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Synthesis and antibacterial activity of some novel sebacic acid derivatives

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ABSTRACT

Diverse biological activities, including antibacterial effects have been reported for sebacic acid and alkyl esters of amino acids. New derivatives of sebacic acid were synthesized in a one pot approach by the formation of amide bond between hydroxyl group of the sebacic acid and amine group of different amino acid alkyl ester hydrochloride salts. The mean synthesis yield for the studied compounds was ~58%. The structures of the newly synthesized compounds were confirmed by inspection of their ^{1}H- NMR, ^{13}C-NMR, IR and elemental analysis. The new compounds were screened for antimicrobial activities against six common strains of Gram-negative and Gram-positive bacteria. The results of the present work show low to moderate antibacterial activity for the studied compounds.

KEY WORDS: Sebacic Acid, Aminoacid Alkylester Hydrochloride, Amide Bond, Antibacterial Activitiy.

1. INTRODUCTION

Compounds containing amide bond show broad spectrum of biological activities including antituberculosis, anticonvulsant, analgesic, anti-inflammatory, insecticidal, antifungal, and antitumor properties. Accordingly these compounds play an important role in research and development of pharmaceutical and agrochemical compounds. It has been shown that compounds obtained from the formation of amide bond between ester derivatives of amino acids and different acids, long chain acids and amines and dicarboxylic acids and amino acids, exhibit considerable biological activities and are used in different areas such as pharmaceutical, agricultural and cosmetic industries. Furthermore, the pharmacological activity of sebacic acid (decanedioic acid) and its derivatives, and ester derivatives of amino acids have been studied. Based on previous studies, it is expected that compounds obtained from the formation of amid bond between amine group of an alkyl ester derivative of amino acid and sebacic acid, show biological activities including bactericidal effects. Amide bonds are typically resulted from the union of carboxylic acids and amines functional groups. However, the unification of these two functional groups does not occur spontaneously at ambient temperature and it is usually necessary to first activate the carboxylic acid.

In order to activate carboxylic acids, one can use so-called coupling reagents, which act as stand-alone reagents to generate compounds such as acid chlorides, (mixed) anhydrides, carbonic anhydrides or active esters. Though the choice of this coupling reagent is critical, and many reviews on coupling reagents have been published. In this study dicyclohexylcarbodiimide (DCC) was used as a coupling reagent and 1-hydroxy-1H-benzotriazole (HOBt) was used as an additive to form the amide bond.

2. EXPERIMENTAL

Chemicals and Apparatus: All used reagents and solvents were purchased from commercial sources and used without further purification except for N, N-dimethylformamide (DMF), which was dried over molecular sieve. Amino acid alkylester hydrochlorides were synthesized by chlorotrimethylsilane as an efficient esterification reagent. Reactions were monitored by thin layer chromatography, silica gel 60 F254 plates (Merck) and were visualized by a 254 nm UV lamp. Melting points were determined on the Electrothermal-9100 melting point apparatus using open capillaries and they are uncorrected. Infrared spectra were recorded (in KBr) on a FT-IR spectrometer (Shimadzu FT-IR 8101 M) and are reported in cm^{-1}. 1H-NMR spectra were recorded in DMSO-d6 solution on a 400 MHz spectrometer (Bruker Spectrospin Avance-400) and following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet and m = multiplet. ^{13}C-NMR spectra were recorded on the same spectrometer (at 100 MHz) with complete proton decoupling. Chemical shifts (δ) were recorded in parts per million (ppm) and were referenced to tetramethylsilane and coupling constants (*J*) in Hz. Elemental analyses were conducted with Vario EL. III Apparatus (Elementar Co).

General procedure for the preparation of Sebacic acid derivatives: Two equivalent of appropriate amino acid alkyl ester hydrochloride salt (0.4 mmol) was suspended with stirring in dry N, N-dimethylformamide (DMF) (6 mL) which was cooled in an ice bath. The mixture was stirred for 3 minutes to allow complete dissolution of the amino acid alkyl ester hydrochloride salt and then triethylamine (0.1 ml) was added. Then one equivalent sebacic acid (0. 2 mmol) and 2.5 equivalent of HOBt (0.5 mmol) and DCC (0.5 mmol) were added one after each other. The mixture was stirred for 1 hour while the temperature was kept at 0°C and for 1 hour in 5°C then at the room temperature for 13 hours. Solvent (DMF) of the reaction mixture was removed under reduced pressure. Then ethyl

acetate (5 mL) was added to the mixture and the precipitated part was filtered and remained solution was concentrated and the residue was purified by silica gel thin layer chromatography (MeOH:CH_2Cl_2 = 1: 20) to afford the last product.

