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Synthesis, Characterization, Antimicrobial and Antitumor Activities of Sucrose Octa(*N*-ethyl)carbamate

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Abstract: Sucrose octa(*N*-ethyl)carbamate was synthesized directly from sucrose and ethyl isocyanate, and its structure was confirmed by various analytical methods, such as ^{1}H and ^{13}C NMR, FTIR, m.p., MS, and optical rotation. Its antibacterial, antifungal and cytotoxic activities were investigated. It exhibited strong inhibition against all bacteria tested, namely *S. aureus* (MIC 0.18±0.006), *B. cereus* (MIC 0.094±0.000), *M. flavus* (MIC 0.28±0.01), *L. monocytogenes* (MIC 0.18±0.006), *P. aeruginosa* (MIC 0.094±0.002), *S. typhimurium* (MIC 0.094±0.002), *E. coli* (MIC 0.18±0.006) and *E. cloacae* (MIC 0.18±0.006) and strong antifungal activity towards *T. viride* (MIC 0.09 ± 0.006), *A. versicolor* (MIC 0.18 ± 0.01), *A. ochraceus* (MIC 0.375 ± 0.01) and *P. ochrochloron* (MIC 0.375 ± 0.04). Furthermore, it showed moderate antitumor potential against human breast (GI_{50} 357.20±14.12), colon (GI_{50} 332.43±11.19) and cervical (GI_{50} 282.67±3.97) cell lines and, more important, without hepatotoxicity.

Keywords: Biological activity, antimicrobial activity, cytotoxic activity, carbamate, carbohydrates, microwave chemistry, sucrose derivatization.

1. INTRODUCTION

The excessive or careless use of antibiotics has contributed to an increased number of drug resistant microorganisms. Although many efforts have been devoted to overcoming this worldwide issue, the present antimicrobial drug market is becoming inadequate and therefore it is necessary to develop new, safe and effective antibacterial and antifungal compounds [1]. Cytotoxic agents for chemotherapy also attract much attention, since cancer is responsible for many deaths worldwide [2]. Recently, there has been an increasing interest in the development of therapeutic compounds that are biodegradable and biocompatible, derived from plant resources and natural compound-based substances [3]. A growing number of compounds with carbamate linkages have shown strong antimicrobial and cytotoxic activities have been reported [4-7].

Various glycosides can be found in natural resources, mainly in the form of glycoconjugates, where the saccharide moiety plays an important role in modulating their biological activities [8]. Glycosyl carbamates find applications as dopamine prodrugs [9], surfactants [10], glycosyl donors [11], for studying carbohydrate–protein interactions [12], in glycopeptide synthesis, [13] or for binding various residues [14]. Their application to these studies results from their stability under basic conditions [15]. Methods for the synthesis of glycosyl carbamates from glycosyl carbonates [16] and from the corresponding lactol and isocyanate in the presence of a base [17] have been reported. The structures of the mentioned glycosides are presented in (Fig. **1**).

The wide variety of potent biological activities of natural and synthetic sugar derivatives encouraged us to develop novel biological active compounds based on sucrose [18, 19]. It is a biorenewable and biocompatible raw material and is a promising starting material for the synthesis of new compounds with biological activity [20]. Sucrose carbamation has been accomplished by reacting sucrose with isocyanates in dipolar aprotic solvents [21] and in water or mixtures of water and a co-solvent to obtain them chemoselectively [22, 23].

Herein, a model study on the polysubstitution of sucrose with ethylcarbamate moieties both under microwave irradiation and conventional conditions is presented. The antimicrobial, antifungal and cytotoxic activities of the products were tested and compared with those of commercial agents – streptomycin and ampicillin (antimicrobial), bifonazole and ketoconazole (antifungal), and ellipticine (cytotoxic).

