Article

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Facile Synthesis of Novel Amino Acids Derivatives as Potential Antibacterial Agents using Sustainable Materials

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Following the principles of green chemistry, cardanol derivatives have been used as renewable, low-cost, and available natural starting materials to construct a variety of protected and unprotected amino acids derivatives. The reaction of cardanol derivatives with different phthaloylamino acids including glycine, alanine, phenylalanine, and valine in the presence *N,N'*-dicyclohexylcarbodiimide (DCC) as coupling reagent afforded high yields of the target compounds. Deprotection of phthaloylamino acids derivatives was achieved by heating with hydrazine hydrate. The chemical structures of all products were confirmed by spectral data (IR, MS, ^{1}H NMR, ^{13}C NMR) and elemental analyses. Antibacterial evaluation of the synthesized products was performed, which exhibited potent to weak activity in comparison with a standard drug.

Keywords: Cardanol; Hydrogenated cardanol; Phthaloylamino acids; Hydrazide; Antibacterial.

INTRODUCTION

Recently, the utilization of renewable feedstock is one of the most important green chemistry principles used in the development of chemicals and organic synthesis.[1–4] Cardanol is a renewable and inexpensive natural organic molecule that can be easily obtained via the vacuum distillation of cashew nut shell liquid (CNSL) obtained from the spongy mesocarp of cashew nut shells (*Anacardium occidentale* L.).[5] The oil CNSL and cardanol have a high potential uses in chemical reactions, resulting in products with innumerable applications like surface-active agents, pesticides, insecticides, phenolic resins and surface coatings, biocides, antioxidants, and pharmaceuticals.[6–13] Cardanol is the main component (about 84%) of CNSL, besides smaller percentages of cardol (11%) and methylcardol (4%) (Figure 1). Cardanol itself is a mixture of 3-(pentadeca-8-enyl)phenol, 3-*n*-pentadecylphenol, 3-(pentadeca-8,11-dienyl)phenol, and 3-(pentadeca-8,11,14-trienyl)phenol (**1a–1d**, respectively).[5] Purification of cardanol afforded 3-(pentadeca-8-enyl)phenol (**1a)** as the main component (95%), so this monoolefinic phenol will be referred to as cardanol.

Amino acid derivatives have been reported to be biologically active as antibacterial,[14–16] antifungal,[17,18] antioxidant,[19] pseudo analogs of the naturally occurring antibiotic sparsomyci,[20] anti-inflammatory,[21] and anticonvulsant agents.[22] They are used also as reactive substrates in the design of bioactive molecules for cancer treatment.[23–25]

Guided by the previous observations, and in continuation of our ongoing interest in the synthesis of biologically active molecules,[26–30] several new cardanol derivatives conjugated with flexible protected and unprotected amino acids as side chains have been designed. This combination has been suggested as an effective means of evaluating the effect of different amino acids on the bioactivity of cardanol derivatives, and therefore these products were tested for their antibacterial activity.

RESULTS AND DISCUSSION

Chemistry

The reaction of cardanol and hydogenated cardanol (3-*n*-pentadecylphenol) (**1a** and **1b)** with N-protected amino acids, namely phthaloylglycine, phthaloylalanine, phthaloylphenylalanine, and phthaloylvaline (**2a–2d)** in tetrahydrofuran in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) afforded the target products **3a–3d** and **5a–5d**, respectively. DCC has

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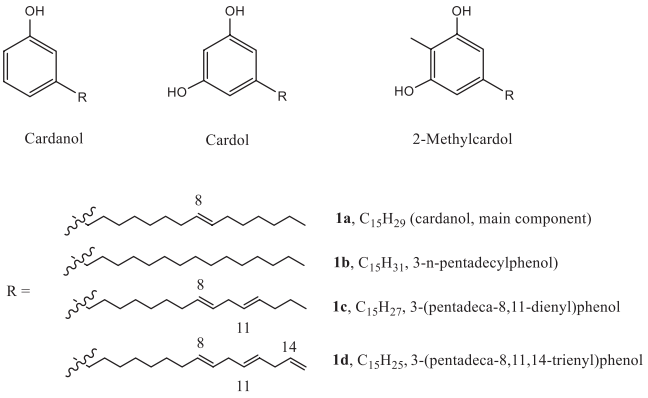
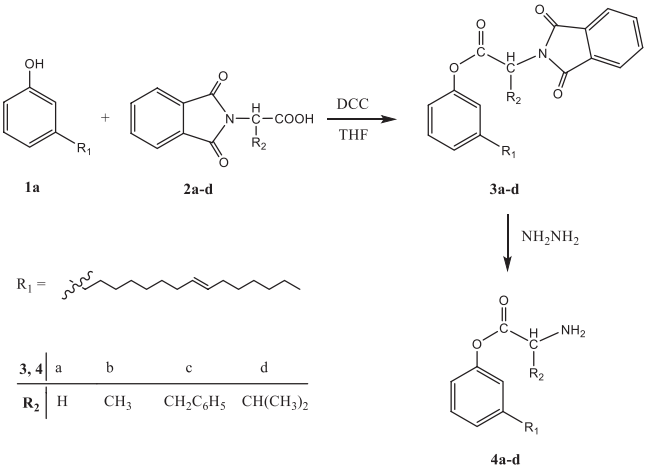


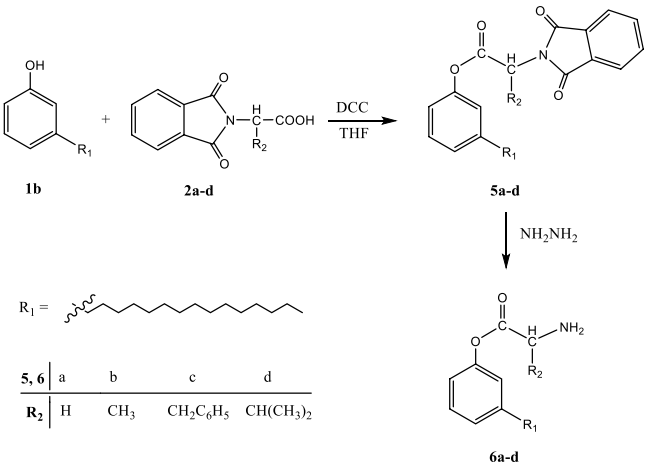
Fig. 1. Main components of cashew nut shell liquid (CNSL).

achieved popularity mainly because of its high-yielding amide and ester coupling reactions and the fact that it is quite inexpensive. Deprotection of phthaloylamino acids derivatives **3a–3d** and **5a–5d** by hydrazine hydrate under refluxing in ethanol afforded the free amino acids derivatives **4a–4d** and **6a–6d**, (Schemes 1 and 2). The structures of compounds were established by both spectral and elemental analyses. The infrared spectra of free amino acids derivatives **4a–4d** and **6a–6d** showed the absorption peaks of amino group at 3335–3180 cm^{-1} and the absence of imide carbonyls in 1775–1725 cm^{-1} range. Also, disappearance of hydroxyl signal of cardanol and hydrogenated cardanol in ^1H NMR spectra and the presence of amino signal confirmed the chemical structures.