Spectral Data of Compounds: [2,2'-diamino-3,3'-bis(1H-indole-3-yl)-N,N'-(1,10-decan-dioyl)]dipropanoic acid dimethyl ester (1): This product was obtained in the form of pale brown oil; Yield 60%; IR (KBr) υ (cm^{-1}): 3410, 3303, 1747, 1658, 1542, 1465, 1444, 1350, 1217, 1102, 747. ^{1}H-NMR (DMSO-*d*6) δ : 1.16(m, 4H, CH_2), 1.36 (m, 2H, CH_2), 2.03 (t, *J* = 7 Hz, 2H, CH_2-CO-NH), 3.06 (two dd, 2H, CH_2), 3.56 (s, 3H, CH_3-O-CO-), 4.47 (m, 1H, CH), 6.97 (t, *J* = 7.2 Hz, 1H, ArH), 7.05 (t, *J* = 7.4 Hz, 1H, ArH), 7.13 (s, 1H, ArH), 7.32 (d, *J* = 7.9 Hz, 1H, ArH), 7.48 (d, *J* = 7.8 Hz, 1H, ArH), 8.24 (d, *J* = 7.4 Hz, 1H, NH-CO), 10.86 (s, 1H, NH-Ar); ^{13}C-NMR (DMSO-*d*6) δ : 172.66, 172.41, 136.10, 127.08, 123.66, 120.99, 118.42, 118.02, 111.46, 109.61, 53.04, 51.80, 34.99, 28.72, 28.55, 27.08, 25.16. Anal. Calc. (%) for $C_{34}H_{42}N_4O_6$ C 67.8, H 7.1, N 9.3. Found (%): C 67.4, H 6.8, N 8.9.

[2,2'-diamino-3,3'-bis(1H-indole-3-yl)-N,N'-(1,10-decan-dioyl)]dipropanoic acid dipropyl ester (2): This product was obtained in the form of pale brown oil; Yield 65%; IR (KBr) υ (cm^{-1}): 3410, 3303, 1739, 1658, 1632, 1546, 1461, 1363, 1209, 1102, 747. ^{1}H-NMR (DMSO-*d*6) δ : 0.77(t, *J* = 7.4 Hz , 3H, CH_3), 1.15(m, 4H, CH_2), 1.42 (m, 2H, CH_2), 1.48 (m, 2H, CH_2) 2.04 (t, 2H, CH_2-CO-NH), 3.07 (two dd, 2H, CH_2), 3.92(t, *J* = 6.5 Hz , 2H, -CH_2-O-CO), 4.48 (m, 1H, CH), 6.97 (t, *J* = 7.2 Hz, 1H, ArH), 7.05 (t, *J* = 7.4 Hz, 1H, ArH), 7.13 (s, 1H, ArH), 7.32 (d, *J* = 8.0 Hz, 1H, ArH), 7.48 (d, *J* = 7.7 Hz, 1H, ArH), 8.22 (d, *J* = 7.4 Hz, 1H,- NH-CO), 10.84 (s, 1H, NH-Ar); ^{13}C-NMR (DMSO-*d*6) δ : 172.32, 172.22, 136.11, 127.07, 123.59, 120.93, 118.35, 117.98, 111.40, 109.61, 65.75, 53.15, 34.98, 28.70, 28.54, 27.13, 25.16, 21.41, 10.11. Anal. Calc. (%) for $C_{38}H_{50}N_4O_6$ C 69.3, H 7.7, N 8.5. Found (%): C 68.8, H 7.4, N 8.2.

