_{28}H_{32}I_2N_8O_6$ (830)	225–226	73	−0.5496 ± 0.0047	40.48 (40.50)	4.02 (3.88)	13.52 (13.49)
6e	I	I	–	–	His-Pro	$C_{28}H_{28}I_2N_6O_4$ (766)	197–198	67	−0.0521 ± 0.0200	43.85 (43.88)	3.70 (3.68)	10.99 (10.97)
6f	I	I	–	–	Ala-Tyr-Gly	$C_{31}H_{31}I_2N_5O_6$ (823)	282–283	72	−0.2880 ± 0.0059	45.19 (45.22)	3.83 (3.79)	8.55 (8.51)
6g	I	I	–	–	Phe-Val-Pro	$C_{36}H_{39}I_2N_5O_5$ (875)	254–255	69	−0.9079 ± 0.0107	49.41 (49.39)	4.50 (4.49)	7.98 (8.00)
6h	I	I	–	–	Gly-Ile-Gly-Thr	$C_{31}H_{38}I_2N_6O_7$ (860)	259–261	74	−0.4542 ± 0.0476	43.29 (43.27)	4.44 (4.45)	9.70 (9.77)
6e$_a$	I	I	–	–	His-Pro	$C_{27}H_{26}I_2N_6O_4$ (752)	188–189	71	−0.2126 ± 0.0124	43.10 (43.10)	3.50 (3.48)	11.21 (11.17)
6f$_a$	I	I	–	–	Ala-Tyr-Gly	$C_{30}H_{29}I_2N_5O_6$ (809)	269–270	74	−0.1401 ± 0.0092	44.49 (44.52)	3.59 (3.61)	8.66 (8.65)
6g$_a$	I	I	–	–	Phe-Val-Pro	$C_{35}H_{37}I_2N_5O_5$ (861)	210–211	68	−0.6585 ± 0.0724	48.77 (48.80)	4.33 (4.33)	8.12 (8.13)
Characterization data of compounds **7a–8g$_a$**												
7a	–	–	H	NO_2	Nitro(Arg)	$C_{21}H_{22}N_8O_8$ (514)	170–171	86	−0.1224 ± 0.0118	48.99 (49.03)	4.29 (4.31)	21.71 (21.78)
7b	–	–	H	NO_2	Trp	$C_{26}H_{21}N_5O_6$ (499)	159–160	81	−0.9542 ± 0.0200	62.50 (62.52)	4.25 (4.24)	13.98 (14.02)
7c	–	–	H	NO_2	Gly-Gly	$C_{19}H_{17}N_5O_7$ (427)	125–126	88	−0.4101 ± 0.0037	53.45 (53.40)	3.98 (4.01)	16.40 (16.39)
7d	–	–	H	NO_2	Pro-Ala	$C_{23}H_{23}N_5O_7$ (481)	196–197	89	−0.4771 ± 0.0229	57.40 (57.38)	4.85 (4.82)	14.49 (14.55)
7e	–	–	H	NO_2	Pro-Pro-Pro	$C_{30}H_{32}N_6O_8$ (604)	168–169	82	−0.1580 ± 0.1104	59.59 (59.60)	5.35 (5.33)	13.93 (13.90)
7f	–	–	H	NO_2	Val-Phe-His	$C_{35}H_{36}N_8O_8$ (696)	175–176	91	−0.0871 ± 0.0048	60.35 (60.34)	5.20 (5.21)	16.05 (16.08)
7g	–	–	H	NO_2	His-Pro-Leu-Gly	$C_{34}H_{39}N_9O_9$ (717)	202–203	83	−0.2688 ± 0.0102	56.89 (56.90)	5.50 (5.48)	17.55 (17.56)
7c$_a$	–	–	H	NO_2	Gly-Gly	$C_{18}H_{15}N_5O_7$ (413)	108–109	92	−0.3679 ± 0.0140	52.27 (52.30)	3.65 (3.66)	16.95 (16.94)
7d$_a$	–	–	H	NO_2	Pro-Ala	$C_{22}H_{21}N_5O_7$ (467)	185–186	81	−0.4319 ± 0.0083	56.52 (56.53)	4.55 (4.53)	15.01 (14.98)
7e$_a$	–	–	H	NO_2	Pro-Pro-Pro	$C_{29}H_{30}N_6O_8$ (590)	152–153	89	−0.1760 ± 0.0071	58.96 (58.98)	5.12 (5.12)	14.20 (14.23)
8a	–	–	CH_3	CH_3	Phe	$C_{26}H_{25}N_3O_4$ (443)	210–211	80	−0.1224 ± 0.0221	70.45 (70.41)	5.64 (5.68)	9.47 (9.47)
8b	–	–	CH_3	CH_3	(Nitro)Arg-Ala	$C_{26}H_{32}N_8O_7$ (568)	222–223	85	−0.0347 ± 0.0109	54.95 (54.92)	5.67 (5.67)	19.69 (19.71)
8c	–	–	CH_3	CH_3	His-His	$C_{29}H_{30}N_8O_5$ (570)	196–197	89	−0.8653 ± 0.0063	61.05 (61.04)	5.28 (5.30)	19.65 (19.64)
8d	–	–	CH_3	CH_3	Leu-Ile	$C_{29}H_{38}N_4O_5$ (522)	188–189	79	−0.0871 ± 0.0094	66.66 (66.64)	7.32 (7.33)	10.72 (10.72)
8e	–	–	CH_3	CH_3	Trp-Ala-Tyr	$C_{40}H_{40}N_6O_7$ (716)	174–175	91	−0.1942 ± 0.0173	66.98 (67.03)	5.64 (5.62)	11.75 (11.72)
8f	–	–	CH_3	CH_3	Ala-Val-Ala	$C_{28}H_{35}N_5O_6$ (537)	250–251	90	−0.5247 ± 0.0428	62.50 (62.55)	6.57 (6.56)	13.06 (13.03)
8g	–	–	CH_3	CH_3	Gly-Trp-Gly-His	$C_{38}H_{39}N_9O_7$ (733)	244–245	90	−0.1047 ± 0.0221	62.16 (62.20)	5.35 (5.36)	17.20 (17.18)
8e$_a$	–	–	CH_3	CH_3	Trp-Ala-Tyr	$C_{39}H_{38}N_6O_7$ (702)	160–161	82	−0.4102 ± 0.0113	66.61 (66.65)	5.49 (5.45)	11.99 (11.96)
8f$_a$	–	–	CH_3	CH_3	Ala-Val-Ala	$C_{27}H_{33}N_5O_6$ (523)	229–230	85	−0.2311 ± 0.0038	61.92 (61.94)	6.36 (6.35)	13.42 (13.38)
8g$_a$	–	–	CH_3	CH_3	Gly-Trp-Gly-His	$C_{37}H_{37}N_9O_7$ (719)	202–203	80	−0.6886 ± 0.0192	61.75 (61.74)	5.15 (5.18)	17.50 (17.51)

[a] $R_M = \log[(1/R_f) - 1]$; data are given as mean ± S.D. ($n = 3$).

Table 2
Antimicrobial activity data

Compound	Diameter of zone of inhibition (mm)							
	Bacterial strains				Fungal strains			
	B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*	*C. albicans*	*M. audouinii*	*A. niger*	*T. mentagrophytes*
5a	13 (6)	11 (12.5)	22 (6)	17 (12.5)	16 (6)	9 (25)	17 (12.5)	13 (6)
5b	14 (12.5)	9 (25)	23 (6)	17 (12.5)	15 (12.5)	8 (12.5)	15 (12.5)	12 (12.5)
5c	10 (6)	9 (12.5)	20 (6)	14 (12.5)	18 (6)	10 (25)	16 (25)	12 (6)
5d	14 (6)	10 (12.5)	19 (12.5)	15 (25)	16 (12.5)	8 (25)	16 (12.5)	13 (6)
5e	13 (12.5)	8 (25)	20 (6)	16 (25)	16 (6)	9 (25)	14 (12.5)	13 (6)
5f	14 (6)	10 (12.5)	20 (6)	18 (12.5)	19 (25)	10 (6)	19 (25)	9 (25)
5b$_a$	15 (12.5)	11 (25)	25 (6)	19 (12.5)	17 (12.5)	10 (12.5)	16 (12.5)	14 (12.5)
5c$_a$	13 (6)	10 (12.5)	23 (6)	17 (12.5)	19 (6)	11 (25)	17 (25)	14 (6)
5d$_a$	13 (6)	11 (12.5)	23 (12.5)	17 (25)	17 (12.5)	10 (25)	17 (12.5)	16 (6)
6a	16 (6)	12 (12.5)	24 (6)	18 (12.5)	18 (6)	11 (25)	14 (12.5)	12 (12.5)
6b	16 (6)	12 (12.5)	25 (6)	19 (12.5)	18 (6)	9 (12.5)	19 (25)	12 (6)
6c	20 (6)	13 (12.5)	23 (6)	16 (12.5)	19 (6)	8 (25)	15 (12.5)	10 (6)
6d	17 (6)	12 (12.5)	27 (6)	18 (12.5)	23 (6)	10 (25)	14 (25)	12 (6)
6e	14 (6)	11 (12.5)	24 (6)	17 (12.5)	16 (6)	9 (25)	13 (12.5)	12 (6)
6f	15 (6)	12 (12.5)	20 (6)	17 (12.5)	15 (6)	9 (12.5)	15 (12.5)	13 (12.5)
6g	16 (6)	12 (25)	22 (12.5)	16 (25)	16 (6)	10 (12.5)	14 (12.5)	12 (6)
6h	15 (6)	12 (12.5)	22 (6)	17 (12.5)	13 (12.5)	9 (25)	18 (25)	9 (25)
6e$_a$	16 (6)	13 (12.5)	27 (6)	18 (12.5)	25 (6)	10 (25)	14 (12.5)	13 (6)
6f$_a$	16 (6)	13 (12.5)	23 (6)	18 (12.5)	16 (6)	11 (12.5)	15 (12.5)	15 (12.5)
6g$_a$	17 (6)	13 (25)	24 (12.5)	18 (25)	17 (6)	11 (12.5)	15 (12.5)	13 (6)
7a	13 (6)	10 (25)	19 (6)	15 (12.5)	15 (12.5)	13 (6)	18 (12.5)	15 (6)
7b	12 (6)	12 (12.5)	20 (12.5)	16 (12.5)	20 (6)	10 (12.5)	16 (12.5)	17 (6)
7c	9 (25)	9 (12.5)	22 (6)	16 (12.5)	18 (6)	13 (6)	17 (12.5)	15 (6)
7d	13 (12.5)	9 (25)	28 (6)	18 (12.5)	22 (6)	12 (6)	16 (12.5)	17 (6)
7e	14 (6)	11 (12.5)	27 (6)	17 (25)	24 (6)	13 (6)	17 (12.5)	17 (12.5)
7f	13 (6)	11 (12.5)	24 (12.5)	16 (12.5)	19 (6)	12 (12.5)	19 (25)	13 (6)
7g	14 (6)	10 (12.5)	24 (6)	14 (12.5)	20 (6)	12 (6)	17 (12.5)	15 (6)
7c$_a$	9 (25)	9 (12.5)	22 (6)	16 (12.5)	18 (6)	13 (6)	17 (12.5)	16 (6)
7d$_a$	13 (12.5)	9 (25)	28 (6)	18 (12.5)	22 (6)	12 (6)	16 (12.5)	17 (6)
7e$_a$	14 (6)	11 (12.5)	28 (6)	17 (25)	24 (6)	13 (6)	17 (12.5)	17 (12.5)
8a	14 (6)	10 (12.5)	24 (6)	17 (12.5)	17 (6)	9 (25)	17 (12.5)	15 (6)
8b	15 (6)	11 (12.5)	22 (6)	17 (12.5)	19 (12.5)	11 (6)	18 (12.5)	10 (6)
8c	13 (6)	11 (12.5)	21 (6)	17 (12.5)	20 (6)	11 (6)	17 (12.5)	15 (6)
8d	15 (6)	10 (12.5)	20 (6)	16 (12.5)	19 (6)	12 (6)	19 (25)	13 (6)
8e	13 (12.5)	10 (12.5)	21 (6)	16 (12.5)	17 (6)	11 (12.5)	16 (12.5)	14 (6)
8f	13 (6)	9 (25)	19 (6)	16 (25)	18 (6)	10 (6)	16 (12.5)	14 (6)
8g	12 (6)	9 (12.5)	23 (6)	17 (12.5)	17 (6)	10 (6)	15 (12.5)	15 (6)
8e$_a$	16 (12.5)	11 (12.5)	22 (6)	18 (12.5)	18 (6)	12 (12.5)	17 (12.5)	15 (6)
8f$_a$	14 (6)	11 (25)	21 (6)	17 (25)	19 (6)	11 (6)	17 (12.5)	15 (6)
8g$_a$	14 (6)	10 (12.5)	24 (6)	18 (12.5)	20 (6)	11 (6)	16 (12.5)	16 (6)
Control	–	–	–	–	–	–	–	–
Ciprofloxacin	20 (6)	20 (12.5)	25 (6)	19 (12.5)	–	–	–	–
Griseofulvin	–	–	–	–	20 (6)	17 (6)	18 (12.5)	20 (6)

Values in bracket are MIC values ($\mu g\,mL^{-1}$).

ester derivatives showed easily distinguishable R–C≡O^+ ion peaks at M − 31 along with characteristic fragmentation pattern after and before the carbonyl moiety in their respective structures. Furthermore, $[CH_3O^+]$ and $[CH_3OCO^+]$ fragment ion peaks appeared at *m/z* values 31 and 59 in mass spectra of compounds **5a–8g**. Peptide derivatives of compounds **5**, **6** and **8** showed characteristic fragment ion peaks at *m/z* value 146 (5,6-dimethylbenzimidazole ion – $[C_9H_{10}N_2]^+$) which dissociated into $[C_8H_9N]^+$ ion by loss of HCN, appeared at *m/z* value 119 which further dissociated into $[C_8H_8N]^+$ ion by loss of hydrogen radical, appeared at *m/z* value 118. Similar pattern of fragmentation appeared in case of amino acid/peptide derivatives of compound **7**, characteristic fragment ion being 6-nitrobenzimidazole ion – $[C_7H_5N_3O_2]^+$, which dissociated into $[C_6H_4N_2O_2]^+$ and $[C_6H_3N_2O_2]^+$ ions by loss of HCN and hydrogen radical, appeared at *m/z* value 136 and 135, respectively.

Structures of hydrolyzed derivatives **5b$_a$–d$_a$**, **6e$_a$–g$_a$**, **7c$_a$–e$_a$** and **8e$_a$–g$_a$** were confirmed by appearance of strong bands at 1716–1705 cm^{-1} (C=O str. COOH) in IR spectra, broad singlets at 9.72–9.80 ppm (for hydroxyl proton of COOH) in ^1H NMR spectra and singlets at 182.2–173.2 ppm (for carbonyl carbon of COOH) in ^{13}C NMR spectra. This fact was further supported by disappearance of medium to strong bands

Table 3
Anthelmintic activity data

Compound	Earthworm species					
	M. konkanensis		*P. corethruses*		*Eudrilus* sp.	
	Mean paralyzing time (min)[a]	Mean death time (min)[a]	Mean paralyzing time (min)[a]	Mean death time (min)[a]	Mean paralyzing time (min)[a]	Mean death time (min)[a]
5a	28.38 ± 0.52	40.58 ± 0.59	35.57 ± 1.26	50.26 ± 1.02	32.25 ± 0.93	45.34 ± 1.62
5b	18.56 ± 0.98	26.56 ± 0.45	21.65 ± 1.44	35.22 ± 1.87	18.67 ± 0.82	28.21 ± 0.82
5c	28.34 ± 0.59	41.40 ± 0.84	37.17 ± 1.88	49.40 ± 1.43	29.73 ± 0.49	42.54 ± 0.93
5d	13.68 ± 1.12	22.59 ± 0.72	17.55 ± 0.23	29.18 ± 2.17	13.49 ± 1.32	23.98 ± 0.44
5e	36.78 ± 0.21	62.48 ± 0.91	49.35 ± 1.65	72.24 ± 1.04	32.82 ± 0.58	53.34 ± 0.62
5f	13.25 ± 0.44	22.52 ± 1.43	17.22 ± 1.24	29.57 ± 1.02	13.59 ± 0.41	24.10 ± 0.60
5b$_a$	18.15 ± 0.52	26.29 ± 0.76	21.51 ± 1.12	34.96 ± 1.04	18.38 ± 0.69	38.12 ± 0.71
5c$_a$	26.29 ± 0.89	40.27 ± 0.92	36.61 ± 1.91	48.39 ± 0.20	32.80 ± 0.85	40.24 ± 0.55
5d$_a$	13.54 ± 0.83	22.18 ± 1.28	17.47 ± 1.47	29.02 ± 1.18	13.44 ± 0.89	23.08 ± 0.38
6a	29.28 ± 0.67	45.46 ± 0.28	34.14 ± 1.23	47.82 ± 0.78	34.34 ± 0.56	46.30 ± 0.49
6b	13.04 ± 0.93	22.28 ± 0.71	17.10 ± 1.08	29.29 ± 0.39	13.50 ± 0.81	24.02 ± 0.96
6c	35.23 ± 1.56	59.23 ± 0.88	40.60 ± 1.33	78.32 ± 0.87	31.22 ± 1.75	69.45 ± 0.78
6d	17.93 ± 0.80	26.34 ± 0.77	22.77 ± 1.56	34.45 ± 1.86	19.43 ± 0.67	30.02 ± 0.59
6e	13.73 ± 1.90	22.73 ± 0.49	17.52 ± 2.23	29.58 ± 1.63	13.48 ± 0.59	23.98 ± 0.97
6f	28.35 ± 0.43	39.13 ± 0.43	34.13 ± 1.31	48.24 ± 0.31	27.42 ± 0.35	45.30 ± 1.13
6g	27.25 ± 0.14	40.35 ± 0.24	33.64 ± 0.46	50.22 ± 1.22	29.24 ± 0.56	45.34 ± 0.35
6h	36.10 ± 0.23	65.13 ± 0.92	57.67 ± 1.90	82.30 ± 0.49	38.45 ± 0.88	70.54 ± 0.76
6e$_a$	13.65 ± 1.56	22.38 ± 2.03	17.38 ± 0.33	29.33 ± 0.28	13.37 ± 1.44	23.86 ± 1.21
6f$_a$	27.23 ± 0.24	40.57 ± 0.34	35.42 ± 1.31	47.45 ± 1.76	26.25 ± 0.35	45.22 ± 1.10
6g$_a$	26.42 ± 0.45	41.85 ± 0.67	34.13 ± 1.06	50.13 ± 1.44	27.10 ± 0.83	44.10 ± 1.02
7a	16.22 ± 0.37	25.56 ± 0.72	20.65 ± 1.25	32.22 ± 1.29	17.98 ± 0.86	28.27 ± 0.81
7b	13.09 ± 1.44	22.46 ± 0.69	17.02 ± 0.53	29.41 ± 1.28	13.37 ± 0.40	23.93 ± 1.44
7c	27.67 ± 0.17	36.48 ± 1.95	31.38 ± 0.74	42.45 ± 1.55	25.74 ± 0.65	36.77 ± 0.87
7d	26.26 ± 1.46	35.22 ± 0.94	31.98 ± 1.17	43.76 ± 0.41	27.23 ± 0.79	35.82 ± 0.48
7e	25.48 ± 0.82	34.12 ± 1.63	30.59 ± 1.01	40.38 ± 1.03	26.67 ± 0.37	37.44 ± 1.42
7f	10.45 ± 2.20	19.58 ± 1.08	11.87 ± 0.49	22.79 ± 0.97	11.55 ± 1.02	21.72 ± 0.88
7g	11.28 ± 0.62	20.03 ± 1.34	13.76 ± 0.51	21.72 ± 0.45	11.23 ± 1.26	20.33 ± 0.53
7c$_a$	27.08 ± 0.45	36.05 ± 0.65	31.18 ± 0.44	42.26 ± 1.12	25.50 ± 0.38	36.70 ± 0.70
7d$_a$	26.14 ± 1.12	35.10 ± 0.51	31.90 ± 1.02	43.55 ± 0.56	27.12 ± 0.61	35.69 ± 0.31
7e$_a$	25.09 ± 0.49	34.03 ± 1.23	30.52 ± 1.55	40.20 ± 1.69	26.54 ± 0.20	37.23 ± 1.69
8a	26.22 ± 0.67	35.54 ± 0.90	30.34 ± 1.12	42.56 ± 1.40	26.78 ± 0.87	37.74 ± 0.56
8b	16.74 ± 0.28	25.40 ± 0.84	20.38 ± 1.09	32.65 ± 1.10	17.35 ± 0.49	28.54 ± 0.85
8c	10.52 ± 0.86	18.28 ± 1.12	12.22 ± 0.77	23.75 ± 0.83	10.38 ± 1.18	21.78 ± 0.58
8d	25.50 ± 0.34	34.12 ± 0.87	29.83 ± 1.45	41.53 ± 1.67	25.69 ± 0.43	36.12 ± 0.66
8e	13.66 ± 0.32	22.74 ± 1.53	17.60 ± 0.13	29.34 ± 0.65	13.41 ± 1.40	24.07 ± 0.85
8f	25.56 ± 0.46	34.67 ± 0.78	29.89 ± 1.22	41.79 ± 1.34	25.55 ± 0.98	36.23 ± 0.45
8g	9.44 ± 0.56	17.49 ± 0.72	14.34 ± 0.68	26.21 ± 0.54	11.06 ± 0.24	20.94 ± 1.03
8e$_a$	13.43 ± 0.67	22.62 ± 0.21	17.02 ± 1.74	29.19 ± 1.02	13.25 ± 0.83	23.98 ± 1.02
8f$_a$	25.23 ± 0.23	34.22 ± 0.69	29.65 ± 1.87	41.60 ± 1.77	25.18 ± 0.38	36.14 ± 0.69
8g$_a$	9.32 ± 0.87	17.36 ± 0.55	12.22 ± 0.51	24.52 ± 0.86	10.89 ± 0.48	19.83 ± 0.16
Control	–	–	–	–	–	–
Mebendazole	13.85 ± 0.64	22.90 ± 0.53	17.85 ± 1.03	29.64 ± 1.20	13.54 ± 0.45	24.05 ± 0.62

[a] Data are given as mean ± S.D. ($n = 3$).

at 1755–1740 cm^{-1} (C=O str. ester) and 1273–1262 cm^{-1} (C–O str. ester) in IR spectra and singlets at 170.4–168.7 ppm (for carbonyl carbon of $C(=O)OCH_3$) in ^{13}C NMR spectra of compounds **5b$_a$**–**8g$_a$**. All hydrolyzed peptide derivatives showed peaks at M − 17 and M − 45 in their mass spectra by loss of OH and COOH, respectively. Moreover, [$COOH^+$] fragment ion peak appeared at *m/z* value 45 in mass spectra of compounds **5b$_a$**–**8g$_a$** along with characteristic fragmentation pattern after and before the carbonyl moiety.

Comparison of antibacterial and antifungal screening data suggested that hydrolyzed peptide derivatives **5b$_a$**–**d$_a$**, **6e$_a$**–**g$_a$** and **8e$_a$**–**g$_a$** are slightly more potent antimicrobial agents than their corresponding methyl ester derivatives except compounds **7c$_a$**–**e$_a$** which are almost as potent as compounds **7c**–**e**. All peptide derivatives exhibited maximum activity against gram negative bacteria *P. aeruginosa*, *E. coli* and pathogenic fungi *C. albicans*, *A. niger* whereas *S. aureus* and *M. audouinii* are found to be least sensitive bacterial and fungal strains. Compounds **6d**, **6e$_a$**, **7d**, **7d$_a$**, **7e** and **7e$_a$** are most active which possessed 8–25% higher activity against *P. aeruginosa* and *C. albicans* in comparison to standard drugs at 10 μg mL^{-1} in DMF and DMSO, respectively. However, compounds **7a** and **8b** possessed antifungal activity against *A. niger*, **5b$_a$** and **6b** showed antibacterial activity against *P. aeruginosa*

Table 4
Cytotoxic activity data

Compound	Conc. ($\mu g\,mL^{-1}$)	DLA cells				EAC cells			
		Live cells counted	No. of dead cells	% Growth inhibition[a]	CTC_{50}[b] (μM)	Live cells counted	No. of dead cells	% Growth inhibition[a]	CTC_{50}[b] (μM)
5d$_a$	500	28	10	26.31		25	3	10.71	
	250	31	7	18.42		26	2	7.14	
	125	30	8	21.00	>883.39	26	2	7.14	>883.39
	62.5	34	4	10.52		27	1	3.57	
	31.25	33	5	13.15		27	1	3.57	
6d	500	6	32	84.21		0	28	100.0	
	250	12	26	68.42		0	28	100.0	
	125	18	20	52.61	114	0	28	100.0	84.34
	62.5	27	11	28.94		18	10	35.71	
	31.25	32	6	15.78		22	6	21.42	
6e$_a$	500	18	20	52.63		18	10	35.71	
	250	22	16	42.10		20	8	28.57	
	125	25	13	34.21	583.11	25	3	10.71	>664.89
	62.5	27	11	28.94		25	3	10.71	
	31.25	33	5	13.15		26	2	7.14	
7d$_a$	500	25	13	34.20		21	7	25.0	
	250	28	10	26.31		23	5	17.85	
	125	30	8	21.00	>1070.66	24	4	14.28	>1070.66
	62.5	31	7	18.42		26	2	7.14	
	31.25	35	3	7.89		26	2	7.14	
7e$_a$	500	13	25	65.78		20	8	28.7	
	250	18	20	52.63		22	6	21.42	
	125	20	18	47.36	322.47	25	3	10.71	>847.46
	62.5	25	13	34.21		26	2	7.14	
	31.25	31	7	18.42		27	1	3.57	
7f	500	22	16	42.10		25	3	10.71	
	250	27	11	28.94		26	2	7.14	
	125	28	10	26.31	>718.39	26	2	7.14	>718.39
	62.5	30	8	21.00		27	1	3.57	
	31.25	34	4	10.52		27	1	3.57	
7g	500	23	15	39.47		20	8	28.7	
	250	26	12	31.57		22	6	21.42	
	125	29	9	23.68	>697.35	25	3	10.71	>697.35
	62.5	32	6	15.78		26	2	7.14	
	31.25	36	2	5.26		27	1	3.57	
8c	500	24	14	36.84		22	6	21.42	
	250	26	12	31.57		24	4	14.28	
	125	30	8	21.00	>877.19	26	2	7.14	>877.19
	62.5	32	6	15.78		26	2	7.14	
	31.25	35	3	7.89		27	1	3.57	
8g	62.5	0	38	100.0		0	28	100.0	
	31.25	5	33	86.84		8	20	71.42	
	15.63	17	21	55.26	15.32	13	15	53.57	18.91
	7.81	21	17	44.73		18	10	35.71	
	3.91	28	10	26.32		26	2	7.14	
8g$_a$	62.5	0	38	100.0		0	28	100.0	
	31.25	0	38	100.0		2	26	92.85	
	15.63	7	31	81.58	6.15	7	21	75.0	12.00
	7.81	15	23	60.52		15	13	46.43	
	3.91	21	17	44.73		25	3	10.71	
Control	500–62.5	38	0	–		28	0	–	
	31.25	38	0	–		28	0	–	
	15.63	38	0	–	–	28	0	–	–
	7.81	38	0	–		28	0	–	
	3.91	38	0	–		28	0	–	

Table 4 (*continued*)

Compound	Conc. ($\mu g\,mL^{-1}$)	DLA cells				EAC cells			
		Live cells counted	No. of dead cells	% Growth inhibition[a]	CTC_{50}[b] (μM)	Live cells counted	No. of dead cells	% Growth inhibition[a]	CTC_{50}[b] (μM)
Standard (5-FU)	62.5	0	38	100.0		0	28	100.0	
	31.25	0	38	100.0		0	28	100.0	
	15.63	10	28	73.68	37.36	11	17	60.71	90.55
	7.81	13	25	65.79		19	9	32.14	
	3.91	22	16	42.11		23	5	17.86	

[a] % Growth inhibition $= 100 - [\{(cell_{total} - cell_{dead}) \times 100\}/cell_{total}]$.
[b] CTC_{50} = cytotoxic conc. inhibiting 50% of percentage growth.

and *E. coli,* **7b**, **7g**, **8c** and **8g$_a$** exhibited antifungal activity against pathogenic *C. albicans*, **6c** possessed antibacterial activity against *B. subtilis*, equal to reference drugs ciprofloxacin and griseofulvin, respectively.

