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Synthesis and Antimicrobial Activities on *Staphylicoccus aureus* of Miscellaneous Atomic Curcumin Derivatives

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Miscellaneous atomic curcumin derivatives were synthesized with biotin, lipolic acid, isonicotinic acid and curcumin, employing the acylchloride method. Their chemical structures were confirmed by IR, MS and ^{1}H NMR spectroscopy. The antimicrobial activities of these new compounds and curcumin were explored with *Staphylicoccus aureus* under the same conditions. The result showed that the antimicrobial activity of these new compounds were better than curcumin especially the MIC of lipolic curcumin was 2.5 mg/mL, which was 4 times better than curcumin.

Key Words: Biotinylated curcumin, Lipolate curcumin, Isonicotinate curcumin, *Staphylicoccus aureus*, Antimicrobial activities.

INTRODUCTION

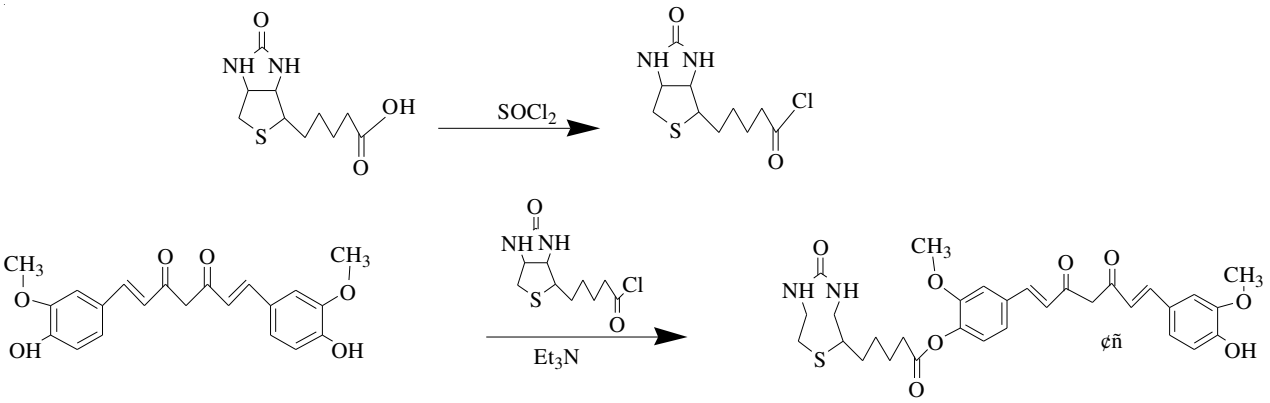
Curcumin is a β-diketone constituent of the turmerichat is obtained from the powdered root of *Curcumaonga Linn*. Curcumin has been used by traditional medicine for liver disease (jaundice), indigestion, urinary tract diseases, rheumatoid arthritis and insect bites. This phytochemical has also been demonstrated to possess both anticancer and antiangiogenic properties[1]. The studies showed that the phenolic groups and the active methylene in curcumin were connected with biomolecular potential target for antibacterial activity and curcumin derivatives containing heteroatoms had stronger efficancy[2,3]. Biotin (vitamin H), as a pure natural product, can help treat diabetes in addition to biotin deficiency and according to a variety of animal experiments, even given excessive biotin, there were no side effects[4]. The lipoic acid has much better antioxidant activity compared with general antioxidants and has been used for the treatment of diabetic neuropathy in Germany for decades[5]. Nicotinic is used as clinical drugs to regulate dyslipidemia[6] and isonicotinic acid as its isomers, there is great significance to explore its antimicrobial activities. So we decided to use biotin, lipoic acid, isonicotinic acid and curcumin to synthesize miscellaneous atomic curcumin. And the antimicrobial activities of these new chemical compounds and curcumin were explored with *Staphylicoccus aureus* under the same conditions in order to provide a theoretical basis for the further expansion of the natural products in the aspect of medicinal value.

EXPERIMENTAL

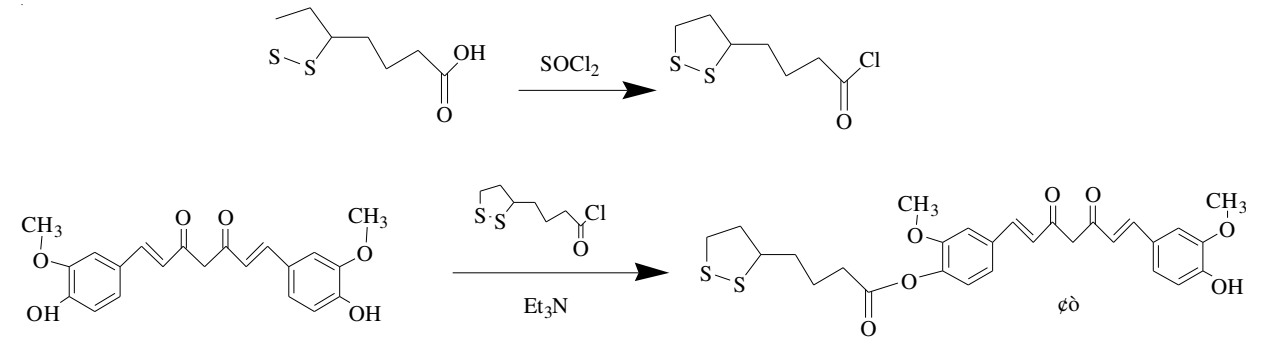
The miscellaneous atomic curcumin derivaives were synthesized with biotin, lipolic acid, isonicotinic acid and curcumin employing the acyl chloride method (**Schemes I-III**).

