



Synthesis, antibacterial activity, and application in the antifouling marine coatings of novel acylamino compounds containing gramine groups



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ABSTRACT

Basing on the previous syntheses of ester compounds containing gramine functional groups, the researchers synthesized two novel acylamino compounds containing gramine groups and the structures of target compound were established using ^1H NMR, ^{13}C NMR, IR spectra, and elemental analysis. The antibacterial activity of the synthesized compounds against *Escherichia coli* and *Staphylococcus aureus*, as well as their antifouling activity were studied. The results showed that these compounds possessed high antibacterial activity and a minimal inhibitory concentration value of 0.03 mg/mL against bacteria. Moreover, their antifouling properties are superior to cuprous oxide and chlorothalonil, which are widely used as antifoulants. Furthermore, quantitative structure activity relationship studies with antibacterial activity of the nine gramine compounds were established. These provide theoretical and technical bases for preparing environment-friendly antifouling coatings with the compounds as antifouling agents.

1. Introduction

Antifouling organotin paints prevent marine biological adhesion for up to 5 years. However, the International Maritime Organization has banned it globally since January 1, 2008 due to its serious damage to the marine ecological environment [1–4]. Since then, new antifouling non-organic tin paints have been widely used. However, in recent years, studies have indicated that effective antifouling coating ingredients, such as the cuprous oxide, chlorothalonil and Irgarol 1051, have caused biological malformation, death [5–7], and coastal enrichment of sediments and organisms [8–10] because of their long half-life, high toxicity, and synergistic effect. Moreover, they have caused various degrees of environmental damage. Therefore, they are expected to be replaced with environment-friendly antifouling agents, especially substances with antifouling activity from secondary metabolites in marine organisms [11–14]. Among these natural antifouling agents, 2,5,6-tribromo-methylgramine deserves consideration because of its simple structure and high antifouling capability [15–17]. Moreover, research on the synthesis and property of its analogues has attracted increasing attention [18].

Based on the previous syntheses of ester compounds containing gramine functional groups¹⁹, two novel acylamino compounds containing gramine groups at the *N*-position of their indole rings were synthesized via the Michael addition reaction. The synthetic routes of the target compounds are shown in Scheme 1. The antibacterial activity

of the synthesized compounds against *Escherichia coli* and *Staphylococcus aureus* was investigated. Moreover, the relationships between inhibitory activity and quantum chemical parameters of the nine compounds against *E. coli* were discussed. Furthermore, their quantitative structure activity relationship (QSAR) studies with the antibacterial activity were established, and the application of the nine compounds on the antifouling marine coating was preliminarily studied. These provided theoretical and technical bases for preparing environment-friendly antifouling coatings using the compounds as antifouling agents.