All peptide derivatives **5a–8g** showed moderate to good anthelmintic activity at 2 mg mL^{-1} in Tween 80 (0.5%) and distilled water. Comparison of anthelmintic activity data revealed that hydrolyzed peptide derivatives **5b$_a$–8g$_a$** are slightly more active than their corresponding ester derivatives **5b–8g**. Compounds **7f**, **8c**, **8g** and **8g$_a$** are most active which possessed higher activity against *M. konkanensis*, *P. corethruses* and *Eudrilus* sp. in comparison to standard drugs and compounds **5d**, **5d$_a$**, **5f**, **6b**, **6e**, **6e$_a$**, **7b**, **7g** and **8e** showed anthelmintic activity comparable to that of reference compounds.

Cytotoxic activity data revealed that compound **8g$_a$** possessed higher cytotoxic activity with CTC_{50} values 6.15 and 12 μM (4.42 and 8.63 $\mu g\,mL^{-1}$, respectively), against DLA and EAC cell lines as compared to 5-fluorouracil (CTC_{50} value – 37.36 and 90.55 μM (4.86 and 11.78 $\mu g\,mL^{-1}$)) whereas compound **8g** exhibited cytotoxicity comparable to standard drug. Moreover, compound **6d** exhibited moderate cytotoxicity with CTC_{50} values 114 and 84.34 μM (94.63 and 70 $\mu g\,mL^{-1}$, respectively), against both cell lines.

Different steric and lipophilicity parameters for selected peptide derivatives exhibiting significant level of activity, were calculated which are needed to describe the intermolecular forces of drug receptor interaction as well as transport and distribution of drugs in a quantitative manner. These physicochemical parameters are standard constant values for newly synthesized compounds which would be helpful for further extension of the present work to SAR and molecular modeling aspects.

5. Conclusions

This study reports the successful synthesis of title compounds via coupling reaction in good yields. For peptide

Table 5
Calculated physicochemical parameters for peptide derivatives

Compound	Molar refractivity (cm^3)	Molar volume (cm^3)	Parachor (cm^3)	Index of refraction	Surface tension (dyne/cm)	Density (g/cm^3)	Polarizability ($10^{-24}\,cm^3$)	Partition coefficient ($\log P$)
5b	126.28 ± 0.5[a]	340.9 ± 7.0	937.3 ± 8.0	1.662 ± 0.05	57.1 ± 7.0	1.41 ± 0.1	50.06 ± 0.5	3.41 ± 0.77
5b$_a$	121.32 ± 0.5	316.5 ± 7.0	892.7 ± 8.0	1.692 ± 0.05	63.2 ± 7.0	1.47 ± 0.1	48.09 ± 0.5	3.08 ± 0.78
5d	160.97 ± 0.3	433.8 ± 3.0	1230.9 ± 4.0	1.664 ± 0.02	64.7 ± 3.0	1.338 ± 0.06	63.81 ± 0.5	4.38 ± 0.67
5d$_a$	156.13 ± 0.3	408.5 ± 3.0	1188.2 ± 4.0	1.689 ± 0.02	71.5 ± 3.0	1.387 ± 0.06	61.89 ± 0.5	3.96 ± 0.67
5f	198.59 ± 0.3	560.3 ± 3.0	1532.5 ± 4.0	1.626 ± 0.02	55.9 ± 3.0	1.263 ± 0.06	78.72 ± 0.5	5.63 ± 0.84
6b	162.69 ± 0.3	403.9 ± 3.0	1154.9 ± 4.0	1.738 ± 0.02	66.8 ± 3.0	1.778 ± 0.06	64.49 ± 0.5	6.91 ± 0.65
6c	132.05 ± 0.3	345.1 ± 3.0	973.2 ± 4.0	1.690 ± 0.02	63.1 ± 3.0	1.834 ± 0.06	52.35 ± 0.5	4.75 ± 0.66
6d	176.89 ± 0.5	435.6 ± 7.0	1240.9 ± 8.0	1.746 ± 0.05	65.8 ± 7.0	1.90 ± 0.1	70.12 ± 0.5	3.20 ± 0.93
6e	167.38 ± 0.3	430.1 ± 3.0	1250.2 ± 6.0	1.706 ± 0.02	71.3 ± 3.0	1.781 ± 0.06	66.35 ± 0.5	5.87 ± 0.79
6e$_a$	162.54 ± 0.3	404.7 ± 3.0	1206.8 ± 6.0	1.735 ± 0.02	79.0 ± 3.0	1.858 ± 0.06	64.43 ± 0.5	5.40 ± 0.79
7a	123.94 ± 0.5	313.0 ± 7.0	926.3 ± 8.0	1.722 ± 0.05	76.6 ± 7.0	1.64 ± 0.1	49.13 ± 0.5	3.45 ± 0.81
7b	135.65 ± 0.3	337.5 ± 3.0	998.9 ± 4.0	1.736 ± 0.02	76.7 ± 3.0	1.479 ± 0.06	53.77 ± 0.5	5.79 ± 0.56
7d$_a$	118.63 ± 0.3	306.0 ± 3.0	923.9 ± 6.0	1.702 ± 0.02	83.0 ± 3.0	1.527 ± 0.06	47.03 ± 0.5	2.21 ± 0.60
7e	155.16 ± 0.3	409.7 ± 3.0	1216.4 ± 6.0	1.681 ± 0.02	77.6 ± 3.0	1.475 ± 0.06	61.51 ± 0.5	5.14 ± 0.74
7e$_a$	150.31 ± 0.3	384.4 ± 3.0	1173.0 ± 6.0	1.710 ± 0.02	86.6 ± 3.0	1.536 ± 0.06	59.59 ± 0.5	4.68 ± 0.73
7f	184.58 ± 0.3	502.3 ± 3.0	1437.8 ± 4.0	1.656 ± 0.02	67.0 ± 3.0	1.386 ± 0.06	73.17 ± 0.5	5.57 ± 0.81
7g	184.58 ± 0.3	508.4 ± 3.0	1481.4 ± 6.0	1.646 ± 0.02	72.0 ± 3.0	1.411 ± 0.06	73.17 ± 0.5	4.73 ± 0.86
8b	144.68 ± 0.5	387.3 ± 7.0	1076.8 ± 8.0	1.670 ± 0.05	59.7 ± 7.0	1.46 ± 0.1	57.35 ± 0.5	3.56 ± 0.89
8c	153.50 ± 0.3	405.4 ± 3.0	1184.6 ± 4.0	1.681 ± 0.02	72.9 ± 3.0	1.407 ± 0.06	60.85 ± 0.5	3.30 ± 0.72
8e	200.09 ± 0.3	529.0 ± 3.0	1505.3 ± 4.0	1.680 ± 0.02	65.5 ± 3.0	1.354 ± 0.06	79.32 ± 0.5	6.61 ± 0.78
8g	199.03 ± 0.3	524.2 ± 3.0	1519.5 ± 4.0	1.684 ± 0.02	70.6 ± 3.0	1.399 ± 0.06	78.90 ± 0.5	3.88 ± 0.86
8g$_a$	194.19 ± 0.3	498.8 ± 3.0	1476.8 ± 4.0	1.706 ± 0.02	76.8 ± 3.0	1.442 ± 0.06	76.98 ± 0.5	3.46 ± 0.86

[a] Data are given as mean ± S.D. ($n = 3$).

coupling, method employing DCC/NMM in DMF solvent proved to be better than DCC/TEA method utilizing THF as solvent, providing 10% extra yields. DCC proved to be a good coupling agent both economically and yieldwise. Synthesized peptide derivatives showed moderate to good antimicrobial activity against all tested microbial strains except *S. aureus* and *M. audouinii*. Presence of iodine atoms in nucleus confers greater antibacterial activity whereas derivatives having nitro group in nucleus possessed more antifungal activity but nitro group in amino acid chain has not much effect on activity. Gram negative bacteria proved to be more sensitive in comparison to gram positive bacteria towards peptide derivatives. The results of anthelmintic studies indicated the good level of activity of synthetic peptide derivatives when compared to the standard drug, mebendazole. Greater anthelmintic activity was found in derivatives with histidine and tryptophan constituents in their amino acid chain. Derivatives bearing salicylic acid moiety in nucleus possessed better anthelmintic and antifungal activity in comparison to compounds having benzoic acid moiety. Hydrolyzed derivatives exhibited more antimicrobial and anthelmintic activity in comparison to their corresponding methyl ester derivatives. Among tested compounds, only **8g$_a$**, **8g** and **6d** possessed significant cytotoxicity against DLA and EAC cell lines in comparison to standard drug.

6. Experimental protocols

6.1. General chemistry

All the reactions requiring anhydrous conditions were conducted in flame dried apparatus. Melting points were determined by open capillary method and are uncorrected. L-Amino acids, di-*tert*-butylpyrocarbonate (Boc_2O), dicyclohexylcarbodiimide (DCC), trifluoroacetic acid (TFA), hydroxybenztriazole (HOBt), triethylamine (TEA) and *N*-methylmorpholine (NMM) were obtained from Spectrochem Limited (Mumbai, India). IR spectra were recorded on Shimadzu 8700 FTIR spectrophotometer (Shimadzu, Japan) using a thin film supported on KBr pellets or utilizing deuterated chloroform. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC NMR spectrometer (300 MHz), (Brucker, USA) using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. The mass spectra were recorded on JMS-DX 303 mass spectrometer (Jeol, Tokyo, Japan) operating at 70 eV by electron spray ionization technique (ESI MS)/fast atom bombardment technique (FAB MS). Optical rotation of synthesized peptides was measured on automatic polarimeter (Optics Tech, Ghaziabad, India) in a 2 dm tube at 25 °C using sodium lamp and methanol as solvent. Elemental analyses of all compounds were performed on Vario EL III elemental analyzer (Elementar, Germany). Purity of all synthesized compounds was checked by TLC on precoated silica gel G plates (Kieselgel 0.25 mm, 60G F_{254}, Merck, Germany) utilizing chloroform/methanol as developing solvent system in different ratios (9:1/8:2/7:3 v/v) and brown spots were detected on exposure to iodine vapours in a tightly closed chamber.

6.1.1. General procedure for the preparation of Boc-di/tri/tetrapeptide methyl esters (**2a–4d**)

Boc-di/tri/tetrapeptide methyl esters **2a–i**, **3a–g** and **4a–d** were prepared by coupling Boc-amino acids/dipeptides with the respective L-amino acid methyl ester hydrochlorides/dipeptide methyl esters using DCC, HOBt and NMM according to Bodanzsky and Bodanzsky procedure with suitable modifications. To remove the Boc group, Boc-di/tri/tetrapeptide methyl ester (0.01 mol) was dissolved in $CHCl_3$ (15 mL) and treated with trifluoroacetic acid (2.28 g). The resulting solution was stirred at RT for 1 h and washed with saturated $NaHCO_3$ solution (25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by crystallization from $CHCl_3$ and petroleum ether (b.p. 40–60 °C) to get pure di/tri/tetrapeptide methyl esters **2a′–i′**, **3a′–g′** and **4a′–d′** which were utilized directly for coupling with compounds **5–8**.

6.1.1.1. Compound ***3a***. Yield: 77%; $[\alpha]_D$ −35.0° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3125 (N–H str.), 3042 (Ar–H str.), 2996–2988 (C–H str., cyclic CH_2), 2826 (C–H str., OCH_3), 1750 (C=O str. ester), 1663, 1640 (C=O str. amide), 1567, 1425 (skeletal bands), 1462 (C–H def. CH_2), 1389, 1370 (C–H def. ^{t}butyl grp), 1270, 930, 770, 708, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (br s, 1H, NH, amide), 7.10 (t, 1H, $J = 6.2$ Hz, *p*-H, Phe), 6.97 (tt, 2H, $J = 7.2$, 4.4 Hz, *m*-H's, Phe), 6.85 (dd, 2H, $J = 8.8$, 4.1 Hz, *o*-H's, Phe), 5.07–5.02 (m, 1H, α-H, Phe), 4.26 (t, 1H, $J = 6.8$ Hz, α-H, Pro^2), 3.97 (t, 1H, $J = 6.85$ Hz, α-H, Pro^1), 3.56 (s, 3H, OCH_3), 3.53 (t, 2H, $J = 7.2$ Hz, δ-H's, Pro^2), 3.21 (t, 2H, $J = 7.15$ Hz, δ-H's, Pro^1), 3.02 (d, 2H, $J = 5.6$ Hz, β-H's, Phe), 2.69–2.61 (m, 4H, β-H's, Pro^1 and Pro^2), 1.96–1.87 (m, 4H, γ-H's, Pro^1 and Pro^2), 1.50 (s, 9H, ^{t}butyl grp); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.2 (C=O, *sec*. amide), 168.8 (C=O, ester), 166.7 (C=O, *tert*. amide), 156.3 (C=O, ^{t}Boc), 138.0 (γ-C, Phe), 129.2 (*o*-C's, Phe), 127.7 (*m*-C's, Phe), 125.1 (*p*-C, Phe), 80.4 (α-C, ^{t}Boc), 63.6, 57.3 (α-C's, Pro^1 and Pro^2), 54.1 (α-C, Phe), 50.5 (OCH_3), 47.0, 46.4 (δ-C's, Pro^2 and Pro^1), 38.8, 31.9 (β-C's, Phe and Pro^1), 29.4 (β-C's, ^{t}Boc), 27.0 (γ-C, Pro^1), 26.5 (β-C, Pro^2), 24.3 (γ-C, Pro^2); $C_{25}H_{35}N_3O_6$ (473): Calcd. C 63.41, H 7.45, N 8.87; Found: C 63.38, H 7.46, N 8.85.

6.1.1.2. Compound ***3a′***. Yield: 73%; $[\alpha]_D$ −14.2° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3498, 3395, 3128 (N–H str.), 3045 (Ar–H str.), 2997–2988 (C–H str., cyclic CH_2), 1752 (C=O str. ester), 1662, 1637 (C=O str. amide), 1565, 1425 (skeletal bands), 1460 (C–H def. CH_2), 1272 (C–O str. ester), 1155 (C–N str. *sec*. amine), 768, 709, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (br s, 1H, NH, amide), 7.11 (t, 1H, $J = 6.15$ Hz, *p*-H, Phe), 6.99 (tt, 2H, $J = 7.2$, 4.35 Hz, *m*-H's, Phe), 6.86 (dd, 2H, $J = 8.75$, 4.15 Hz, *o*-H's, Phe), 6.8 (br s, 1H, NH, Pro^1), 5.08–5.00 (m, 1H, α-H, Phe), 4.14 (t, 1H, $J = 6.85$ Hz, α-H, Pro^2), 3.58 (t, 1H, $J = 6.85$ Hz, α-H, Pro^1), 3.55 (s, 3H, OCH_3), 3.43 (t, 2H, $J = 7.15$ Hz, δ-H's, Pro^2), 2.98 (d, 2H, $J = 5.6$ Hz, β-H's, Phe), 2.75 (t, 2H, $J = 7.2$ Hz, δ-H's, Pro^1), 2.69–2.65 (m, 2H, β-H's, Pro^2), 1.95–1.84 (m,

4H, γ-H's, Pro^2 and β-H's, Pro^1), 1.78–1.70 (m, 2H, γ-H's, Pro^1); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.1 (C=O, *sec*. amide), 169.2 (C=O, ester), 166.4 (C=O, *tert*. amide), 138.0 (γ-C, Phe), 129.3 (*o*-C's, Phe), 127.9 (*m*-C's, Phe), 125.3 (*p*-C, Phe), 63.3, 57.8 (α-C's, Pro^1 and Pro^2), 54.6 (α-C, Phe), 50.6 (OCH_3), 47.4, 46.1 (δ-C's, Pro^2 and Pro^1), 38.8, 31.6 (β-C's, Phe and Pro^1), 25.2 (β-C, Pro^2), 26.5, 23.7 (γ-C's, Pro^1 and Pro^2); $C_{20}H_{27}N_3O_4$ (373): Calcd. C 64.32, H 7.29, N 11.25; Found: C 64.29, H 7.30, N 11.27.

6.1.1.3. Compound ***3b***. Yield: 81%; $[\alpha]_D$ −7.8° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3135, 3128 (N–H str.), 3370 (O–H str., Tyr), 3066, 3042 (Ar–H str.), 2960, 2925, 2919 (C–H str. CH_3 and CH_2), 1745 (C=O str. ester), 1638, 1627 (C=O str. amide), 1556, 1412 (skeletal bands), 1530 (NH def. amide), 1463 (C–H def. CH_2), 1392, 1368, 1271, 929, 828, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (br s, 1H, NH, amide), 7.11 (br s, 1H, NH, amide), 6.99–6.89 (m, 4H, *o*- and *m*-H's, Tyr), 6.62 (br s, 1H, NH, amide), 5.95 (br s, 1H, OH, Tyr), 4.58–4.52 (m, 1H, α-H, Tyr), 4.39–4.32 (m, 1H, α-H, Ala), 4.03 (d, 2H, $J = 5.15$ Hz, CH_2, Gly), 3.65 (s, 3H, OCH_3), 2.78 (d, 2H, $J = 5.45$ Hz, β-H's, Tyr), 1.59 (d, 3H, $J = 5.85$ Hz, β-H's, Ala), 1.54 (s, 9H, ^{t}butyl grp); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.8, 169.4 (C=O, amide), 168.2 (C=O, ester), 156.9 (C=O, ^{t}Boc), 152.7 (*p*-C, Tyr), 132.4 (γ-C, Tyr), 130.6 (*o*-C's, Tyr), 128.3 (*m*-C's, Tyr), 79.8 (α-C, ^{t}Boc), 53.6 (α-C, Ala), 52.1 (α-C, Tyr), 50.4 (OCH_3), 41.8 (CH_2, Gly), 37.3 (β-C, Tyr), 29.4 (β-C's, ^{t}Boc), 19.5 (β-C, Ala); $C_{20}H_{29}N_3O_7$ (423): Calcd. C 56.73, H 6.90, N 9.92; Found: C 56.69, H 6.94, N 9.90.

6.1.1.4. Compound ***3b′***. Yield: 76%; $[\alpha]_D$ −44.6° (*c* 0.9, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 8.28 (br s, 1H, NH, amide), 7.00–6.88 (m, 4H, *o*- and *m*-H's, Tyr), 6.50 (br s, 1H, NH, amide), 4.88–4.83 (m, 1H, α-H, Tyr), 4.02 (d, 2H, $J = 5.1$ Hz, CH_2, Gly), 3.63 (s, 3H, OCH_3), 3.55–3.49 (m, 1H, α-H, Ala), 2.97 (br s, 3H, NH_2 and OH), 2.76 (d, 2H, $J = 5.5$ Hz, β-H's, Tyr), 1.11 (d, 3H, $J = 5.9$ Hz, β-H's, Ala); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.8, 169.6 (C=O, amide), 168.5 (C=O, ester), 153.2 (*p*-C, Tyr), 132.2 (γ-C, Tyr), 130.4 (*o*-C's, Tyr), 126.6 (*m*-C's, Tyr), 53.2 (α-C, Ala), 52.6 (α-C, Tyr), 50.1 (OCH_3), 41.3 (CH_2, Gly), 37.6 (β-C, Tyr), 18.9 (β-C, Ala); $C_{15}H_{21}N_3O_5$ (323): Calcd. C 55.72, H 6.55, N 13.00; Found: C 55.75, H 6.52, N 12.97.

6.1.1.5. Compound ***3c***. Yield: 86%; $[\alpha]_D$ −9.3° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3129, 3118 (N–H str.), 3062 (Ar–H str.), 2995, 2992 (C–H str. cyclic CH_2), 2962, 2926 (C–H str. CH_3 and CH_2), 1748 (C=O str. ester), 1658, 1629 (C=O str. amide), 1554, 1420 (skeletal bands), 1390, 1369 (C–H def. ^{t}butyl grp), 1385, 1363 (C–H def. isopropyl grp), 1268, 931, 923, 766, 707, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (br s, 1H, NH, amide), 7.50 (tt, 2H, $J = 7.2$, 4.35 Hz, *m*-H's, Phe), 6.91 (t, 1H, $J = 6.15$ Hz, *p*-H, Phe), 6.84 (dd, 2H, $J = 8.8$, 4.15 Hz, *o*-H's, Phe), 6.57 (br s, 1H, NH, amide), 4.46–4.41 (m, 2H, α-H's, Phe and Val), 3.62 (t, 1H, $J = 6.85$ Hz, α-H, Pro), 3.63 (s, 3H, OCH_3), 3.15–2.92 (m, 4H, β-H's, Phe and δ-H's, Pro), 2.09–1.96 (m, 5H, β-, γ-H's, Pro and β-H, Val), 1.54 (s, 9H, ^{t}butyl grp), 1.04 (d, 6H, $J = 4.6$ Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.5 (C=O, *sec*. amide), 168.6 (C=O, ester), 165.8 (C=O, *tert*. amide), 152.4 (C=O, ^{t}Boc), 137.7 (γ-C, Phe), 132.3 (*o*-C's, Phe), 129.0 (*m*-C's, Phe), 128.8 (*p*-C, Phe), 79.9 (α-C, ^{t}Boc), 58.0 (α-C, Pro), 55.9 (α-C, Phe), 53.8 (α-C, Val), 53.1 (OCH_3), 45.6 (δ-C, Pro), 34.2 (β-C, Phe), 29.8 (β-C, Val), 29.2 (β-C's, ^{t}Boc), 28.7 (β-C, Pro), 24.9 (γ-C, Pro), 18.2 (γ-C's, Val); $C_{25}H_{37}N_3O_6$ (475): Calcd. C 63.14, H 7.84, N 8.84; Found: C 63.15, H 7.82, N 8.84.

6.1.1.6. Compound ***3c′***. Yield: 70%; $[\alpha]_D$ −16.9° (*c* 0.9, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (tt, 2H, $J = 7.15$, 4.4 Hz, *m*-H's, Phe), 6.96 (t, 1H, $J = 6.2$ Hz, *p*-H, Phe), 6.90 (br s, 1H, NH, amide), 6.72 (dd, 2H, $J = 8.75$, 4.15 Hz, *o*-H's, Phe), 4.31 (t, 1H, $J = 5.8$ Hz, α-H, Val), 3.61 (t, 1H, $J = 6.85$ Hz, α-H, Pro), 3.62 (s, 3H, OCH_3), 3.60–3.57 (m, 1H, α-H, Phe), 3.11 (t, 2H, $J = 7.15$ Hz, δ-H, Pro), 2.76 (d, 2H, $J = 5.65$ Hz, β-H's, Phe), 2.10–1.94 (m, 5H, β- and γ-H's, Pro and β-H, Val), 1.82 (2H, br s, NH_2), 1.05 (d, 6H, $J = 4.55$ Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.2 (C=O, *sec*. amide), 168.8 (C=O, ester), 165.4 (C=O, *tert*. amide), 138.2 (γ-C, Phe), 131.8 (*o*-C's, Phe), 129.7 (*m*-C's, Phe), 128.4 (*p*-C, Phe), 58.3 (α-C, Pro), 56.2 (α-C, Phe), 54.3 (α-C, Val), 53.5 (OCH_3), 45.6 (δ-C, Pro), 34.8 (β-C, Phe), 30.6 (β-C, Val), 28.7 (β-C, Pro), 24.5 (γ-C, Pro), 17.8 (γ-C's, Val); $C_{20}H_{29}N_3O_4$ (375): Calcd. C 63.98, H 7.78, N 11.19; Found: C 64.00, H 7.75, N 11.21.

6.1.1.7. Compound ***3d***. Yield: 82%; $[\alpha]_D$ +8.2° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 2997–2985 (C–H str., cyclic CH_2), 2826 (C–H str., OCH_3), 1750 (C=O str. ester), 1663, 1658 (C=O str. *tert*. amide), 1389, 1370 (C–H def. ^{t}butyl grp), 1271, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.35 (t, 1H, $J = 6.8$ Hz, α-H, Pro^2), 4.27–4.16 (m, 2H, α-H's, Pro^1 and Pro^3), 3.72 (t, 2H, $J = 7.2$ Hz, δ-H's, Pro^3), 3.62 (s, 3H, OCH_3), 3.53 (t, 2H, $J = 7.15$ Hz, δ-H's, Pro^2), 3.23 (t, 2H, $J = 7.2$ Hz, δ-H's, Pro^1), 2.70–2.55 (m, 4H, β-H's, Pro^1 and Pro^2), 2.07–1.88 (m, 8H, β- and γ-H's, Pro^3 and γ-H's, Pro^1 and Pro^2), 1.50 (s, 9H, ^{t}butyl grp); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.4, 168.3 (C=O, amide), 166.5 (C=O, ester), 157.2 (C=O, ^{t}Boc), 80.9 (α-C, ^{t}Boc), 62.7, 58.8, 55.2 (α-C's, Pro^{1-3}), 53.7 (OCH_3), 46.9, 45.7 (δ-C's, $Pro^{1,2}$), 41.1 (δ-C, Pro^3), 32.0, 29.7, 28.8 (β-C's, Pro^{1-3}), 27.4 (β-C's, ^{t}Boc), 24.5, 23.2, 22.7 (γ-C's, Pro^{1-3}); $C_{21}H_{33}N_3O_6$ (423): Calcd. C 59.56, H 7.85, N 9.92; Found: C 59.55, H 7.85, N 9.96.

6.1.1.8. Compound ***3d′***. Yield: 76%; $[\alpha]_D$ +16.7° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3502, 3398 (N–H str.), 2998–2985 (C–H str., cyclic CH_2), 2828 (C–H str., OCH_3), 1748 (C=O str. ester), 1660, 1657 (C=O str. *tert*. amide), 1270 (C–O str. ester), 1159 (C–N str. *sec*. amine) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.80 (br s, 1H, NH, amide), 4.28–4.18 (m, 2H, α-H's, Pro^2 and Pro^3), 3.73 (t, 2H,

$J = 7.1$ Hz, δ-H's, Pro[3]), 3.63 (s, 3H, OCH_3), 3.57 (t, 1H, $J = 6.85$ Hz, α-H, Pro[1]), 3.43 (t, 2H, $J = 7.15$ Hz, δ-H's, Pro[2]), 2.80–2.65 (m, 4H, δ-H's, Pro[1] and β-H's, Pro[2]), 2.07–1.84 (m, 8H, β-H's, Pro[1] and Pro[3] and γ-H's, Pro[2] and Pro[3]), 1.77–1.68 (m, 2H, γ-H's, Pro[1]); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.9, 168.2 (C=O, *tert*. amide), 166.8 (C=O, ester), 62.2, 59.1, 55.3 (α-C's, Pro[1–3]), 53.4 (OCH_3), 47.2, 45.5 (δ-C's, Pro[1,2]), 41.7 (δ-C, Pro[3]), 31.6, 29.5, 28.2 (β-C's, Pro[1–3]), 25.0, 23.4, 22.8 (γ-C's, Pro[1–3]); $C_{16}H_{25}N_3O_4$ (323): Calcd. C 59.43, H 7.79, N 12.99; Found: C 59.45, H 7.82, N 13.00.