An extension of this study, 2-(3-pentadecylphenoxy)acetohydrazide **8** was allowed to react with the



Scheme 1. Synthesis of protected and unprotected amino acids from cardanol **1a**.

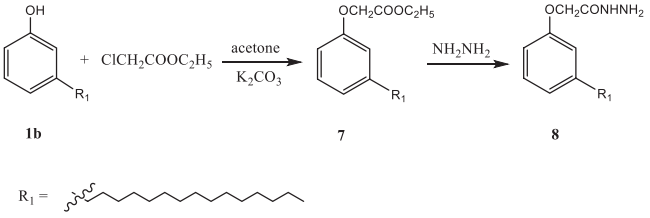


Scheme 2. Synthesis of protected and unprotected amino acids from cardanol **1b**.

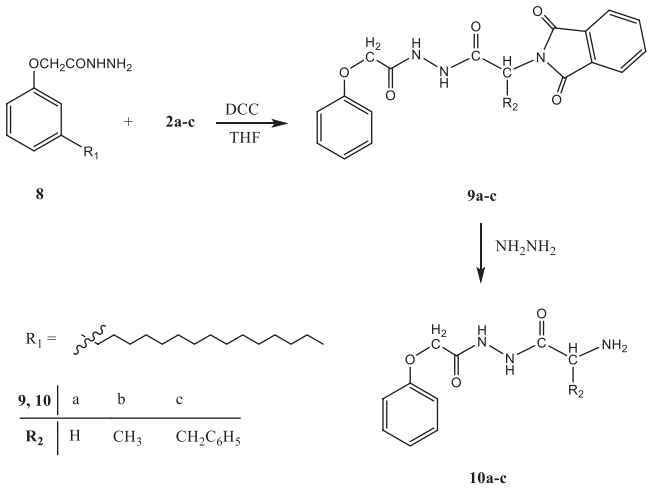
same protected amino acids **2a–2c** to illustrate the effect of the combination of amino acids with different cardanol derivatives in their antibacterial activities.

Thus, the reaction of hydrogenated cardanol **1b** with ethyl chloroacetate in dry acetone in the presence of anhydrous potassium carbonate furnished ethyl-2-(3-pentadecylphenoxy)acetate **7**. The structure of ester **7** was established by its infrared spectrum, which showed the absorption peak of the ester group at 1745 cm^{-1}. Also, the ^1H NMR spectrum exhibited triplet and quartet signals at 1.11 and 4.15 ppm besides a singlet signal at 4.72 ppm of the methylene protons. ^{13}C NMR detected the presence of the carbonyl group at 169.5 ppm. Treatment of ester **7** with hydrazine hydrate gave the target structure 2-(3-pentadecylphenoxy)acetohydrazide **8**. Its infrared spectrum showed the characteristic absorption peaks of NH_2 and NH groups and the absence of the absorption peak of the ester group (Scheme 3).

Treatment of hydrazide **8** with phthaloylamino acids **2a–2c** under the same conditions described above afforded the protected amino acids **9a–9c**. Deprotection



Scheme 3. Synthesis of 2-(3-pentadecylphenoxy) acetohydrazide **8**.



Scheme 4. Synthesis of protected and unprotected amino acids from hydrazide **8**.

of **9a–9c** by hydrazine hydrate furnished free amino acids derivatives **10a–10c** (Scheme 4).

Antibacterial activity

The synthesized products were evaluated for their antibacterial activity against two Gram-positive bacteria *Streptococcus spp.* and *Bacillus subtilis* and two Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*. Ampicillin was used as the standard drug to evaluate the potency of the tested compounds under the same conditions.

Agar diffusion method[31] was used for the determination of the preliminary antibacterial activity, and the results were recorded for each tested compound as the average diameter of inhibition zones (*d*) of bacterial growth around the disks in millimeters at the concentration of 100 μg/mL in dimethyl sulfoxide. The observed data on the antibacterial activity of the compounds and the control drug are given in Table 1.

From the results given in Table 1, it is seen that the synthesized products show varying degrees of inhibition against the tested microorganisms. Most of the tested compounds exhibit high activity against both *E. coli* and *P. aeruginosa*, comparable to that of the standard drug ampicillin. Among the tested products, compounds **4a**, **6a**, **6b**, and **10a** are more potent against all bacteria. Also, the presence of the hydrazide moiety in compounds **8**, **9a**, **10a**, and **10b** enhanced their antibacterial activity against both *E. coli* and *P. aeruginosa*. It is clear that coupling of amino acid derivatives with the starting materials cardanol, saturated cardanol, and hydrazide enhanced their antibacterial activity, especially against Gram-negative bacteria.

EXPERIMENTAL

Materials and instruments

The chemical reagents were purchased from Sigma-Aldrich. Solvents were commercially available from El-nasr Chemicals Co. in analytical grade and were used without further purification. Thin-layerchromatography (TLC) was performed on pre-coated silica gel polyester sheets (Kieselgel 60 F254, 0.20 mm; Merck).

Melting points reported are uncorrected. FT-IR spectra were recorded on a JASCO FT-IR 660 Plus spectrometer; NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer using DMSO and $CDCl_3$ as solvents; and mass spectra were obtained using a Shimadzu GCMS-QP 1000 EX mass spectrometer.