2. RESULTS AND DISCUSSION

2.1. Chemistry

A comparison of the results of experiments carried out under microwave irradiation and conventional heating for the

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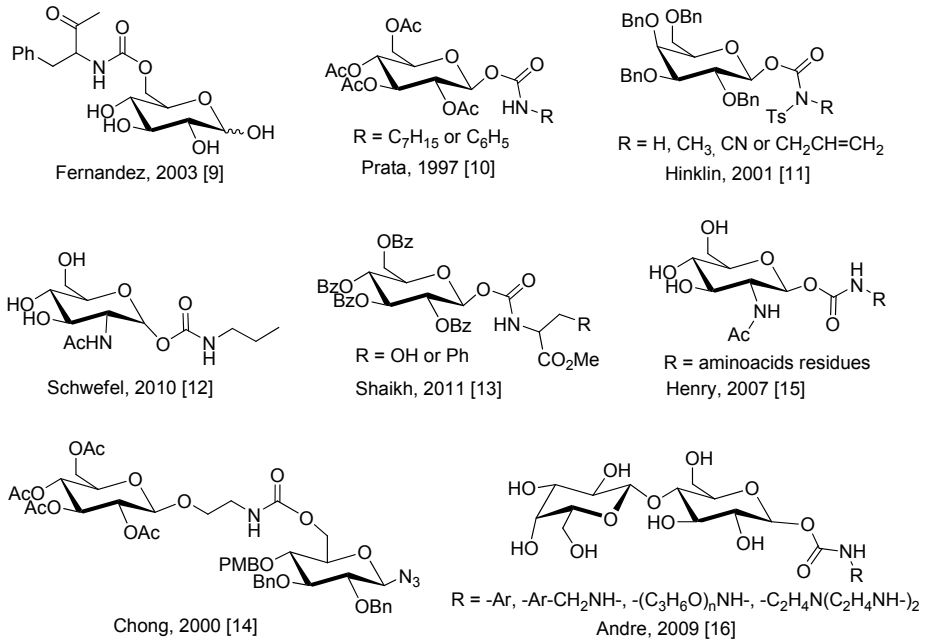
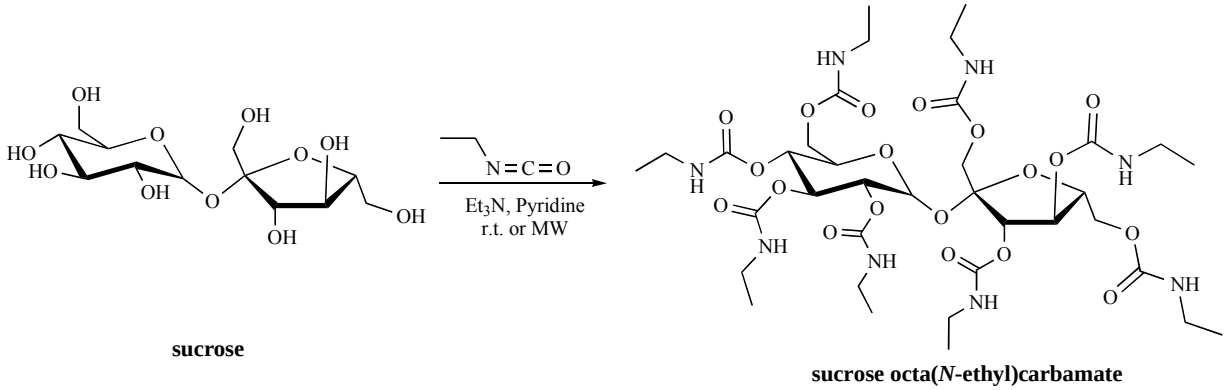


Fig. (1). Structures of some synthetic glycosyl carbamates found in the literature.



sucrose **sucrose octa(*N*-ethyl)carbamate**

Scheme 1. Synthesis of sucrose octa(*N*-ethyl)carbamate.

Table 1. Comparison of the results from conventional conditions and microwave assisted synthesis (EtNCO, Et_3N, pyridine, r.t. or MW).

