Design and synthesis of curcumin-bioconjugates to improve systemic delivery

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ABSTRACT
Di-O-glycinoyl curcumin (I), di-O-glycinoyl-C⁴-glycyl-curcumin (II), 5'-deoxy-5'-curcuminyl thymidine (5'-cur-T) (III) and 2'-deoxy-2'-curcuminyl uridine (2'-cur-U) (IV) have been synthesized and characterised by elemental analysis & ¹H NMR. The antibacterial activities of these four bioconjugates has been tested particularly for multiresistant micro-organisms. Best results are shown by I & IV. These bioconjugates serve dual purpose of systemic delivery as well as therapeutic agents against viral diseases.

INTRODUCTION
The primary goal of today’s pharmaceutical industries is to enhance the specificity of therapeutic drugs and thereby improving their delivery on the specific sites. The past decade has seen extensive use of liposomes and lipid based delivery system to improve pharmacological properties of the variety of drugs¹-³. Lipid-oligonucleotides complexes can provide levels of encapsulation but their size and charge severely impair their ability to distribute systematically after parenteral administration. Keeping this rational in mind, a bioconjugate may be synthesized comprising of amino acid / nucleoside and any suitable neutral molecule. In the present work, bioconjugates of curcumin (coloring agent of turmeric having immense biological importance⁴), 1,7-bis(4-hydroxy-5-methoxyphenyl)-1,6-heptadiene -3,5-dione / diferuloyl methane have been synthesized viz, di-O-glycinoyl curcumin (I), di-O-glycinoyl-C⁴-glycyl-curcumin (II), 5'-deoxy-5'-curcuminyl thymidine (5'-cur-T) (III) and 2'-deoxy-2'-curcuminyl uridine (2'-cur-U) (IV). Curcumin has interesting structure with two phenolic rings and active methylene function, which are potential site for attaching biomolecules.

The meager absorption of curcumin through the intestinal wall on oral intake needs to be improved in order to achieve significant concentration inside the cells for appropriate activity henceforth, the nucleoside-curcumin bioconjugate can serve dual purpose of systemic delivery as well as therapeutic agent against viral diseases.

MATERIALS AND METHOD
Curcumin, glycine, allyl bromide and triphenylphosphite were purchased from Merck-Schuchardt, Germany. Nucleosides were purchased from Sigma Chemical Company, USA. Mueller-Hinton Broth, Agar and sterile discs were purchased from Hi Media laboratory Ltd., Mumbai, India.

RESULT AND DISCUSSION
Di-O-glycinoyl curcumin (I), di-O-glycinoyl-C⁴-glycyl-curcumin (II) were synthesized by condensing curcumin with N-phthaloyl glycinoyl chloride in anhydrous pyridine. In case of (II) a strong base NaOEt was taken whereas in case of (I) curcumin itself was treated with N-phthaloyl glycinoyl chloride. 5'-Deoxy-5'-curcuminyl thymidine (5'-cur-T) (III) and 2'-deoxy-2'-curcuminyl uridine (2'-cur-U) (IV) were synthesized by taking 5'-deoxy-5'-bromothymidine and 2'-deoxy-2'-chloro uridine in pyridine mixed with sodium salt of (I). The antibacterial activity of bioconjugates (I), (II), and (IV) were compared with curcumin from known macro-dilution broth susceptibility test method. These were serially diluted (30, 15, 7.5, 3.75, 1.88, 0.94 µmol/L) and made in Muller-Hinton broth, after which a standardized bacterial suspension was added. The lowest concentration of curcumin bioconjugates in µmol/mL that prevent the in vitro growth of micro-
organism has been represented as MIC (Minimum Inhibitory Concentration, shown in Table 1.

Curcumin conjugates
I ; \( R_1 = R_3 = \text{CO-CH}_2\text{-NH}_2 \), \( R_2 = \text{H} \)

II ; \( R_1 = R_2 = R_3 = \text{-CO-CH}_2\text{-NH}_2 \)

III ; \( R_1 = R_3 = \text{H}, R_2 = 5'\text{-Deoxy thymidine} \)

IV ; \( R_1 = R_3 = \text{H}, R_2 = 2'\text{-Deoxy uridine} \)

Each test was performed in triplicate and the MICs reported represent the result of at least two repetitions. Out of four, three conjugates show positive result on multi-resistant micro-organisms. The most encouraging result was found against Streptococcus pyogenis with (I) having MIC 1.88 \( \mu \text{mol/ mL} \) against Streptococcus pyogenes and compared with one of the best marketed antibiotic, viz. Amoxyclyav which show MIC 7 \( \mu \text{mol / mL} \) (6 \( \mu \text{mol / mL} \) reported) where as (I) shows MIC 1.88 \( \mu \text{mol / mL} \) which is 3.7 times more effective than amoxyclyav. The results with 5'-deoxy-5'-curuminoyl thymidine (III) were not satisfactory among the selected bacterial strains, which may be due the fact that thymidine is not a natural component of bacterial DNA (data not shown).

### CONCLUSION

It is apparent from the above discussion that the amino acid bioconjugates are bacteriologically more active than nucleoside bioconjugate, since amino acid is the main component of bacterial cell wall.

### ACKNOWLEDGEMENT

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### REFERENCES


### Table 1

<table>
<thead>
<tr>
<th>S.No</th>
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MIC Correlation Diagram (in \( \mu \text{mol/mL} \)) I = Di-O-glycinoyl curcumin, II = di-O-glycinoyl-\( C' \)-glycyl-curcumin and IV = 2'-deoxy-2'-curcuminyl uridine (2'-cur-U), Cur = Curcumin, R = Resistant (below 10 mm). I shows best result against *Streptococcus pyogenes*. Results with 5'-deoxy-5'-curcuminyl thymidine (5'-Cur-I) are not included.