General procedure for the synthesis of 3a–3d and 5a–5d

A mixture of cardanol derivatives **1a** and **1b** (0.01 mol) and phthaloylamino acids **2a–2d**, namely glycine, alanine, phenylalanine, and valine (0.01 mol), was dissolved in tetrahydrofuran (THF) (30 mL). The mixture was cooled to 0°C, and then *N*,*N*-dicyclohexylcarbodiimide (DCC) (0.01 mol) dissolved in THF (10 mL) was added. The reaction mixture was stirred for 24 h at 0°C, which was continued for another 24 h at room temperature. The precipitated *N*,*N*-diclohexylurea was filtered off and removed. The filtrate was evaporated *in vacuo* and the residue was tritrated with 25 mL ethyl acetate. The formed mixture was filtrated off again from *N*,*N*-dicyclohexylurea. The products obtained after evaporation of the filtrate in *vacuo* were filtered off and recrystallized to give **3a–3d** and **5a–5d**.

General procedures for the synthesis of free amino acids 4a–4d and 6a–6d

A mixture of protected amino acid derivatives **3a–3d** or **5a–5d** (0.01 mol) and hydrazine hydrate (0.8 ml) in ethanol (20 mL) was refluxed for 2 h on a water bath and left for 24 h at room temperature. Evaporation of the solvent under vacuum gave a solid material, to which was added water (10 mL), and the solution was

Table 1. Antibacterial activity of compounds **1–10**[a]

Compounds	*Streptococcus* spp.	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
1a	++	+	+	+
1b	++	++	++	-
3a	++	+++	++	++
3b	++	++	+++	+
3c	++	+++	++	+
4a	+++	+++	+++	+++
4b	+++	++	+++	++
4c	+++	+++	+++	++
5a	++	+++	+++	+++
5c	++	+++	+++	+++
6a	+++	+++	+++	+++
6b	+++	+++	+++	+++
8	++	++	+++	+++
9a	+++	+	+++	+++
9b	++	++	++	+++
10a	+++	++	+++	+++
10b	+++	+++	+++	+++
Ampicillin	+++	+++	+++	+++

[a] Inhibition zone diameter: +++ (d > 12 mm, highly active); ++ (d = 9–12 mm, moderately active); + (d = 6–9 mm, slightly active); − (d < 6 mm, inactive).

acidified with AcOH till pH = 6. The reaction mixture was heated for 1 h on a water bath, and the suspension was diluted with water (25 mL), cooled to room temperature, and filtrated off. The filtrate was concentrated and cooled to give a solid, which was recrystallized to give pure powder of **4a–4d** and **6a–6d**.

3-(Pentadec-8-en-1-yl)phenyl-2-(1,3-dioxoisoindolin-2-yl) acetate 3a

Yield: 79%; m.p. 72–74°C. IR spectrum (KBr, ν, cm^{-1}): 2922, 2852 (CH aliphatic), 1772–1719 (CO); ^1H NMR (DMSO, δ ppm): 1.00 (t, 3H, CH_3, J = 7.2 Hz), 1.08–2.27 (m, 22H, $11CH_2$), 2.51 (t, 2H, benzylic CH_2), 3.74 (s, 2H, $COCH_2$), 5.30–5.80 (dd, 2H, vinylic protons), 7.12–7.56 (m, 8H, Ar-H); ^{13}C NMR, 15.6, 22.3, 23.1, 25.7, 26.2, 26.8, 27.5, 28.3, 29.3, 31.5, (aliphatic carbon chain), 42.2 (CH_2 glycine), 114.5, 116.3, 121.5, 122.3, 125.5, 126.4, 126.8, 127.5, 128.3, 128.8, 129.3, 130.5, 131.5, 144.3, 155.5 (aromatic and vinylic carbons), 169.5, 171.3 (CO); MS: m/z = 489 (M^+); Anal. calcd. for $C_{31}H_{39}NO_4$ (489.66): C, 76.04%; H, 8.03%; N, 2.86%. Found: C, 75.95%; H, 7.95%; N, 2.75%.

3-(Pentadec-8-en-1-yl)phenyl-2-(1,3-dioxoisoindolin-2-yl) propanoate 3b

Yield: 83%; m.p. 77–79°C. IR spectrum (KBr, ν, cm^{-1}): 2920, 2851 (CH aliphatic), 1773–1726 (CO); ^1H NMR ($CDCl_3$, δ ppm): 1.05 (t, 3H, CH_3, J = 7.1 Hz), 1.40 (d, 3H, $CHCH_3$, J = 7.1 Hz), 1.30–2.20 (m, 22H, $11CH_2$), 2.53 (t, 2H, benzylic CH_2, J = 7.3 Hz), 4.12–4.17 (q, 1H, $CHCH_3$, J = 7.1 Hz), 6.50–6.80 (dd, 2H, vinylic protons), 6.95–7.80 (m, 8H, Ar-H); ^{13}C NMR, 16.2, 18.7, 21.5, 23.2, 25.4, 25.8, 26.3, 28.1, 28.6, 28.9, 32.1, (aliphatic carbon chain), 55.5 (CH alanine), 115.2, 115.7, 120.0, 121.2, 125.1, 125.4, 126.2, 126.5, 127.0, 127.5, 128.1, 128.4, 129.2, 145.3, 155.3 (aromatic and vinylic carbons), 167.5, 170.2 (CO); MS: m/z = 503 (M^+); Anal. calcd. for $C_{32}H_{41}NO_4$ (503.68): C, 76.31%; H, 8.21%; N, 2.78%. Found: C, 76.24%; H, 8.15%; N, 2.69%.

3-(Pentadec-8-en-1-yl)phenyl-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate 3c

Yield: 77%; m.p. 80–82°C. IR spectrum (KBr, ν, cm^{-1}): 2925, 2848 (CH aliphatic), 1775–1723 (CO); ^1H NMR (DMSO, δ ppm): 1.12 (t, 3H, CH_3, J = 7.2 Hz), 1.39–2.12 (m, 22H, $11CH_2$), 2.46 (t, 2H, benzylic CH_2,

J = 7.4 Hz), 2.91 (d, 2H, $CHCH_2$, J = 7.2 Hz), 4.42 (t, 1H, $CHCH_2$, J = 7.1 Hz), 5.22–5.53 (dd, 2H, vinylic protons), 6.90–7.80 (m, 13H, Ar-H); ^{13}C NMR, 14.5, 22.5, 27.3, 28.2 28.5, 29.5, 29.8, 31.3, 32.5, 35.2, 36.3 (aliphatic carbon chain), 41.5 (CH_2 phenylalanine), 56.5 (CH phenylalanine), 117.5, 118.2, 122.5, 126.5, 127.5, 128.3, 130.5, 132.5, 146.6, 155.1, (aromatic carbons), 167.2, 170.0 (CO); MS: m/z = 579 (M^+), 580 (M^{+1}); Anal. calcd. for $C_{38}H_{45}NO_4$ (579.78): C, 78.72%; H, 7.82%; N, 2.42%. Found: C, 78.64%; H, 7.74%; N, 2.35%.