	Reaction Temperature	Reaction Time	Yield
Conventional synthesis	20 °C	28 h	89 %
Microwave irradiation (300 W)	105 °C	15 min	69 %

formation of sucrose octa(*N*-ethyl)carbamate (Scheme **1**) are presented in Table **1**.

Although we experimented the carbamate synthesis described by Christian *et al.* in water-alcohol mixtures [22], we did not obtain the desired product probably because the isocyanate reacted with the hydroxylic solvents. Therefore, a synthesis using a polar aprotic solvent such as pyridine was attempted, and the desired sucrose octa(*N*-ethyl)carbamate was formed in good yield (Scheme **1**). Under these conditions only the octa-substituted product, and not a mixture of compounds with different degrees of substitution, was formed. Both microwave assisted and conventional (room temperature) syntheses proceeded smoothly in pyridine using triethylamine as a base. Carbamation at room temperature was complete within 28 h and yielded 89 % octacarbamate. Increasing the reaction temperature did not lead to better results because degradation processes occurred. Although microwave irradiation usually leads to higher yields, in this case the reaction was not complete and some of the starting material was recovered. Thus, the octacarbamate was synthesized under microwave irradiation in 15 min to afford only a 69 % yield. Further irradiation for longer times did not lead

Table 2. Antibacterial activity of sucrose octa(*N*-ethyl)carbamate, mg/mL.

Bacteria	Sucrose Octa(*N*-ethyl)carbamate MIC[a] MBC[b]	Streptomycin MIC[a] MBC[b]	Ampicillin MIC[a] MBC[b]
Staphylococcus aureus	0.18±0.006 0.375±0.01	0.04±0.003 0.09±0.006	0.25±0.03 0.37±0.03
Bacillus cereus	0.094±0.000 0.375±0.04	0.09±0.000 0.17±0.01	0.25±0.03 0.37±0.01
Micrococcus flavus	0.28±0.01 0.375±0.04	0.17±0.01 0.34±0.02	0.25±0.01 0.37±0.02
Listeria monocytogenes	0.18±0.006 0.375±0.04	0.17±0.006 0.34±0.01	0.37±0.02 0.49±0.09
Pseudomonas aeruginosa	0.094±0.002 0.18±0.02	0.17±0.01 0.34±0.02	0.74±0.02 1.24±0.02
Salmonella typhimurium	0.094±0.002 0.18±0.01	0.17±0.000 0.34±0.03	0.37±0.02 0.49±0.006
Escherichia coli	0.18±0.006 0.375±0.01	0.17±0.006 0.34±0.006	0.25±0.03 0.49±0.006
Enterobacter cloacae	0.18±0.006 0.375±0.000	0.26±0.02 0.52±0.01	0.37±0.02 0.74±0.02

[a] Minimum inhibitory concentration. [b] Minimum bactericidal concentration.

to higher yields and the conditions reported here are the ones which provided the optimum results. Despite the somewhat lower yield using microwave irradiation, the drastic decrease in the reaction time is noteworthy.