[2,2'-diamino-3,3'-bis(1H-indole-3-yl)-N,N'-(1,10-decan-dioyl)]dipropanoic acid dipentyl ester (3): This product was obtained in the form of pale brown oil; Yield 70%; IR (KBr) υ (cm^{-1}): 3410, 3303, 1739, 1658, 1555, 1465, 1358, 1205, 1102, 747. ^{1}H-NMR (DMSO-*d*6) δ : 0.81(t, *J* = 7.0 Hz , 3H, CH_3), 1.18(m, 6H, CH_2), 1.24 (m, 2H, CH_2), 1.43 (m, 4H, CH_2) 2.04 (t, 2H, CH_2-CO-NH), 3.06 (two dd, 2H, CH_2), 3.93(t, *J* = 6.4 Hz , 2H, -CH_2-O-CO), 4.46 (m, 1H, CH), 6.97 (t, *J* = 7.2 Hz, 1H, ArH), 7.05 (t, *J* = 7.4 Hz, 1H, ArH), 7.13 (s, 1H, ArH), 7.32 (d, *J* = 8.0 Hz, 1H, ArH), 7.47 (d, *J* = 7.8 Hz, 1H, ArH), 8.21 (d, *J* = 7.4 Hz, 1H,- NH-CO), 10.84 (s, 1H, NH-Ar); ^{13}C-NMR (DMSO-*d*6) δ : 172.37, 172.21, 136.14, 127.09, 123.59, 120.96, 118.37, 117.98, 111.44, 109.61, 64.30, 53.20, 35.02, 28.74, 28.59, 27.69, 27.41, 27.16, 25.19, 21.75, 13.84. Anal. Calc. (%) for $C_{42}H_{58}N_4O_6$ C 70.8, H 8.2, N 7.9 Found (%): C 70.4, H 7.8, N 8.1.

[2,2'-diamino-3,3'-bis(4-hidroxyphenyl)-N,N'-(1,10-decan-dioyl)]dipropanoic acid dimethyl ester (4): This product was obtained in the form of pale yellow solid Yield 72%; m.p. 143–144°C. IR (KBr) υ (cm^{-1}): 3346, 3100, 1730, 1658, 1564, 1521, 1450, 1371, 1273, 1226, 1175, 1042, 833. ^{1}H-NMR (DMSO-*d*6) δ : 1.15(m, 4H, CH_2), 1.41 (m, *J* = 7.0 Hz, 2H, CH_2), 2.04 (t, *J* = 7.2 Hz, 2H, CH_2-CO-NH), 2.81 (two dd, 2H, CH_2), 3.57(s, 3H, CH_3-O-CO-), 4.34 (m, 1H, CH), 6.64 (d, *J* = 8.3 Hz, 2H, ArH), 6.98 (d, *J* = 8.3 Hz, 2H, ArH), 8.19 (d, *J* = 7.7 Hz, 1H,- NH-CO), 9.26 (s, 1H, OH); ^{13}C-NMR (DMSO-*d*6) δ : 172.41, 172.33, 155.98, 129.95, 127.27, 114.98, 53.81, 51.72, 35.98, 34.96, 28.70, 28.49, 25.16. Anal Calc. (%) for $C_{35}H_{40}N_2O_8$ C 64.8, H 7.3, N 5.1. Found (%): C 64.4, H 7.0 N 5.3.

[2,2'-diamino-3,3'-bis(4-hidroxyphenyl)-N,N'-(1,10-decan-dioyl)]dipropanoic acid dipropyl ester (5): This product was obtained in the form of pale yellow solid Yield 73%; m.p. 125–126°C. IR (KBr) υ (cm^{-1}): 3367, 3303, 1740, 1653, 1521, 1461, 1367, 1252, 1064, 837. ^{1}H-NMR (DMSO-*d*6) δ : 0.81(t, *J* = 7.4 Hz , 3H, CH_3), 1.15 (m, 4H, CH_2), 1.40 (m, *J* = 6.4 Hz , 2H, CH_2), 1.50 (m, *J* = 7.0 Hz , 2H, CH_2), 2.04 (t, *J* = 7.2 Hz, 2H, CH_2-CO-NH), 2.81 (two dd, 2H, CH_2), 3.93 (t, *J* = 6.5 Hz, 2H, -CH_2-O-CO-), 4.34 (m, 1H, CH), 6.63 (d, *J* = 8.3 Hz, 2H, ArH), 6.98 (d, *J* = 8.3 Hz, 2H, ArH), 8.17 (d, *J* = 7.7 Hz, 1H, - NH-CO), 9.22 (s, 1H, OH); ^{13}C-NMR (DMSO-*d*6) δ: 172.29, 171.97, 155.97, 129.94, 127.28, 114.96, 65.76, 53.93, 36.06, 34.97, 28.71, 28.51, 25.18, 21.46, 10.18. Anal Calc. (%) for $C_{34}H_{48}N_2O_8$ C 66.6, H 7.9, N 4.6. Found (%): C 66.8, H 7.5, N 4.8.