3-(Pentadec-8-en-1-yl)phenyl-2-(1,3-dioxoisoindolin-2-yl)-3-methylbutanoate 3d

Yield: 84%; m.p. 77–79°C. IR spectrum (KBr, ν, cm^{-1}): 2918, 2849 (CH aliphatic), 1774–1721 (CO); ^{1}H NMR ($CDCl_3$, δ ppm): 0.96 (t, 3H, CH_3, J = 7.2 Hz), 1.05 (d, 6H, $2CH_3$, J = 7.1 Hz), 1.15–2.10 (m, 22H, $11CH_2$), 2.57 (t, 2H, benzylic CH_2, J = 7.3 Hz), 2.90–2.93 (m, 1H, $CH(CH_3)_2$), 4.20 (d, 1H, CH), 5.55–5.68 (dd, 2H, vinylic protons), 7.25–7.80 (m, 8H, Ar-H); ^{13}C NMR, 14.4, 22.5, 23.2, 25.6, 28.3, 29.5, 30.6, 31.2, 32.5, 35.3, 36.7 (aliphatic carbon chain), 18.8 ($2CH_3$ valine), 27.8 (CH valine), 51.2 (CH valine), 118.5, 122.4, 127.5, 127.8, 128.2, 129.3, 136.3, 145.2, 152.5 (aromatic carbons), 170.2, 172.6 (CO); MS: m/z = 531 (M^+); Anal. calcd. for $C_{34}H_{45}NO_4$ (531.74): C, 76.80%; H, 8.53%; N, 2.63%. Found: C, 76.72%; H, 8.42%; N, 2.55%.

3-(Pentadec-8-en-1-yl)phenyl glycinate 4a

Yield: 75%; m.p. 106–108°C. IR spectrum (KBr, ν, cm^{-1}): 3352–3192 (NH_2), 2927, 2853 (CH aliphatic), 1738 (CO); ^{1}H NMR ($CDCl_3$, δ ppm): 1.05 (t, 3H, CH_3, J = 7.1 Hz), 1.18–2.27 (m, 22H, $11CH_2$), 2.53(t, 2H, benzylic CH_2), 4.28 (s, 2H, $COCH_2$), 5.55 (s, 2H, NH_2, exchangeable), 6.52–6.73 (dd, 2H, vinylic protons), 7.05–7.92 (m, 4H, Ar-H); ^{13}C NMR, 16.5, 22.2, 23.5, 27.5, 28.2, 29.5, 30.8, 31.5, 32.5, 33.3, 35.2 (aliphatic carbon chain), 42.5 (CH_2 glycine), 114.3, 119.3, 122,5, 126.5, 127.3, 128,2, 136.3,, 144.5, 147.2 (aromatic carbons), 170.5 (CO); MS: m/z = 359 (M^+); Anal. calcd. for $C_{23}H_{37}NO_2$ (359.55): C, 76.83%; H, 10.37%; N, 3.90%. Found: C, 76.74%; H, 10.30%; N, 3.82%.

3-(Pentadec-8-en-1-yl)phenyl alaninate 4b

Yield: 69%; m.p. 113–115°C. IR spectrum (KBr, ν, cm^{-1}): 3315–3155 (NH_2), 2930, 2862 (CH aliphatic), 1745 (CO); ^{1}H NMR ($CDCl_3$, δ ppm): 0.97 (t, 3H, CH_3, J = 7.1 Hz), 1.12 (d, 3H, $CHCH_3$, J = 7.0 Hz), 1.25–2.20 (m, 22H, $11CH_2$), 2.48(t, 2H, benzylic CH_2, J = 7.2 Hz), 4.10–4.13 (q, 1H, $CHCH_3$, J = 8.2 Hz), 5.42 (s, 2H, NH_2, exchangeable), 6.48–6.81 (dd, 2H, vinylic protons), 7.12–8.02 (m, 4H, Ar-H); ^{13}C NMR, 15.2, 22.3, 22.8, 28,2, 28.5, 29.3, 30.5, 31.7, 32.2, 34.5, 36.5 (aliphatic carbon chain), 18.5 (CH_3 alanine), 49.5 (CH alanine), 115.3, 121.5, 126.3, 127.2, 128.5, 129.2, 135.5, 144.3, 148.5 (aromatic carbons), 169.5 (CO); MS: m/z = 373 (M^+), 374 (M^{+1}); Anal. calcd. for $C_{24}H_{39}NO_2$ (373.58): C, 77.16%; H, 10.52%; N, 3.75%. Found: C, 77.07%; H, 10.45%; N, 2.65%.

3-(Pentadec-8-en-1-yl)phenyl phenylalaninate 4c

Yield: 67%; m.p. 110–112°C. IR spectrum (KBr, ν, cm^{-1}): 3418–3180 (NH_2), 2961, 2850 (CH aliphatic), 1717 (CO); ^{1}H NMR ($CDCl_3$, δ ppm): 0.90 (t, 3H, CH_3, J = 7.1 Hz), 1.12–2.28 (m, 22H, $11CH_2$), 2.49 (t, 2H, benzylic CH_2, J = 7.4 Hz), 2.90 (d, 2H, $CHCH_2$), 4.02 (t, 1H, $CHCH_2$, J = 7.2 Hz), 5.13–5.50 (dd, 2H, vinylic protons), 6.69–7.70 (m, 9H, Ar-H), 8.62 (s, 2H, NH_2, exchangeable); ^{13}C NMR, 14.2, 22.3, 26.5, 27,5, 28.3, 29.5, 30.5, 31.3, 31.5, 32.2, 36.4 (aliphatic carbon chain), 37.2 (CH_2 phenylalanine), 49.5 (CH phenylalanine) 117.3, 121.5, 126.4, 127.5, 127.8, 128.2, 129.5, 130.2, 131.5, 138.2, 145.7, 156.2 (aromatic and vinylic carbons), 168.4 (CO); MS: m/z = 449 (M^+), 450 (M^{+1}); Anal. calcd. for $C_{30}H_{43}NO_2$ (449.68): C, 80.13%; H, 9.64%; N, 3.11%. Found: C, 80.06%; H, 9.57%; N, 3.03%.