Analysis of FTIR and NMR spectra of the obtained compound proved it to be the desired product. In the FTIR spectra (Fig. **S1**, Supporting Information) it was possible to observe the relevant N-H stretching (3334 and 1533 cm^{-1}) and C=O stretching (1708 cm^{-1}) corresponding to the carbamate groups. In ^{1}H NMR (Fig. **S2**, Supporting Information), the peaks for the protons of the carbamate group (N-H), with integration corresponding to eight protons between 6.25 and 4.84 ppm, were present, as well as the anomeric (H-1) proton at 5.62 ppm and the rest of the sucrose protons between 5.53 and 3.93 ppm. Methyl and methylene protons from the ethyl groups were approximately at 1 and 3 ppm, respectively, with integration corresponding to eight ethyl groups. In ^{13}C NMR and DEPT, (Figs. **S3** and **S4**, Supporting Information) it was possible to verify the presence of carbonyl carbons between 157 and 154 ppm. Since C-2' of the sucrose core was the only quaternary carbon present, its characteristic shift at 102.6 ppm was observed in ^{13}C NMR, but was not present in DEPT, as expected. The anomeric carbon peak of the glucose unit was at 91.0 ppm. The peaks for all of the other sucrose core carbons appeared between 78 and 62 ppm, and the peaks of methylene at 36 ppm and methyl carbons at 15 ppm were corresponding to the ethyl groups. The DEPT spectre allowed us to distinguish the methylene groups from methine and methyl groups – the three primary positions of sucrose 1', 6, and 6' at 63.4, 63.3 and 62.6 ppm and the methylene carbons from the ethylcarbamate groups at 36 ppm. Bi-dimensional NMR spectra (COSY, Fig. **S5**, and HMQC, Fig. **S6**, Supporting Information) were used as an aid to assess and attribute all the signals mentioned previously. Thus, the HMQC (Fig. **S6**) spectre allowed us to distinguish which protons were not attached to a carbon atom and those were attributed to the carbamate group (N-H) protons. In the COSY spectre (Fig. **S5**) these signals exhibited cross-peaks with the CH_2-signals at 3.18 ppm, which confirmed their neighbouring positions in the carbamate groups. Further, in the COSY spectre were observed the cross peaks corresponding to the glucose core, as the one between the characteristic signals H-1 and H-2 at 5.62 – 4.65 ppm. Then, the cross peak at 4.65 – 5.30 ppm was attributed to H-2 – H-3 interaction; H-3 – H-4 was observed at 5.30 – 4.72 ppm; H-4 – H-5 at 4.72 – 4.29 ppm; and H-5 – H-6 at 4.29 – 3.93 ppm. The cross peaks corresponding to the fructose core appeared as follows: H-4' – H-5' at 5.53 – 4.09 ppm; and H-5' – H-6' at 4.09 – 4.34 ppm. After attributing all the signals in the ^{1}H NMR spectre, it was possible to assign all the carbon peaks from the corresponding cross peaks in the HMQC spectre. The elemental analysis results (Fig. **S7**, Supporting Information) confirmed the proposed structure, and by mass spectrometry it was possible to detect the expected molecular peak $[M+Na]^{+}$ at 933.3955 mass units (Fig. **S8**, Supporting Information).

2.2. Antibacterial Activity

The synthesized carbamate exhibited high antibacterial activity against all tested bacterial species (Table **2**, Figs. **2** and **3**), with MIC in the range of 0.094 - 0.280 mg/mL, and MBC in the range of 0.180 - 0.375 mg/mL. Comparing the results obtained for the synthetic compound with commercial antibiotic streptomycin (Table **2**), it was noticed that the

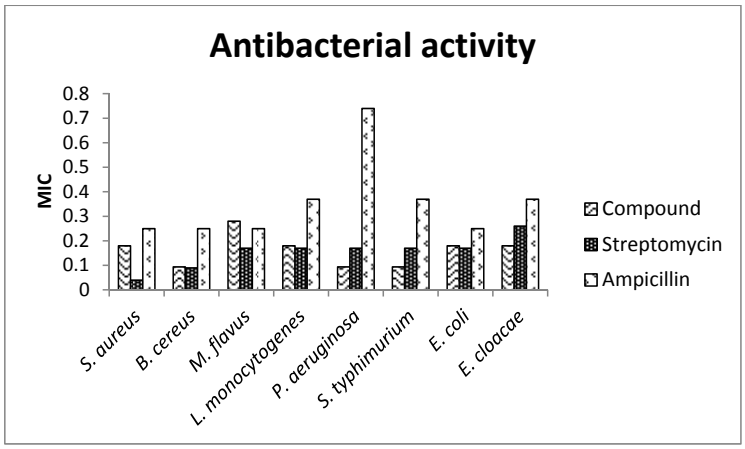


Fig. (2). MIC comparison of the antibacterial activity of sucrose octa(*N*-ethyl)carbamate, streptomycin and ampicillin.