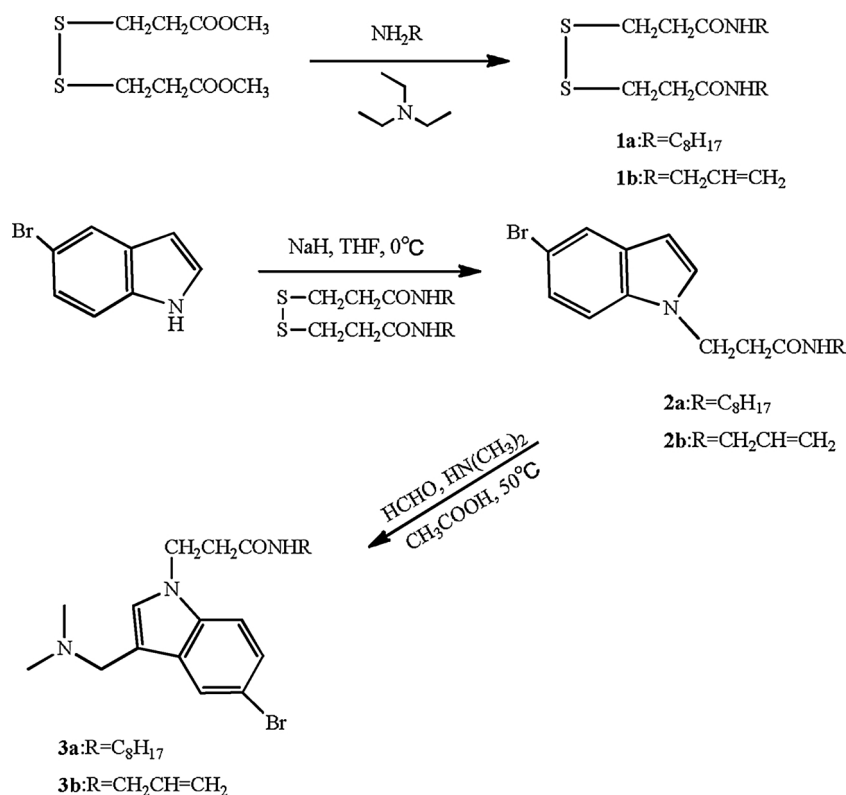
2. Experimental

2.1. Instruments and reagents

This study used the following for the investigation: MLR-350H incubator (Sanyo, Japan), HZQ-F160 incubator shaker (Harbin Donglian company), SCV-4A1 bechtop (ESCO, Singapore), and MLS-3750 autoclave sterilizer (Sanyo, Japan). IR spectra were recorded for KBr disc on an AVATAR-360 Fourier Transform Infrared Spectrometer (Nicolet, America). ^1H NMR and ^{13}C NMR spectra were recorded with AVANCE III (600 MHz) instrument (Bruker, Switzerland) in CDCl_3 as the solvent, using TMS as an internal standard, and chemical shifts were indicated in parts per million (δ). Elemental analyses were performed using FLASH EA1112 Analyzer, and results for C, H, N, were within $\pm 0.4\%$

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Scheme 1. Synthetic routes of compounds.

of the calculated values. Allylamine was purchased from Sigma-Aldrich, and *n*-octylamine and 5-bromo-1*H*-indole were obtained from Aladdin, Silica gel (200–300 meshes) was purchased from Qingdao Haiyang Chemical Co. Ltd. Other reagents were analytically or chemically pure, and all solvents were analytically pure.

2.2. Synthesis of compounds

2.2.1. Syntheses of compounds 1a and 1b

The compounds were synthesized according to a reference [20]. The 1b target compounds were used as examples. A three-necked flask (500 mL) equipped with a stirrer was placed in an ice bath. Allylamine (17.1 g, 0.3 mol) and triethylamine (2.5 mL) was added, and dimethyl 3,3'-dithiobispropionate (23.8 g, 0.1 mol) was dropwise dispersed in the flask. The reaction mixture was stirred at room temperature for 48 h after dripping. The white solid was obtained by washing with deionized water. And the crude product was purified by recrystallization with ethanol to afford compound 1b. The yield of 1a was 86.5%, with melting point at 122.3 °C to 122.8 °C; the yield of 1b was 88.4%, with melting point at 135.7 °C to 137.2 °C.

2.2.2. Syntheses of intermediate 2a and 2b

Compounds 2a and 2b were synthesized according to the reference [19,21,22]. The 2b target compounds were used as examples. A three-necked flask (100 mL) equipped with a stirrer was placed in an ice bath. Anhydrous tetrahydrofuran (THF) (20 mL) was added, and sodium hydride (60%, 1.8 g, 0.036 mol) and 5-bromo-1*H*-indole (3.9 g, 0.02 mol) were dispersed successively in anhydrous THF (20 mL) by stirring. After stirring for 0.5 h, a solution of 1b (6.0 g, 0.02 mol) in anhydrous THF (10 mL) was added dropwise. The reaction mixture was stirred at 0 °C to 5 °C for approximately 3.5 h and the reaction was quenched with saturated ammonium chloride solution (20 mL). After extraction with ethyl acetate, the combined organic layers were washed with saturated brine and deionized water, and dried over anhydrous MgSO₄. After removing the solvent in reduced pressure distillation, the

yellow oily substances were obtained and dissolved in ethyl acetate. The substances were purified via column chromatography with ethyl acetate and petroleum ether (volume ratio 1:1) as an eluent. The extract was concentrated to dryness to afford intermediate 2b (2.1 g).