6.1.1.9. Compound ***3e***. Yield: 85%; $[\alpha]_D$ −41.5° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3489, 3129 (N–H str.), 3052, 3040 (Ar–H str.), 2920, 2851 (C–H str. CH_2), 1750 (C=O str. ester), 1642, 1638 (C=O str. amide), 1568, 1425 (skeletal bands), 1392, 1370 (C–H def. ^{t}butyl grp), 1383, 1362 (C–H def. isopropyl grp), 1269, 930, 922, 884, 768, 707, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.12 (br s, 1H, NH, amide), 7.74 (d, 1H, $J = 8.0$ Hz, β-H, Imz), 7.60 (s, 1H, δ-H, Imz), 7.56 (br s, 1H, NH, amide), 7.16 (tt, 2H, $J = 7.2$, 4.3 Hz, *m*-H's, Phe), 6.99 (t, 1H, $J = 6.2$ Hz, *p*-H, Phe), 6.94 (br s, 1H, NH, amide), 6.81 (dd, 2H, $J = 8.8$, 4.15 Hz, *o*-H's, Phe), 6.44 (br s, 1H, NH, amide), 4.38–4.33 (m, 1H, α-H, Phe), 4.20–4.16 (m, 1H, α-H, Val), 4.14–4.09 (m, 1H, α-H, His), 3.55 (s, 3H, OCH_3), 3.03–2.86 (m, 4H, β-H's, Phe and His), 1.87–1.76 (m, 1H, β-H, Val), 1.54 (s, 9H, ^{t}butyl grp), 1.05 (d, 6H, $J = 4.55$ Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): δ 172.8 (C=O, ester), 171.1, 169.2 (C=O, amide), 156.7 (C=O, ^{t}Boc), 142.8 (C_2, Imz), 135.6 (γ-C, Phe), 130.4 (*o*-C's, Phe), 128.8 (*m*-C's, Phe), 127.2 (*p*-C, Phe), 124.8 (C_4, Imz), 115.5 (C_5, Imz), 79.7 (α-C, ^{t}Boc), 60.6, 53.9, 51.4 (α-C's, Val, His and Phe), 50.3 (OCH_3), 38.2, 29.6 (β-C, Phe and Val), 27.5 (β-C's, ^{t}Boc), 22.8 (β-C, His), 18.2 (γ-C's, Val); $C_{26}H_{37}N_5O_6$ (515): Calcd. C 60.57, H 7.23, N 13.58; Found: C 60.55, H 7.26, N 13.59.

6.1.1.10. Compound ***3e′***. Yield: 75%; $[\alpha]_D$ −32.8° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3504, 3395 (N–H str.), 3049, 3042 (Ar–H str.), 2922, 2850 (C–H str. CH_2), 1747 (C=O str. ester), 1640, 1637 (C=O str. amide), 1611 (N–H def. amine), 1565, 1428 (skeletal bands), 1381, 1363 (C–H def. isopropyl grp), 1268, 1233, 924, 887, 765, 704, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 1H, $J = 7.95$ Hz, β-H, Imz), 7.59 (s, 1H, δ-H, Imz), 7.55 (br s, 1H, NH, amide), 7.18 (tt, 2H, $J = 7.15$, 4.35 Hz, *m*-H's, Phe), 6.99 (t, 1H, $J = 6.15$ Hz, *p*-H, Phe), 6.93 (br s, 1H, NH, amide), 6.83 (dd, 2H, $J = 8.8$, 4.2 Hz, *o*-H's, Phe), 5.95 (br s, 3H, NH, Imz and NH_2, Val), 4.36–4.30 (m, 1H, α-H, Phe), 4.15–4.08 (m, 1H, α-H, His), 3.54 (s, 3H, OCH_3), 3.52–3.49 (m, 1H, α-H, Val), 3.05–2.90 (m, 4H, β-H's, Phe and His), 1.76–1.66 (m, 1H, β-H, Val), 1.00 (d, 6H, $J = 4.55$ Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.1 (C=O, ester), 170.9, 169.0 (C=O, amide), 143.1 (C_2, Imz), 135.3 (γ-C, Phe), 129.8 (*o*-C's, Phe), 128.3 (*m*-C's, Phe), 127.1 (*p*-C, Phe), 125.0 (C_4, Imz), 115.2 (C_5, Imz), 61.2, 53.0, 51.5 (α-C's, Val, His and Phe), 50.0 (OCH_3), 37.9, 30.1 (β-C, Phe and Val), 23.1 (β-C, His), 18.3 (γ-C's, Val); $C_{21}H_{29}N_5O_4$ (415): Calcd. C 60.71, H 7.03, N 16.86; Found: C 60.72, H 6.99, N 16.88.

6.1.1.11. Compound ***3f***. Yield: 86%; $[\alpha]_D$ −74.6° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3492, 3124 (N–H str.), 3358 (O–H str. Tyr), 3032, 3023 (Ar–H str.), 2966, 2925, 2922 (C–H str. CH_3 and CH_2), 1752 (C=O str. ester), 1642, 1635 (C=O str. amide), 1546, 1422 (skeletal bands), 1530, 1528 (NH def. amide), 1390, 1373 (C–H def. ^{t}butyl grp), 1271, 929, 828, 742, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.75 (br s, 1H, NH, amide), 7.45 (br s, 2H, NH, Indole and OH, Tyr), 7.27–7.09 (m, 4H, δ–η-H's, Indole), 6.90 (dd, 2H, $J = 8.5$, 5.2 Hz, *o*-H's, Tyr), 6.79 (dd, 2H, $J = 8.6$, 4.9 Hz, *m*-H's, Tyr), 6.76 (br s, 1H, NH, amide), 6.58 (br s, 1H, NH, amide), 6.23 (d, 1H, $J = 7.85$ Hz, β-H, Indole), 4.84–4.77 (m, 1H, α-H, Trp), 4.46–4.37 (m, 1H, α-H, Ala), 3.96–3.89 (m, 1H, α-H, Tyr), 3.55 (s, 3H, OCH_3), 3.15–2.96 (m, 4H, β-H's, Tyr and Trp), 1.54 (s, 9H, ^{t}butyl grp), 1.50 (d, 3H, $J = 5.85$ Hz, β-H's, Ala); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.8, 172.2 (C=O, amide), 168.8 (C=O, ester), 154.3 (*p*-C, Tyr), 152.3 (C=O, ^{t}Boc), 138.8 ($C_{2'}$, Indole), 129.7 (*o*-C's, Tyr), 128.5 (*m*-C's, Tyr), 126.1 ($C_{3'}$, Indole), 124.3 (C_2, Indole), 121.7, 120.4, 118.3 (C_{4-6}, Indole), 116.2 (γ-C, Tyr), 113.7 (C_7, Indole), 108.9 (C_3, Indole), 79.7 (α-C, ^{t}Boc), 65.3 (α-C, Trp), 55.4 (α-C, Tyr), 54.1 (α-C, Ala), 52.6 (OCH_3), 38.9 (β-C, Tyr), 28.8 (β-C, Trp), 27.2 (β-C's, ^{t}Boc), 18.9 (β-C, Ala); $C_{29}H_{36}N_4O_7$ (552): Calcd. C 63.03, H 6.57, N 10.14; Found: C 62.99, H 6.60, N 10.15.

6.1.1.12. Compound ***3f′***. Yield: 80%; $[\alpha]_D$ −115.7° (*c* 0.9, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H, NH, amide), 7.28–7.17 (m, 4H, δ–η-H's, Indole), 6.94 (d, 1H, $J = 7.8$ Hz, β-H, Indole), 6.90 (dd, 2H, $J = 8.55$, 5.2 Hz, *o*-H's, Tyr), 6.80 (br s, 1H, NH, amide), 6.78 (dd, 2H, $J = 8.6$, 4.95 Hz, *m*-H's, Tyr), 4.60 (br s, 4H, NH, Indole and NH_2, OH), 4.52–4.47 (m, 1H, α-H, Ala), 4.17–4.13 (m, 1H, α-H, Trp), 3.94 (t, 1H, $J = 8.0$ Hz, α-H, Tyr), 3.54 (s, 3H, OCH_3), 3.07–2.95 (m, 4H, β-H's, Tyr and Trp), 1.49 (d, 3H, $J = 5.9$ Hz, β-H's, Ala); ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.9, 172.8 (C=O, amide), 169.2 (C=O, ester), 154.1 (*p*-C, Tyr), 138.2 ($C_{2'}$, Indole), 129.8 (*o*-C's, Tyr), 127.8 (*m*-C's, Tyr), 126.8 ($C_{3'}$, Indole), 124.9 (C_2, Indole), 122.0, 119.8, 118.5 (C_{4-6}, Indole), 115.7 (γ-C, Tyr), 113.0 (C_7, Indole), 109.3 (C_3, Indole), 64.6 (α-C, Trp), 56.0 (α-C, Tyr), 54.6 (α-C, Ala), 52.9 (OCH_3), 38.5 (β-C, Tyr), 29.4 (β-C, Trp), 18.0 (β-C, Ala); $C_{24}H_{28}N_4O_5$ (452): Calcd. C 63.70, H 6.24, N 12.38; Found: C 63.68, H 6.25, N 12.40.

6.1.1.13. Compound ***3g***. Yield: 85%; $[\alpha]_D$ +17.0° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3127, 3123 (N–H str.), 2962, 2958, 2874 (C–H str. CH_3), 1750 (C=O str. ester), 1640, 1636 (C=O str. amide), 1533, 1525 (NH def. amide), 1393, 1372 (C–H def. ^{t}butyl grp), 1385, 1362, 1267, 932, 923 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (br s, 1H, NH, amide), 6.81 (br s, 1H, NH, amide), 6.53 (br s, 1H, NH, amide),

4.46 (t, 1H, $J = 5.75$ Hz, α-H, Val), 4.25–4.17 (m, 1H, α-H, Ala[1]), 3.60 (s, 3H, OCH_3), 3.54–3.43 (m, 1H, α-H, Ala[2]), 2.10–1.95 (m, 1H, β-H, Val), 1.58 (d, 3H, $J = 5.9$ Hz, β-H's, Ala[1]), 1.55 (s, 9H, ^{t}butyl grp), 1.30 (d, 3H, $J = 5.85$ Hz, β-H's, Ala[2]), 1.04 (d, 6H, $J = 4.6$ Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): δ 176.4 (C=O, amide), 173.2 (C=O, ester), 169.2 (C=O, amide), 152.5 (C=O, ^{t}Boc), 80.2 (α-C, ^{t}Boc), 60.5 (α-C, Ala[1]), 53.3 (α-C, Val), 50.2 (OCH_3), 47.5 (α-C, Ala[2]), 28.4 (β-C, Val), 26.8 (β-C's, ^{t}Boc), 21.4 (β-C, Ala[1]), 18.5 (γ-C's, Val), 17.6 (β-C, Ala[2]); $C_{17}H_{31}N_3O_6$ (373): Calcd. C 54.68, H 8.37, N 11.25; Found: C 54.71, H 8.37, N 11.21.

*6.1.1.14. Compound **3g′***. Yield: 81%; $[\alpha]_D$ +10.2° (*c* 0.9, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (br s, 1H, NH, amide), 6.82 (br s, 1H, NH, amide), 4.43 (t, 1H, $J = 6.85$ Hz, α-H, Val), 3.59 (s, 3H, OCH_3), 3.53–3.44 (m, 1H, α-H, Ala[2]), 3.29–3.22 (m, 1H, α-H, Ala[1]), 2.11–1.97 (m, 1H, β-H, Val), 1.49 (br s, 2H, NH_2, Ala[1]), 1.29 (d, 3H, $J = 5.9$ Hz, β-H's, Ala[2]), 1.13 (d, 3H, $J = 5.85$ Hz, β-H's, Ala[1]), 1.05 (d, 6H, $J = 4.55$ Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.0 (C=O, ester), 170.8, 169.1 (C=O, amide), 55.9 (α-C, Val), 52.4 (α-C, Ala[1]), 50.1 (OCH_3), 48.5 (α-C, Ala[2]), 28.4 (β-C, Val), 21.5 (β-C, Ala[2]), 18.4 (γ-C's, Val), 17.7 (β-C, Ala[1]); $C_{12}H_{23}N_3O_4$ (273): Calcd. C 52.73, H 8.48, N 15.37; Found: C 52.75, H 8.47, N 15.40.

*6.1.1.15. Compound **4a***. Yield: 78%; $[\alpha]_D$ −21.6° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3492, 3128, 3124 (N–H str.), 3064 (Ar–H str.), 2965–2938, 2866–2848 (C–H str. CH_3 and CH_2), 1752 (C=O str. ester), 1640, 1628 (C=O str. amide), 1542, 1426 (skeletal bands), 1525, 1520 (NH def. amide), 1395, 1371 (C–H def. ^{t}butyl grp), 1271, 930, 748, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.95 (br s, 1H, NH, Indole), 7.94 (br s, 1H, NH, amide), 7.25–7.02 (m, 4H, δ–η-H's, Indole), 7.09 (br s, 1H, NH, amide), 6.68 (br s, 1H, NH, amide), 6.57 (br s, 1H, NH, amide), 6.21 (d, 1H, $J = 7.8$ Hz, β-H, Indole), 4.84–4.80 (m, 1H, α-H, Trp), 4.21 (t, 1H, $J = 8.6$ Hz, α-H, Ile), 4.10 (d, 2H, $J = 5.1$ Hz, CH_2, Gly), 3.76 (t, 1H, $J = 4.1$ Hz, α-H, Ala), 3.60 (s, 3H, OCH_3), 3.43 (d, 2H, $J = 5.7$ Hz, β-H's, Trp), 2.07–1.95 (m, 1H, β-H, Ile), 1.68–1.57 (m, 2H, γ-H's, Ile), 1.55 (s, 9H, ^{t}butyl grp), 1.29 (d, 3H, $J = 5.85$ Hz, β-H's, Ala), 1.03 (d, 3H, $J = 5.9$ Hz, γ′-H's, Ile), 0.97 (t, 3H, $J = 7.7$ Hz, δ-H's, Ile); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.2 (C=O, ester), 171.8, 170.7, 165.9 (C=O, amide), 154.6 (C=O, ^{t}Boc), 138.0 ($C_{2'}$, Indole), 127.5 ($C_{3'}$, Indole), 124.2 (C_2, Indole), 121.7, 119.5, 117.3, 112.7 (C_{4-7}, Indole), 106.9 (C_3, Indole), 80.2 (α-C, ^{t}Boc), 65.4, 50.5 (α-C's, Trp and Ile), 49.8 (OCH_3), 47.6 (α-C, Ala), 40.7 (CH_2, Gly), 35.9, 30.0 (β-C's, Ile and Trp), 27.4 (β-C's, ^{t}Boc), 22.7 (γ-C, Ile), 17.7 (β-C, Ala), 13.2 (γ′-C, Ile), 10.9 (δ-C, Ile); $C_{28}H_{41}N_5O_7$ (559): Calcd. C 60.09, H 7.38, N 12.51; Found: C 60.10, H 7.41, N 12.50.

*6.1.1.16. Compound **4a′***. Yield: 72%; $[\alpha]_D$ −4.3° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3502–3496, 3403, 3129–3122 (N–H str.), 3068 (Ar–H str.), 2966–2938, 2865–2849 (C–H str. CH_3 and CH_2), 1747 (C=O str. ester), 1643, 1629 (C=O str. amide), 1615 (N–H def. amine), 1540, 1424 (skeletal bands), 1523 (NH def. amide), 1269, 1235, 1154, 745, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H, NH, amide), 7.32–7.06 (m, 4H, δ–η-H's, Indole), 7.03 (br s, 1H, NH, amide), 6.95 (d, 1H, $J = 5.65$ Hz, β-H, Indole), 6.69 (br s, 1H, NH, amide), 4.22 (t, 1H, $J = 8.55$ Hz, α-H, Ile), 4.18 (br s, 3H, NH_2, Trp and NH, Indole), 4.16–4.10 (m, 1H, α-H, Trp), 4.06 (d, 2H, $J = 5.15$ Hz, CH_2, Gly), 3.81–3.70 (m, 1H, α-H, Ala), 3.62 (s, 3H, OCH_3), 3.00 (d, 2H, $J = 5.65$ Hz, β-H's, Trp), 2.10–1.96 (m, 1H, β-H, Ile), 1.69–1.56 (m, 2H, γ-H's, Ile), 1.30 (d, 3H, $J = 5.85$ Hz, β-H's, Ala), 1.03–0.95 (m, 6H, γ′- and δ-H's, Ile); ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.7 (C=O, ester), 172.2, 169.9, 165.7 (C=O, amide), 138.5, 128.3 ($C_{2',3'}$, Indole), 124.6 (C_2, Indole), 122.2, 119.4, 118.1, 112.3 (C_{4-7}, Indole), 107.1 (C_3, Indole), 61.8, 50.3 (α-C's, Trp and Ile), 49.8 (OCH_3), 47.5 (α-C, Ala), 41.3 (CH_2, Gly), 36.2, 30.3 (β-C's, Ile and Trp), 23.0 (γ-C, Ile), 17.7 (β-C, Ala), 13.0 (γ′-C, Ile), 10.1 (δ-C, Ile); $C_{23}H_{33}N_5O_5$ (459): Calcd. C 60.11, H 7.24, N 15.24; Found: C 60.12, H 7.20, N 15.25.

*6.1.1.17. Compound **4b***. Yield: 88%; $[\alpha]_D$ −54.6° (*c* 0.9, MeOH); IR ($CHCl_3$): ν 3332 (O–H str.), 3133, 3129 (N–H str.), 2960, 2872, 2850 (C–H str. CH_3 and CH_2), 1753 (C=O str. ester), 1645, 1643 (C=O str. amide), 1535, 1532 (NH def. amide), 1457 (C–H def. CH_2), 1422, 1329 (O–H def.), 1391, 1370 (C–H def. ^{t}butyl grp), 1269, 1091, 929, 662 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.90 (br s, 1H, NH, amide), 7.72 (br s, 1H, NH, amide), 6.50 (br s, 1H, NH, amide), 6.24 (br s, 1H, NH, amide), 4.62–4.54 (m, 1H, β-H, Thr), 4.23 (t, 1H, $J = 8.6$ Hz, α-H, Ile), 3.81 (d, 2H, $J = 5.15$ Hz, CH_2, Gly[2]), 3.77 (t, 1H, $J = 3.9$ Hz, α-H, Thr), 3.62 (s, 3H, OCH_3), 3.51 (d, 2H, $J = 5.15$ Hz, CH_2, Gly[1]), 3.26 (br s, 1H, OH, Thr), 1.60–1.56 (m, 2H, γ-H's, Ile), 1.54 (s, 9H, ^{t}butyl grp), 1.53–1.49 (m, 1H, β-H, Ile), 1.31 (d, 3H, $J = 4.9$ Hz, γ-H's, Thr), 1.01–0.94 (m, 6H, γ′- and δ-H's, Ile); ^{13}C NMR (300 MHz, $CDCl_3$): δ 177.6, 174.5 (C=O, amide), 171.7 (C=O, ester), 165.8 (C=O, amide), 154.5 (C=O, ^{t}Boc), 79.5 (α-C, ^{t}Boc), 68.8 (β-C, Thr), 58.1, 55.3 (α-C's, Thr and Ile), 50.5 (OCH_3), 48.3, 44.2 (CH_2, Gly[2] and Gly[1]), 36.8 (β-C, Ile), 28.3 (β-C's, ^{t}Boc), 27.6, 20.0 (γ-C's, Ile and Thr), 13.7 (γ′-C, Ile), 9.9 (δ-C, Ile); $C_{20}H_{36}N_4O_8$ (460): Calcd. C 52.16, H 7.88, N 12.17; Found: C 52.20, H 7.90, N 12.15.

*6.1.1.18. Compound **4b′***. Yield: 70%; $[\alpha]_D$ −2.9° (*c* 0.9, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (br s, 1H, NH, amide), 7.46 (br s, 1H, NH, amide), 6.23 (br s, 1H, NH, amide), 4.66–4.54 (m, 2H, β-H, Thr and α-H, Ile), 3.82 (d, 2H, $J = 5.15$ Hz, CH_2, Gly[2]), 3.78 (t, 1H, $J = 3.95$ Hz, α-H, Thr), 3.63 (s, 3H, OCH_3), 3.61 (d, 2H, $J = 5.15$ Hz, CH_2, Gly[1]), 3.56 (br s, 3H, OH, Thr and NH_2), 1.59–1.35 (m, 3H, β- and γ-H's, Ile), 1.32 (d, 3H, $J = 4.95$ Hz, γ-H's, Thr), 1.00–0.93 (m, 6H, γ′- and δ-H's, Ile); ^{13}C NMR (300 MHz, $CDCl_3$): δ 176.9 (C=O, amide),

171.6 (C=O, ester), 169.9, 167.8 (C=O, amide), 68.5 (β-C, Thr), 58.0, 56.2 (α-C's, Thr and Ile), 51.2 (OCH_3), 46.8, 44.3 (CH_2, Gly^2 and Gly^1), 37.0 (β-C, Ile), 27.5, 19.8 (γ-C's, Ile and Thr), 13.5 (γ′-C, Ile), 9.8 (δ-C, Ile); $C_{15}H_{28}N_4O_6$ (360): Calcd. C 49.99, H 7.83, N 15.55; Found: C 50.00, H 7.85, N 15.56.

6.1.1.19. Compound ***4c***. Yield: 84%; $[\alpha]_D$ +43.0° (*c* 0.9, MeOH); IR ($CHCl_3$): *ν* 3480, 3124, 3120 (N–H str.), 3055 (Ar–H str.), 2997, 2994 (C–H str., cyclic CH_2), 2926, 2920, 2854 (C–H str. CH_2), 1749 (C=O str. ester), 1660, 1643 (C=O str. amide), 1562, 1424 (skeletal bands), 1536 (NH def. amide), 1395, 1371 (C–H def. ^{t}butyl grp), 1386, 1365 (C–H def. isopropyl grp), 1268, 929, 921, 886, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 9.10 (br s, 1H, NH, Imz), 8.95 (br s, 1H, NH, amide), 7.89 (d, 1H, $J = 7.95$ Hz, β-H, Imz), 7.15 (br s, 1H, NH, amide), 6.46 (br s, 1H, NH, amide), 6.44 (s, 1H, δ-H, Imz), 4.80–4.75 (m, 1H, α-H, His), 4.59–4.54 (m, 1H, α-H, Leu), 4.46 (t, 1H, $J = 6.9$ Hz, α-H, Pro), 4.02 (d, 2H, $J = 5.1$ Hz, CH_2, Gly), 3.69 (t, 2H, $J = 7.15$ Hz, δ-H's, Pro), 3.65 (s, 3H, OCH_3), 3.09 (d, 2H, $J = 5.9$ Hz, β-H's, His), 2.70–2.65 (m, 2H, β-H's, Pro), 1.96–1.88 (m, 2H, γ-H's, Pro), 1.82 (t, 2H, $J = 7.95$ Hz, β-H's, Leu), 1.54 (s, 9H, ^{t}butyl grp), 1.52–1.44 (m, 1H, γ-H, Leu), 0.98 (d, 6H, $J = 6.2$ Hz, δ-H's, Leu); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 172.5 (C=O, *tert*. amide), 171.2, 169.6 (C=O, *sec*. amide), 168.1 (C=O, ester), 154.6 (C=O, ^{t}Boc), 142.3, 120.2, 112.5 ($C_{2,4,5}$, Imz), 79.9 (α-C, ^{t}Boc), 65.7, 56.2 (α-C's, His and Pro), 52.4 (OCH_3), 49.3 (α-C, Leu), 47.2 (δ-C, Pro), 44.6 (β-C, Leu), 39.5 (CH_2, Gly), 28.5 (β-C's, ^{t}Boc), 26.5, 25.2 (β- and γ-C's, Pro), 23.9 (γ-C, Leu), 23.3 (β-C, His), 21.1 (δ-C's, Leu); $C_{25}H_{40}N_6O_7$ (536): Calcd. C 55.96, H 7.51, N 15.66; Found: C 55.99, H 7.52, N 15.65.

6.1.1.20. Compound ***4c′***. Yield: 72%; $[\alpha]_D$ +19.8° (*c* 0.9, MeOH); IR ($CHCl_3$): *ν* 3503, 3395, 3122 (N–H str.), 3058 (Ar–H str.), 2996, 2992 (C–H str., cyclic CH_2), 2925, 2920, 2855 (C–H str. CH_2), 1748 (C=O str. ester), 1662, 1642 (C=O str. amide), 1613 (N–H def. amine), 1560, 1424 (skeletal bands), 1534 (NH def. amide), 1384, 1362 (C–H def. isopropyl grp), 1272, 1232, 920, 885, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.98 (br s, 1H, NH, amide), 7.84 (d, 1H, $J = 7.95$ Hz, β-H, Imz), 7.50 (s, 1H, δ-H, Imz), 6.52 (br s, 1H, NH, amide), 4.84–4.69 (m, 1H, α-H, Leu), 4.55 (br s, 3H, NH, Imz and NH_2, His), 4.32 (t, 1H, $J = 6.85$ Hz, α-H, Pro), 4.16–4.11 (m, 1H, α-H, His), 4.03 (d, 2H, $J = 5.15$ Hz, CH_2, Gly), 3.63 (s, 3H, OCH_3), 3.57 (t, 2H, $J = 7.15$ Hz, δ-H's, Pro), 2.95 (d, 2H, $J = 5.85$ Hz, β-H's, His), 2.69–2.64 (m, 2H, β-H's, Pro), 1.97–1.87 (m, 2H, γ-H's, Pro), 1.74 (t, 2H, $J = 7.9$ Hz, β-H's, Leu), 1.51–1.40 (m, 1H, γ-H, Leu), 0.99 (d, 6H, $J = 6.15$ Hz, δ-H's, Leu); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 171.1, 170.8 (C=O, *sec*. amide), 170.3 (C=O, *tert*. amide), 168.3 (C=O, ester), 142.8, 121.7, 111.9 ($C_{2,4,5}$, Imz), 57.6, 54.7 (α-C's, Pro and His), 51.8 (OCH_3), 49.3 (α-C, Leu), 47.8 (δ-C, Pro), 44.1 (β-C, Leu), 40.6 (CH_2, Gly), 26.5, 26.0 (β-C's Pro and His), 24.2, 23.8 (γ-C's, Pro and Leu), 21.6 (δ-C's, Leu); $C_{20}H_{32}N_6O_5$ (436): Calcd. C 55.03, H 7.39, N 19.25; Found: C 55.01, H 7.40, N 19.25.