[2,2'-diamino-3,3'-bis(4-hidroxyphenyl)-N,N'-(1,10-decan-dioyl)]dipropanoic acid dibenzyl ester (6): This product was obtained in the form of yellow oil; Yield 56%; IR (KBr) υ (cm^{-1}): 3346, 3303, 1747, 1658, 1634, 1517, 1457, 1388, 1239, 1111, 833, 743, 700. ^{1}H-NMR (DMSO-*d*6) δ : 1.13(m, 4H, CH_2), 1.39 (m, 2H, CH_2), 2.04 (t, *J* = 7.2 Hz, 2H, CH_2-CO-NH), 2.84 (two dd, 2H, CH_2), 4.41 (m, 1H, CH), 5.05 (dd, 2H, -CH_2-Ph); 6.63 (d, *J* = 8.1 Hz, 2H, ArH), 6.98 (d, *J* = 8.1 Hz, 2H, ArH), 7.24 (m, 5H, ArH), 8.23 (d, *J* = 7.6 Hz, 1H,- NH-CO), 9.24 (s, 1H, OH); ^{13}C-NMR (DMSO-*d*6) δ : 172.42, 171.79, 156.02, 135.86, 130.00, 128.36, 128.00, 127.77, 127.18, 115.02, 65.82, 53.99, 35.97, 35.00, 28.69, 28.54, 25.18. Anal Calc. (%) for $C_{42}H_{48}N_2O_8$ C 71.2, H 6.8, N 3.9. Found (%) C 71.4, H 7.0, N 3.7.

[2,2'-diamino-3,3'-diphenyl-N,N'-(1,10-decan-dioyl)]dipropanoic acid diethyl ester (7): This product was obtained in the form of pale yellow solid Yield 63%; m.p. 104–105°C. IR (KBr) υ (cm^{-1}): 3303, 1760, 1735, 1650, 1547, 1370, 1277, 1247, 1217, 1034, 756, 705. ^{1}H-NMR (DMSO-*d*6) δ : 1.10 (m, 7H, CH_2,CH_3), 1.38 (m, *J* = 6.5 Hz, 2H, CH_2), 2.03 (t, *J* = 7.1 Hz, 2H, CH_2-CO-NH), 2.93 (two dd, 2H, CH_2), 4.03 (q, *J* = 7.0 Hz, 2H, -CH_2-O-CO-), 4.42 (m, 1H, CH), 7.21 (m, 5H, ArH), 8.22 (d, *J* = 7.7 Hz, 1H,- NH-CO); ^{13}C-NMR (DMSO-*d*6) δ : 172.25,

171.72, 137.30, 129.02, 128.12, 126.42, 60.36, 53.44, 36.70, 34.94, 28.64, 28.39, 25.13, 13.93. Anal Calc. for $C_{32}H_{44}N_2O_6$ C 69.5, H 8.0, N 5.1. Found (%): C 69.8, H 8.2, N 5.3.

[2,2'-diamino-3,3'-diphenyl-N,N'-(1,10-decan-dioyl)]dipropanoic acid dipropyl ester (8): This product was obtained in the form of pale yellow solid Yield 60%; m.p. 94–95°C. IR (KBr) υ (cm^{-1}): 3303, 1752, 1740, 1653, 1547, 1457, 1384, 1299, 1273, 1217, 1183, 756, 704. ^{1}H-NMR (DMSO-*d*6) δ : 0.81 (t, *J* = 7.4 Hz , 3H, CH_3), 1.12 (m, 4H, CH_2), 1.38 (m, *J* = 6.5 Hz , 2H, CH_2), 1.50 (m, *J* = 7.0 Hz , 2H, CH_2), 2.03 (t, *J* = 7.2 Hz, 2H, CH_2-CO-NH), 2.94 (two dd, 2H, CH_2), 3.95 (t, *J* = 7.0 Hz, 2H, -CH_2-O-CO-), 4.44 (m, 1H, CH), 7.22 (m, 5H, ArH), 8.23 (d, *J* = 7.7 Hz, 1H,- NH-CO); ^{13}C-NMR (DMSO-*d*6) δ : 172.24, 171.81, 137.33, 129.00, 128.15, 126.44, 65.82, 53.49, 36.73, 34.96, 28.66, 28.42, 25.15, 21.43, 10.15. Anal Calc. (%) for $C_{34}H_{48}N_2O_6$ C 70.3, H 8.3, N 4.8. Found (%): C 70.5, H 8.5, N 4.6.