3-(Pentadec-8-en-1-yl)phenyl valinate 4d

Yield: 70%; m.p. 108–110°C. IR spectrum (KBr, ν, cm^{-1}): 3334–3165 (NH_2), 2925, 2855 (CH aliphatic), 1728 (CO); ^{1}H NMR ($CDCl_3$, δ ppm): 0.97 (t, 3H, CH_3, J = 7.2 Hz), 1.18 (d, 6H, $2CH_3$, J = 7.1 Hz), 1.21–2.24 (m, 22H, $11CH_2$), 2.32–2.35 (m, 1H, $CH(CH_3)_2$), 2.51 (t, 2H, benzylic CH_2, J = 7.3 Hz), 5.20 (d, 1H, CH, J = 7.1 Hz), 5.59–5.64 (dd, 2H, vinylic protons), 5.82 (s, 2H, NH_2, exchangeable), 6.85–7.42 (m, 4H, Ar-H); ^{13}C NMR, 14.6, 22.2, 23.5, 26.5, 28.8, 29.2, 30.2, 31.5, 32.5, 35.2, 36.5 (aliphatic

carbon chain), 17.5 ($2CH_3$ valine), 28.2 (CH valine), 48.3 (CH valine), 116.3, 122.5, 126.3, 127.2, 128.5, 135.2,, 146.8, 154.5 (aromatic and vinylic carbons), 167.8 (CO); MS: m/z = 401 (M^+), 402 (M^{+1}); Anal. calcd. for $C_{26}H_{43}NO_2$ (401.64): C, 77.75%; H, 10.79%; N, 3.49%. Found: C, 77.68%; H, 10.71%; N, 3.43%.

3-Pentadecylphenyl-2-(1,3-dioxoisoindolin-2-yl) acetate 5a

Yield: 76%; m.p. 102–104°C. IR spectrum (KBr, ν, cm^{-1}): 2933, 2852 (CH aliphatic), 1775–1723 (CO); ^1H NMR (DMSO, δ ppm): 1.09 (t, 3H, CH_3, J = 7.2 Hz), 1.24–2.29 (m, 26H, $13CH_2$), 2.37 (t, 2H, benzylic CH_2, J = 7.2 Hz), 4.50 (s, 2H, $COCH_2$), 7.10–7.90 (m, 8H, Ar-H); ^{13}C NMR, 15.8, 21.5, 25.3, 27.5, 28.2, 29.3, 31.3, 31.7, 32.3, 36.2 (aliphatic carbon chain), 45.8 (CH_2 glycine) 116.3, 122.0, 123.5, 125.5, 127.2, 128.5, 135.2, 145.5, 154.3 (aromatic carbons), 170.2, 171.5 (CO); MS: m/z = 491 (M^+); Anal. calcd. for $C_{31}H_{41}NO_4$ (491.67): C, 75.73%; H, 8.41%; N, 2.85%. Found: C, 75.60%; H, 8.31%; N, 2.73%.

3-Pentadecylphenyl-2-(1,3-dioxoisoindolin-2-yl) propanoate 5b

Yield: 80%; m.p. 112–114°C. IR spectrum (KBr, ν, cm^{-1}): 2923, 2855 (CH aliphatic), 1770–1725 (CO); ^1H NMR ($CDCl_3$, δ ppm): 0.96 (t, 3H, CH_3, J = 7.1 Hz), 1.21–2.23 (m, 26H, $13CH_2$), 1.53 (d, 3H, $CHCH_3$, J = 7.0 Hz), 2.55 (t, 2H, benzylic CH_2, J = 7.4 Hz), 5.24 (q, 1H, $CHCH_3$, J = 7.2 Hz), 6.87–7.65 (m, 8H, Ar-H); ^{13}C NMR, 14.3, 22.5, 25.5, 28.3, 29.1, 29.5, 30.2, 31.5, 32.5, 35.3 (aliphatic carbon chain), 15.5 (CH_3 alanine), 55.4 (CH alanine) 117.5, 121.2, 123.2, 126.3, 127.5, 128.4, 136.5, 148.2, 155.3 (aromatic carbons), 169.5, 171.3 (CO); MS: m/z = 505 (M^+); Anal. calcd. for $C_{32}H_{43}NO_4$ (505.70): C, 76.00%; H, 8.57%; N, 2.77%. Found: C, 75.92%; H, 8.46%; N, 2.68%.

3-Pentadecylphenyl-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate 5c

Yield: 79%; m.p. 121–123°C. IR spectrum (KBr, ν, cm^{-1}): 2980, 2860 (CH aliphatic), 1767–1704 (CO); ^1H NMR ($CDCl_3$, δ ppm): 0.98 (t, 3H, CH_3, J = 7.0 Hz), 1.25–2.20 (m, 26H, $13CH_2$), 2.54 (t, 2H, benzylic CH_2, J = 7.3 Hz), 2.90 (d, 2H, $CHCH_2$, J = 7.0 Hz), 4.85 (t, 1H, $CHCH_2$, J = 7.2 Hz), 6.72–8.25 (m, 13H, Ar-H); ^{13}C NMR, 18.5, 23.2, 26.5, 28.8, 29.3, 30.0, 30.7, 32.3, 32.6, 36.3 (aliphatic carbon chain), 36.8 (CH_2 phenylalanine), 59.2 (CH phenylalanine), 114.5, 116.2, 117.1, 118.5, 121.5, 126.3, 127.2, 127.8, 128.1, 130.2, 138.2, 147.5, 154.5, 158.2 (aromatic carbons), 167.2, 170.0 (CO); MS: m/z = 581 (M^+); Anal. calcd. for $C_{38}H_{47}NO_4$ (581.80): C, 78.45%; H, 8.14%; N, 2.41%. Found: C, 78.36%; H, 8.07%; N, 2.32%.

