



Synthesis and biological evaluation of novel lipoamino acid derivatives



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ARTICLE INFO

Article history:

Received 9 September 2015

Revised 26 October 2015

Accepted 29 October 2015

Available online 2 November 2015

Keywords:

Fatty acid

Lipoamino acid

Amino acid

Antimicrobial activity

Antibiofilm activity

ABSTRACT

Seven novel lipoamino acid conjugates were synthesized from methyl oleate and amino acids. Methyl oleate was grafted to different amino acids using thioglycolic acid as a spacer group. Seven derivatives (**3a–g**) were prepared and characterized by spectral data (NMR, IR and MS spectral studies). All the derivatives were studied for their antimicrobial, anti-biofilm and anticancer activities. Among all the derivatives, it was found that compound **3b** was the most potent antibacterial compound which showed good activity against four Gram positive bacterial strains and also exhibited excellent antifungal activity against a fungal strain. In the anti-biofilm assay, compound **3b** showed promising activity with IC₅₀ value of 2.8 μM against *Bacillus subtilis* MTCC 121. All the compounds showed anticancer activities with **3c** showing promising anticancer activity (IC₅₀ = 15.3–22.4 μM) against the four cell lines tested.

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Emergence of antimicrobial resistance increases the number of diseases and poses a threat in prevention and treatment of infections caused by various bacteria, viruses, fungi and parasites.¹ This is a global concern and thus necessitated the interest and search for new and more promising potential antibiotics. Production of novel hybrid molecules by combining two biologically important and biocompatible molecules is a well known strategy for the synthesis of novel bioactives.^{2,3} Fatty acids, one of the building blocks of biomolecules are reported to assist in host defense against pathogenic microorganisms. Fatty acids and their derivatives exhibit broad spectrum of antibacterial action with potencies comparable to some natural antimicrobial peptides.^{4,5} The broad spectrum of bioactivity with non-specific mode of action makes them attractive substrates for antimicrobial agents for application in medicine, agriculture, cosmetics and nutraceutical areas.

Combination of fatty acids with natural amino acids produces amphiphilic lipoamino acids with combined properties of both lipids and amino acids.⁶ Lipoamino acid derivatives are reported to be employed in the preparation of lipid core peptide systems for application in the delivery of genes, drugs and vaccines.⁷ The lipoamino acid derivatives are expected to possess membrane like properties which could help in the passage of drugs through the biological membranes.⁸ Studies of biological activities of

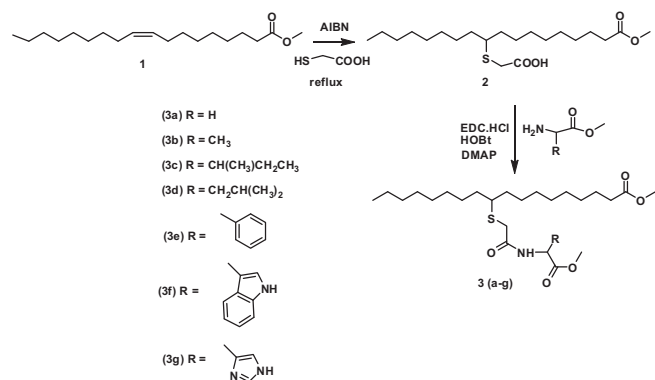
N-palmitoylated amino acids and *N*-stearyl amino acids showed that these compounds function as potential biostatic additives.^{9,10} Therefore, conjugation of amino acids with a fatty acid derivative changes the lipophilicity which influences the membrane permeability of the synthetic molecule. These types of lipoamino acid conjugates are used to enhance the oral absorption of drugs like peptides, β-lactam antibiotics and alkaloid-based molecules.¹¹ Moreover, products like lipoaminoacids and derivatives have been reported to be biodegradable and can find wide range of applications in food, pharmaceutical and cosmetic formulations.¹²

In the present study, we describe the functionalization of methyl oleate with thioglycolic acid group by thiol-ene coupling, followed by condensation of the carboxylic acid moiety with amine group of amino acid esters to produce novel lipoamino acid derivatives. Synthesis was carried out as shown in Scheme 1. Initially methyl oleate was functionalized with thioglycolic acid based on a reported method via thiol-ene coupling reaction using AIBN as initiator to give the corresponding product in 92.5% yield.¹³ The second step was condensation of the acid group with amine group of different amino acid esters catalyzed by EDC.HCl (*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride) and HOBt (1-hydroxybenzotriazole hydrate) reagent which resulted in the final products (**3a–g**) in yields ranging from 78% to 82%.

Biological activities: All the prepared compounds were tested for biological activities such as antimicrobial, anti-biofilm and cytotoxic activities.

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Scheme 1. Synthetic route for lipoamino acid conjugates.

Antimicrobial activity: The antimicrobial activities of the novel lipoamino acid esters were determined using well diffusion method¹⁴ against different pathogenic strains. The synthesized compounds were evaluated for antimicrobial activity against seven bacterial organisms, namely *Micrococcus luteus* (*M. luteus*) MTCC 2470, *Staphylococcus aureus* (*S. aureus*) MTCC 96, *S. aureus* MLS-16 MTCC 2940, *Bacillus subtilis* (*B. subtilis*) MTCC 121, *Escherichia coli* (*E. coli*) MTCC 739, *Pseudomonas aeruginosa* (*P. aeruginosa*) MTCC 2453 and *Klebsiella planticola* (*K. planticola*) MTCC 530 and also against a fungal strain, *Candida albicans* (*C. albicans*) MTCC 3017. The MIC (Minimum inhibitory concentration) was determined by comparing the standard Ciprofloxacin and Miconazole as reference drugs for evaluating the antibacterial and antifungal activities, respectively. Out of the compounds tested, two compounds showed both antibacterial and antifungal activity and two compounds showed only antibacterial activity. The results of antimicrobial evaluation are presented in Table 1. The compounds whose MIC was less than 125 µg/mL were considered as active antimicrobial compounds and were taken up for further evaluation.