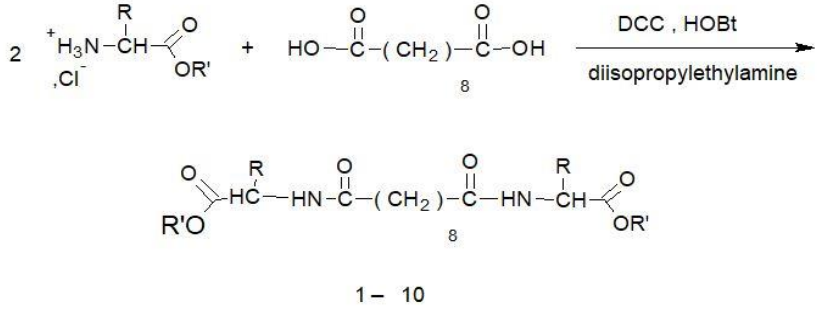
[2,2'-diamino-3,3'-diphenyl-N,N'-(1,10-decan-dioyl)] dipropanoic acid dibenzyl ester (9): This product was obtained in the form of pale yellow solid Yield 60%; m.p. 105–106°C. IR (KBr) υ (cm^{-1}): 3320, 1740, 1650, 1538, 1457, 1388, 1354, 1081, 756, 700. ^{1}H-NMR (DMSO-*d*6) δ : 1.10(m, 4H, CH2), 1.37 (m, *J* = 6.4 Hz , 2H, CH_2), 2.03 (t, *J* = 7.2 Hz, 2H, CH_2-CO-NH), 2.95 (two dd, 2H, CH_2), 4.51 (m, 1H, CH), 5.07 (dd, 2H, -CH_2-Ph), 7.27 (m, 10H, ArH), 8.29 (d, *J* = 7.7 Hz, 1H, - NH-CO); ^{13}C-NMR (DMSO-*d*6) δ : 172.35, 171.64, 137.24, 135.81, 129.05, 128.35, 128.18, 127.85,127.76, 126.47, 65.88, 53.54, 36.61, 34.98, 28.64, 28.44, 25.15. Anal Calc. (%) for $C_{42}H_{48}N_2O_6$ C 74.5, H 7.2, N 4.1. Found (%): C 74.7, H 7.4, N 4.3.

N,N'-(1,10-decan-dioyl)-bis(pyrrolidine2-carboxylicacid)dibenzyl ester (10): This product was obtained in the form of pale yellow liquid; Yield 65%; IR (KBr) υ (cm^{-1}): 1747, 1653, 1427, 1277, 1175, 1098, 740, 704. ^{1}H-NMR (DMSO-*d*6) δ : 1.22 (m, 4H, CH_2), 1.46 (m, *J* = 6.4 Hz, 2H, CH_2), 1.85 (m, 3H, CH_2(pyrrolidine)), 2.16 (m, 1H, CH_2(pyrrolidine)) 2.24 (t, *J* = 7.2 Hz, 2H, CH_2-CO-NH), 3.50 (m, 2H, CH_2(pyrrolidine)), 4.32 (dd, 1H, CH), 5.09 (dd, 2H, -CH_2-Ph), 7.31 (m, 5H, ArH); ^{13}C-NMR (DMSO-*d*6) δ : 171.98, 170.85, 136.05, 128.37, 127.93, 127.60, 65.61, 58.28, 46.52, 33.46, 28.77, 28.72, 28.61, 24.41, 24.21.Anal Calc. (%) for $C_{34}H_{44}N_2O_6$ C 70.8, H 7.7, N 4.9. Found (%): C 70.6, H 7.9, N 4.8.

Antimicrobial Assay: The newly synthesized compounds were screened for their antimicrobial activities *in vitro* against four Gram-negative *Entrobacter aerogenes* (ATCC 13048), *Klebsiella pneumoniae* (ATCC 700603), *Escherichia coli* (ATCC 25922) and *Proteus mirabilis* (ATCC 43071) and two Gram-positive *Enterococcus faecalis* (ATCC 29212) and *Staphylococcus aureus* (ATCC 25952) on Mueller-Hinton agar media. The activities of these compounds were tested using the paper disc agar diffusion method. The area of inhibition was measured using Ciprofloxacin (0.5 mg per disc) as standard antibiotic and 0.5 mg of the tested compounds. The inhibition zones were measured in millimeters at the end of an incubation period of 24 hours at 37°C. Test results are shown in Table.2.