6.1.1.21. Compound ***4d***. Yield: 87%; $[\alpha]_D$ +1.2° (*c* 0.9, MeOH); IR ($CHCl_3$): *ν* 3490, 3486, 3125 (N–H str.), 3066, 3045 (Ar–H str.), 2928, 2925, 2850 (C–H str. CH_2), 2826 (C–H str, OCH_3), 1747 (C=O str. ester), 1633, 1628 (C=O str. amide), 1543, 1421 (skeletal bands), 1530, 1524 (NH def. amide), 1392, 1369 (C–H def. ^{t}butyl grp), 1270 (C–O str. ester), 928, 867, 738, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 9.05 (br s, 2H, NH's, Indole and Imz), 8.46 (br s, 1H, NH, amide), 8.26 (br s, 1H, NH, amide), 7.75 (d, 1H, $J = 7.95$ Hz, β-H, Imz), 7.60 (s, 1H, δ-H, Imz), 7.25 (d, 1H, $J = 7.85$ Hz, β-H, Indole), 7.22–7.08 (m, 4H, δ–η-H's, Indole), 6.32 (br s, 1H, NH, amide), 6.23 (br s, 1H, NH, amide), 4.70–4.63 (m, 1H, α-H, Trp), 4.16–4.10 (m, 1H, α-H, His), 3.82 (d, 2H, $J = 5.15$ Hz, CH_2, Gly^2), 3.72 (d, 2H, $J = 5.15$ Hz, CH_2, Gly^1), 3.54 (s, 3H, OCH_3), 3.21–3.09 (m, 4H, β-H's, Trp and His), 1.55 (s, 9H, ^{t}butyl grp); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 178.2 (C=O, amide), 172.3 (C=O, ester), 170.7 (C=O, amide), 168.8 (C=O, amide), 156.6 (C=O, ^{t}Boc), 142.3 (C_2, Imz), 136.1 ($C_{2'}$, Indole), 129.3 ($C_{3'}$, Indole), 126.8 (C_4, Imz), 122.6 (C_2, Indole), 120.8, 119.7, 118.8 (C_{4-6}, Indole), 114.5 (C_5, Imz), 113.1 (C_3, Indole), 110.9 (C_7, Indole), 79.5 (α-C, ^{t}Boc), 55.6 (α-C, Trp), 51.9 (α-C, His), 50.2 (OCH_3), 48.3 (CH_2, Gly^2), 43.2 (CH_2, Gly^1), 32.8 (β-C, Trp), 27.5 (β-C's, ^{t}Boc), 24.2 (β-C, His); $C_{27}H_{35}N_7O_7$ (569): Calcd. C 56.93, H 6.19, N 17.21; Found: C 56.95, H 6.17, N 17.20.

6.1.1.22. Compound ***4d′***. Yield: 76%; $[\alpha]_D$ +18.0° (*c* 0.9, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.34 (br s, 1H, NH, amide), 8.25 (br s, 1H, NH, amide), 7.74 (d, 1H, $J = 8.0$ Hz, β-H, Imz), 7.59 (s, 1H, δ-H, Imz), 7.26 (d, 1H, $J = 7.8$ Hz, β-H, Indole), 7.23–7.11 (m, 4H, δ–η-H's, Indole), 6.30 (br s, 1H, NH, amide), 4.79 (br s, 4H, NH's, Indole, Imz and NH_2), 4.75–4.71 (m, 1H, α-H, Trp), 4.17–4.12 (m, 1H, α-H, His), 3.81 (d, 2H, $J = 5.15$ Hz, CH_2, Gly^2), 3.62 (t, 2H, $J = 6.6$ Hz, CH_2, Gly^1), 3.55 (s, 3H, OCH_3), 3.20–3.11 (m, 4H, β-H's, Trp and His); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 178.0 (C=O, amide), 172.8 (C=O, ester), 170.0, 169.1 (C=O, amide), 141.8 (C_2, Imz), 136.6 ($C_{2'}$, Indole), 128.9 ($C_{3'}$, Indole), 127.0 (C_4, Imz), 122.8 (C_2, Indole), 121.2, 119.6, 119.0 (C_{4-6}, Indole), 114.7 (C_5, Imz), 111.3 (C_3, Indole), 110.0 (C_7, Indole), 51.8, 50.0 (α-C's, His and Trp), 49.6 (OCH_3), 48.0, 42.9 (CH_2, Gly^2 and Gly^1), 33.1, 23.7 (β-C's, Trp and His); $C_{22}H_{27}N_7O_5$ (469): Calcd. C 56.28, H 5.80, N 20.88; Found: C 56.25, H 5.76, N 20.90.

*6.1.2. General method for the synthesis of 4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-benzoic acid (**5**)/4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-3,5-diiodobenzoic acid (**6**)/2-hydroxy-5-(6-nitro-1H-benzo[d]imidazol-2-yl)-benzoic acid (**7**)/5-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-2-hydroxybenzoic acid (**8**)*

A mixture of PABA (6.9 g), dilute hydrochloric acid (15%, 30 mL) and water (45 mL) was heated to get a clear solution. After cooling to 0 °C, the solution was diazotized by the

addition of sodium nitrite solution (30%, 12 mL). To the filtrate of diazotized salt solution, 5,6-dimethylbenzimidazole (7.3 g) and aqueous cupric chloride solution (1.3 g in 5 mL water) were added with stirring followed by slow addition of water (25 mL), maintaining the temperature between 5 and 10 °C. Stirring was continued for 6 h and finally reaction mixture was kept overnight in the refrigerator. The separated solid was collected by filtration and washed with cold water. The crude product was recrystallized from acetone to get the title compound **6**. Similarly, reaction of diazotized 4-amino-3, 5-diiodobenzoic acid **1a** (19.4 g) with 5,6-dimethylbenzimidazole (7.3 g), 5-aminosalicylic acid (7.7 g) with 6-nitrobenzimidazole **1b** (8.2 g), 5-aminosalicylic acid (7.7 g) with 5, 6-dimethylbenzimidazole (7.3 g) in aqueous $CuCl_2$ afforded compounds **7**, **8** and **9**, repectively.

*6.1.2.1. Compound **5***. Yield: 83%; m.p. 152–153 °C; IR (KBr): ν 3480 (N–H str.), 3290–2508 (O–H str. COOH), 3062, 3055 (Ar–H str.), 2960, 2874 (C–H str. CH_3), 1692 (C=O str. COOH), 1554, 1423 (skeletal bands), 1407 (O–H def. COOH), 1372 (C–H def. CH_3), 873, 828 (C–H def. rings) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.84 (br s, 2H, NH, BzImz and OH, COOH), 8.40 (dd, 2H, $J = 8.95$, 6.7 Hz, *m*-H's, Ar–COOH), 8.06 (dd, 2H, $J = 8.9$, 6.55 Hz, *o*-H's, Ar –COOH), 7.29 (singlet overlapped over singlet (ss), 2H, δ- and η-H's, BzImz), 2.27 (ss, 6H, ε- and ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 168.4 (C=O, COOH), 152.1 (C_2, BzImz), 140.2 ($C_{2'}$, BzImz), 137.7 ($C_{3'}$, BzImz), 134.2 (C_5, BzImz), 132.4 (C_4, Ar–COOH), 131.8 (C_6, BzImz), 131.2 (*o*-C's, Ar–COOH), 130.5 (C_1, Ar–COOH), 127.6 (*m*-C's, Ar–COOH), 124.2 (C_4, BzImz), 115.8 (C_7, BzImz), 20.3 (5-CH_3, BzImz), 18.8 (6-CH_3, BzImz); $C_{16}H_{14}N_2O_2$ (266): Calcd. C 72.17, H 5.30, N 10.52; Found: C 72.19, H 5.33, N 10.50.

*6.1.2.2. Compound **6***. Yield: 78%; m.p. 179–180 °C; IR (KBr): ν 3483 (N–H str.), 3294–2511 (O–H str. COOH), 3064, 3059 (Ar–H str.), 2963, 2875 (C–H str. CH_3), 1693 (C=O str. COOH), 1553, 1421 (skeletal bands), 1405 (O–H def. COOH), 1369 (C–H def. CH_3), 875, 869 (C–H def. rings), 591 (C–I str.) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.85 (br s, 2H, NH, BzImz and OH, COOH), 8.12 (ss, 2H, *o*-H's, Ar–COOH), 7.25 (ss, 2H, δ- and η-H's, BzImz), 2.26 (ss, 6H, ε- and ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 168.5 (C=O, COOH), 152.4 (C_2, BzImz), 140.0 ($C_{2'}$, BzImz), 137.3 ($C_{3'}$, BzImz), 136.6 (*m*-C's, Ar–COOH), 133.9 (C_5, BzImz), 133.0 (C_4, Ar–COOH), 131.5 (C_6, BzImz), 130.8 (C_1, Ar–COOH), 123.7 (C_4, BzImz), 116.0 (C_7, BzImz), 109.5 (*o*-C's, Ar–COOH), 20.2 (5-CH_3, BzImz), 18.9 (6-CH_3, BzImz); $C_{16}H_{12}I_2N_2O_2$ (518): Calcd. C 37.09, H 2.33, N 5.41; Found: C 37.10, H 2.33, N 5.40.

*6.1.2.3. Compound **7***. Yield: 75%; m.p. 141–142 °C; IR (KBr): ν 3490 (N–H str.), 3365 (O–H str. Ar–OH), 3296–2502 (O–H str. COOH), 3065, 3028 (Ar–H str.), 1695 (C=O str. COOH), 1582, 1433 (skeletal bands), 1540, 1349 (NO_2 str.), 1409 (O–H def. COOH), 1198, 869, 834, 825, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.6 (br s, 3H, NH, BzImz and OH's, Ar(OH)COOH), 8.86 (s, 1H, ζ-H, Ar (OH)COOH), 8.80 (d, 1H, $J = 7.5$ Hz, δ-H, Ar(OH)COOH), 8.43 (s, 1H, η-H, BzImz), 8.02 (d, 1H, $J = 7.8$ Hz, ε-H, BzImz), 7.66 (d, 1H, $J = 7.6$ Hz, δ-H, BzImz), 6.80 (d, 1H, $J = 7.15$ Hz, γ-H, Ar(OH)COOH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.0 (C=O, COOH), 164.4 (C_2, Ar(OH)COOH), 152.6 (C_2, BzImz), 141.0 ($C_{2'}$, BzImz), 139.1 ($C_{3'}$, BzImz), 142.2 (C_6, BzImz), 135.0 (C_6, Ar(OH)COOH), 130.2 (C_4, Ar (OH)COOH), 122.2 (C_5, Ar(OH)COOH), 121.5 (C_5, BzImz), 117.3 (C_4, BzImz), 118.8 (C_3, Ar(OH)COOH), 111.5 (C_1, Ar (OH)COOH), 108.4 (C_7, BzImz); $C_{14}H_9N_3O_5$ (299): Calcd. C 56.19, H 3.03, N 14.04; Found: C 56.22, H 3.00, N 14.06.

*6.1.2.4. Compound **8***. Yield: 79%; m.p. 166–167 °C; IR (KBr): ν 3488 (N–H str.), 3362 (O–H str. Ar–OH), 3295–2502 (O–H str. COOH), 3066, 3025 (Ar–H str.), 2962, 2959, 2870 (C–H str. CH_3), 1693 (C=O str. COOH), 1580, 1433 (skeletal bands), 1408 (O–H def. COOH), 1196, 871, 823, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.5 (br s, 3H, NH, BzImz and OH's, Ar(OH)COOH), 8.87 (s, 1H, ζ-H, Ar(OH)-COOH), 8.81 (d, 1H, $J = 7.55$ Hz, δ-H, Ar(OH)COOH), 7.31 (ss, 2H, δ- and η-H's, BzImz), 6.81 (d, 1H, $J = 7.2$ Hz, γ-H, Ar(OH)COOH), 2.26 (ss, 6H, ε- and ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.4 (C=O, COOH), 164.5 (C_2, Ar(OH)COOH), 153.2 (C_2, BzImz), 140.1 ($C_{2'}$, BzImz), 138.5 ($C_{3'}$, BzImz), 135.6 (C_6, Ar(OH)COOH), 133.9, 131.5 ($C_{5,6}$, BzImz), 130.4 (C_4, Ar(OH)COOH), 127.2 (C_4, BzImz), 123.1 (C_5, Ar(OH)COOH), 119.2 (C_3, Ar(OH)COOH), 114.0 (C_7, BzImz), 111.3 (C_1, Ar(OH)COOH), 20.3 (5-CH_3, BzImz), 18.9 (6-CH_3, BzImz); $C_{16}H_{14}N_2O_3$ (282): Calcd. C 68.08, H 5.00, N 9.92; Found: C 68.05, H 4.96, N 9.90.

*6.1.3. General method for the synthesis of amino acid/peptide derivatives of 4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-benzoic acid (**5**)/4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-3,5-diiodobenzoic acid (**6**)*

Amino acid methyl ester hydrochloride/di/tri/tetrapeptide methyl ester (0.01 mol) was dissolved in THF (75 mL). To this, TEA (2.9 mL) was added at 0 °C and the reaction mixture was stirred for 15 min. Compound **5/6** (26.6/51.8 g, 0.01 mol) in THF (75 mL) and DCC (2.1 g) were added to the above mixture with stirring. After 36 h, the reaction mixture was filtered and the residue was washed with THF (30 mL). Then, filtrate was washed with 5% $NaHCO_3$ and saturated NaCl solutions (25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The crude product was recrystallized from a mixture of chloroform and *n*-hexane followed by cooling at 0 °C.

*6.1.3.1. Compound **5a***. $[\alpha]_D$ −77.0° (*c* 0.1, MeOH); IR (KBr): ν 3488 (N–H str.), 3065, 3052 (Ar–H str.), 2998, 2995 (C–H str, cyclic CH_2), 2962, 2872 (C–H str. CH_3), 1748 (C=O str. ester), 1660 (C=O str. *tert*. amide), 1558, 1425 (skeletal bands), 1269, 876, 832 (C–H def. rings) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.90 (br s, 1H, NH, BzImz), 8.40 (dd, 2H, $J = 9.0$, 6.75 Hz, *m*-H's, Ar–CO), 8.05 (dd, 2H, $J = 8.9$,

6.55 Hz, *o*-H's, Ar–CO), 7.32 (s, 1H, δ-H, BzImz), 7.29 (s, 1H, η-H, BzImz), 4.14 (t, 1H, $J = 6.85$ Hz, α-H, Pro), 3.68 (t, 2H, $J = 7.2$ Hz, δ-H, Pro), 3.62 (s, 3H, OCH_3), 2.27 (s, 3H, ε-CH_3, BzImz), 2.25 (s, 3H, ζ-CH_3, BzImz), 2.23–2.14 (m, 2H, γ-H's, Pro), 2.06–1.98 (m, 2H, β-H's, Pro); ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.6 (C=O, Ar–CO), 170.5 (C=O, ester), 152.5 (C_2, BzImz), 139.7 ($C_{2'}$, BzImz), 136.9 ($C_{3'}$, BzImz), 133.4 (C_1, Ar–CO), 132.9 (C_5, BzImz), 132.5 (C_4, Ar–CO), 132.0 (C_6, BzImz), 130.8 (*o*-C's, Ar–CO), 128.2 (*m*-C's, Ar–CO), 124.9 (C_4, BzImz), 116.1 (C_7, BzImz), 63.5 (α-C, Pro), 52.4 (OCH_3), 46.2 (δ-C, Pro), 28.0 (β-C, Pro), 25.8 (γ-C, Pro), 20.4 (5-CH_3, BzImz), 19.1 (6-CH_3, BzImz); MS (*m*/*z*, %): 379 (2.6), 378 (3.1), 377 (M^+, 5.8), 362 (7.5), 346 (16.2), 318 (9.9), 249 (21.5), 221 (100), 146 (30.5), 119 (10.3), 118 (8.9), 59 (18.6), 51 (10.8), 42 (10.7), 39 (9.3), 31 (12.5), 15 (5.2).

6.1.3.2. Compound ***5b***. $[\alpha]_D$ −59.5° (*c* 0.1, MeOH); IR (KBr): ν 3494, 3332, 3122 (N–H str.), 3068, 3049 (Ar–H str.), 2959, 2926, 2919 (C–H str. CH_3 and CH_2), 2825 (C–H str., OCH_3), 1752 (C=O str. ester), 1630 (C=O str. *sec*. amide), 1546, 1418 (skeletal bands), 1535 (NH def. amide), 1372 (NO_2 str.), 1269 (C–O str. ester), 1160 (C–N str. *sec*. amine), 875, 833, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (dd, 2H, $J = 8.9$, 6.75 Hz, *m*-H's, Ar–CO), 8.06 (dd, 2H, $J = 8.95$, 6.5 Hz, *o*-H's, Ar–CO), 7.52 (br s, 1H, NH, amide), 7.31 (s, 1H, δ-H, BzImz), 7.29 (s, 1H, η-H, BzImz), 7.20 (br s, 4H, NH's, BzImz and guanidino grp), 4.36 (q, 1H, $J = 9.4$ Hz, α-H, Arg), 3.84 (q, 2H, $J = 7.0$ Hz, δ-H's, Arg), 3.64 (s, 3H, OCH_3), 2.26 (s, 3H, ε-CH_3, BzImz), 2.24 (s, 3H, ζ-CH_3, BzImz), 2.03–1.60 (m, 4H, β- and γ-H's, Arg); ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.8 (C=O, ester), 167.4 (C=O, Ar–CO), 160.5 (C=NH, Arg), 152.9 (C_2, BzImz), 138.9 ($C_{2'}$, BzImz), 137.4 ($C_{3'}$, BzImz), 134.7 (C_1, Ar–CO), 133.5 (C_5, BzImz), 133.0 (C_4, Ar–CO), 130.8 (C_6, BzImz), 130.1 (*o*-C's, Ar–CO), 127.9 (*m*-C's, Ar–CO), 124.4 (C_4, BzImz), 115.0 (C_7, BzImz), 53.9 (α-C, Arg), 50.6 (OCH_3), 40.0 (δ-C, Arg), 27.9 (β-C, Arg), 24.3 (γ-C, Arg), 19.5 (5-CH_3, BzImz), 18.3 (6-CH_3, BzImz).

6.1.3.3. Compound ***5c***. $[\alpha]_D$ −9.7° (*c* 0.1, MeOH); IR (KBr): ν 3489, 3332, 3126 (N–H str.), 3069, 3036 (Ar–H str.), 2960, 2925, 2917 (C–H str. CH_3 and CH_2), 1746 (C=O str. ester), 1630, 1626 (C=O str. *sec*. amide), 1552, 1423 (skeletal bands), 1531 (NH def. amide), 1386, 1370 (C–H def. $CH(CH_3)_2$), 1270, 879, 835, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (br s, 1H, NH, BzImz), 8.28 (dd, 2H, $J = 8.9$, 6.75 Hz, *o*-H's, Ar–CO), 8.24 (dd, 2H, $J = 8.9$, 6.55 Hz, *m*-H's, Ar–CO), 7.75 (br s, 1H, NH, amide), 7.30 (s, 1H, δ-H, BzImz), 7.28 (s, 1H, η-H, BzImz), 6.52 (br s, 1H, NH, amide), 4.41 (q, 1H, $J = 6.7$ Hz, α-H, Leu), 4.02 (d, 2H, $J = 5.1$ Hz, CH_2, Gly), 3.64 (s, 3H, OCH_3), 2.27 (s, 3H, ε-CH_3, BzImz), 2.24 (s, 3H, ζ-CH_3, BzImz), 1.76–1.41 (m, 3H, β- and γ-H's, Leu), 1.02 (d, 6H, $J = 6.2$ Hz, δ-H's, Leu); ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.0 (C=O, amide), 168.1 (C=O, ester), 166.2 (C=O, Ar–CO), 153.1 (C_2, BzImz), 140.2 ($C_{2'}$, BzImz), 138.0 ($C_{3'}$, BzImz), 135.9 (C_1, Ar–CO), 133.7 (C_5, BzImz), 132.6 (C_6, BzImz), 132.4 (C_4, Ar–CO), 131.6 (*o*-C's, Ar–CO), 128.3 (*m*-C's, Ar–CO), 125.6 (C_4, BzImz), 114.0 (C_7, BzImz), 54.5 (α-C, Leu), 48.3 (OCH_3), 44.6 (β-C, Leu), 40.6 (CH_2, Gly), 25.2 (γ-C, Leu), 21.7 (δ-C's, Leu), 19.9 (5-CH_3, BzImz), 19.0 (6-CH_3, BzImz); MS (*m*/*z*, %): 451 (2.6), 450 (M^+, 8.2), 435 (7.8), 419 (15.5), 391 (100), 362 (20.2), 334 (14.8), 249 (10.2), 221 (27.1), 146 (21.4), 119 (10.2), 118 (8.8), 59 (19.2), 57 (18.4), 51 (9.8), 43 (15.5), 39 (6.3), 31 (8.6), 30 (10.7), 15 (8.3).

6.1.3.4. Compound ***5d***. $[\alpha]_D$ +15.6° (*c* 0.1, MeOH); IR (KBr): ν 3492, 3489, 3120 (N–H str.), 3373 (O–H str., Tyr), 3069, 3042, 3035 (Ar–H str.), 2958, 2919 (C–H str. CH_3 and CH_2), 1742 (C=O str. ester), 1633, 1625 (C=O str. amide), 1556, 1424, 1419 (skeletal bands), 1530, 1527 (NH def. amide), 1462 (C–H def. CH_2), 1272, 882, 879, 837, 831, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.38 (br s, 1H, NH, amide), 8.28–8.22 (m, 4H, *o*- and *m*-H's, Ar–CO), 7.98 (br s, 3H, NH's and OH), 7.65 (s, 1H, δ-H, Imz), 7.35 (d, 1H, $J = 7.95$ Hz, β-H, Imz), 7.31 (s, 1H, δ-H, BzImz), 7.28 (s, 1H, η-H, BzImz), 6.95 (br s, 1H, NH, amide), 6.90 (dd, 2H, $J = 8.55$, 5.25 Hz, *o*-H's, Tyr), 6.78 (dd, 2H, $J = 8.6$, 4.9 Hz, *m*-H's, Tyr), 5.01 (q, 1H, $J = 9.0$ Hz, α-H, His), 3.92 (q, 1H, $J = 7.9$ Hz, α-H, Tyr), 3.54 (s, 3H, OCH_3), 3.05–2.74 (m, 4H, β-H's, Tyr and His), 2.26 (s, 3H, ε-CH_3, BzImz), 2.24 (s, 3H, ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.8 (C=O, amide), 170.1 (C=O, ester), 166.3 (C=O, Ar–CO), 154.1 (C–OH, Tyr), 152.2 (C_2, BzImz), 141.7 (C_2, Imz), 139.6 ($C_{2'}$, BzImz), 137.3 ($C_{3'}$, BzImz), 136.4 (C_1, Ar–CO), 134.0 (C_5, BzImz), 132.5 (C_6, BzImz), 131.0 (C_4, Ar–CO), 132.7 (*o*-C's, Ar–CO), 128.9 (*o*-C's, Tyr), 128.5 (*m*-C's, Tyr), 128.0 (*m*-C's, Ar–CO), 126.0 (C_4, BzImz), 123.2 (C_4, Imz), 118.5 (γ-C, Tyr), 115.3 (C_5, Imz), 113.9 (C_7, BzImz), 59.8, 52.5 (α-C, His and Tyr), 51.0 (OCH_3), 38.8 (β-C, Tyr), 20.4 (5-CH_3, BzImz), 18.9 (6-CH_3, BzImz), 16.1 (β-C, His); MS (*m*/*z*, %): 558 (M^+, 4.8), 565 (19.3), 549 (8.7), 521 (22.4), 415 (8.4), 386 (34.8), 358 (12.4), 249 (46.7), 221 (100), 145 (29.3), 118 (12.2), 117 (8.9), 107 (11.5), 93 (19.5), 81 (13.3), 77 (4.6), 67 (9.4), 59 (18.1), 51 (8.2), 39 (6.7), 31 (10.5), 15 (6.8).

6.1.3.5. Compound ***5e***. $[\alpha]_D$ −7.3° (*c* 0.1, MeOH); IR (KBr): ν 3493, 3125 (N–H str.), 3064, 3045, 3033 (Ar–H str.), 2996, 2993, 2989 (C–H str. cyclic CH_2), 2963, 2958, 2919 (C–H str. CH_3 and CH_2), 1747 (C=O str. ester), 1668, 1660, 1626 (C=O str. *tert*. and *sec*. amide), 1554, 1548, 1420 (skeletal bands), 1528 (NH def. amide), 1268 (C–O str. ester), 877, 835, 768, 712, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (br s, 1H, NH, BzImz), 8.62 (br s, 1H, NH, amide), 8.25–8.13 (m, 4H, *o*- and *m*-H's, Ar–CO), 7.33 (s, 1H, δ-H, BzImz), 7.28 (s, 1H, η-H, BzImz), 7.11 (t, 1H, $J = 6.25$ Hz, *p*-H, Phe), 6.98 (tt, 2H, $J = 6.75$, 4.45 Hz, *m*-H's, Phe), 6.85 (dd, 2H, $J = 8.8$, 4.15 Hz, *o*-H's, Phe), 5.04 (q, 1H, $J = 5.5$ Hz, α-H, Phe), 4.45–4.39 (m, 2H, α-H's, Pro^1 and Pro^2), 3.68 (t, 2H, $J = 7.15$ Hz, δ-H's, Pro^2), 3.57 (t, 2H, $J = 7.2$ Hz, δ-H's, Pro^1), 3.53 (s, 3H, OCH_3), 3.02 (d, 2H, $J = 5.6$ Hz, β-H's, Phe), 2.70–2.63 (m, 4H, β-H's, Pro^1 and

Pro^2), 2.28 (s, 3H, ε-CH_3, BzImz), 2.26 (s, 3H, ζ-CH_3, BzImz), 2.02–1.87 (m, 4H, γ-H's, Pro^1 and Pro^2); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.0 (C=O, Ar–CO), 170.2 (C=O, *sec*. amide), 169.8 (C=O, ester), 164.6 (C=O, *tert*. amide), 153.0 (C_2, BzImz), 140.2 ($C_{2'}$, BzImz), 138.0 (γ-C, Phe), 136.7 ($C_{3'}$, BzImz), 135.2 (C_4, Ar–CO), 134.7 (C_1, Ar–CO), 133.9 (C_5, BzImz), 131.4 (C_6, BzImz), 132.3 (*o*-C's, Ar–CO), 129.0 (*o*-C's, Phe), 128.5 (*m*-C's, Phe), 127.6 (*m*-C's, Ar–CO), 126.3 (*p*-C, Phe), 124.1 (C_4, BzImz), 114.8 (C_7, BzImz), 59.2, 55.0, 53.7 (α-C's, Pro^1, Pro^2 and Phe), 50.6 (OCH_3), 47.3, 42.7 (δ-C's, Pro^1 and Pro^2), 38.0 (β-C, Phe), 33.4, 28.5 (β- and γ-C's, Pro^1), 25.4, 23.1 (β- and γ-C's, Pro^2), 20.1 (5-CH_3, BzImz), 19.2 (6-CH_3, BzImz).