From the antimicrobial activity data, it was observed that four compounds showed activity out of the total seven compounds screened. Among the four active compounds, compounds **3a** and **3b** exhibited both antibacterial and antifungal activity with compound **3b** being more potent than **3a**. Compound **3b** exhibited good antimicrobial activity with MIC value of 7.8, 15.6, 7.8 and 3.9 µg/mL against *M. luteus* MTCC 2470, *S. aureus* MTCC 96, *S. aureus* MLS-16 MTCC 2940 and *B. subtilis* MTCC 121, respectively.

Table 1
Antimicrobial activity of the lipoamino acid conjugates **3 (a–g)**

S. No	Test compounds	Minimum inhibitory concentration (µg/ml)							
		<i>M l</i> ^a	<i>S a</i> ^b	<i>S a</i> ^c	<i>B s</i> ^d	<i>E c</i> ^e	<i>P a</i> ^f	<i>K p</i> ^g	<i>C a</i> ^h
1	3a	15.6	>125	>125	7.8	>125	>125	>125	31.2
2	3b	7.8	15.6	7.8	3.9	>125	>125	>125	7.8
3	3c	31.2	31.2	>125	>125	>125	>125	>125	>125
4	3d	>125	>125	>125	>125	>125	>125	>125	>125
5	3e	>125	>125	>125	>125	>125	>125	>125	>125
6	3f	>125	>125	>125	>125	>125	>125	>125	>125
7	3g	3.9	>125	>125	3.9	>125	>125	>125	>125
	Ciprofloxacin (Standard)	0.9	0.9	0.9	0.9	0.9	0.9	0.9	>125
	Miconazole (Standard)	>125	>125	>125	>125	>125	>125	>125	7.8

^a *M. luteus* MTCC 2470.

^b *S. aureus* MTCC 96.

^c *S. aureus* MLS-16 MTCC 2940.

^d *B. subtilis* MTCC 121.

^e *E. coli* MTCC 739.

^f *P. aeruginosa* MTCC 2453.

^g *K. planticola* MTCC 530.

^h *C. albicans* MTCC 3017.

Compound **3c** showed moderate antibacterial activity (MIC value of 31.2 µg/mL) against both *M. luteus* MTCC 2470 and *S. aureus* MTCC 96. Compound **3g** showed promising antibacterial activity (MIC value of 3.9 µg/mL) against both *M. luteus* MTCC 2470 and *B. subtilis* MTCC 121.

Based on the preliminary antibacterial activity data screening, further studies on minimum bactericidal concentration (MBC) and biofilm inhibition assay was conducted on four bacterial strains.¹⁵ The compounds which showed antibacterial activity were tested for determining the MBC and it was found that compound **3b** was the most potent compound showing very good activity against all the four Gram positive microbes, namely *M. luteus* MTCC 2470, *S. aureus* MTCC 96, *S. aureus* MLS-16 MTCC 2940 and *B. subtilis* MTCC 121.

The results of the MBC data are presented in Table 2. All the compounds showed activity against *M. luteus* MTCC 2470 with compounds **3b** and **3g** being the most potent compounds, both showing MIC value of 7.8 µg/mL. Compounds **3a** and **3g** showed promising bactericidal activity against *B. subtilis* MTCC 121 with MIC value of 3.9 µg/mL. However, the values were than the standard reference drug, Ciprofloxacin which had MIC values ranging between 0.9 and 1.9 µg/mL.

These four compounds were also tested for biofilm inhibition assay according to a reported protocol.¹⁶ The bacteria which caused biofilm formation were reported to tolerate antibiotics which posed a major threat in treatment of bacterial infections.¹⁷ The compounds prepared in the present study are derived from amino acids and fatty acid and therefore can be projected as new molecules which can prevent the formation of biofilm. Accordingly, the compounds which showed activity in the preliminary antimicrobial assay were screened for biofilm inhibition assay and the results to this regard are presented in Table 3. It was observed that compound **3g** showed excellent anti-biofilm activity against *B. subtilis* MTCC 121 and *M. luteus* MTCC 2470 with IC₅₀ values of 1.9 and 2.1 µM, respectively. Compound **3b** showed anti-biofilm activity against all the strains with IC₅₀ values ranging from 2.8 to 9.3 µM. Compound **3a** showed moderate activity against *M. luteus* MTCC 2470 and *B. subtilis* MTCC 121, whereas compound **3c** showed lowest activity among all the compounds tested for biofilm inhibition assay.

From a structure–activity relationship perspective, the prepared lipoamino acid ester derivatives (**3a–g**) indicated that compound **3b** derived from alanine showed promising activity with respect to the evaluation of antimicrobial and anti-biofilm activities. The lipoamino acid from glycine (**3a**) and alanine (**3b**) were found to

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