3. RESULTS AND DISCUSSION

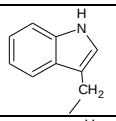
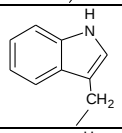
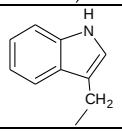
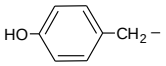
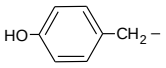
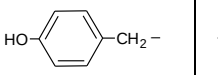
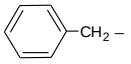
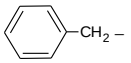
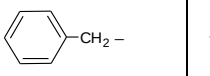
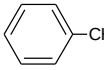
Chemistry: The designated compounds were synthesized by the one-pot five-component procedure according to Scheme.1.



Scheme.1. Synthesis of new sebacic acid derivatives (compounds 1-10)

Diisopropylethylamine were used as hydrochloride scavenger. The substituted side chains (R and R'), reaction times and yields for newly synthesized compounds (1-10) are listed in Table.1.

Table.1. Reaction time and yield for the reaction of different amino acid alkyl ester hydrochloride salts

Compound	R	R'	Amino acid alkyl ester hydrochloride used in reaction	Reaction time (hour)	(Yield %)
1		CH_3 –	Tryptophan methyl ester hydrochloride	15	60
2		CH_3 -(CH_2)$_2$ –	Tryptophan propyl ester hydrochloride	15	65
3		CH_3 -(CH_2)$_4$ –	Tryptophan n-amyle ester hydrochloride	15	70
4		CH_3 –	Tyrosine methyl ester hydrochloride	15	72
5		CH_3 -(CH_2)$_2$ -	Tyrosine propyl ester hydrochloride	15	73
6			Tyrosine benzyl ester hydrochloride	15	56
7		CH_3 - CH_2 -	Phenylalanine ethyl ester hydrochloride	15	63
8		CH_3 -(CH_2)$_2$ -	Phenylalanine propyl ester hydrochloride	15	60
9			Phenylalanine benzyl ester hydrochloride	15	60
10	–		Proline benzyl ester hydrochloride	15	65

The chemical structures of these newly synthesized compounds were confirmed by IR, ^{1}H-NMR, and ^{13}C-NMR spectral measurements and elemental analysis were in good agreement with the proposed structures.

Antimicrobial Activities: The antimicrobial activities of the newly synthesized compounds were evaluated by the paper disc agar diffusion method. Six common strains of Gram-negative and Gram-positive bacteria were assayed on Mueller Hinton agar medium, and related results are listed in Table.2.

Table.2. Antimicrobial activities of the newly synthesized compounds

Compound	Antimicrobial Activity (zone of inhibition mm)					
	P. mirabilis ATCC 43071	*S. aureus* ATCC 25952	*E.faecalis* ATCC 29212	*E. coli* ATCC 25922	*K.pneumoniae* ATCC 700603	*E.aerogenes* ATCC 13048
1	-	10	-	-	-	-
2	11	-	-	11	-	-
3	17	-	-	-	-	-
4	14	-	-	-	-	-
5	-	-	-	-	-	-
6	8	10	8	8	-	-
7	12	9	-	-	-	-
8	-	10	-	-	-	-
9	-	-	-	-	-	-
10	-	-	-	-	-	-
Ciprofloxacin	31	32	14	31	22	35

4. CONCLUSION

In summary, 10 new sebacic acid derivatives were designed and synthesized using a one pot approach by the formation of amide bond between hydroxyl group of the sebacic acid and amine group of a number of amino acid alkyl ester hydrochloride salts by DCC as a coupling reagent and HOBt as an additive. The mean synthesis yield

for the studied compounds was ~58%. The structures of the obtained compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR, IR and elemental analysis. The biological evaluation showed that some of them exhibit low to moderate growth inhibition activity against, *Escherichia coli*, *Proteus mirabilis*, *Enterococcus faecalis*, *Staphylococcus aureus* in comparison to ciprofloxacin as a positive control compound. Among them, compound 6 shows more promising results.

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