6.1.3.6. Compound ***5f***. $[\alpha]_D$ −11.8° (*c* 0.1, MeOH); IR (KBr): ν 3495, 3488, 3127 (N–H str.), 3066, 3028 (Ar–H str.), 2964–2937, 2868–2849 (C–H str. CH_3 and CH_2), 1745 (C=O str. ester), 1638, 1625 (C=O str. *sec*. amide), 1549, 1544, 1425 (skeletal bands), 1526, 1522 (NH def. amide), 1270, 885, 832, 745, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.35 (br s, 1H, NH, amide), 8.92 (br s, 2H, NH's, BzImz and Indole), 8.29–8.23 (m, 4H, *o*- and *m*-H's, Ar–CO), 8.22 (br s, 1H, NH, amide), 7.31 (s, 1H, δ-H, BzImz), 7.29 (s, 1H, η-H, BzImz), 7.25 (d, 1H, $J = 7.85$ Hz, β-H, Indole), 7.23–7.10 (m, 4H, δ–η-H's, Indole), 7.07 (br s, 1H, NH, amide), 6.68 (br s, 1H, NH, amide), 4.75–4.68 (m, 1H, α-H, Trp), 4.08 (t, 1H, $J = 8.6$ Hz, α-H, Ile), 3.83 (d, 2H, $J = 5.15$ Hz, CH_2, Gly), 3.81–3.72 (m, 1H, α-H, Ala), 3.59 (s, 3H, OCH_3), 3.20 (d, 2H, $J = 5.65$ Hz, β-H's, Trp), 2.27 (s, 3H, ε-CH_3, BzImz), 2.26 (s, 3H, ζ-CH_3, BzImz), 1.57–1.32 (m, 3H, β- and γ-H's, Ile), 1.28 (d, 3H, $J = 5.85$ Hz, β-H's, Ala), 1.01–0.94 (m, 6H, γ′- and δ-H's, Ile); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.1 (C=O, ester), 169.8 (C=O, amide), 167.4 (C=O, Ar–CO), 165.9 (C=O, amide), 163.6 (C=O, amide), 152.7 (C_2, BzImz), 139.5 ($C_{2'}$, BzImz), 137.2 ($C_{3'}$, BzImz), 136.4 ($C_{2'}$, Indole), 134.8 (C_4, Ar–CO), 133.2 (C_5, BzImz), 131.3 (C_6, BzImz), 129.4 (*m*-C's, Ar–CO), 129.1 (C_1, Ar–CO), 127.2 (*o*-C's, Ar–CO), 126.1 ($C_{3'}$, Indole), 124.2 (C_4, BzImz), 122.5 (C_2, Indole), 120.6, 119.2, 118.3 (C_{4-6}, Indole), 114.8 (C_7, BzImz), 111.9 (C_3, Indole), 109.6 (C_7, Indole), 59.1 (α-C, Trp), 52.5 (α-C, Ile), 49.2 (OCH_3), 47.5 (α-C, Ala), 40.6 (CH_2, Gly), 34.5, 26.4 (β- and γ-C's, Ile), 22.5 (β-C, Trp), 20.2, 19.1 (5,6-CH_3, BzImz), 17.7 (β-C, Ala), 14.3 (γ′-C, Ile), 9.7 (δ-C, Ile); MS (*m*/*z*, %): 709 (4.2), 708 (3.2), 707 (M^+, 6.2), 692 (11.8), 676 (19.5), 605 (15.5), 577 (9.2), 492 (28.4), 464 (100), 435 (19.2), 407 (7.3), 249 (11.6), 221 (30.2), 146 (22.5), 130 (9.5), 119 (11.8), 118 (9.4), 116 (7.7), 59 (20.2), 51 (7.9), 43 (15.1), 39 (5.5), 31 (9.6), 30 (12.3), 29 (4.8), 15 (8.2).

6.1.3.7. Compound ***6a***. $[\alpha]_D$ −38.5° (*c* 0.1, MeOH); IR (KBr): ν 3482, 3479, 3125 (N–H str.), 3069, 3062 (Ar–H str.), 2955, 2923 (C–H str. CH_3 and CH_2), 1745 (C=O str. ester), 1642 (C=O str. amide), 1559, 1422, 1416 (skeletal bands), 1545 (NH def. amide), 1466 (C–H def. CH_2), 1270 (C–O str. ester), 882, 878, 872 (C–H def. ring), 588 (C–I str.) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (br s, 2H, NH's, BzImz and Imz), 8.39 (ss, 2H, *o*-H's, Ar–CO), 7.92 (br s, 1H, NH, amide), 7.75 (d, 1H, $J = 8.0$ Hz, β-H, Imz), 7.59 (s, 1H, δ-H, Imz), 7.26 (ss, 2H, δ- and η-H, BzImz), 4.84 (q, 1H, $J = 9.0$ Hz, α-H, His), 3.54 (s, 3H, OCH_3), 2.99 (d, 2H, $J = 5.9$ Hz, β-H's, His), 2.26 (ss, 6H, ε- and ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.3 (C=O, ester), 170.5 (C=O, Ar–CO), 156.4 (C_2, BzImz), 145.8 (C_1, Ar–CO), 141.9 (C_2, Imz), 139.2 ($C_{2'}$, BzImz), 136.4 (*m*-C's, Ar–CO), 135.0 (C_4, Ar–CO), 134.3 ($C_{3'}$, BzImz), 133.5 (C_5, BzImz), 132.2 (C_6, BzImz), 126.3 (C_4, Imz), 122.6 (C_4, BzImz), 114.5 (C_5, Imz), 111.7 (C_7, BzImz), 103.5 (*o*-C's, Ar–CO), 52.2 (α-C, His), 49.6 (OCH_3), 21.2 (β-C, His), 20.4 (5-CH_3, BzImz), 19.0 (6-CH_3, BzImz); MS (*m*/*z*, %): 670 (2.2), 669 (M^+, 6.2), 654 (10.6), 638 (19.2), 610 (8.6), 501 (100), 473 (25.8), 329 (4.8), 203 (6.2), 146 (22.3), 127 (5.5), 119 (10.8), 118 (9.4), 81 (12.5), 67 (9.2), 59 (16.5), 31 (12.8), 30 (8.3), 15 (5.2).

6.1.3.8. Compound ***6b***. $[\alpha]_D$ −20.5° (*c* 0.1, MeOH); IR (KBr): ν 3479, 3475, 3122 (N–H str.), 3066, 3059, 3031 (Ar–H str.), 2957, 2926 (C–H str. CH_3 and CH_2), 2829 (C–H str. OCH_3), 1742 (C=O str. ester), 1640 (C=O str. amide), 1558, 1551, 1425, 1419 (skeletal bands), 1539 (NH def. amide), 1464 (C–H def. CH_2), 1267, 885, 876, 770, 705, 593 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.94 (br s, 2H, NH's, BzImz and Imz), 8.37 (ss, 2H, *o*-H's, Ar–CO), 7.93 (br s, 1H, NH, amide), 7.51 (d, 1H, $J = 7.8$ Hz, β-H, Indole), 7.26 (ss, 2H, δ- and η-H, BzImz), 7.16–7.02 (m, 4H, δ–η-H's, Indole), 4.95–4.87 (m, 1H, α-H, Trp), 3.55 (s, 3H, OCH_3), 3.26 (d, 2H, $J = 5.7$ Hz, β-H's, Trp), 2.26 (ss, 6H, ε- and ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.8 (C=O, ester), 168.4 (C=O, Ar–CO), 156.3 (C_2, BzImz), 144.7 (C_4, Ar–CO), 139.6 ($C_{2'}$, BzImz), 136.5 (*o*-C's, Ar–CO), 135.4 ($C_{2'}$, Indole), 134.7 (C_1, Ar–CO), 134.1 ($C_{3'}$, BzImz), 133.5 (C_5, BzImz), 132.4 (C_6, BzImz), 128.2 ($C_{3'}$, Indole), 122.8 (C_2, Indole), 121.9 (C_4, BzImz), 119.8, 118.9, 118.1, 114.7 (C_{3-6}, Indole), 112.7 (C_7, BzImz), 110.2 (C_7, Indole), 104.5 (*m*-C's, Ar–CO), 55.6 (α-C, Trp), 49.3 (OCH_3), 19.7, 19.2 (5,6-CH_3, BzImz), 16.8 (β-C, Trp).

6.1.3.9. Compound ***6c***. $[\alpha]_D$ −96.4° (*c* 0.1, MeOH); IR (KBr): ν 3480, 3128 (N–H str.), 3065, 3030 (Ar–H str.), 2957, 2870 (C–H str. CH_3), 1740 (C=O str. ester), 1641 (C=O str. amide), 1562, 1420, 1418 (skeletal bands), 1538 (NH def. amide), 1422, 1329 (O–H def.), 1269, 1093, 883, 875, 660, 602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (ss, 2H, *o*-H's, Ar–CO), 7.47 (br s, 1H, NH, amide), 7.26 (ss, 2H, δ- and η-H, BzImz), 6.10 (br s, 2H, NH, BzImz and OH, Thr), 4.62–4.53 (m, 1H, β-H, Thr), 4.49 (t, 1H, $J = 3.95$ Hz, α-H, Thr), 3.62 (s, 3H, OCH_3), 2.28 (ss, 6H, ε- and ζ-CH_3, BzImz), 1.34 (d, 3H, $J = 4.9$ Hz, γ-H's, Thr); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.6 (C=O, ester), 168.7 (C=O, Ar–CO), 156.4 (C_2, BzImz), 143.8 (C_1, Ar–CO), 140.0 ($C_{2'}$, BzImz), 138.5 (*m*-C's, Ar–CO), 137.2 (C_4, Ar–CO), 135.0 ($C_{3'}$, BzImz), 133.9 (C_5, BzImz), 132.4 (C_6, BzImz), 122.5 (C_4, BzImz),

112.7 (C_7, BzImz), 104.2 (*o*-C's, Ar–CO), 68.4 (β-C, Thr), 57.9 (α-C, Thr), 52.1 (OCH_3), 20.2 (γ-C, Thr), 19.7 (5-CH_3, BzImz), 19.1 (6-CH_3, BzImz); MS (*m/z*, %): 635 (2.1), 634 (3.5), 633 (M^+, 4.6), 618 (11.5), 602 (18.9), 574 (12.6), 501 (25.1), 473 (100), 329 (5.9), 203 (6.7), 146 (20.2), 127 (8.2), 119 (6.8), 118 (12.4), 59 (14.6), 45 (7.2), 31 (11.9), 17 (1.4), 15 (5.5).

6.1.3.10. Compound ***6d***. $[\alpha]_D$ +26.5° (*c* 0.1, MeOH); IR (KBr): *ν* 3490, 3125 (N–H str.), 3069, 3053 (Ar–H str.), 2997, 2992 (C–H str. cyclic CH_2), 2960, 2925, 2917 (C–H str. CH_3 and CH_2), 1750 (C=O str. ester), 1659, 1623 (C=O str. *tert*. and *sec*. amide), 1548, 1420 (skeletal bands), 1533 (NH def. amide), 1370 (NO_2 str.), 1268, 1159, 884, 873, 698, 596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.62 (br s, 1H, NH, amide), 8.44 (ss, 2H, *o*-H's, Ar–CO), 7.26 (ss, 2H, δ- and η-H's, BzImz), 7.22 (br s, 4H, NH's, guanidino group and BzImz), 4.80–4.75 (m, 1H, α-H, Arg), 4.31–4.28 (m, 1H, α-H, Pro), 3.87–3.82 (m, 2H, δ-H's, Arg), 3.65 (s, 3H, OCH_3), 3.45–3.41 (m, 2H, δ-H's, Pro), 2.69–2.64 (m, 2H, β-H's, Pro), 2.27 (s, 3H, ε-CH_3, BzImz), 2.26 (s, 3H, ζ-CH_3, BzImz), 2.02–1.60 (m, 6H, β- and γ-H's, Arg and γ-H's, Pro); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 170.4 (C=O, ester), 169.7 (C=O, amide), 165.6 (C=O, Ar–CO), 160.2 (C=NH), 155.4 (C_2, BzImz), 143.5 (C_4, Ar–CO), 139.2 (*o*-C's, Ar–CO), 136.6 ($C_{2'}$, BzImz), 134.5 (C_1, Ar–CO), 134.1 ($C_{3'}$, BzImz), 133.8 (C_5, BzImz), 130.2 (C_6, BzImz), 122.7 (C_4, BzImz), 113.7 (C_7, BzImz), 104.3 (*m*-C's, Ar–CO), 58.2 (α-C, Pro), 51.7 (OCH_3), 48.4 (α-C, Arg), 43.5, 40.4 (δ-C's, Pro and Arg), 29.8, 27.7 (β-C's, Pro and Arg), 24.2, 22.3 (γ-C's, Arg and Pro), 19.3, 18.9 (5,6-CH_3, BzImz); MS (*m/z*, %): 830 (M^+, 6.8), 815 (11.2), 799 (24.4), 771 (14.8), 598 (100), 571 (14.7), 501 (19.6), 473 (29.4), 329 (8.9), 203 (6.2), 146 (16.2), 127 (6.6), 119 (6.9), 118 (11.3), 59 (14.2), 46 (3.7), 42 (5.5), 31 (10.2), 30 (4.9), 15 (3.7).

6.1.3.11. Compound ***6e***. $[\alpha]_D$ +6.0° (*c* 0.1, MeOH); IR (KBr): *ν* 3479, 3475, 3122 (N–H str.), 3078, 3055 (Ar–H str.), 2996, 2990 (C–H str. cyclic CH_2), 2957, 2922 (C–H str. CH_3 and CH_2), 1744 (C=O str. ester), 1655, 1626 (C=O str. amide), 1557, 1420, 1414 (skeletal bands), 1463 (C–H def. CH_2), 1271, 886, 876, 870, 595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.97 (br s, 2H, NH's, BzImz and Imz), 8.86 (br s, 1H, NH, amide), 8.52 (ss, 2H, *o*-H's, Ar–CO), 7.68 (d, 1H, $J = 7.95$ Hz, β-H, Imz), 7.50 (s, 1H, δ-H, Imz), 7.25 (ss, 2H, δ- and η-H, BzImz), 4.87 (q, 1H, $J = 9.0$ Hz, α-H, His), 3.92 (t, 1H, $J = 6.85$ Hz, α-H, Pro), 3.62 (s, 3H, OCH_3), 3.39 (t, 2H, $J = 7.2$ Hz, δ-H's, Pro), 2.95 (d, 2H, $J = 5.85$ Hz, β-H's, His), 2.28 (ss, 6H, ε- and ζ-CH_3, BzImz), 2.07–1.95 (m, 4H, β- and γ-H's, Pro); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 173.7 (C=O, ester), 169.0 (C=O, Ar–CO), 164.3 (C=O, *tert*. amide), 155.7 (C_2, BzImz), 143.2 (C_1, Ar–CO), 140.4 (C_2, Imz), 139.0 ($C_{2'}$, BzImz), 136.4 (*m*-C's, Ar–CO), 135.6 ($C_{3'}$, BzImz), 134.2 (C_4, Ar–CO), 133.9 (C_5, BzImz), 132.7 (C_6, BzImz), 129.0 (C_4, Imz), 121.9 (C_4, BzImz), 117.2 (C_5, Imz), 111.8 (C_7, BzImz), 103.5 (*o*-C's, Ar–CO), 58.9 (α-C, Pro), 56.7 (α-C, His), 53.6 (OCH_3), 45.5 (δ-C, Pro), 29.6 (β-C, Pro), 24.8 (γ-C, Pro), 19.9, 19.2 (5,6-CH_3, BzImz), 16.9 (β-C, His).

6.1.3.12. Compound ***6f***. $[\alpha]_D$ −76.8° (*c* 0.1, MeOH); IR (KBr): *ν* 3490, 3130 (N–H str.), 3372 (O–H str., Tyr), 3065, 3045, 3033 (Ar–H str.), 2962, 2955, 2917 (C–H str. CH_3 and CH_2), 1748 (C=O str. ester), 1631, 1622 (C=O str. amide), 1558, 1425, 1417 (skeletal bands), 1532, 1527 (NH def. amide), 1465 (C–H def. CH_2), 1268, 881, 872, 825, 690, 590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.96 (br s, 1H, NH, amide), 9.32 (br s, 1H, NH, amide), 8.45 (ss, 2H, *o*-H's, Ar–CO), 7.42 (br s, 2H, NH, BzImz and OH, Tyr), 7.26 (ss, 2H, δ- and η-H, BzImz), 7.12 (br s, 1H, NH, amide), 7.01–6.88 (m, 4H, *o*- and *m*-H's, Tyr), 4.33 (q, 1H, $J = 8.0$ Hz, α-H, Tyr), 4.28–4.23 (m, 1H, α-H, Ala), 4.03 (d, 2H, $J = 5.15$ Hz, CH_2, Gly), 3.65 (s, 3H, OCH_3), 2.88 (d, 2H, $J = 5.5$ Hz, β-H's, Tyr), 2.27 (ss, 6H, ε- and ζ-CH_3, BzImz), 1.51 (d, 3H, $J = 5.9$ Hz, β-H's, Ala); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 170.1 (C=O, ester), 168.5 (C=O, amide), 166.8 (C=O, amide), 163.9 (C=O, Ar–CO), 156.3 (C_2, BzImz), 153.5 (C–OH, Tyr), 144.7 (C_4, Ar–CO), 138.8 (*o*-C's, Ar–CO), 137.5 ($C_{2'}$, BzImz), 136.1 (C_1, Ar–CO), 134.9 ($C_{3'}$, BzImz), 133.6 (C_5, BzImz), 132.4 (C_6, BzImz), 130.6 (*o*-C's, Tyr), 128.8 (*m*-C's, Tyr), 126.5 (γ-C, Tyr), 122.2 (C_4, BzImz), 115.7 (C_7, BzImz), 105.8 (*m*-C's, Ar–CO), 53.4 (OCH_3), 50.5 (α-C, Ala), 47.5 (α-C, Tyr), 41.6 (CH_2, Gly), 36.3 (β-C, Tyr), 20.4, 18.8 (5,6-CH_3, BzImz), 17.4 (β-C, Ala); MS (*m/z*, %): 824 (2.2), 823 (M^+, 6.2), 808 (10.2), 792 (17.4), 764 (12.4), 735 (38.2), 707 (14.9), 572 (100), 544 (10.5), 501 (16.4), 473 (26.5), 329 (12.9), 203 (5.3), 146 (15.1), 127 (8.7), 119 (9.9), 118 (12.5), 107 (11.2), 93 (3.8), 59 (14.5), 31 (14.8), 30 (4.4), 15 (2.5).

6.1.3.13. Compound ***6g***. $[\alpha]_D$ −19.9° (*c* 0.1, MeOH); IR (KBr): *ν* 3470, 3116 (N–H str.), 3071, 3052 (Ar–H str.), 2997, 2992 (C–H str. cyclic CH_2), 2961, 2924 (C–H str. CH_3 and CH_2), 1752 (C=O str. ester), 1659, 1628 (C=O str. amide), 1556, 1422, 1417 (skeletal bands), 1462 (C–H def. CH_2), 1385, 1369 (C–H def. isopropyl grp), 1269, 883, 870, 765, 705, 595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.38 (br s, 1H, NH, amide), 8.90 (br s, 1H, NH, BzImz), 8.46 (ss, 2H, *o*-H's, Ar–CO), 7.84 (br s, 1H, NH, amide), 7.26 (ss, 2H, δ- and η-H, BzImz), 7.19 (tt, 2H, $J = 7.15$, 4.4 Hz, *m*-H's, Phe), 7.00 (t, 1H, $J = 6.2$ Hz, *p*-H, Phe), 6.83 (dd, 2H, $J = 8.75$, 4.15 Hz, *o*-H's, Phe), 4.53 (q, 1H, $J = 5.55$ Hz, α-H, Phe), 4.18 (t, 1H, $J = 5.85$ Hz, α-H, Val), 3.66 (t, 1H, $J = 6.85$ Hz, α-H, Pro), 3.62 (s, OCH_3), 3.11 (t, 2H, $J = 7.2$ Hz, δ-H's, Pro), 2.79 (d, 2H, $J = 5.65$ Hz, β-H's, Phe), 2.27 (ss, 6H, ε- and ζ-CH_3, BzImz), 2.07–1.96 (m, 5H, β- and γ-H's, Pro and β-H, Val), 1.04 (d, 6H, $J = 4.55$ Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 169.7 (C=O, ester), 166.9 (C=O, amide), 166.3 (C=O, amide), 165.5 (C=O, Ar–CO), 157.2 (C_2, BzImz), 145.2 (C_4, Ar–CO), 140.8 (C_1, Phe), 138.9 (*o*-C's, Ar–CO), 136.8 ($C_{2'}$, BzImz), 136.1 (C_1, Ar–CO), 134.5 ($C_{3'}$, BzImz), 133.3 (C_5, BzImz), 131.5 (C_6, BzImz), 130.4 (*o*-C's, Phe),

128.6 (*m*-C's, Phe), 127.2 (*p*-H, Phe), 122.0 (C_4, BzImz), 113.7 (C_7, BzImz), 104.7 (*m*-C's, Ar–CO), 59.1 (α-C, Pro), 54.7 (α-C, Phe), 53.4 (OCH_3), 52.1 (α-C, Val), 45.6 (δ-C, Pro), 38.1 (β-C, Phe), 30.5 (β-C, Val), 28.8, 24.7 (β- and γ-C, Pro), 20.3, 19.1 (5,6-CH_3, BzImz), 18.4 (γ-C's, Val).

6.1.3.14. Compound ***6h***. $[\alpha]_D$ −113.8° (*c* 0.1, MeOH); IR (KBr): *ν* 3490, 3135 (N–H str.), 3074, 3036 (Ar–H str.), 2962, 2955, 2873 (C–H str. CH_3), 1755 (C=O str. ester), 1647, 1642 (C=O str. amide), 1566, 1426, 1417 (skeletal bands), 1538, 1535 (NH def. amide), 1459 (C–H def. CH_2), 1420, 1332 (O–H def.), 1267, 1089, 879, 871, 658, 597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.25 (br s, 1H, NH, amide), 8.49 (ss, 2H, *o*-H's, Ar–CO), 8.45 (br s, 1H, NH, amide), 7.25 (ss, 2H, δ- and η-H, BzImz), 6.67 (br s, 1H, NH, amide), 6.25 (br s, 1H, NH, amide), 6.09 (br s, 2H, NH, BzImz and OH, Thr), 4.65–4.56 (m, 1H, β-H, Thr), 4.09 (t, 1H, $J = 8.6$ Hz, α-H, Ile), 3.94 (d, 2H, $J = 5.1$ Hz, CH_2, Gly^1), 3.92 (d, 2H, $J = 5.1$ Hz, CH_2, Gly^2), 3.78 (t, 1H, $J = 3.95$ Hz, α-H, Thr), 3.60 (s, 3H, OCH_3), 2.25 (ss, 6H, ε- and ζ-CH_3, BzImz), 2.10–2.02 (m, 1H, β-H, Ile), 1.67–1.52 (m, 2H, γ-H's, Ile), 1.32 (d, 3H, $J = 4.95$ Hz, γ-H's, Thr), 1.02 (d, 3H, $J = 5.9$ Hz, γ′-H's, Ile), 0.96 (t, 3H, $J = 7.75$ Hz, δ-H's, Ile); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 176.0 (C=O, amide), 172.2 (C=O, ester), 171.2, 169.8 (C=O, amide), 167.1 (C=O, Ar–CO), 156.1 (C_2, BzImz), 143.7 (C_1, Ar–CO), 138.6 (*m*-C's, Ar–CO), 137.8 ($C_{2'}$, BzImz), 136.8 (C_4, Ar–CO), 134.6 ($C_{3'}$, BzImz), 133.9 (C_5, BzImz), 132.1 (C_6, BzImz), 121.9 (C_4, BzImz), 113.0 (C_7, BzImz), 102.7 (*o*-C's, Ar–CO), 67.8 (β-C, Thr), 58.1 (α-C, Thr), 53.0 (OCH_3), 48.9 (α-C, Ile), 46.3, 42.4 (CH_2, Gly^2 and Gly^1), 33.9 (β-C, Ile), 28.4 (γ-C, Ile), 20.4 (γ-C, Thr), 19.8, 18.9 (5,6-CH_3, BzImz), 15.1 (γ′-C, Ile), 10.2 (δ-C, Ile); MS (*m*/*z*, %): 862 (2.4), 861 (3.1), 860 (M^+, 6.4), 845 (11.8), 829 (19.7), 801 (7.3), 728 (30.5), 700 (12.5), 671 (100), 643 (17.3), 558 (32.2), 530 (10.7), 501 (28.3), 473 (21.3), 329 (11.5), 203 (6.8), 146 (26.3), 127 (12.2), 119 (12.4), 118 (8.5), 59 (17.4), 57 (8.6), 31 (11.3), 30 (15.8), 29 (6.1), 15 (3.2).

*6.1.4. General method for the synthesis of amino acid/peptide derivatives of 2-hydroxy-5-(6-nitro-1H-benzo[d]imidazol-2-yl)-benzoic acid (**7**)/5-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-2-hydroxybenzoic acid (**8**)*

To a mixture of L-amino acid methyl ester hydrochloride/di/tri/tetrapeptide methyl ester (0.01 mol) in DMF (50 mL), NMM (2.3 mL) was added at 0 °C with stirring. Compound **7/8** (29.9/28.2 g, 0.01 mol) in DMF (50 mL) and DCC (2.1 g) were added to the above mixture and stirring was done for 24 h. After 24 h, the reaction mixture was filtered. To the filtrate, water is added in equal proportions and aqueous layer was washed with ether (150 mL) in three proportions. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The product obtained was dissolved in chloroform, washed with 10% HCl, saturated $NaHCO_3$ solution and water (25 mL) followed by evaporation in vacuum. Crude product was crystallized from a mixture of ethyl acetate and petroleum ether.

6.1.4.1. Compound ***7a***. $[\alpha]_D$ −86.2° (*c* 0.1, MeOH); IR (KBr): *ν* 3496, 3115 (N–H str.), 3368 (O–H str., Ar–CO), 3069, 3032 (Ar–H str.), 2925, 2918, 2850 (C–H str. CH_2), 2822 (C–H str., OCH_3), 1750 (C=O str. ester), 1638 (C=O str. *sec*. amide), 1585, 1435 (skeletal bands), 1542, 1350 (NO_2 str.), 1538 (NH def. amide), 1267, 1202, 1160, 871, 840, 829, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.75 (s, 1H, ζ-H, Ar–CO), 8.59 (d, 1H, $J = 7.45$ Hz, δ-H, Ar–CO), 8.43 (s, 1H, η-H, BzImz), 8.03 (d, 1H, $J = 7.75$ Hz, ε-H, BzImz), 7.67 (d, 1H, $J = 7.65$ Hz, δ-H, BzImz), 7.52 (d, 1H, $J = 7.2$ Hz, γ-H, Ar–CO), 6.62 (br s, 5H, NH's, BzImz, guanidino grp and OH, Ar–CO), 6.52 (br s, 1H, NH, amide), 4.36 (q, 1H, $J = 9.45$ Hz, α-H, Arg), 3.84 (q, 2H, $J = 6.95$ Hz, δ-H, Arg), 3.65 (s, 3H, OCH_3), 2.01–1.60 (m, 4H, β- and γ-H's, Arg); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 173.2 (C=O, amide), 170.3 (C=O, ester), 160.6 (C=NH), 156.2 (C_2, Ar–CO), 153.2 (C_2, BzImz), 145.1 ($C_{3'}$, BzImz), 142.3 (C_6, BzImz), 139.2 ($C_{2'}$, BzImz), 134.8 (C_4, Ar–CO), 128.6 (C_6, Ar–CO), 124.5 (C_1, Ar–CO), 121.1 (C_5, Ar–CO), 119.5 (C_5, BzImz), 118.4 (C_4, BzImz), 116.2 (C_3, Ar–CO), 110.4 (C_7, BzImz), 54.2 (α-C, Arg), 50.7 (OCH_3), 39.7 (δ-C, Arg), 27.8 (β-C, Arg), 24.2 (γ-C, Arg); MS (*m*/*z*, %): 515 (2.2), 514 (M^+, 4.8), 499 (12.6), 483 (19.2), 455 (16.1), 282 (100), 254 (25.7), 163 (15.8), 145 (19.4), 136 (11.6), 135 (26.2), 131 (18.9), 117 (16.6), 103 (7.3), 66 (10.3), 65 (12.2), 59 (16.6), 46 (5.4), 31 (10.9), 17 (2.3), 15 (1.4).