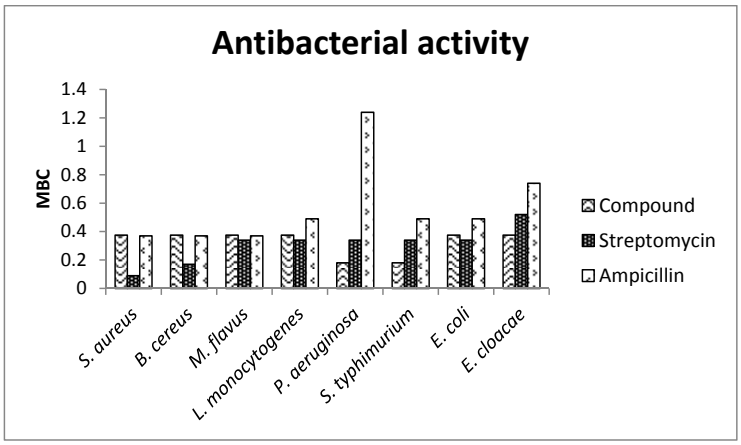


Fig. (3). MBC comparison between sucrose octa(*N*-ethyl)carbamate, streptomycin and ampicillin.

sample exhibited similar antibacterial activity for most of the bacteria tested with higher antibacterial activity towards *P. aeruginosa*, *S. typhimonium* and *E. cloacae* and lower activity towards *M. flavus*. Compared to ampicillin (Table **2**), compound **2** showed higher antibacterial activity and the only exception found was for slightly lower activity towards *M. flavus*.

2.3. Antifungal Activity

Sucrose octa(*N*-ethyl)carbamate also showed some antifungal potential (Table **3**, Figs. **4** and **5**). Inhibitory activity was in the range of 0.090 - 0.375 mg/mL, while fungicidal effects were observed in the range from 0.180 - 1.500 mg/mL. Sucrose octacarbamate possessed higher antifungal activity than bifonazole and ketoconazole against *T. viride*, and greater antifungal activity than ketoconazole towards *A. versicolor*, *A. ochraceus* and *P. ochrochloron*.

The results showed that the growth of the various types of bacteria tested responded differently to the synthetic compound. This indicates that it may have different modes of action on the different species or that the metabolism of some bacteria is able to overcome the effect of the compound or adapt to it. It is known that Gram (+) bacteria are more susceptible to antimicrobial agents than Gram (-) bacteria and fungi are more susceptible than bacteria in general [24, 25].

2.4. Antitumor Activity and Hepatotoxicity

The synthesized carbamate showed low activity against human breast, colon and cervical carcinoma cell lines, the latter being the most susceptible one (Table **4**). Up to 400 μg/mL, the sucrose octa(*N*-ethyl)carbamate did not present any activity towards lung and hepatocellular carcinoma cell lines. GI_{50} values were higher (lower antitumor activity) than the ones of the standard ellipticine. Nevertheless, it was noted that the tested compound did not show toxicity for non-tumor cells (porcine liver cells primary culture; PLP2), while the standard proved to be strongly hepatotoxic (2.96 μg/mL).

CONCLUSIONS

In summary, a novel derivative of sucrose with all eight hydroxyl groups substituted with (*N*-ethyl)carbamate moieties was synthesized and fully characterized. Synthetic procedures using microwave irradiation resulted in shorter reaction times but lower yields. The antibacterial, antifungal and

Table 3. Antifungal activity of sucrose octa(*N*-ethyl)carbamate, mg/mL.