2a: red brown liquid; the yield is 39.2%; ¹HNMR(CDCl₃, 600 MHz) δ: 0.87(t, *J* = 7.2 Hz, 3H, CH₃), 1.13(m, 2H, C₈H₁₇, 2-H), 1.20(m, 2H, C₈H₁₇, 3-H), 1.20(m, 2H, C₈H₁₇, 4-H), 1.20(m, 2H, C₈H₁₇, 5-H), 1.24(m, 2H, C₈H₁₇, 6-H), 1.24(m, 2H, C₈H₁₇, 7-H), 2.57(t, *J* = 6.6 Hz, 2H, CH₂CO), 3.08(t, *J* = 9.6 Hz, 2H, NHCH₂), 4.47(t, *J* = 6.3 Hz, 2H, NCH₂), 5.20(s, 1H, NH), 6.43(s, 1H, PyH), 7.09(m, 1H, PyH), 7.09~7.59(d, 3H, PhH); ¹³CNMR(CDCl₃, 150 MHz) δ: 14.11(1C, C₈H₁₇, 1-C), 22.64(1C, C₈H₁₇, 2-C), 26.75(1C, C₈H₁₇, 3-C), 29.15(1C, C₈H₁₇, 4-C), 29.17(1C, C₈H₁₇, 5-C), 29.26(1C, C₈H₁₇, 6-C), 31.77(1C, C₈H₁₇, 7-C), 37.44(1C, CH₂CO, 1-C), 39.67(1C, C₈H₁₇, 8-C), 42.61(1C, NCH₂), 101.42(1C, PyC), 109.16(1C, PhC), 119.45(1C, PhC), 121.06(1C, PhC), 121.54(1C, PhCBr), 128.70(1C, PyC), 130.89(1C, Py-PhC), 135.47(1C, Py-PhC), 170.11(1C, CO); IR(KBr) ν: 735.5, 1238.9, 1456.8, 1556.8, 1659.8, 2922.6, 3287.6 cm⁻¹.

2b: yellow liquid; the yield is 35.0%; ¹HNMR(CDCl₃, 600 MHz) δ: 2.59(t, *J* = 6.6 Hz, 2H, CH₂CO), 3.72(t, 2H, NHCH₂), 4.43(t, *J* = 6.3 Hz, 2H, NCH₂), 5.00(d, *J* = 16.8 Hz, 1H, CH=CHH), 5.03(d, *J* = 10.2 Hz, 1H, CH=CHH), 5.47(s, 1H, NH), 5.62(m, 1H, CH), 6.40(s, 1H, PyH), 7.09(d, 1H, PyH), 7.21~7.73(m, 3H, PhH); ¹³CNMR(CDCl₃, 150 MHz) δ: 37.06(1C, CH₂CO, 1-C), 41.97(1C, NHCH₂), 42.55(1C, NCH₂), 101.07(1C, PyC), 110.67(1C, PhC), 112.74(1C, =CH₂), 116.61(1C, PhC), 123.44(1C, PhC), 124.35(1C, PhCBr), 129.39(1C, PyC), 130.32(1C, Py-PhC), 133.50(1C, =CH), 134.19(1C, Py-PhC), 169.83(1C, CO); IR(KBr) ν: 717.9, 1174.2, 1468.5, 1506.8, 1642.2, 2946.2, 3066.9, 3249.4 cm⁻¹.

2.2.3. Syntheses of target compounds 3a and 3b

The synthetic method of 3a is similar to 3b; therefore, we used the target compounds of 3b as examples. A three-necked flask (100 mL) equipped with a stirrer and thermometer was placed in an ice bath, and an aqueous dimethylamine solution (33%, 3 mL, 0.02 mol) was frozen

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