6.1.4.2. Compound ***7b***. $[\alpha]_D$ −68.3° (*c* 0.1, MeOH); IR (KBr): *ν* 3496, 3489, 3115 (N–H str.), 3366 (O–H str., Ar–CO), 3066, 3048, 3035 (Ar–H str.), 2923, 2852 (C–H str. CH_2), 2826 (C–H str., OCH_3), 1745 (C=O str. ester), 1642 (C=O str. *sec*. amide), 1588, 1430, 1422 (skeletal bands), 1548 (NH def. amide), 1539, 1352 (NO_2 str.), 1273, 1197, 870, 844, 827, 758, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.76 (s, 1H, ζ-H, Ar–CO), 8.58 (d, 1H, $J = 7.45$ Hz, δ-H, Ar–CO), 8.45 (s, 1H, η-H, BzImz), 8.02 (d, 1H, $J = 7.75$ Hz, ε-H, BzImz), 7.67 (d, 1H, $J = 7.6$ Hz, δ-H, BzImz), 7.52 (d, 1H, $J = 7.8$ Hz, β-H, Indole), 7.35 (br s, 3H, NH's, BzImz, Indole and OH, Ar–CO), 7.16–6.97 (m, 5H, δ–η-H's, Indole and γ-H, Ar–CO), 6.50 (br s, 1H, NH, amide), 4.93 (q, 1H, $J = 6.1$ Hz, α-H, Trp), 3.56 (s, 3H, OCH_3), 3.21 (d, 2H, $J = 5.65$ Hz, β-H's, Trp); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 174.7 (C=O, Ar–CO), 169.6 (C=O, ester), 156.4 (C_2, Ar–CO), 153.3 (C_2, BzImz), 144.2 ($C_{3'}$, BzImz), 142.0 (C_6, BzImz), 139.1 ($C_{2'}$, BzImz), 135.9 ($C_{2'}$, Indole), 134.6 (C_4, Ar–CO), 129.4 ($C_{3'}$, Indole), 128.2 (C_6, Ar–CO), 122.6 (C_2, Indole), 121.8 (C_6, Indole), 121.0 (C_1, Ar–CO), 119.9 (C_5, Ar–CO), 119.2 (C_5, Indole), 118.6 (C_5, BzImz), 118.4 (C_4, BzImz), 118.0 (C_4, Indole), 116.6 (C_3, Ar–CO), 111.2 (C_7, Indole), 109.5 (C_3, Indole), 107.9 (C_7, BzImz), 55.5 (α-C, Trp), 49.3 (OCH_3), 28.3 (β-C, Trp).

6.1.4.3. Compound ***7c***. $[\alpha]_D$ −7.2° (*c* 0.1, MeOH); IR (KBr): *ν* 3492, 3127, 3112 (N–H str.), 3362 (O–H str., Ar–CO), 3066, 3028 (Ar–H str.), 2922, 2852, 2845 (C–H str. CH_2), 2825

(C–H str., OCH_3), 1747 (C=O str. ester), 1644, 1636 (C=O str. *sec*. amide), 1589, 1432 (skeletal bands), 1544 (NH def. amide), 1539, 1348 (NO_2 str.), 1262, 1198, 872, 840, 828, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.95 (s, 1H, ζ-H, Ar–CO), 8.66 (br s, 1H, NH, amide), 8.59 (d, 1H, $J = 7.45$ Hz, δ-H, Ar–CO), 8.42 (s, 1H, η-H, BzImz), 8.14 (br s, 1H, NH, amide), 8.02 (d, 1H, $J = 7.75$ Hz, ε-H, BzImz), 7.66 (d, 1H, $J = 7.6$ Hz, δ-H, BzImz), 7.01 (d, 1H, $J = 7.15$ Hz, γ-H, Ar–CO), 6.58 (br s, 2H, NH, BzImz and OH, Ar–CO), 4.02 (d, 2H, $J = 5.15$ Hz, CH_2, Gly^2), 3.91 (d, 2H, $J = 5.15$ Hz, CH_2, Gly^1), 3.50 (s, OCH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.1 (C=O, ester), 168.5 (C=O, amide), 166.6 (C=O, Ar–CO), 157.4 (C_2, Ar–CO), 153.2 (C_2, BzImz), 144.3 ($C_{3'}$, BzImz), 141.2 (C_6, BzImz), 139.1 ($C_{2'}$, BzImz), 136.8 (C_4, Ar–CO), 127.7 (C_6, Ar–CO), 124.5 (C_1, Ar–CO), 121.3 (C_5, Ar–CO), 119.6 (C_5, BzImz), 118.5 (C_4, BzImz), 116.4 (C_3, Ar–CO), 109.2 (C_7, BzImz), 53.4 (OCH_3), 40.4, 40.1 (CH_2, Gly^1 and Gly^2); MS (*m/z*, %): 428 (1.2), 427 (M^+, 5.6), 412 (12.2), 396 (18.7), 368 (14.8), 339 (100), 311 (9.7), 282 (54.8), 254 (20.4), 163 (19.3), 136 (10.4), 135 (25.7), 66 (9.8), 65 (10.8), 59 (14.5), 46 (7.3), 31 (11.5), 17 (1.8), 15 (0.8).

6.1.4.4. Compound ***7d***. $[\alpha]_D$ −16.2° (*c* 0.1, MeOH); IR (KBr): ν 3488, 3138 (N–H str.), 3359 (O–H str., Ar–CO), 3060, 3053 (Ar–H str.), 2996, 2990 (C–H str., cyclic CH_2), 2959, 2871 (C–H str. CH_3), 2824 (C–H str., OCH_3), 1748 (C=O str. ester), 1662, 1639 (C=O str. amide), 1566, 1424 (skeletal bands), 1543 (NH def. amide), 1538, 1348 (NO_2 str.), 1262, 1204, 870, 842, 826, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.90 (s, 1H, ζ-H, Ar–CO), 8.59 (d, 1H, $J = 7.5$ Hz, δ-H, Ar–CO), 8.57 (br s, 1H, NH, amide), 8.42 (s, 1H, η-H, BzImz), 8.03 (d, 1H, $J = 7.8$ Hz, ε-H, BzImz), 7.67 (d, 1H, $J = 7.65$ Hz, δ-H, BzImz), 7.05 (br s, 2H, NH, BzImz and OH, Ar–CO), 7.00 (d, 1H, $J = 7.2$ Hz, γ-H, Ar–CO), 4.92–3.85 (m, 1H, α-H, Ala), 4.09 (t, 1H, $J = 6.85$ Hz, α-H, Pro), 3.59 (s, 3H, OCH_3), 3.43 (t, 2H, $J = 7.15$ Hz, δ-H's, Pro), 2.76–2.69 (m, 2H, β-H's, Pro), 2.02–1.95 (m, 2H, γ-H's, Pro), 1.28 (d, 3H, $J = 5.9$ Hz, β-H's, Ala); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.9 (C=O, ester), 172.0 (C=O, amide), 167.2 (C=O, Ar–CO), 157.3 (C_2, Ar–CO), 153.0 (C_2, BzImz), 146.1 (C_6, BzImz), 144.9 ($C_{3'}$, BzImz), 139.3 ($C_{2'}$, BzImz), 135.7 (C_4, Ar–CO), 127.1 (C_6, Ar–CO), 124.6 (C_1, Ar–CO), 121.4 (C_5, Ar–CO), 120.5 (C_4, BzImz), 118.3 (C_5, BzImz), 118.7 (C_3, Ar–CO), 109.2 (C_7, BzImz), 64.3 (α-C, Pro), 51.1 (OCH_3), 46.4 (α-C, Ala), 43.1 (δ-C, Pro), 31.0 (γ-C, Pro), 28.1, 17.8 (β-C's, Pro and Ala).

6.1.4.5. Compound ***7e***. $[\alpha]_D$ −5.0° (*c* 0.1, MeOH); IR (KBr): ν 3492 (N–H str.), 3361 (O–H str, Ar–CO), 3059, 3045 (Ar–H str.), 2998–2989 (C–H str., cyclic CH_2), 2827 (C–H str., OCH_3), 1751 (C=O str. ester), 1662, 1659 (C=O str. *tert*. amide), 1569, 1428 (skeletal bands), 1540, 1350 (NO_2 str.), 1272, 1202, 871, 828, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.90 (s, 1H, ζ-H, Ar–CO), 8.59 (d, 1H, $J = 7.15$ Hz, δ-H, Ar–CO), 8.41 (s, 1H, η-H, BzImz), 8.03 (d, 1H, $J = 7.75$ Hz, ε-H, BzImz), 7.67 (d, 1H, $J = 7.65$ Hz, δ-H, BzImz), 7.05 (br s, 2H, NH, BzImz and OH, Ar–CO), 7.00 (d, 1H, $J = 7.2$ Hz, γ-H, Ar–CO), 4.41 (t, 1H, $J = 6.8$ Hz, α-H, Pro^1), 4.23–4.18 (m, 2H, α-H's, Pro^2 and Pro^3), 3.73 (t, 2H, $J = 7.15$ Hz, δ-H's, Pro^3), 3.65 (t, 2H, $J = 5.85$ Hz, δ-H's, Pro^2), 3.61 (s, OCH_3), 3.52 (t, 2H, $J = 7.2$ Hz, δ-H's, Pro^1), 2.79–2.68 (m, 4H, β-H's, $Pro^{1,2}$), 2.08–1.88 (m, 8H, β-H's, Pro^3 and γ-H's, Pro^{1-3}); ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.4 (C=O, amide), 168.7 (C=O, ester), 168.2 (C=O, amide), 166.2 (C=O, Ar–CO), 157.7 (C_2, Ar–CO), 153.3 (C_2, BzImz), 144.5 ($C_{3'}$, BzImz), 141.2 (C_6, BzImz), 138.4 ($C_{2'}$, BzImz), 135.9 (C_4, Ar–CO), 127.5 (C_6, Ar–CO), 124.2 (C_1, Ar–CO), 121.4 (C_5, Ar–CO), 119.6 (C_5, BzImz), 118.7 (C_4, BzImz), 116.1 (C_3, Ar–CO), 109.7 (C_7, BzImz), 59.4, 57.6, 55.2 (α-C's, Pro^{1-3}), 53.7 (OCH_3), 46.7, 44.5, 43.1 (δ-C's, Pro^{1-3}), 30.6, 29.4, 28.1 (β-C's, Pro^{1-3}), 27.3, 24.5, 23.2 (γ-C's, Pro^{1-3}); MS (*m/z*, %): 604 (M^+, 8.8), 589 (11.1), 573 (20.2), 545 (13.7), 476 (19.2), 448 (14.3), 379 (100), 351 (16.3), 282 (51.1), 254 (17.4), 163 (17.1), 136 (12.6), 135 (27.7), 66 (11.3), 65 (14.2), 59 (19.7), 46 (9.3), 42 (29.7), 31 (10.5), 17 (2.5), 15 (1.7).

6.1.4.6. Compound ***7f***. $[\alpha]_D$ −34.2° (*c* 0.1, MeOH); IR (KBr): ν 3492, 3488, 3132 (N–H str.), 3358 (O–H str, Ar–CO), 3055, 3042, 3110 (Ar–H str.), 2922, 2852 (C–H str. CH_2), 1754 (C=O str. ester), 1644, 1640 (C=O str. amide), 1567, 1560, 1267, 1426, 1420 (skeletal bands), 1539, 1351 (NO_2 str.), 1389, 1367 (C–H def. isopropyl grp), 1268, 1205, 869, 845, 840, 829, 765, 709, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.95 (s, 1H, ζ-H, Ar–CO), 8.58 (d, 1H, $J = 7.45$ Hz, δ-H, Ar–CO), 8.41 (s, 1H, η-H, BzImz), 8.02 (d, 1H, $J = 7.8$ Hz, ε-H, BzImz), 7.94 (br s, 1H, NH, amide), 7.85 (br s, 1H, NH, amide), 7.74 (d, 1H, $J = 8.0$ Hz, β-H, Imz), 7.66 (d, 1H, $J = 7.6$ Hz, δ-H, BzImz), 7.60 (s, 1H, δ-H, Imz), 7.39 (br s, 3H, NH's, BzImz, Imz and OH, Ar–CO), 7.20–7.14 (m, 2H, *m*-H's, Phe), 7.00 (t, 1H, $J = 6.15$ Hz, *p*-H, Phe), 6.95 (br s, 1H, NH, amide), 6.91 (d, 1H, $J = 7.2$ Hz, γ-H, Ar–CO), 6.84 (dd, 2H, $J = 8.8$, 4.15 Hz, *o*-H's, Phe), 4.33 (t, 1H, $J = 5.85$ Hz, α-H, Val), 4.21 (q, 1H, $J = 5.45$ Hz, α-H, Phe), 4.10 (q, 1H, $J = 9.0$ Hz, α-H, His), 3.54 (s, 3H, OCH_3), 3.03–2.89 (m, 4H, β-H's, Phe and His), 1.60–1.46 (m, 1H, β-H, Val), 0.97 (d, 6H, $J = 4.6$ Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.1 (C=O, ester), 171.2, 169.6 (C=O, amide), 166.8 (C=O, Ar–CO), 156.8 (C_2, Ar–CO), 153.2 (C_2, BzImz), 145.2 ($C_{3'}$, BzImz), 141.2 (C_6, BzImz), 139.8 (C_2, Imz), 139.2 ($C_{2'}$, BzImz), 135.9 (C_4, Ar–CO), 133.2 (γ-C, Phe), 130.3 (*o*-C's, Phe), 128.0 (*m*-C's, Phe), 127.7 (*p*-C, Phe), 126.8 (C_4, Imz), 125.8 (C_6, Ar–CO), 124.3 (C_1, Ar–CO), 122.0 (C_5, Ar–CO), 119.7 (C_4, BzImz), 118.5 (C_5, BzImz), 117.5 (C_3, Ar–CO), 113.4 (C_5, Imz), 108.6 (C_7, BzImz), 57.7 (α-C, Val), 53.0 (α-C, His), 50.8 (α-C, Phe), 49.6 (OCH_3), 38.5 (β-C, Phe), 28.5 (β-C, Val), 23.2 (β-C, His), 18.6 (γ-C's, Val).

6.1.4.7. Compound ***7g***. $[\alpha]_D$ +33.3° (*c* 0.1, MeOH); IR (KBr): ν 3489, 3483, 3130 (N–H str.), 3359 (O–H str., Ar–CO), 3052, 3115 (Ar–H str.), 2998, 2992 (C–H str., cyclic CH_2), 2924, 2919, 2850 (C–H str. CH_2), 1747 (C=O str. ester),

1662, 1640, 1636 (C=O str. amide), 1565, 1427, 1422 (skeletal bands), 1549 (NH def. amide), 1544, 1347 (NO_2 str.), 1390, 1365 (C–H def. isopropyl grp), 1266, 1201, 870, 845, 839, 827, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.96 (br s, 1H, NH, amide), 8.93 (s, 1H, ζ-H, Ar–CO), 8.60 (d, 1H, $J = 7.45$ Hz, δ-H, Ar–CO), 8.42 (s, 1H, η-H, BzImz), 8.02 (d, 1H, $J = 7.75$ Hz, ε-H, BzImz), 7.86 (br s, 1H, NH, amide), 7.69 (d, 1H, $J = 7.95$ Hz, β-H, Imz), 7.66 (d, 1H, $J = 7.6$ Hz, δ-H, BzImz), 7.50 (s, 1H, δ-H, Imz), 7.40 (br s, 3H, NH's, BzImz, Imz and OH, Ar–CO), 7.02 (d, 1H, $J = 7.2$ Hz, γ-H, Ar–CO), 6.52 (br s, 1H, NH, amide), 4.84–4.78 (m, 1H, α-H, Leu), 4.70–4.63 (m, 1H, α-H, His), 4.03 (d, 2H, $J = 5.1$ Hz, CH_2, Gly), 3.90 (t, 1H, $J = 6.8$ Hz, α-H, Pro), 3.64 (s, 3H, OCH_3), 3.33 (t, 2H, $J = 7.2$ Hz, δ-H's, Pro), 2.94 (d, 2H, $J = 5.85$ Hz, β-H's, His), 2.77–2.72 (m, 2H, β-H's, Pro), 1.97–1.86 (m, 2H, γ-H's, Pro), 1.73 (t, 2H, $J = 7.95$ Hz, β-H's, Leu), 1.51–1.40 (m, 1H, γ-H, Leu), 1.00 (d, 6H, $J = 6.15$ Hz, δ-H's, Leu); ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.8, 171.6 (C=O, amide), 169.5 (C=O, ester), 168.7 (C=O, amide), 167.6 (C=O, Ar–CO), 156.2 (C_2, Ar–CO), 152.4 (C_2, BzImz), 144.8 ($C_{3'}$, BzImz), 142.2 (C_6, BzImz), 139.8 (C_2, Imz), 138.2 ($C_{2'}$, BzImz), 136.6 (C_4, Ar–CO), 128.4 (C_4, Imz), 124.6 (C_6, Ar–CO), 122.8 (C_1, Ar–CO), 120.3 (C_5, Ar–CO), 119.2 (C_5, BzImz), 118.5 (C_4, BzImz), 116.6 (C_3, Ar–CO), 115.8 (C_5, Imz), 107.2 (C_7, BzImz), 59.1 (α-C, His), 56.5 (α-C, Pro), 51.4 (OCH_3), 47.2 (δ-C, Pro), 45.3 (α-C, Leu), 41.7 (CH_2, Gly), 38.4 (β-C, Leu), 27.5, 25.6 (β-C's, Pro and His), 24.2, 22.8 (γ-C's, Pro and Leu), 20.9 (δ-C's, Leu); MS (*m/z*, %): 719 (1.2), 718 (2.5), 717 (M^+, 7.3), 702 (11.8), 686 (19.6), 658 (13.7), 629 (16.7), 601 (19.5), 516 (37.2), 488 (14.9), 419 (100), 391 (17.9), 282 (48.9), 254 (15.8), 163 (14.1), 136 (10.5), 135 (26.2), 81 (14.7), 67 (9.2), 66 (14.2), 65 (14.9), 59 (19.2), 57 (29.5), 46 (9.9), 43 (11.7), 42 (29.2), 31 (10.5), 30 (16.6), 29 (11.5), 17 (2.8), 15 (1.1).

6.1.4.8. Compound ***8a***. $[\alpha]_D$ −44.0° (*c* 0.1, MeOH); IR (KBr): ν 3492, 3120 (N–H str.), 3355 (O–H str., Ar–CO), 3066, 3042, 3030 (Ar–H str.), 2964, 2958, 2917 (C–H str. CH_3 and CH_2), 1748 (C=O str. ester), 1640 (C=O str. *sec*. amide), 1544, 1416 (skeletal bands), 1532 (NH def. amide), 1398, 1268, 1196, 879, 825, 752, 705, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.75 (s, 1H, ζ-H, Ar–CO), 8.60 (d, 1H, $J = 7.55$ Hz, δ-H, Ar–CO), 7.31 (s, 1H, δ-H, BzImz), 7.30 (s, 1H, η-H, BzImz), 7.11 (t, 1H, $J = 6.15$ Hz, *p*-H, Phe), 7.01–6.96 (m, 3H, γ-H, Ar–CO and *m*-H's, Phe), 7.85 (dd, 2H, $J = 8.75$, 4.1 Hz, *o*-H's, Phe), 6.58 (br s, 2H, NH, BzImz and OH, Ar–CO), 6.50 (br s, 1H, NH, amide), 4.66 (q, 1H, $J = 5.55$ Hz, α-H, Phe), 3.56 (s, 3H, OCH_3), 2.97 (d, 2H, $J = 5.6$ Hz, β-H's, Phe), 2.27 (s, 3H, ε-CH_3, BzImz), 2.26 (s, 3H, ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 172.8 (C=O, Ar–CO), 170.4 (C=O, ester), 157.6 (C_2, Ar–CO), 152.2 (C_2, BzImz), 140.3 ($C_{2'}$, BzImz), 138.4 (C_1, Phe), 137.2 ($C_{3'}$, BzImz), 135.8 (C_4, Ar–CO), 134.1, 132.5 (C_5 and C_6, BzImz), 128.9, 128.1, 126.8 (*o*-, *m*- and *p*-C's, Phe), 126.2 (C_4, BzImz), 124.9 (C_6, Ar–CO), 123.2 (C_1, Ar–CO), 120.7 (C_5, Ar–CO), 117.2 (C_3, Ar–CO), 114.0 (C_7, BzImz), 57.4 (α-C, Phe), 52.5 (OCH_3), 38.8 (β-C, Phe), 20.4, 18.8 (5,6-CH_3, BzImz); MS (*m/z*, %): 444 (2.1), 443 (M^+, 8.2), 428 (11.5), 412 (18.8), 384 (10.2), 265 (100), 237 (14.8), 146 (33.5), 119 (11.5), 118 (12.8), 91 (17.3), 77 (4.5), 66 (9.5), 65 (19.9), 59 (16.4), 31 (14.1), 17 (8.8), 15 (6.2).

6.1.4.9. Compound ***8b***. $[\alpha]_D$ −36.3° (*c* 0.1, MeOH); IR (KBr): ν 3490, 3124, 3117 (N–H str.), 3359 (O–H str., Ar–CO), 3060, 3033 (Ar–H str.), 2962, 2925, 2919 (C–H str. CH_3 and CH_2), 2823 (C–H str., OCH_3), 1750 (C=O str. ester), 1640, 1637 (C=O str. amide), 1540, 1412 (skeletal bands), 1530 (NH def. amide), 1468, 1445, 1372, 1272, 1198, 1158, 875, 828, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.92 (s, 1H, ζ-H, Ar–CO), 8.59 (d, 1H, $J = 7.5$ Hz, δ-H, Ar–CO), 7.98 (br s, 1H, NH, amide), 7.32 (s, 1H, δ-H, BzImz), 7.30 (s, 1H, η-H, BzImz), 7.11 (br s, 1H, NH, amide), 7.01 (d, 1H, $J = 7.2$ Hz, γ-H, Ar–CO), 6.62 (br s, 5H, NH's, BzImz, guanidino grp and OH, ArCO), 4.63 (q, 1H, $J = 9.45$ Hz, α-H, Arg), 3.90 (q, 2H, $J = 7.0$ Hz, δ-H's, Arg), 3.80–3.71 (m, 1H, α-H, Ala), 3.60 (s, 3H, OCH_3), 2.27 (s, 3H, ε-CH_3, BzImz), 2.25 (s, 3H, ζ-CH_3, BzImz), 2.18–1.74 (m, 4H, β- and γ-H's, Arg), 1.30 (d, 3H, $J = 5.9$ Hz, β-H's, Ala); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.7 (C=O, ester), 172.0 (C=O, amide), 170.9 (C=O, Ar–CO), 159.6 (C=NH), 156.8 (C_2, Ar–CO), 153.0 (C_2, BzImz), 139.9 ($C_{2'}$, BzImz), 137.1 ($C_{3'}$, BzImz), 135.6 (C_4, Ar–CO), 133.8, 132.4 (C_5 and C_6, BzImz), 128.1 (C_4, BzImz), 125.3 (C_6, Ar–CO), 124.5 (C_1, Ar–CO), 122.0 (C_5, Ar–CO), 118.4 (C_3, Ar–CO), 113.7 (C_7, BzImz), 52.7 (α-C, Arg), 51.0 (OCH_3), 47.6 (α-C, Ala), 38.5 (δ-C, Arg), 27.8 (β-C, Arg), 24.4 (γ-C, Arg), 20.1, 19.1 (5,6-CH_3, BzImz), 17.8 (β-C, Ala).

6.1.4.10. Compound ***8c***. $[\alpha]_D$ −13.4° (*c* 0.1, MeOH); IR (KBr): ν 3498, 3494, 3125 (N–H str.), 3362 (O–H str., Ar–CO), 3062, 3035, 3022 (Ar–H str.), 2960, 2924, 2916 (C–H str. CH_3 and CH_2), 1753 (C=O str. ester), 1642, 1635 (C=O str. amide), 1544, 1426, 1420 (skeletal bands), 1534 (NH def. amide), 1465, 1447, 1270, 1195, 879, 872, 869, 824, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.93 (s, 1H, ζ-H, Ar–CO), 8.59 (d, 1H, $J = 7.6$ Hz, δ-H, Ar–CO), 7.98 (br s, 1H, NH, amide), 7.82 (br s, 4H, NH's, BzImz, Imz's and OH, Ar–CO), 7.74 (d, 1H, $J = 7.95$ Hz, β-H, Imz^2), 7.65 (s, 1H, δ-H, Imz^1), 7.60 (s, 1H, δ-H, Imz^2), 7.37 (d, 1H, $J = 8.0$ Hz, β-H, Imz^1), 7.31 (s, 1H, δ-H, BzImz), 7.30 (s, 1H, η-H, BzImz), 7.01 (d, 1H, $J = 7.15$ Hz, γ-H, Ar–CO), 6.93 (br s, 1H, NH, amide), 5.01 (q, 1H, $J = 8.95$ Hz, α-H, His^1), 4.13 (q, 1H, $J = 9.0$ Hz, α-H, His^2), 3.55 (s, 3H, OCH_3), 3.07–2.76 (m, 4H, β-H's, His), 2.27 (s, 3H, ε-CH_3, BzImz), 2.26 (s, 3H, ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.3 (C=O, amide), 170.2 (C=O, ester), 168.8 (C=O, Ar–CO), 158.2 (C_2, Ar–CO), 153.1 (C_2, BzImz), 142.7 (C_2, $Imz^{1,2}$), 138.9, 136.2 ($C_{2',3'}$, BzImz), 135.8 (C_4, Ar–CO), 134.2, 132.8 ($C_{5,6}$, BzImz), 126.9, 125.6 (C_4, $Imz^{1,2}$), 124.1 (C_4, BzImz), 122.9 (C_6, Ar–CO), 121.8 (C_5, Ar–CO), 120.2 (C_1, Ar–CO), 118.4 (C_3, Ar–CO), 116.3, 114.6 (C_5, $Imz^{1,2}$), 111.8 (C_7, BzImz), 62.7, 52.8 (α-C,

His[1,2]), 49.1 (OCH_3), 25.8, 23.3 (β-C, His[1,2]), 20.3, 18.7 (5,6-CH_3, BzImz); MS (*m/z*, %): 572 (3.2), 571 (1.3), 570 (M^+, 4.6), 555 (11.5), 539 (18.2), 511 (10.7), 402 (100), 374 (21.3), 265 (32.6), 237 (15.3), 146 (30.9), 119 (10.5), 118 (11.6), 81 (20.3), 67 (12.5), 66 (10.4), 65 (17.7), 59 (15.9), 31 (10.7), 17 (7.8), 15 (5.5).