Fungi	Sucrose Octa(*N*-ethyl) carbamate MIC[a] MFC[b]	Bifonazole MIC[a] MFC[b]	Ketoconazole MIC[a] MFC[b]
Aspergillus fumigatus	0.375 ± 0.001 0.75 ± 0.000	0.15 ± 0.03 0.20 ± 0.03	0.20 ± 0.00 0.50 ± 0.10
Aspergillus versicolor	0.18 ± 0.01 0.375 ± 0.01	0.10 ± 0.06 0.20 ± 0.06	0.20 ± 0.06 0.50 ± 0.06
Aspergillus ochraceus	0.375 ± 0.01 0.75 ± 0.03	0.15 ± 0.03 0.20 ± 0.00	1.50 ± 0.00 2.0 ± 0.30
Aspergillus niger	0.375 ± 0.01 0.75 ± 0.00	0.15 ± 0.03 0.20 ± 0.06	0.20 ± 0.03 0.50 ± 0.03
Trichoderma viride	0.09 ± 0.006 0.18 ± 0.000	0.15 ± 0.03 0.20 ± 0.00	1.0 ± 0.00 1.0 ± 0.30
Penicillium funiculosum	0.375 ± 0.04 0.75 ± 0.03	0.20 ± 0.06 0.25 ± 0.03	0.20 ± 0.03 0.50 ± 0.00
Penicillium ochrochloron	0.375 ± 0.04 0.75 ± 0.08	0.20 ± 0.06 0.25 ± 0.03	2.5 ± 0.30 3.5 ± 0.10
Penicillium verrucosum	0.75 ± 0.000 1.5 ± 0.300	0.10 ± 0.00 0.20 ± 0.00	0.20 ± 0.00 0.30 ± 0.00

[a] Minimum inhibitory concentration. [b] Minimum fungal concentration.

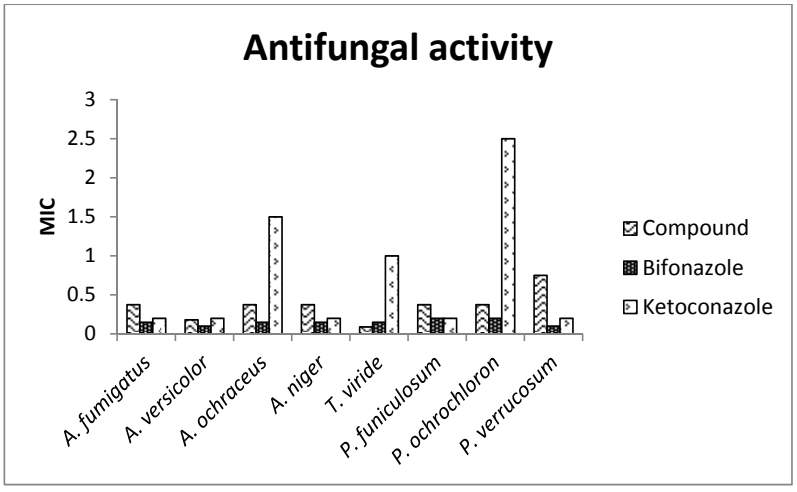


Fig. (4). MIC comparison of the antifungal activity of sucrose octa(*N*-ethyl)carbamate, bifonazole and ketoconazole.

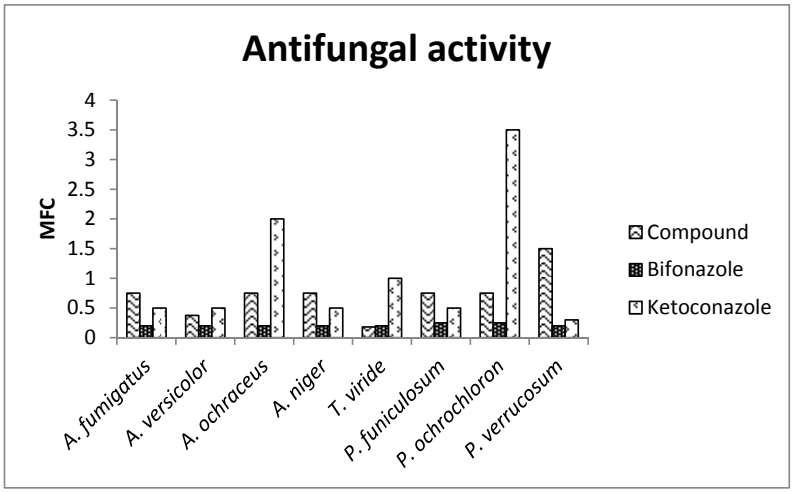


Fig. (5). MFC comparison between sucrose octa(*N*-ethyl)carbamate, bifonazole and ketoconazole.