3-Pentadecylphenyl-2-(1,3-dioxoisoindolin-2-yl)-3-methylbutanoate 5d

Yield: 76%; m.p. 132–134°C. IR spectrum (KBr, ν, cm^{-1}): 2948, 2850 (CH aliphatic), 1771–1738 (CO); ^1H NMR ($CDCl_3$, δ ppm): 0.91 (t, 3H, CH_3, J = 7.1 Hz), 1.01 (d, 6H, $2CH_3$, J = 7.1 Hz), 1.21–2.12 (m, 26H, $13CH_2$), 2.15–2.30 (m, 1H, $CH(CH_3)_2$), 2.56 (t, 2H, benzylic CH_2, J = 7.3 Hz), 4.96–5.02 (d, 1H, CH, J = 7.1 Hz), 6.70–7.63 (m, 8H, Ar-H); ^{13}C NMR, 15.3, 21,8, 23.5, 28.5, 29.4, 30.3, 30.6, 31.6, 32.2, 35.5 (aliphatic carbon chain), 18.2 ($2CH_3$ valine), 26.5 (CH valine), 53.5 (CH valine), 115.3, 122.5, 123.5, 126.2, 128.3, 1229.5, 135.2, 146.5, 156.3 (aromatic carbons), 167.3, 170.5 (CO); MS: m/z = 533 (M^+), 534 (M^{+1}); Anal. calcd. for $C_{34}H_{47}NO_4$ (533.75): C, 76.51%; H, 8.88%; N, 2.62%. Found: C, 76.43%; H, 8.77%; N, 2.50%.

3-Pentadecylphenyl glycinate 6a

Yield: 70%; m.p. 135–137°C. IR spectrum (KBr, ν, cm^{-1}): 3327–3156 (NH_2), 2928, 2898 (CH aliphatic), 1726 (CO); ^1H NMR ($CDCl_3$, δ ppm): 0.98 (t, 3H, CH_3, J = 7.2 Hz), 1.16–2.21 (m, 26H, $13CH_2$), 2.46 (t, 2H, benzylic CH_2, J = 7.4 Hz), 4.42 (s, 2H, $COCH_2$), 5.53 (s, 2H, NH_2, exchangeable), 7.10–7.82 (m, 4H, Ar-H); ^{13}C NMR, 16.3, 21.3, 25.5, 28.2, 28.6, 29.2, 30.7, 31.3, 32.5, 36.5 (aliphatic carbon chain), 45.2 (CH_2 glycine), 115.5, 120.2, 125.3, 126.3, 144.5, 154.5 (aromatic carbons), 169.5 (CO); MS: m/z = 361 (M^+); Anal. calcd. for $C_{23}H_{39}NO_2$ (361.57): C, 76.40%; H, 10.87%; N, 3.87%. Found: C, 76.33%; H, 10.78%; N, 3.76%.

3-Pentadecylphenylalaninate 6b

Yield: 66%; m.p. 142–144°C. IR spectrum (KBr, ν, cm^{-1}): 3315–3195 (NH_2), 2932, 2856 (CH aliphatic), 1740 (CO); ^1H NMR ($CDCl_3$, δ ppm): 1.02 (t, 3H, CH_3, J = 7.1 Hz), 1.42 (d, 3H, $CHCH_3$, J = 7.1 Hz),

1.20–2.18 (m, 26H, $13CH_2$), 2.50 (t, 2H, benzylic CH_2, J = 7.4 Hz), 4.65 (q, 1H, $CHCH_3$, J = 7.2 Hz), 5.76 (s, 2H, NH_2, exchangeable), 7.23–7.88 (m, 4H, Ar-H); ^{13}C NMR, 15.5, 22.2, 26.3, 28.5, 29.3, 29.6, 30.5, 31.2, 32.3, 35.2 (aliphatic carbon chain), 17.3 (CH_3 alanine), 46.5 (CH alanine) 117.2, 121.5, 126.5, 128.8, 146.5, 152,3 (aromatic carbons), 166.7 (CO); MS: m/z = 375 (M^+), 376 (M^{+1}); Anal. calcd. for $C_{24}H_{41}NO_2$ (375.60): C, 76.75%; H, 11.00%; N, 3.73%. Found: C, 76.66%; H, 10.91%; N, 3.65%.

3-Pentadecylphenylphenylalaninate 6c

Yield: 65%; m.p. 155–157°C. IR spectrum (KBr, ν, cm^{-1}): 3321–3200 (NH_2), 2922, 2855 (CH aliphatic), 1737 (CO); ^1H NMR ($CDCl_3$, δ ppm): 0.98 (t, 3H, CH_3, J = 7.1 Hz), 1.20–2.18 (m, 26H, $13CH_2$), 2.58 (t, 2H, benzylic CH_2, J = 7.2 Hz), 3.10 (d, 2H, $CHCH_2$, J = 7.2 Hz), 3.85 (t, 1H, $CHCH_2$, J = 7.3 Hz), 5.85 (s, 2H, NH_2, exchangeable), 7.11–7.95 (m, 9H, Ar-H); ^{13}C NMR, 13.8, 22.5, 26.1, 28.3, 29.6, 30.2, 31.7, 32.5, 35.2 (aliphatic carbon chain), 42.5 (CH_2 phenylalanine), 52.5 (CH phenylalanine) 118.5, 122.5, 127.3, 127.5, 128.5, 130.5, 131.2, 138.5, 144.5, 155.5 (aromatic carbons), 169.2 (CO); MS: m/z = 451 (M^+), 452 (M^{+1}); Anal. calcd. for $C_{30}H_{45}NO_2$ (451.70): C, 79.77%; H, 10.04%; N, 3.10%. Found: C, 79.83%; H, 10.10%; N, 3.07%.

3-Pentadecylphenyl valinate 6d

Yield: 68%; m.p. 138–140°C. IR spectrum (KBr, ν, cm^{-1}): 3370–3160 (NH_2), 2917, 2849 (CH aliphatic), 1730 (CO); ^1H NMR ($CDCl_3$, δ ppm): 0.95 (t, 3H, CH_3, J = 7.2 Hz), 1.11 (d, 6H, $2CH_3$, J = 7.2 Hz), 1.22–2.23 (m, 26H, $13CH_2$), 2.32–2.36 (m, 1H, $CH(CH_3)_2$), 2.61 (t, 2H, benzylic CH_2, J = 7.3 Hz), 4.92 (d, 1H, CH, J = 7.0 Hz), 6.70–7.63 (m, 4H, Ar-H), 8.52 (s, 2H, NH_2, exchangeable); MS: m/z = 403 (M^+), 404 (M^{+1}); Anal. calcd. for $C_{26}H_{45}NO_2$ (403.65): C, 77.37%; H, 11.24%; N, 3.47%. Found: C, 77.32%; H, 11.17%; N, 3.39%.