6.1.4.11. Compound ***8d***. $[\alpha]_D$ −7.5° (*c* 0.1, MeOH); IR (KBr): *ν* 3496, 3116 (N−H str.), 3358 (O−H str., Ar−CO), 3061, 3034 (Ar−H str.), 2963, 2925, 2919 (C−H str. CH_3 and CH_2), 1744 (C=O str. ester), 1640, 1632 (C=O str. amide), 1540, 1425, 1422 (skeletal bands), 1536, 1466, 1445, 1387, 1365, 1273, 1198, 875, 830, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.98 (s, 1H, ζ-H, Ar−CO), 8.60 (d, 1H, *J* = 7.6 Hz, δ-H, Ar−CO), 7.60 (br s, 1H, NH, amide), 7.31 (s, 1H, δ-H, BzImz), 7.29 (s, 1H, η-H, BzImz), 7.01 (d, 1H, *J* = 7.2 Hz, γ-H, Ar−CO), 6.78 (br s, 1H, NH, amide), 6.58 (br s, 2H, NH, BzImz and OH, ArCO), 4.39 (q, 1H, *J* = 6.7 Hz, α-H, Leu), 3.83 (t, 1H, *J* = 8.65 Hz, α-H, Ile), 3.51 (s, 3H, OCH_3), 2.26 (s, 3H, ε-CH_3, BzImz), 2.24 (s, 3H, ζ-CH_3, BzImz), 2.06−1.96 (m, 1H, β-H, Ile), 1.75 (t, 2H, *J* = 7.95 Hz, β-H's, Leu), 1.67−1.62 (m, 2H, γ-H's, Ile), 1.51−1.46 (m, 1H, γ-H, Leu), 0.99 (d, 6H, *J* = 6.25 Hz, δ-H's, Leu), 0.93 (t, 3H, *J* = 7.75 Hz, δ-H's, Ile), 0.88 (d, 3H, *J* = 5.9 Hz, γ′-H's, Ile); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 174.9 (C=O, ester), 170.2 (C=O, amide), 168.7 (C=O, Ar−CO), 156.2 (C_2, Ar−CO), 153.2 (C_2, BzImz), 140.3 ($C_{2'}$, BzImz), 137.3 ($C_{3'}$, BzImz), 135.5 (C_4, Ar−CO), 133.9, 132.6 (C_5 and C_6, BzImz), 128.9 (C_4, BzImz), 124.6 (C_6, Ar−CO), 123.6 (C_1, Ar−CO), 121.8 (C_5, Ar−CO), 118.1 (C_3, Ar−CO), 114.0 (C_7, BzImz), 58.5 (α-C, Ile), 53.4 (OCH_3), 51.4 (α-C, Leu), 40.6 (β-C, Ile), 36.4 (β-C, Leu), 24.7 (γ-C, Ile), 24.0 (γ-C, Leu), 22.5 (δ-C's, Leu), 19.8, 19.0 (5,6-CH_3, BzImz), 15.2 (γ′-C, Ile), 9.9 (δ-C, Ile).

6.1.4.12. Compound ***8e***. $[\alpha]_D$ +10.2° (*c* 0.1, MeOH); IR (KBr): *ν* 3497, 3493, 3121 (N−H str.), 3360, 3357 (O−H str., Ar−CO and Tyr), 3067, 3034, 3020 (Ar−H str.), 2964, 2928, 2923 (C−H str. CH_3 and CH_2), 1748 (C=O str. ester), 1640, 1633 (C=O str. amide), 1544, 1424, 1418 (skeletal bands), 1532, 1528 (NH def. amide), 1466, 1449, 1269, 1198, 875, 824, 818, 738, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.94 (s, 1H, ζ-H, Ar−CO), 8.58 (d, 1H, *J* = 7.55 Hz, δ-H, Ar−CO), 8.15 (br s, 1H, NH, amide), 7.98 (br s, 1H, NH, amide), 7.32 (s, 1H, δ-H, BzImz), 7.30 (s, 1H, η-H, BzImz), 7.25 (d, 1H, *J* = 7.8 Hz, β-H, Indole), 7.22−7.08 (m, 4H, δ−η-H's, Indole), 7.03 (d, 1H, *J* = 7.2 Hz, γ-H, Ar−CO), 6.99 (br s, 4H, NH's, BzImz, Indole and OH's, Ar−CO, Tyr), 6.92−6.77 (m, 4H, *o*- and *m*-H's, Tyr), 6.80 (br s, 1H, NH, amide), 4.94 (q, 1H, *J* = 6.15 Hz, α-H, Trp), 4.32−4.27 (m, 1H, α-H, Ala), 3.93 (q, 1H, *J* = 7.95 Hz, α-H, Tyr), 3.55 (s, 3H, OCH_3), 3.21 (d, 2H, *J* = 5.65 Hz, β-H's, Trp), 2.82 (d, 2H, *J* = 5.5 Hz, β-H's, Tyr), 2.27 (s, 3H, ε-CH_3, BzImz), 2.25 (s, 3H, ζ-CH_3, BzImz), 1.49 (d, 3H, *J* = 5.9 Hz, β-H's, Ala); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 175.3, 172.7 (C=O, amide), 169.9 (C=O, ester), 166.2 (C=O, Ar−CO), 157.4 (C_2, Ar−CO), 153.9 (*p*-C, Tyr), 152.7 (C_2, BzImz), 138.8, 137.0 ($C_{2',3'}$, BzImz), 136.3 ($C_{2'}$, Indole), 135.5 (C_4, Ar−CO), 133.7, 132.5 ($C_{5,6}$, BzImz), 129.8, 128.4 (*o*- and *m*-C's, Tyr), 127.2 ($C_{3'}$, Indole), 126.0 (C_4, BzImz), 124.8 (C_6, Ar−CO), 122.5 (C_2, Indole), 122.1 (C_5, Ar−CO), 121.5 (C_1, Ar−CO), 120.8, 119.0 ($C_{5,6}$, Indole), 118.4 (C_3, Ar−CO), 117.8 (C_4, Indole), 117.0 (γ-C, Tyr), 113.9 (C_7, BzImz), 111.2 (C_7, Indole), 109.3 (C_3, Indole), 62.6 (α-C, Trp), 56.5 (α-C, Ala), 54.5 (α-C, Tyr), 52.6 (OCH_3), 37.9 (β-C, Tyr), 30.3 (β-C, Trp), 20.2, 19.0 (5,6-CH_3, BzImz), 16.9 (β-C, Ala); MS (*m/z*, %): 717 (3.2), 716 (M^+, 8.2), 701 (10.5), 685 (19.6), 657 (13.1), 522 (17.8), 494 (17.4), 451 (100), 423 (20.8), 265 (30.6), 237 (13.8), 146 (28.7), 130 (12.9), 119 (10.7), 118 (14.9), 116 (18.4), 107 (6.9), 93 (16.3), 66 (13.2), 65 (16.2), 59 (13.6), 31 (11.2), 17 (7.3), 15 (6.2).

6.1.4.13. Compound ***8f***. $[\alpha]_D$ +41.8° (*c* 0.1, MeOH); IR (KBr): *ν* 3490, 3130, 3122 (N−H str.), 3362 (O−H str. ArCO), 3062, 3032 (Ar−H str.), 2964, 2959, 2876 (C−H str. CH_3), 1748 (C=O str. ester), 1642, 1631 (C=O str. amide), 1541, 1420 (skeletal bands), 1535, 1527 (NH def. amide), 1449, 1392, 1362, 1271, 1196, 878, 828, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.32 (br s, 1H, NH, amide), 8.92 (s, 1H, ζ-H, Ar−CO), 8.59 (d, 1H, *J* = 7.55 Hz, δ-H, Ar−CO), 7.96 (br s, 1H, NH, amide), 7.31 (s, 1H, δ-H, BzImz), 7.30 (s, 1H, η-H, BzImz), 7.02 (d, 1H, *J* = 7.25 Hz, γ-H, Ar−CO), 6.82 (br s, 1H, NH, amide), 6.57 (br s, 2H, NH, BzImz and OH, Ar−CO), 4.53−4.44 (m, 1H, α-H, Ala[1]), 3.96 (t, 1H, *J* = 5.85 Hz, α-H, Val), 3.60 (s, 3H, OCH_3), 3.53−3.44 (m, 1H, α-H, Ala[2]), 2.27 (s, 3H, ε-CH_3, BzImz), 2.26 (s, 3H, ζ-CH_3, BzImz), 1.58−1.45 (m, 1H, β-H, Val), 1.29 (d, 3H, *J* = 5.9 Hz, β-H's, Ala[2]), 1.23 (d, 3H, *J* = 5.85 Hz, β-H's, Ala[1]), 0.97 (d, 6H, *J* = 4.55 Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 171.5, 169.1 (C=O, amide), 170.2 (C=O, ester), 165.4 (C=O, Ar−CO), 156.1 (C_2, Ar−CO), 152.2 (C_2, BzImz), 140.7, 137.1 ($C_{2',3'}$, BzImz), 135.9 (C_4, Ar−CO), 134.1, 132.5 ($C_{5,6}$, BzImz), 129.2 (C_4, BzImz), 125.5 (C_6, Ar−CO), 123.7 (C_1, Ar−CO), 122.0 (C_5, Ar−CO), 119.4 (C_3, Ar−CO), 113.8 (C_7, BzImz), 58.5 (α-C, Ala[1]), 52.4 (α-C, Val), 50.1 (OCH_3), 47.5 (α-C, Ala[2]), 28.3 (β-C, Val), 20.2, 19.2 (5,6-CH_3, BzImz), 18.8 (β-C, Ala[1]), 18.1 (γ-C's, Val), 17.5 (β-C, Ala[2]).

6.1.4.14. Compound ***8g***. $[\alpha]_D$ −1.8° (*c* 0.1, MeOH); IR (KBr): *ν* 3492, 3488, 3124 (N−H str.), 3359 (O−H str. ArCO), 3065, 3046, 3033 (Ar−H str.), 2958, 2925, 2850 (C−H str. CH_3 and CH_2), 2824 (C−H str., OCH_3), 1744 (C=O str. ester), 1630, 1628 (C=O str. amide), 1545, 1419 (skeletal bands), 1532 (NH def. amide), 1448, 1267, 1197, 878, 872, 824, 739, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.49 (br s, 1H, NH, amide), 8.96 (s, 1H, ζ-H, Ar−CO), 8.59 (d, 1H, *J* = 7.6 Hz, δ-H, Ar−CO), 8.25 (br s, 1H, NH, amide), 8.10 (br s, 1H, NH, amide), 7.80 (br s, 4H, NH's, BzImz, Indole, Imz and OH, Ar−CO), 7.74 (d, 1H, *J* = 7.95 Hz, β-H, Imz), 7.60 (s, 1H, δ-H, Imz), 7.31 (s, 1H, δ-H, BzImz), 7.28 (s, 1H, η-H, BzImz), 7.24 (d, 1H, *J* = 7.8 Hz, β-H, Indole), 7.21−7.07 (m, 4H, δ−η-H's, Indole), 7.01 (d, 1H,

$J = 7.2$ Hz, γ-H, Ar–CO), 6.32 (br s, 1H, NH, amide), 4.24 (q, 1H, $J = 6.1$ Hz, α-H, Trp), 4.15 (q, 1H, $J = 9.0$ Hz, α-H, His), 3.93 (d, 2H, $J = 5.1$ Hz, CH_2, Gly^1), 3.82 (d, 2H, $J = 5.1$ Hz, CH_2, Gly^2), 3.54 (s, 3H, OCH_3), 3.22 (d, 2H, $J = 5.65$ Hz, β-H's, Trp), 3.07 (d, 2H, $J = 5.9$ Hz, β-H's, His), 2.26 (s, 3H, ε-CH_3, BzImz), 2.24 (s, 3H, ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 176.5 (C═O, ester), 174.3, 169.4, 167.1 (C═O, amide), 166.7 (C═O, Ar–CO), 156.7 (C_2, Ar–CO), 153.2 (C_2, BzImz), 142.0 (C_2, Imz), 138.7, 137.0 ($C_{2',3'}$, BzImz), 135.8 ($C_{2'}$, Indole), 135.8 (C_4, Ar–CO), 133.8, 132.6 ($C_{5,6}$, BzImz), 127.0 ($C_{3'}$, Indole), 126.8 (C_4, Imz), 126.2 (C_4, BzImz), 124.7 (C_6, Ar–CO), 124.0 (C_1, Ar–CO), 122.5 (C_2, Indole), 121.8 (C_5, Ar–CO), 120.2, 119.6, 118.6 (C_{4-6}, Indole), 118.0 (C_3, Ar–CO), 114.5 (C_5, Imz), 113.8 (C_7, BzImz), 110.9 (C_7, Indole), 109.2 (C_3, Indole), 56.9 (α-C, Trp), 51.6 (α-C, His), 50.3 (OCH_3), 46.3 (CH_2, Gly^2), 41.0 (CH_2, Gly^1), 29.3 (β-C, Trp), 20.1 (β-C, His), 19.9, 18.9 (5,6-CH_3, BzImz); MS (*m/z*, %): 735 (2.4), 734 (1.6), 733 (M^+,6.7), 718 (10.2), 702 (18.6), 674 (12.3), 565 (17.3), 537 (16.7), 508 (100), 480 (22.4), 322 (15.8), 294 (20.4), 265 (35.2), 237 (15.6), 146 (25.9), 130 (13.4), 119 (11.3), 118 (14.4), 116 (18.9), 81 (16.1), 67 (10.7), 66 (14.8), 65 (18.1), 59 (11.6), 31 (10.7), 17 (6.8), 15 (5.1).

*6.1.5. General method for the hydrolysis of amino acid/peptide derivatives of 4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-benzoic acid (**5**)/4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-3,5-diiodobenzoic acid (**6**)/2-hydroxy-5-(6-nitro-1H-benzo[d]imidazol-2-yl)-benzoic acid (**7**)/5-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-2-hydroxybenzoic acid (**8**)*

To a solution of the amino acid/peptide methyl esters (0.01 mol) in THF:H_2O (1:1, 36 mL), LiOH (0.36 g) was added at 0 °C. The mixture was stirred at RT for 1 h and then acidified to pH 3.5 with 1 N H_2SO_4. The aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were crystallized from methanol and ether to get hydrolyzed peptide derivatives **$5b_a$–d_a**, **$6e_a$–g_a**, **$7c_a$–e_a** and **$8e_a$–g_a**.

*6.1.5.1. Compound **$5b_a$**.* $[\alpha]_D$ −20.2° (*c* 0.3, MeOH); IR (KBr): ν 3495, 3338, 3125 (N–H str.), 3283–2490 (O–H str. COOH), 3069, 3052 (Ar–H str.), 2960, 2928, 2916 (C–H str. CH_3 and CH_2), 1710 (C═O str. COOH), 1635 (C═O str. *sec*. amide), 1544, 1418 (skeletal bands), 1531 (NH def. amide), 1411 (C–OH def. COOH), 1375 (NO_2 str.), 1164 (C–N str. *sec*. amine), 876, 835, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (br s, 1H, NH, amide), 8.41 (dd, 2H, $J = 9.0$, 6.65 Hz, *m*-H's, Ar–CO), 8.20 (br s, 5H, NH's, BzImz, guanidino grp and OH, COOH), 8.02 (dd, 2H, $J = 8.9$, 6.55 Hz, *o*-H's, Ar–CO), 7.31 (s, 1H, δ-H, BzImz), 7.30 (s, 1H, η-H, BzImz), 4.40 (q, 1H, $J = 9.35$ Hz, α-H, Arg), 3.84 (q, 2H, $J = 6.95$ Hz, δ-H's, Arg), 2.27 (s, 3H, ε-CH_3, BzImz), 2.25 (s, 3H, ζ-CH_3, BzImz), 2.04–1.59 (m, 4H, β- and γ-H's, Arg); ^{13}C NMR (300 MHz, $CDCl_3$): δ 182.2 (C═O, COOH), 167.5 (C═O, Ar–CO), 159.8 (C═NH), 152.2 (C_2, BzImz), 139.6 ($C_{2'}$, BzImz), 137.8 ($C_{3'}$, BzImz), 135.4 (C_4, Ar–CO), 133.8 (C_5, BzImz), 132.6 (C_6, BzImz), 131.4 (C_1, Ar–CO), 130.2 (*m*-C's, Ar–CO), 128.1 (*o*-C's, Ar–CO), 125.2 (C_4, BzImz), 115.9 (C_7, BzImz), 54.1 (α-C, Arg), 39.3 (δ-C, Arg), 27.8 (β-C, Arg), 24.0 (γ-C, Arg), 19.2, 18.5 (5,6-CH_3, BzImz); MS (*m/z*, %): 467 (M^+, 5.9), 450 (4.5), 422 (15.2), 249 (18.5), 221 (100), 146 (27.5), 119 (10.9), 118 (10.2), 60 (24.8), 51 (10.5), 45 (11.2), 39 (9.7), 30 (16.5), 15 (7.8).

*6.1.5.2. Compound **$5c_a$**.* $[\alpha]_D$ −65.3° (*c* 0.3, MeOH); IR (KBr): ν 3495, 3336, 3125 (N–H str.), 3295–2525 (O–H str. COOH), 3067, 3037 (Ar–H str.), 2964, 2927, 2915 (C–H str. CH_3 and CH_2), 1708 (C═O str. COOH), 1633, 1625 (C═O str. *sec*. amide), 1553, 1428 (skeletal bands), 1530 (NH def. amide), 1406 (C–OH def. COOH), 1389, 1368 (C–H def. $CH(CH_3)_2$), 880, 833, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.3 (br s, 2H, NH, BzImz and OH, COOH), 8.31–8.22 (m, 4H, *o*- and *m*-H's, Ar–CO), 7.79 (br s, 1H, NH, amide), 7.70 (br s, 1H, NH, amide), 7.31 (s, 1H, δ-H, BzImz), 7.29 (s, 1H, η-H, BzImz), 5.16 (q, 1H, $J = 6.75$ Hz, α-H, Leu), 4.17 (d, 2H, $J = 5.1$ Hz, CH_2, Gly), 2.26 (s, 3H, ε-CH_3, BzImz), 2.25 (s, 3H, ζ-CH_3, BzImz), 1.81–1.40 (m, 3H, β- and γ-H's, Leu), 1.00 (d, 6H, $J = 6.15$ Hz, δ-H's, Leu); ^{13}C NMR (300 MHz, $CDCl_3$): δ 178.2 (C═O, COOH), 170.6 (C═O, amide), 166.1 (C═O, Ar–CO), 152.8 (C_2, BzImz), 139.8, 137.6 ($C_{2',3'}$, BzImz), 134.4 (C_4, Ar–CO), 133.6, 132.5 ($C_{5,6}$, BzImz), 131.7 (C_1, Ar–CO), 130.8, 127.1 (*m*- and *o*-C's, Ar–CO), 125.2 (C_4, BzImz), 114.2 (C_7, BzImz), 55.6, 45.1 (α- and β-C's, Leu), 41.8 (CH_2, Gly), 24.7 (γ-C, Leu), 21.7 (δ-C's, Leu), 19.5, 18.8 (5,6-CH_3, BzImz).

*6.1.5.3. Compound **$5d_a$**.* $[\alpha]_D$ −90.0° (*c* 0.3, MeOH); IR (KBr): ν 3495, 3122 (N–H str.), 3375 (O–H str., Tyr), 3290–2495 (O–H str. COOH), 3048, 3033 (Ar–H str.), 2959, 2923 (C–H str. CH_3 and CH_2), 1705 (C═O str. COOH), 1636, 1622 (C═O str. amide), 1555, 1425, 1420 (skeletal bands), 1535, 1528 (NH def. amide), 1410, 880, 878, 835, 830, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.37 (br s, 1H, NH, amide), 8.98 (br s, 4H, NH's, Imz and BzImz and OH's, Tyr and COOH), 8.29–8.20 (m, 4H, *o*- and *m*-H's, Ar–CO), 7.66 (s, 1H, δ-H, Imz), 7.38 (d, 1H, $J = 7.95$ Hz, β-H, Imz), 7.31 (s, 1H, δ-H, BzImz), 7.30 (s, 1H, η-H, BzImz), 7.24 (br s, 1H, NH, amide), 7.18 (dd, 2H, $J = 8.5$, 5.15 Hz, *o*-H's, Tyr), 6.76 (dd, 2H, $J = 8.55$, 4.9 Hz, *m*-H's, Tyr), 5.78 (q, 1H, $J = 9.0$ Hz, α-H, His), 4.18 (q, 1H, $J = 8.0$ Hz, α-H, Tyr), 3.12–2.73 (m, 4H, β-H's, Tyr and His), 2.27 (s, 3H, ε-CH_3, BzImz), 2.26 (s, 3H, ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.2 (C═O, COOH), 170.5 (C═O, amide), 167.8 (C═O, Ar–CO), 154.7 (C–OH, Tyr), 152.4 (C_2, BzImz), 142.2 (C_2, Imz), 138.5, 136.8 ($C_{2',3'}$, BzImz), 135.1 (C_4, Ar–CO), 133.7, 132.2 ($C_{5,6}$, BzImz), 131.5 (*m*-C's, Ar–CO), 130.1 (C_1, Ar–CO), 128.6, 128.5 (*o*- and *m*-C's, Tyr), 126.2 (*o*-C's, Ar–CO), 125.0, 123.6 (C_4, BzImz and Imz), 118.2 (γ-C, Tyr), 115.3 (C_5, Imz), 112.8 (C_7, BzImz), 58.7, 52.9 (α-C's, His and Tyr), 37.3 (β-C, Tyr), 20.2, 19.1 (5,6-CH_3,

BzImz), 16.7 (β-C, His); MS (*m*/*z*, %): 566 (M^+, 8.5), 549 (5.3), 521 (22.4), 415 (9.8), 386 (30.8), 358 (11.7), 249 (42.7), 221 (100), 146 (22.6), 119 (12.8), 118 (8.4), 107 (12.6), 93 (21.6), 81 (14.6), 67 (12.8), 51 (8.6), 45 (10.7), 39 (7.6), 30 (15.9), 15 (4.7).

6.1.5.4. Compound ***6e**$_a$*. $[\alpha]_D$ −31.0° (*c* 0.3, MeOH); IR (KBr): *ν* 3480, 3470 (N−H str.), 3285−2505 (O−H str. COOH), 3069, 3052 (Ar−H str.), 2997, 2990 (C−H str. cyclic CH_2), 2958, 2920 (C−H str. CH_3 and CH_2), 1710 (C=O str. COOH), 1652, 1626 (C=O str. amide), 1558, 1424, 1416 (skeletal bands), 1467 (C−H def. CH_2), 1405, 888, 875, 868, 597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.50 (br s, 3H, NH's, BzImz, Imz and OH, COOH), 8.89 (br s, 1H, NH, amide), 8.45 (ss, 2H, *o*-H's, Ar−CO), 7.69 (d, 1H, *J* = 7.95 Hz, β-H, Imz), 7.49 (s, 1H, δ-H, Imz), 7.26 (ss, 2H, δ- and η-H, BzImz), 5.85 (q, 1H, *J* = 8.95 Hz, α-H, His), 4.11 (t, 1H, *J* = 6.85 Hz, α-H, Pro), 3.38 (t, 2H, *J* = 7.2 Hz, δ-H's, Pro), 2.94 (d, 2H, *J* = 5.85 Hz, β-H's, His), 2.27 (ss, 6H, ε- and ζ-CH_3, BzImz), 2.06−1.97 (m, 4H, β- and γ-H's, Pro); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 177.2 (C=O, COOH), 168.2 (C=O, Ar−CO), 163.5 (C=O, amide), 155.2 (C_2, BzImz), 142.6 (C_4, Ar−CO), 140.3 (C_2, Imz), 138.7 ($C_{2'}$, BzImz), 136.2 (*o*-C's, Ar−CO), 135.1 ($C_{3'}$, BzImz), 134.3 (C_1, Ar−CO), 133.7 (C_5, BzImz), 132.4 (C_6, BzImz), 128.3 (C_4, Imz), 122.6 (C_4, BzImz), 116.5 (C_5, Imz), 112.4 (C_7, BzImz), 104.6 (*m*-C's, Ar−CO), 60.4 (α-C, Pro), 57.3 (α-C, His), 46.2 (δ-C, Pro), 30.1 (β-C, Pro), 24.0 (γ-C, Pro), 20.1, 19.5 (5,6-CH_3, BzImz), 16.8 (β-C, His); MS (*m*/*z*, %): 752 (M^+, 2.8), 735 (8.7), 707 (16.2), 638 (24.5), 610 (11.6), 501 (100), 473 (19.6), 329 (14.2), 203 (8.2), 146 (25.7), 127 (10.3), 119 (11.5), 118 (12.2), 81 (9.4), 67 (8.8), 45 (10.5), 42 (9.2), 15 (4.6).

6.1.5.5. Compound ***6f**$_a$*. $[\alpha]_D$ −6.4° (*c* 0.3, MeOH); IR (KBr): *ν* 3488, 3125 (N−H str.), 3369 (O−H str., Tyr), 3295−2520 (O−H str. COOH), 3068, 3044, 3030 (Ar−H str.), 2960, 2956, 2915 (C−H str. CH_3 and CH_2), 1708 (C=O str. COOH), 1636, 1624 (C=O str. amide), 1559, 1422, 1418 (skeletal bands), 1530, 1526 (NH def. amide), 1462 (C−H def. CH_2), 1403, 1269, 883, 870, 823, 692, 596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.98 (br s, 1H, NH, amide), 9.34 (br s, 1H, NH, amide), 8.82 (br s, 3H, NH, OH's, BzImz and Tyr, COOH), 8.46 (ss, 2H, *o*-H's, Ar−CO), 7.67 (br s, 1H, NH, amide), 7.27 (ss, 2H, δ- and η-H, BzImz), 6.99 (dd, 2H, *J* = 8.65, 4.95 Hz, *m*-H's, Tyr), 6.90 (dd, 2H, *J* = 8.5, 5.2 Hz, *o*-H's, Tyr), 4.87 (q, 1H, *J* = 8.0 Hz, α-H, Tyr), 4.80−4.72 (m, 1H, α-H, Ala), 4.18 (d, 2H, *J* = 5.1 Hz, CH_2, Gly), 2.79 (d, 2H, *J* = 5.5 Hz, β-H's, Tyr), 2.26 (ss, 6H, ε- and ζ-CH_3, BzImz), 1.25 (d, 3H, *J* = 5.9 Hz, β-H's, Ala); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 177.2 (C=O, COOH), 168.3 (C=O, amide), 167.2 (C=O, amide), 162.0 (C=O, Ar−CO), 155.9 (C_2, BzImz), 153.2 (C−OH, Tyr), 142.8 (C_1, Ar−CO), 138.2 (*m*-C's, Ar−CO), 137.8 ($C_{2'}$, BzImz), 135.9 (C_4, Ar−CO), 134.4 ($C_{3'}$, BzImz), 133.8 (C_5, BzImz), 131.6 (C_6, BzImz), 129.5 (*o*-C's, Tyr), 127.8 (γ-C, Tyr), 125.1 (*m*-C's, Tyr), 121.7 (C_4, BzImz), 114.9 (C_7, BzImz), 104.4 (*o*-C's, Ar−CO), 52.4 (α-C, Ala), 48.8 (α-C, Tyr), 42.0 (CH_2, Gly), 37.1 (β-C, Tyr), 20.1, 18.6 (5,6-CH_3, BzImz), 17.9 (β-C, Ala).