Table 4. Antitumor activity of sucrose octa(*N*-ethyl)carbamate, µg/mL.

Cell Line	Sucrose Octa(*N*-ethyl)carbamate GI_{50}[a]	Ellipticine
MCF7 (human breast carcinoma)	357.20±14.12	0.91±0.04
NCI-H460 (human lung carcinoma)	> 400	1.42±0.00
HCT15 (human colon carcinoma)	332.43±11.19	1.91±0.06
HeLa (human cervical carcinoma)	282.67±3.97	1.14±0.21
HepG2 (human hepatocellular carcinoma)	> 400	3.22±0.67
PLP2 (non-tumor porcine liver primary cells)	> 400	2.06±0.03

[a] Growth inhibition by 50 %.

cytotoxic activities of sucrose octa(*N*-ethyl)carbamate were tested with the view to potential applications. It exhibited higher antibacterial activity than streptomycin against all Gram (-) bacteria, with the exception of *E. coli*, where this potential was almost the same. It was obvious that the compound tested possesses a wide spectrum of activity, depending on the bacterial and fungal species. It exhibited moderate to low antitumor potential (towards human breast, lung, colon, cervical, hepatocellular carcinoma cell lines, MCF7, NCI-H460, HCT15, HeLa and HepG2 cells respectively), but without hepatotoxicity towards non-tumor procine liver primary cells, PLP2.

MATERIALS AND METHODS

General Methods

The ^{1}H NMR (400 Hz) and ^{13}C NMR (100 Hz) were recorded on Bruker ARX 400 spectrometer in $CDCl_3$ solutions. Chemical shift values (δ) are expressed in parts per million and reported downfield from TMS (0.00 ppm). Melting point was determined on Electrothermal Melting Point Apparatus. Optical rotation was measured in chloroform solution using an AA-1000 Polarimeter Optical Activity LTD (0.5 dm cell) at 589 nm. FTIR specter was recorded on a Bruker Tensor 27 spectrometer in KBr dispersion. Mass spectra were recorded on a MALDI-TOF (Matrix-Assisted Laser Desorption and Ionization Time of Flight) spectrometer (Voyager-DETM Pro Workstation model). The microwave-assisted syntheses was performed as previously described [26]. Flash chromatography was performed on silica gel (Merck, 200-400 mesh). Pyridine and triethylamine were distilled from KOH prior to use [27].

Sucrose Octa(N-ethyl)carbamate

Conventional synthesis: Sucrose (1.00 g, 2.92 mmol) was dissolved in pyridine (15 mL) with magnetic stirring and under inert atmosphere (argon). Triethylamine (150 mmol, 2.1 mL) was added and after 30 min the reaction mixture was cooled in an ice bath. Ethyl isocyanate (351 mmol, 2.8 mL) was then added dropwise within 15 min. The reaction mixture was let to reach r.t. After 28 h all of the sucrose had reacted (TLC, eluent, acetone/metanol/water 5/2/1) and the pyridine was evaporated azeotropically using toluene. The crude product was purified by flash chromatography (ether, then ethyl acetate) to afford the desired product as a white solid (2.38 g, 89 %).

Microwave Synthesis

Sucrose (1.00 g, 2.92 mmol) was dissolved in pyridine (15 mL) and triethylamine (150 mmol, 2.1 mL) was added with magnetic stirring and under an inert atmosphere (argon). After 30 minutes the reaction mixture was cooled in an ice bath and ethyl isocyanate (351 mmol, 2.8 mL) was added dropwise within 15 min. The reaction mixture was subjected to microwave irradiation (max 300 W at constant temperature 105 °C) for 15 minutes. The pyridine was evaporated using toluene, and the crude product was purified by flash chromatography (ether, then ethyl acetate) to afford the desired compound as a white solid (1.84 g, 69 %).