Synthesis of ethyl-2-(3-pentadecyl phenoxy) acetate 7

A mixture of cardanol **1b** (0.01 mol), ethyl chloroacetate (0.01 mol) in dry acetone (30 mL) containing anhydrous potassium carbonate (0.5 g) was heated under reflux for 24 h. After cooling, the reaction mixture was poured into cold water and the formed solid was filtered off, dried and crystallized from ethanol. Yield: 76%; m.p. 95–97°C. IR spectrum (KBr, ν, cm^{-1}): 2919, 2850 (CH aliphatic), 1745 (CO), 1594 (C=C); ^1H NMR (DMSO-d_6, δ ppm): 0.85 (t, 3H, CH_3, J = 7.1 Hz), 1.11 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.23–1.53 (m, 26H, $13CH_2$), 2.49 (t, 2H, benzylic CH_2, J = 7.3 Hz), 4.15–4.17 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 4.72 (s, 2H, OCH_2), 6.69–7.17 (m, 4H, Ar-H); ^{13}C NMR, 14.9, 15.1, 22.5, 29.9, 30.0, 30.2, 31.5, 32.5, 36.2, 36.5 (aliphatic carbon chain), 59.2 (OCH_2), 65.3 (OCH_2CO), 112.2, 115.8, 120.7, 129.9, 145.1, 156.3 (aromatic carbons), 169.5 (CO); MS: m/z = 390 (M^+); Anal. calcd. for $C_{25}H_{42}O_3$ (390.61): C, 76.87%; H, 10.84%. Found: C, 76.78%; H, 10.72%.

Synthesis of 2-(3-pentadecylphenoxy)acetohydrazide 8

Hydrazine hydrate (0.01 mol) was added to ester **7** (0.01 mol) in absolute ethanol (20 mL). The reaction mixture was heated under reflux for 6 h. The separated solid after cooling was collected by filtration, dried, and crystallized from ethanol to give the pure powder of hydrazide **8**.

Yield: 84%; m.p. 103–105°C. IR spectrum (KBr, ν, cm^{-1}): 3350–3187 (NH, NH_2), 2923, 2854 (CH aliphatic), 1680 (CO); ^1H NMR (DMSO, δ ppm): 0.83 (t, 3H, CH_3, J = 7.2 Hz), 1.23–1.53 (m, 26H, $13CH_2$), 2.43 (t, 2H, benzylic CH_2, J = 7.3 Hz), 4.91 (s, 2H, OCH_2), 6.53–7.05 (m, 4H, Ar-H), 6.56 (s, 2H, NH_2, exchangeable), 9.15 (s, 1H, NH, exchangeable); ^{13}C NMR, 18.7, 22.5, 27.1, 28.8, 29.1, 29.5, 30.0, 31.5, 31.8, 36.1 (aliphatic carbon chain), 112.5, 116.1, 121.2, 129.3, 130.1, 159.5 (aromatic carbons), 173.3 (CO); MS: m/z = 376 (M^+), 377 (M^{+1}); Anal. calcd. for $C_{23}H_{40}N_2O_2$ (376.59): C, 73.36%; H, 10.71%; N, 7.44%. Found: C, 73.29%; H, 10.63%; N, 7.33%.

General procedures for the synthesis of 9a–9c

The same procedures described for the synthesis of **3a–3d** and **5a–5d** were used.

2-(1,3-Dioxoisoindolin-2-yl)-N-(2-(3-pentadecylphenoxy) acetyl)acetohdrazide 9a

Yield: 79%; m.p. 111–113°C. IR spectrum (KBr, ν, cm^{-1}): 3463–3270 (NH), 2931, 2866 (CH aliphatic), 1772–1726 (CO), 1682 (CO amide), ^1H NMR ($CDCl_3$, δ ppm): 0.97 (t, 3H, CH_3, J = 7.2 Hz), 1.18–2.23 (m, 26H, $13CH_2$), 2.54 (t, 2H, benzylic CH_2, J = 7.3 Hz), 4.31 (s, 2H, $COCH_2$), 4.93 (s, 2H, OCH_2), 6.95–7.92 (m, 8H, Ar-H), 8.55, 9.34 (2 s, 2H, 2NH,

exchangeable); ^{13}C NMR, 15.3, 21.5, 27.2, 28.5, 29.5, 30.3, 31.5, 31.2, 32.6, 35.5 (aliphatic carbon chain), 46.5 (CH_2 glycine), 51.3 (OCH_2), 116.3, 121.5, 122.2, 125.5, 127.3, 128.5, 135.5, 148.3, 151.5 (aromatic carbons), 167.5, 168.7, 175.5 (CO); MS: *m/z* = 563 (M^+); Anal. calcd. for $C_{33}H_{45}N_3O_5$ (563.74): C, 70.31%; H, 8.05%; N, 7.45%. Found: C, 70.24%; H, 7.96%; N, 7.39%.

2-(1,3-Dioxoisoindolin-2-yl)-N-(2-(3-pentadecylphenoxy) acetyl)propanehdrazide 9b

Yield: 76%; m.p. 123–125°C. IR spectrum (KBr, ν, cm^{-1}): 3344–3200 (NH), 2927, 2853 (CH aliphatic), 1770–1730 (CO), 1685 (CO amide), ^{1}H NMR ($CDCl_3$, δ ppm): 0.93 (t, 3H, CH_3, *J* = 7.2 Hz), 1.16 (d, 3H, CH_3CH, *J* = 7.3 Hz), 1.25–2.25 (m, 26H, $13CH_2$), 2.50 (t, 2H, benzylic CH_2, *J* = 7.4 Hz), 4.75 (q, 1H, $CHCH_3$, *J* = 7.2 Hz), 5.35 (s, 2H, OCH_2), 6.70–7.98 (m, 8H, Ar-H), 8.25, 8.40 (2s, 2H, 2NH, exchangeable); ^{13}C NMR, 14.5, 22.3, 28.5, 28.9, 29.2, 29.7, 31.6, 31.8, 32.8, 36.3 (aliphatic carbon chain), 16.2 (CH_3 alanine), 56.2 (CH alanine) 118.8, 122.5, 123.5, 126.2, 128.5, 128.7, 136.2, 149.5, 155.5 (aromatic carbons), 168.4, 169.5, 172.2 (CO); MS: *m/z* = 577 (M^+), 578 (M^{+1}); Anal. calcd. for $C_{34}H_{47}N_3O_5$ (577.77): C, 70.68%; H, 8.20%; N, 7.27%. Found: C, 70.61%; H, 8.11%; N, 7.17%.