Screening for antimicrobial activity[7,8]: Activate *Staphylococcus aureus* at the optimum temperature for 2 h then transfer to the freshly prepared activation medium. After shaking for 24 h, dilute the bacter solution into10^8 cfu/mL. Antimicrobial activity was tested by the agar-well diffusion method. Different concentrations of the products (0.25-100 mg/mL) were dissolved in ethanol. The antibacterial assay plates were incubated at 37 ºC for 24 h. The standard discs (6 mm diameter) of the products and sterile saline served as a negative control, while ethanol was used as a positive control. The diameter of the zones of inhibition around each of the discs was taken as measure of the antimicrobial activity. Each experiment was carried out in triplicate and the mean diameter of the inhibition zone was recorded (Tables 1 and 2).

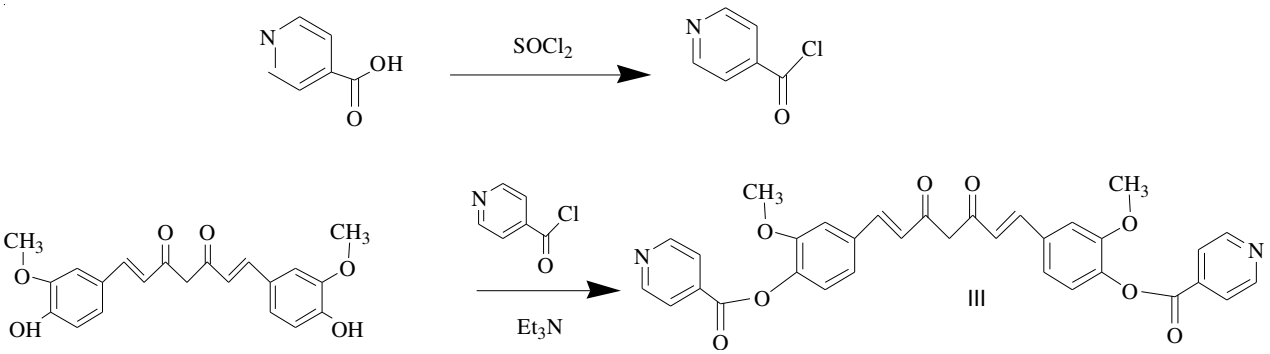
Minimum inhibitory concentration (MIC): Transfer 0.1 mL of 108 cfu/mL *Staphylococcus aureus* to each petri dish and applied to each petri dish with 0.625-200 mg/mL miscellaneous atomic curcumin and curcumin. The MIC values were interpreted as the lowest concentration of the sample, which showed clear fluid with no development of turbidity. All tests were performed in triplicate (Tables 1 and 2).



Scheme-I: Synthesis of biotinylated curcumin. Reagents and conditions: (a) biotin 1 mmol, $SOCl_2$ 4 mL, reflux, 40 ºC, oil bath for 7 h. (b) biotin chloride, curcumin 0.2 mmol, Et_3N 2 mL, N_2, 37 ºC, reflux, for 24 h



Scheme-II: Synthesis of lipolate curcumin. Reagents and conditions: (a) alpha lipoic acid 1 mmol, $SOCl_2$ 4 mL, reflux, 40 ºC, oil bath for 7 h. (b) curcumin 0.2 mmol, Et_3N 2 mL, N_2, 37 ºC, reflux, for 24 h



Scheme-III: Synthesis of isonicotinate curcumin. Reagents and conditions: (a) Isonicotinic acid 24.4 mmol, $SOCl_2$ 20 mL, DMF 0.2 mL, reflux, ice bath then heated to 77 ºC oil bath for 4 h. (b) curcumin 5 mmol, Et_3N 8 mL, N_2, 37 ºC, reflux, for 12 h

RESULTS AND DISCUSSION

From the date, it is observed that the MICs of lipolate curcumin, biotinylated curcumin, isonicotinate curcumin and curcumin were 2.5, 5, 5 and 10 mg/mL. The result showed that the antimicrobial activity of lipolate curcumin was at least 4 times as good as curcumin. And curcumin derivatives modified with sulphur atoms had higher antibacterial activity than that with nitrogen atoms. Because *Staphylococcus aureus* is harm to body and curcumin derivatives modfided with heteroatoms have strong inhibitory effect, it is of great significance in clinical applications.

TABLE-1
MIC OF THE PRODUCTS ON *Staphylicoccus aureus* (CULTURED 24 h AT 37 ºC)

Treatment (mg/mL)	Curcumin	Lipolate curcumin	Biotinylated curcumin	Isonicotinate curcumin	Negative control (Sterile saline)	Positive control (ethanol)
200	–	–	–	–	+++++	++
100	–	–	–	–	+++++	++
10	–	–	–	–	+++++	++
5	+++++	–	–	–	+++++	++
2.5	+++++	–	++	+++	+++++	++
1.25	+++++	+++	+++++	+++++	+++++	++
0.625	+++++	+++++	+++++	+++++	+++++	++

TABLE-2
INHIBITION ZONE OF THE PRODUCTS ON *Staphylicoccus aureus* (CULTURED 24 h AT 37 ºC)

Treatment	Curcumin	Lipolate curcumin	Biotinylated curcumin	Isonicotinate curcumin
100 mg/mL	12	18	16	16
10 mg/mL	9	18	12	12
5 mg/mL	7	13	10	9
2.5 mg/mL	7	10	8	8
Positive control (ethanol)	7	7	7	7
Negative control (sterile saline)	6	6	6	6

Conclusion

Curcumin derivatives in particular modefied with heteroatoms will expand the medicinal value of curcumin and provide theoretical basis for the mechanism of the antibacterial activity.

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