$[\alpha]_D^{24}$ +14.7 (*c* 1.00, $CHCl_3$); mp 113-115 °C; FTIR (K-Br, cm^{-1}) ν_{max}: 3334 (N-H stretch), 2975, 2935 (C-H stretch), 1708 (C=O stretch), 1533 (N-H stretch), 1452, 1381, 1359 (C-H stretch), 1250 (N-CO-O assymetric stretch), 969 (N-CO-O symetric stretch); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.25 (1H, s, N-H), 6.10 (1H, s, N-H), 5.80 (2H, s, N-H), 5.62 (1H, s, H-1), 5.53 (2H, s, H-3', 4'), 5.32-5.28 (1H, m, H-3), 5.09 (1H, s, N-H), 4.93-4.91 (2H, m, N-H), 4.84 (1H, s, N-H), 4.72 (1H, t, *J* = 9.78 Hz, H-4), 4.65 (1H, d, *J* = 7.7 Hz, H-2), 4.40-4.23 (5H, m, H-5, 2×H-1', 2×H-6'), 4.11-4.08 (2H, m, H-5', 6), 3.93 (1H, t, *J* = 10.4 Hz, H-6), 3.19-3.17 (16H, m, C*H*$_2$), 1.18-1.07 (24H, m, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 156.5, 156.4, 155.8, 155.7, 155.0, 154.9, 154.6 (C=O), 102.6 (C-2'), 91.0 (C-1), 78.2 (C-5'), 75.6, 72.8 (C-3',C-4'), 71.4 (C-2), 70.8 (C-3), 69.8 (C-4), 68.3 (C-5), 63.4, 63.3, 62.6 (C-1', C-6, C-6'), 36.0, 35.9, 35.8 (*C*H$_2$), 15.2, 15.0, 14.9, 14.8, 14.6 (*C*H$_3$); Anal. calcd. for $C_{36}H_{62}N_8O_{19}$: C, 47.47; H, 6.86; N, 12.30; found: C, 47.60; H, 6.69; N, 12.65. MALDI-TOF MS m/z calcd. for $C_{36}H_{62}N_8O_{19}Na$ ($[M+Na]^+$) 933.4023; found: 933.3955.

Antibacterial Activity

The Gram-positive bacteria *Staphylococcus aureus* (ATCC 6538), *Bacillus cereus* (clinical isolate), *Listeria monocytogene*s (NCTC 7973), and *Micrococcus flavus* (ATCC 10240), and the Gram-negative bacteria *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 35210), *Salmonella typhimurium* (ATCC 13311), and *En-*

terobacter cloacae (human isolate), were used. The antibacterial assay was carried out by a microdilution method as previously described [28, 29].

Antifungal Activity

Aspergillus fumigatus (human isolate), *Aspergillus versicolor* (ATCC 11730), *Aspergillus ochraceus* (ATCC 12066), *Aspergillus niger* (ATCC 6275), *Trichoderma viride* (IAM 5061), *Penicillium funiculosum* (ATCC 36839), *Penicillium ochrochloron* (ATCC 9112) and *Penicillium verrucosum* var. *cyclopium* (food isolate), were used. Commercial fungicides, bifonazole (Srbolek, Belgrade, Serbia) and ketoconazole (Zorkapharma, Šabac, Serbia), were used as positive controls (1-3000 μg/mL). To investigate the antifungal activity, a modified microdilution technique was used [30, 31].

Antitumor Activity and Hepatotoxicity

Five human tumor cell lines were used: MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), HCT-15 (colon carcinoma), HeLa (cervical carcinoma) and HepG2 (hepatocellular carcinoma). The tests were performed as described in [32]. GI_{50} values (sample concentration that inhibited 50 % of the net cell growth) were determined and ellipticine was used as standard.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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SUPPLEMENTARY MATERIAL

FTIR, NMR, mass spectra and elemental analysis of sucrose octa(*N*-ethyl)carbamate are presented. Supplementary material is available on the publishers Web site along with the published article.

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