2-(1,3-Dioxoisoindolin-2-yl)-N-(2-(3-pentadecylphenoxy) acetyl)-3-phenylpropane hydrazide 9c

Yield: 78%; m.p. 135–137°C. IR spectrum (KBr, ν, cm^{-1}): 3436–3185 (NH), 2923, 2853 (CH aliphatic), 1773–1725 (CO), 1678 (CO amide); ^{1}H NMR ($CDCl_3$, δ ppm): 0.99 (t, 3H, CH_3, *J* = 7.1 Hz), 1.18–2.23 (m, 26H, $13CH_2$), 2.52, (t, 2H, benzylic CH_2, *J* = 7.4 Hz), 2.90 (d, 2H, CH_2, *J* = 7.2 Hz), 4.72 (t, 1H, $CHCH_2$, *J* = 7.1 Hz), 5.40 (s, 2H, OCH_2), 6.70–8.10 (m, 8H, Ar-H), 8.30, 8.52 (2s, 2H, 2NH, exchangeable); ^{13}C NMR, 15.2, 22.5, 27.8, 28.5, 29.5, 30.3, 31.5, 32.2, 33.5, 35.2 (aliphatic carbon chain), 37.1 (CH_2 phenylalanine), 56.4 (CH phenylalanine), 116.5, 117.3, 117.8, 118.2, 122.5, 126.5, 127.6, 128.2, 128.5, 131.5, 138.5, 148.3, 155.2, 156.5 (aromatic carbons), 167.8, 171.3, 172.5 (CO); MS: *m/z* = 653 (M^+); 654 (M^{+1}); Anal. calcd. for $C_{40}H_{51}N_3O_5$ (653.86): C, 73.48%; H, 7.86%; N, 6.43% Found: C, 73.37%; H, 7.71%; N, 6.32%.

General procedures for synthesis of free amino acids 10a–10c

The same procedures described for the synthesis of free amino acids **4a–4d** and **6a–6d** were used.

2-Amino-*N*-(2-(3-pentadecylphenoxy)acetyl) acetohdrazide 10a

Yield: 67%; m.p. 150–152°C. IR spectrum (KBr, ν, cm^{-1}): 3430–3175 (NH_2, NH), 2933, 2863 (CH aliphatic), 1680, 1665 (CO amide); ^{1}H NMR (DMSO, δ ppm): 0.81 (t, 3H, CH_3, *J* = 7.2 Hz), 1.18–1.46 (m, 26H, $13CH_2$), 2.42 (t, 2H, benzylic CH_2, *J* = 7.3 Hz), 4.40 (s, 2H, $COCH_2$), 5.25 (s, 2H, OCH_2), 5.60 (s, 2H, NH_2, exchangeable); 6.52–6.96 (m, 4H, Ar-H), 8.60, 9.20 (2 s, 2H, 2NH, exchangeable); Anal. calcd. for $C_{25}H_{43}N_3O_3$ (433.64): C, 69.25%; H, 10.00%; N, 9.69%. Found: C, 69.12%; H, 9.83%; N, 9.56%.

2-Amino-*N*-(2-(3-pentadecylphenoxy)acetyl) propanehdrazide 10b

Yield: 63%; m.p. 146–148°C. IR spectrum (KBr, ν, cm^{-1}): 3425–3151 (NH_2, NH), 2925, 2845 (CH aliphatic), 1683, 1676 (CO amide); ^{1}H NMR ($CDCl_3$, δ ppm): 0.97 (t, 3H, CH_3, *J* = 7.1 Hz), 1.18 (d, 3H, CH_3CH, *J* = 7.0 Hz), 1.23–2.18 (m, 26H, $13CH_2$), 2.57 (t, 2H, benzylic CH_2, *J* = 7.4 Hz), 4.22 (q, 1H, $CHCH_3$, *J* = 7.3 Hz), 5.16 (s, 2H, OCH_2), 5.89 (s, 2H, NH_2, exchangeable); 7.05–7.65 (m, 4H, Ar-H), 8.45, 8.96 (2s, 2H, 2NH, exchangeable); ^{13}C NMR, 14.3, 22.8, 28.3, 28.7, 29.5, 29.8, 31.5, 32.5, 32.7, 36.5 (aliphatic carbon chain), 17.4 (CH_3 alanine), 50.3 (CH alanine) 118.3, 122.2, 123.7, 126.5, 128.5, 129.3, 136.5, 148.5, 155.2 (aromatic carbons), 167.5, 168.2, 171.7 (CO); Anal. calcd. for $C_{26}H_{45}N_3O_3$ (447.66): C, 69.76%; H, 10.13%; N, 9.39%. Found: C, 69.64%; H, 9.98%; N, 9.26%.

2-Amino-*N*-(2-(3-pentadecylphenoxy)acetyl)-3-phenylpropanehydrazide 10c

Yield: 65%; m.p. 131–133°C. IR spectrum (KBr, ν, cm^{-1}): 3430–3170 (NH_2, NH), 2928, 2850 (CH aliphatic), 1680, 1672 (CO amide), ^{1}H NMR ($CDCl_3$, δ ppm): 0.98 (t, 3H, CH_3, *J* = 7.2 Hz), 1.23–2.18 (m, 26H, $13CH_2$), 2.10 (d, 2H, CH_2CH, *J* = 7.2 Hz), 2.47 (t, 2H, benzylic CH_2, *J* = 7.3 Hz), 4.16 (t, 1H, $CHCH_2$, *J* = 7.2 Hz), 5.27 (s, 2H, OCH_2), 6.11 (s, 2H, NH_2, exchangeable); 6.88–7.79 (m, 9H, Ar-

H), 8.15, 9,23 (2s, 2H, 2NH, exchangeable); MS: *m/z* = 523 (M^+), 524 (M^{+1}); Anal. calcd. for $C_{32}H_{49}N_3O_3$ (523.76): C, 73.38%; H, 9.43%; N, 8.02%. Found: C, 73.24%; H, 9.30%; N, 7.90%.

CONCLUSIONS

I reported the facile and convenient synthesis of a new series of cardanol derivatives conjugated with protected and unprotected amino acids as a suitable side chain using DCC. In addition, the synthesized products were examined for their antibacterial activity, which was comparable to that of ampicillin.

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