6.1.5.6. Compound ***6g**$_a$*. $[\alpha]_D$ −37.0° (*c* 0.3, MeOH); IR (KBr): *ν* 3477, 3120 (N−H str.), 3290−2515 (O−H str. COOH), 3066, 3050 (Ar−H str.), 2998, 2995 (C−H str. cyclic CH_2), 2962, 2925 (C−H str. CH_3 and CH_2), 1712 (C=O str. COOH), 1656, 1629 (C=O str. amide), 1558, 1425, 1420 (skeletal bands), 1460 (C−H def. CH_2), 1408, 1388, 1372, 882, 872, 768, 708, 592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.72 (br s, 2H, NH, OH, BzImz and COOH), 9.35 (br s, 1H, NH, amide), 8.45 (ss, 2H, *o*-H's, Ar−CO), 7.82 (br s, 1H, NH, amide), 7.28 (ss, 2H, δ- and η-H, BzImz), 7.17 (tt, 2H, *J* = 6.15, 4.35 Hz, *m*-H's, Phe), 7.01 (t, 1H, *J* = 6.15 Hz, *p*-H, Phe), 6.84 (dd, 2H, *J* = 8.8, 4.15 Hz, *o*-H's, Phe), 4.90 (t, 1H, *J* = 5.85 Hz, α-H, Val), 4.37 (q, 1H, *J* = 5.5 Hz, α-H, Phe), 3.78 (t, 1H, *J* = 6.85 Hz, α-H, Pro), 3.14 (t, 2H, *J* = 7.2 Hz, δ-H, Pro), 2.76 (d, 2H, *J* = 5.6 Hz, β-H's, Phe), 2.26 (ss, 6H, ε- and ζ-CH_3, BzImz), 2.08−1.95 (m, 4H, β- and γ-H's, Pro), 1.57−1.44 (m, 1H, β-H, Val), 0.97 (d, 6H, *J* = 4.6 Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 178.2 (C=O, COOH), 168.5 (C=O, amide), 166.9 (C=O, *tert*. amide), 165.6 (C=O, Ar−CO), 156.9 (C_2, BzImz), 144.6 (C_1, Ar−CO), 139.9 (γ-C, Phe), 138.7 (*m*-C's, Ar−CO), 136.4 ($C_{2'}$, BzImz), 137.0 (C_4, Ar−CO), 134.9 ($C_{3'}$, BzImz), 133.7 (C_5, BzImz), 131.8 (C_6, BzImz), 130.1 (*o*-C's, Phe), 128.2 (*m*-C's, Phe), 126.4 (*p*-C, Phe), 122.5 (C_4, BzImz), 114.4 (C_7, BzImz), 103.2 (*o*-C's, Ar−CO), 61.0 (α-C, Pro), 54.3 (α-C, Phe), 52.6 (α-C, Val), 45.5 (δ-C, Pro), 37.9 (β-C, Phe), 30.0 (β-C, Val), 28.3, 23.4 (β- and γ-C's, Pro), 19.8, 18.9 (5,6-CH_3, BzImz), 17.9 (γ-C's, Val); MS (*m*/*z*, %): 861 (M^+, 5.4), 844 (7.8), 816 (11.7), 747 (20.1), 719 (10.3), 648 (100), 620 (11.4), 501 (26.7), 473 (18.8), 329 (14.3), 203 (7.8), 146 (23.7), 127 (11.4), 119 (10.2), 118 (12.9), 91 (15.4), 77 (6.5), 65 (8.9), 45 (8.1), 43 (7.2), 29 (11.5), 15 (2.6).

6.1.5.7. Compound ***7c**$_a$*. $[\alpha]_D$ −14.8° (*c* 0.3, MeOH); IR (KBr): *ν* 3488, 3115 (N−H str.), 3359 (O−H str., Ar−CO), 3295−2510 (O−H str. COOH), 3062, 3025 (Ar−H str.), 2920, 2848 (C−H str. CH_2), 1715 (C=O str. COOH), 1642, 1632 (C=O str. amide), 1587, 1430 (skeletal bands), 1548, 1539, 1410, 1348, 1196, 871, 842, 827, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.96 (s, 1H, ζ-H, Ar−CO), 8.59 (d, 1H, *J* = 7.45 Hz, δ-H, Ar−CO), 8.40 (s, 1H, η-H, BzImz), 8.25 (br s, 3H, NH, BzImz and OH's, Ar−CO, COOH), 8.13 (br s, 1H, NH, amide), 8.10 (br s, 1H, NH, amide), 8.03 (d, 1H, *J* = 7.8 Hz, ε-H, BzImz), 7.66 (d, 1H, *J* = 7.6 Hz, δ-H, BzImz), 7.01 (d, 1H, *J* = 7.2 Hz, γ-H, Ar−CO), 4.17 (d, 2H, *J* = 5.1 Hz, CH_2, Gly^2), 3.89 (d, 2H, *J* = 5.1 Hz, CH_2, Gly^1); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 179.2 (C=O, COOH), 168.2 (C=O, amide), 166.7 (C=O, Ar−CO), 156.8 (C_2, Ar−CO), 153.2 (C_2, BzImz), 143.1 ($C_{3'}$, BzImz), 141.0 (C_6, BzImz), 139.2 ($C_{2'}$, BzImz), 135.6 (C_4, Ar−CO), 127.0 (C_6, Ar−CO), 123.9 (C_1, Ar−CO), 120.7 (C_5, Ar−CO),

119.2 (C_4, BzImz), 118.8 (C_5, BzImz), 116.2 (C_3, Ar–CO), 108.7 (C_7, BzImz), 40.7, 39.8 (CH_2, Gly^1 and Gly^2).

6.1.5.8. Compound ***7d**$_a$*. $[\alpha]_D$ −69.1° (*c* 0.3, MeOH); IR (KBr): *ν* 3494, 3130 (N–H str.), 3357 (O–H str., Ar–CO), 3290–2515 (O–H str. COOH), 3057, 3052 (Ar–H str.), 2995, 2989 (C–H str., cyclic CH_2), 2958, 2872 (C–H str. CH_3), 1716 (C=O str. COOH), 1660, 1636 (C=O str. amide), 1568, 1426 (skeletal bands), 1544, 1495, 1414, 1347, 1201, 870, 843, 828, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.30 (br s, 1H, NH, amide), 8.91 (s, 1H, ζ-H, Ar–CO), 8.70 (br s, 3H, NH, BzImz and OH's, Ar–CO, COOH), 8.60 (d, 1H, $J = 7.2$ Hz, δ-H, Ar–CO), 8.42 (s, 1H, η-H, BzImz), 8.02 (d, 1H, $J = 7.75$ Hz, ε-H, BzImz), 7.65 (d, 1H, $J = 7.6$ Hz, δ-H, BzImz), 7.00 (d, 1H, $J = 7.15$ Hz, γ-H, Ar–CO), 4.86–4.77 (m, 1H, α-H, Ala), 4.10 (t, 1H, $J = 6.85$ Hz, α-H, Pro), 3.50 (t, 2H, $J = 7.2$ Hz, δ-H's, Pro), 2.69–2.64 (m, 2H, β-H's, Pro), 2.04–1.93 (m, 2H, γ-H's, Pro), 1.34 (d, 3H, $J = 5.9$ Hz, β-H's, Ala); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 177.4 (C=O, COOH), 170.2 (C=O, amide), 165.4 (C=O, Ar–CO), 156.9 (C_2, Ar–CO), 153.2 (C_2, BzImz), 144.6 ($C_{3'}$, BzImz), 141.1 (C_6, BzImz), 140.0 ($C_{2'}$, BzImz), 135.8 (C_4, Ar–CO), 125.4 (C_6, Ar–CO), 123.9 (C_1, Ar–CO), 120.5 (C_5, Ar–CO), 119.6 (C_5, BzImz), 118.4 (C_4, BzImz), 116.2 (C_3, Ar–CO), 110.7 (C_7, BzImz), 62.4 (α-C, Pro), 45.2 (α-C, Ala), 42.5 (δ-C, Pro), 30.4 (γ-C, Pro), 26.3, 17.6 (β-C's, Pro and Ala); MS (*m*/*z*, %): 467 (M^+, 5.9), 450 (9.4), 422 (16.6), 379 (100), 351 (19.6), 282 (44.8), 254 (19.3), 163 (15.2), 136 (11.8), 135 (25.3), 66 (9.9), 65 (16.5), 46 (11.6), 45 (10.4), 42 (19.5), 17 (2.1).

6.1.5.9. Compound ***7e**$_a$*. $[\alpha]_D$ −50.0° (*c* 0.3, MeOH); IR (KBr): *ν* 3489 (N–H str.), 3360 (O–H str., Ar–CO), 3294–2512 (O–H str. COOH), 3055, 3042 (Ar–H str.), 2997–2989 (C–H str., cyclic CH_2), 1709 (C=O str. COOH), 1660, 1654 (C=O str. *tert*. amide), 1565, 1432 (skeletal bands), 1542, 1492, 1410, 1350, 1203, 869, 843, 826, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.91 (s, 1H, ζ-H, Ar–CO), 8.60 (d, 1H, $J = 7.5$ Hz, δ-H, Ar–CO), 8.42 (s, 1H, η-H, BzImz), 8.20 (br s, 3H, NH, BzImz and OH's, Ar–CO, COOH), 8.00 (d, 1H, $J = 7.75$ Hz, ε-H, BzImz), 7.65 (d, 1H, $J = 7.6$ Hz, δ-H, BzImz), 6.99 (d, 1H, $J = 7.2$ Hz, γ-H, Ar–CO), 4.40 (t, 1H, $J = 6.8$ Hz, α-H, Pro^3), 4.20 (t, 1H, $J = 6.85$ Hz, α-H, Pro^1), 4.04 (t, 1H, $J = 6.85$ Hz, α-H, Pro^2), 3.77–3.63 (m, 4H, δ-H's, $Pro^{2,3}$), 3.43 (t, 2H, $J = 7.15$ Hz, δ-H's, Pro^1), 2.78–2.71 (m, 4H, β-H's, $Pro^{1,2}$), 2.06–1.87 (m, 8H, β-H's, Pro^3 and γ-H's, Pro^{1-3}); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 178.7 (C=O, COOH), 170.2 (C=O, Ar–CO), 166.8, 161.9 (C=O, *tert*. amide), 157.0 (C_2, Ar–CO), 153.0 (C_2, BzImz), 143.6 ($C_{3'}$, BzImz), 141.0 (C_6, BzImz), 139.6 ($C_{2'}$, BzImz), 135.7 (C_4, Ar–CO), 127.6 (C_6, Ar–CO), 124.0 (C_1, Ar–CO), 119.9 (C_5, Ar–CO), 119.2 (C_5, BzImz), 118.9 (C_4, BzImz), 116.7 (C_3, Ar–CO), 110.2 (C_7, BzImz), 59.2, 58.6, 56.0 (α-C's, Pro^{1-3}), 46.4, 44.2, 42.9 (δ-C's, Pro^{1-3}), 29.7, 29.2, 27.8 (β-C's, Pro^{1-3}), 28.4, 24.0, 23.5 (γ-C's, Pro^{1-3}); MS (*m*/*z*, %): 590 (M^+, 6.8), 573 (9.3), 545 (15.8), 476 (48.7), 448 (12.9), 379 (100), 351 (14.8), 282 (49.7), 254 (16.8), 163 (16.5), 136 (11.5), 135 (26.9), 66 (10.6), 65 (15.8), 46 (10.3), 45 (11.8), 42 (18.1), 17 (1.8).

6.1.5.10. Compound ***8e**$_a$*. $[\alpha]_D$ −54.9° (*c* 0.3, MeOH); IR (KBr): *ν* 3495, 3492, 3124 (N–H str.), 3362, 3355 (O–H str., Ar–CO and Tyr), 3282–2518 (O–H str. COOH), 3065, 3033, 3023 (Ar–H str.), 2965, 2926, 2922 (C–H str. CH_3 and CH_2), 1712 (C=O str. COOH), 1645, 1632 (C=O str. amide), 1546, 1425, 1416 (skeletal bands), 1533, 1526 (NH def. amide), 1465, 1446, 1407, 1196, 876, 822, 819, 739, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.95 (s, 1H, ζ-H, Ar–CO), 8.59 (d, 1H, $J = 7.55$ Hz, δ-H, Ar–CO), 8.14 (br s, 1H, NH, amide), 8.03 (br s, 5H, NH's, BzImz, Indole and OH's, Ar–CO, Tyr, COOH), 7.97 (br s, 1H, NH, amide), 7.53 (br s, 1H, NH, amide), 7.31 (s, 1H, δ-H, BzImz), 7.30 (s, 1H, η-H, BzImz), 7.25 (d, 1H, $J = 7.8$ Hz, β-H, Indole), 7.23–7.07 (m, 6H, δ–η-H's, Indole and *o*-H's, Tyr), 7.02 (d, 1H, $J = 7.25$ Hz, γ-H, Ar–CO), 6.76 (dd, 2H, $J = 8.6$ Hz, *m*-H's, Tyr), 4.94 (q, 1H, $J = 6.15$ Hz, α-H, Trp), 4.79–4.72 (m, 1H, α-H, Ala), 4.16 (q, 1H, $J = 8.0$ Hz, α-H, Tyr), 3.23–2.95 (m, 4H, β-H's, Trp and Tyr), 2.27 (s, 3H, ε-CH_3, BzImz), 2.26 (s, 3H, ζ-CH_3, BzImz), 1.50 (d, 3H, $J = 5.85$ Hz, β-H's, Ala); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 173.4 (C=O, COOH), 172.0, 169.2 (C=O, amide), 167.8 (C=O, Ar–CO), 158.0 (C_2, Ar–CO), 154.6 (*p*-C, Tyr), 153.2 (C_2, BzImz), 139.7, 137.2 ($C_{2',3'}$, BzImz), 136.0 ($C_{2'}$, Indole), 134.7 (C_4, Ar–CO), 133.9, 132.4 ($C_{5,6}$, BzImz), 129.5, 128.1 (*o*- and *m*-C's, Tyr), 127.3 ($C_{3'}$, Indole), 126.2 (C_4, BzImz), 124.6 (C_6, Ar–CO), 122.7 (C_2, Indole), 121.9 (C_5, Ar–CO), 121.2 (C_1, Ar–CO), 120.6, 119.2 ($C_{5,6}$, Indole), 118.6 (C_3, Ar–CO), 118.0 (C_4, Indole), 116.5 (γ-C, Tyr), 114.1 (C_7, BzImz), 111.2 (C_7, Indole), 109.5 (C_3, Indole), 62.5 (α-C, Trp), 57.3 (α-C, Ala), 51.1 (α-C, Tyr), 36.3 (β-C, Tyr), 30.5 (β-C, Trp), 20.4, 18.9 (5,6-CH_3, BzImz), 17.8 (β-C, Ala).

6.1.5.11. Compound ***8f**$_a$*. $[\alpha]_D$ −1.7° (*c* 0.3, MeOH); IR (KBr): *ν* 3495, 3136, 3120 (N–H str.), 3361 (O–H str. ArCO), 3295–2510 (O–H str. COOH), 3058, 3030 (Ar–H str.), 2962, 2958, 2877 (C–H str. CH_3), 1715 (C=O str. COOH), 1645, 1629 (C=O str. amide), 1540, 1422 (skeletal bands), 1536 (NH def. amide), 1452, 1406, 1390, 1361, 1198, 880, 826, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.33 (br s, 1H, NH, amide), 8.91 (s, 1H, ζ-H, Ar–CO), 8.60 (d, 1H, $J = 7.55$ Hz, δ-H, Ar–CO), 8.38 (br s, 3H, NH, BzImz and OH's, ArCO, COOH), 8.32 (br s, 1H, NH, amide), 7.31 (s, 1H, δ-H, BzImz), 7.29 (s, 1H, η-H, BzImz), 7.04 (d, 1H, $J = 7.2$ Hz, γ-H, Ar–CO), 7.01 (br s, 1H, NH, amide), 5.02 (t, 1H, $J = 5.8$ Hz, α-H, Val), 4.47–4.40 (m, 1H, α-H, Ala^1), 3.45–3.39 (m, 1H, α-H, Ala^2), 2.27 (s, 3H, ε-CH_3, BzImz), 2.24 (s, 3H, ζ-CH_3, BzImz), 1.58–1.53 (m, 1H, β-H, Val), 1.49 (d, 3H, $J = 5.9$ Hz, β-H's, Ala^1), 1.35 (d, 3H, $J = 5.9$ Hz, β-H's, Ala^2), 0.97 (d, 6H, $J = 4.6$ Hz, γ-H's, Val); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 178.3 (C=O, COOH), 168.7, 167.5 (C=O, amide), 164.6 (C=O, Ar–CO), 156.0 (C_2, Ar–CO), 153.2 (C_2, BzImz), 142.6, 140.1 ($C_{3',2'}$, BzImz),

135.6 (C_4, Ar–CO), 133.8, 132.3 ($C_{5,6}$, BzImz), 127.9 (C_4, BzImz), 125.5 (C_6, Ar–CO), 124.0 (C_1, Ar–CO), 121.8 (C_5, Ar–CO), 118.5 (C_3, Ar–CO), 114.3 (C_7, BzImz), 58.9 (α-C, Val), 55.0 (α-C, Ala^1), 47.8 (α-C, Ala^2), 28.5 (β-C, Val), 20.0, 19.3 (5,6-CH_3, BzImz), 18.5 (γ-C's, Val), 18.2 (β-C, Ala^1), 17.6 (β-C, Ala^2); MS (*m/z*, %): 523 (M^+,4.5), 506 (8.3), 478 (13.4), 435 (28.2), 407 (15.5), 336 (100), 308 (20.4), 265 (31.5), 237 (11.8), 146 (21.4), 119 (11.1), 118 (15.3), 66 (11.3), 65 (15.9), 45 (10.4), 43 (12.7), 29 (8.8), 17 (4.5), 15 (5.2).

6.1.5.12. Compound ***8g**$_a$*. $[\alpha]_D$ −17.4° (*c* 0.3, MeOH); IR (KBr): *ν* 3490, 3486, 3128 (N–H str.), 3352 (O–H str. ArCO), 3290–2515 (O–H str. COOH), 3066, 3042, 3035 (Ar–H str.), 2960, 2926, 2852 (C–H str. CH_3 and CH_2), 1716 (C=O str. COOH), 1633 (C=O str. amide), 1540, 1415 (skeletal bands), 1535 (NH def. amide), 1446, 1402, 1198, 877, 873, 825, 741, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.95 (s, 1H, ζ-H, Ar–CO), 8.65 (br s, 5H, NH's, BzImz, Indole, Imz and OH's, Ar–CO, COOH), 8.58 (d, 1H, $J = 7.55$ Hz, δ-H, Ar–CO), 8.26 (br s, 1H, NH, amide), 8.14 (br s, 1H, NH, amide), 8.03 (d, 1H, $J = 7.95$ Hz, β-H, Imz), 7.75 (br s, 1H, NH, amide), 7.65 (s, 1H, δ-H, Imz), 7.31 (s, 1H, δ-H, BzImz), 7.30 (s, 1H, η-H, BzImz), 7.25 (d, 1H, $J = 7.85$ Hz, β-H, Indole), 7.23–7.06 (m, 4H, δ–η-H's, Indole), 7.02 (d, 1H, $J = 7.2$ Hz, γ-H, Ar–CO), 6.57 (br s, 1H, NH, amide), 4.44 (q, 1H, $J = 6.1$ Hz, α-H, Trp), 4.38 (q, 1H, $J = 8.95$ Hz, α-H, His), 3.95 (d, 2H, $J = 5.15$ Hz, CH_2, Gly^1), 3.80 (d, 2H, $J = 5.15$ Hz, CH_2, Gly^2), 3.21–2.96 (m, 4H, β-H's, Trp and His), 2.27 (s, 3H, ε-CH_3, BzImz), 2.26 (s, 3H, ζ-CH_3, BzImz); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 176.5 (C=O, COOH), 174.6, 170.7, 167.5 (C=O, amide), 165.3 (C=O, Ar–CO), 158.4 (C_2, Ar–CO), 153.2 (C_2, BzImz), 140.1 (C_2, Imz), 138.9, 137.2 ($C_{2',3'}$, BzImz), 136.1 ($C_{2'}$, Indole), 135.6 (C_4, Ar–CO), 133.9, 132.5 ($C_{5,6}$, BzImz), 129.3 (C_4, Imz), 127.2 ($C_{3'}$, Indole), 126.1 (C_4, BzImz), 124.9 (C_6, Ar–CO), 124.0 (C_1, Ar–CO), 122.3 (C_2, Indole), 121.5 (C_5, Ar–CO), 120.2, 119.5, 118.4 (C_{4-6}, Indole), 117.5 (C_3, Ar–CO), 116.1 (C_5, Imz), 114.0 (C_7, BzImz), 111.2 (C_7, Indole), 109.5 (C_3, Indole), 56.5 (α-C, Trp), 51.1 (α-C, His), 46.5 (CH_2, Gly^2), 41.3 (CH_2, Gly^1), 30.2 (β-C, Trp), 20.4 (β-C, His), 19.5, 18.7 (5,6-CH_3, BzImz); MS (*m/z*, %): 719 (M^+,6.7), 702 (9.3), 674 (14.7), 565 (100), 537 (14.3), 508 (27.4), 480 (20.3), 322 (14.4), 294 (20.2), 265 (31.5), 237 (14.8), 146 (23.6), 130 (12.8), 119 (11.8), 118 (14.1), 116 (18.3), 81 (17.5), 67 (10.3), 66 (14.2), 65 (18.5), 45 (9.8), 30 (7.9), 17 (6.1), 15 (5.3).

6.2. Biological experimental section

6.2.1. Antibacterial studies

The synthesized peptide derivatives were screened for their antibacterial activity against two gram positive bacterial strains *B. subtilis*, *S. aureus* and two gram negative bacterial strains *P. aeruginosa*, *E. coli* by using modified Kirby–Bauer disc diffusion method. MIC values of test compounds were determined by tube dilution technique. All the synthesized compounds were dissolved separately to prepare a stock solution of 1 mg mL^{-1} using DMF. Stock solution was aseptically transferred and suitably diluted with sterile broth medium to have seven different concentrations of each test compound ranging from 200 to 3.1 μg mL^{-1} in different test tubes. All the tubes were inoculated with one loopful of one of the test bacteria. The process was repeated with different test bacteria and different samples. Tubes inoculated with bacterial cultures were incubated at 37 °C for 18 h and the presence/absence of growth of the bacteria was observed. From these results, MIC of each test compound was determined against each test bacterium. A spore suspension in sterile distilled water was prepared from five-days-old culture of the test bacteria growing on nutrient broth media. About 20 mL of the growth medium was transferred into sterilized petri plates and inoculated with 1.5 mL of the spore suspension (spore concentration − 6×10^4 spores mL^{-1}). Filter paper disks of 6 mm diameter and 2 mm thickness were sterilized by autoclaving at 121 °C (15 psig) for 15 min. Each petri plate was divided into five equal portions along the diameter to place one disc. Three discs of test sample were placed on three portions together with one disc with reference drug ciprofloxacin and a disk impregnated with the solvent (DMF) as negative control. Test sample and reference drugs were tested at the concentration of 10 μg mL^{-1}. The petri plates inoculated with bacterial cultures were incubated at 37 °C for 18 h. Diameters of the zones of inhibition (mm) were measured and the average diameters for test sample were calculated in triplicate sets. The diameters obtained for the test sample were compared with that produced by the standard drug ciprofloxacin. The results of antibacterial studies are presented in Table 2.

6.2.2. Antifungal studies

Serial plate dilution method was used in the present study for the evaluation of antifungal activity against diamorphic fungal strain *C. albicans* and three other fungal strains, including *A. niger* and two cutaneous fungal strains *M. audouinii* and *T. mentagrophytes*. MIC values of test compounds were determined by employing the same technique as used for antibacterial studies using DMSO instead of DMF and tubes inoculated with fungal cultures were incubated at 37 °C for 48 h. After incubation, the presence/absence of growth of the fungi was observed and MIC of test compounds was determined against each test fungus. A spore suspension in normal saline was prepared from culture of the test fungi on sabouraud's broth media. After transferring growth medium, petri plates were inoculated with spore suspension. After drying, wells were made using an agar punch and test samples, reference drug and negative control (DMSO) were placed in labeled wells in each Petri plate. Test samples and reference drug, griseofulvin, were tested at 10 μg mL^{-1} concentration. The petri plates inoculated with fungal cultures were incubated at 37 °C for 48 h. Antifungal activity was determined by measuring the diameter of the inhibition zone for triplicate sets. Activity of each compound was compared with griseofulvin as standard drug. The results of antifungal studies are given in Table 2 along with the results of antibacterial studies.

6.2.3. Anthelmintic studies

Anthelmintic activity studies were carried out against three different species of earthworms *M. konkanensis*, *P. corethruses* and *Eudrilus* sp. by Garg and Atal method at 2 mg mL^{-1} concentration. Suspensions of samples were prepared by triturating synthesized compounds (100 mg) with Tween 80 (0.5%) and distilled water and the resulting mixtures were stirred using a mechanical stirrer for 30 min. The suspensions were diluted to contain 0.2% w/v of the test samples. Suspension of reference drug, mebendazole, was prepared with the same concentration in a similar way. Three sets of five earthworms of almost similar sizes (2 inch in length) were placed in Petri plates of 4 inch diameter containing 50 mL of suspension of test sample and reference drug at RT. Another set of five earthworms was kept as control in 50 mL suspension of distilled water and Tween 80 (0.5%). The paralyzing and death times were noted and their mean was calculated for triplicate sets. The death time was ascertained by placing the earthworms in warm water (50 °C) which stimulated the movement, if the worm was alive. The results of anthelmintic studies are tabulated in Table 3.

6.2.4. Cytotoxicity studies

Selected peptide derivatives were subjected to short term in vitro cytotoxicity study at 500–31.5 μg mL^{-1} using 5-fluorouracil (5-FU) as the reference compound. Activity was assessed by determining the percentage inhibition of DLA and EAC cells according to the Kuttan method. Both cells were cultured in the peritoneal cavity of healthy albino mice by injecting the suspension of cells (1×10^6 cells/mL) intraperitoneally. After 15–20 days, cells were withdrawn from the peritoneal cavity of the mice with the help of sterile syringe and counted using haemocytometer and adjusted to 1×10^6 cells/mL. Different dilution of all selected compounds ranging from 500 to 31.25 μg mL^{-1} were prepared in Dulbeccos minimum essential medium and 0.1 mL of each diluted test compound was added to 0.1 mL of DLA cells (1×10^6 cells/mL) and EAC cells (1×10^6 cells/mL). Resulted suspensions were incubated at 37 °C for 3 h. After 3 h, tryphan blue dye exclusion test was performed and percentage growth inhibition was calculated. Selected compounds **8g** and **$8g_a$** were also tested at lower concentrations of 15.63–3.91 μg mL^{-1} using 5-fluorouracil (5-FU) as reference compound. CTC_{50} values were determined by graphical extrapolation method. Controls were also tested at 500–3.91 μg mL^{-1} against both cell lines. The results of cytotoxicity studies are listed in Table 4.

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