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Synthesis of Organic Nanoparticle of Aryl Tetralin Compounds and Study of their Biological Activities for Targeted Delivery System

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ABSTRACT
Aryl tetralin is a naturally occurring lignan compound which exhibits anticancer, anti AIDS and other biological activities. In the present work, new tetralone intermediates of aryl tetralin analogues were synthesized in very good yields by chalcone route. All the products were characterized by spectral and elemental analysis data. These types of drug intermediates were synthesized and incorporated into the nanoparticle system and the drug delivery targeting mechanism to be investigated in vitro.

Keywords: *Podophyllotoxin, Aryl tetralin, Nanoparticle, Drug Delivery*

1. INTRODUCTION

In recent years, more interest has been paid to protect food stuffs and human beings against microbes and diseases such as cancer, malaria etc. Therefore prevention has to be taken in order to reduce the problems for example synthesis of new compounds or natural drugs to control microorganisms and cancerous malignant cells. Their large size can make it difficult to evade organs such as spleen, liver etc. in addition the must be able to differentiate between normal and infected tissues. Indeed it is only recently that researchers have begun to successively engineered nanoparticle that can effectively evade the immune system and actively targeting affected sites [1-3].
The lignans are a large family of secondary metabolites widely encountered in the plant kingdom. Within this large family of lignans are the aryltetralin lignans **1** and **2** and aryltetralin lignan lactones **3**-**5** (Figure 1), which have long been recognized as particularly important natural products.

The most prominent member of this group of natural products is podophyllotoxin (**5**). This compound, together with analogues **6**-**8** are aryltetralin lignan lactones isolated from the American Mayapple (Podophyllum peltatum) and related Indian species (Podophyllum emodi) (Figure 2).

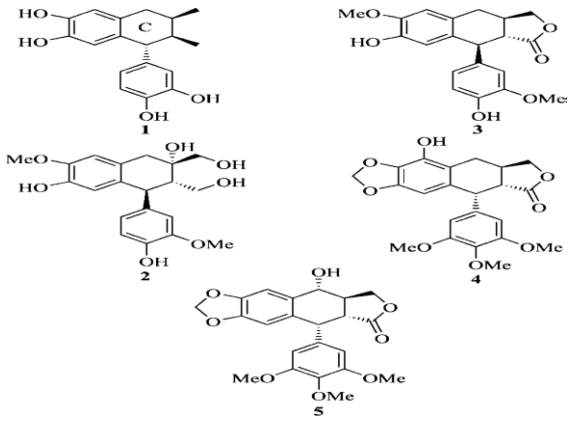

Figure1: Typical examples of aryl tetralin lignans.

These aryl tetralin based compounds exhibit wide variety of biological activities such as antimalarial, antifungal, antibacterial, antimitotic, anti-inflammatory, anticancer and anti-HIV(AIDS). There have been many synthetic modifications to the podophyllotoxin structure including the generation of the three potent anticancer agents **9**, **10** and **11** (Figure 4). Etoposide (**9**) and tenoposide (**10**) are DNA topoisomeraseII inhibitors presently in clinical use for the treatment of many cancers [5-8]. In the present study, we have synthesized podophyllotoxin derivatives and then converted

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into a nanoparticle by attrition method and studied the biological activities.

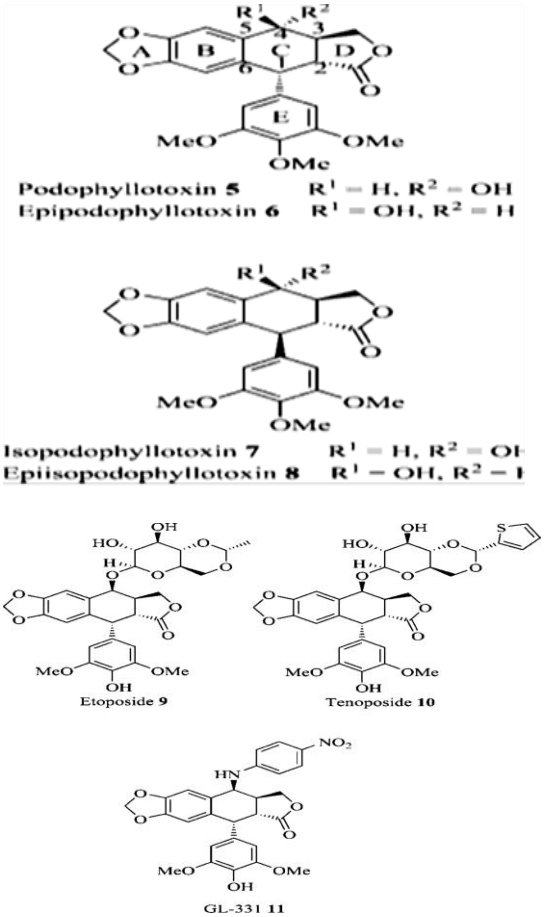
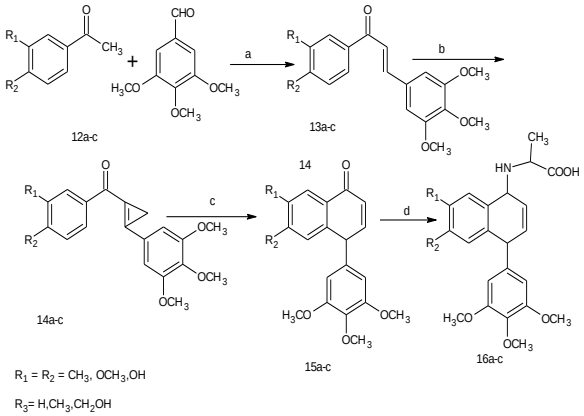


Figure2: Podophyllotoxin and trans-fused stereoisomers.

2. EXPERIMENTAL SECTION

Melting points were determined by open capillary method and are uncorrected. The IR spectra were recorded on a FT-IR in KBr disc or in nujol mull. The 1H NMR spectra were recorded on Joel 60MHz and Joel GSX-400 spectrophotometer using CDCl3 as solvent and TMS as an internal reference. The chemical shifts are expressed in δ values. The mass spectra were recorded on Hitachi RMU-61 spectrophotometer and important fragments were given with the percentage of abundance in the bracket. The purity of the compounds was checked by TLC on silica gel glass plates in benzene and ethyl acetate solvent mixture (7:0.5). The compounds were purified by column chromatography using silica gel (60-120 mesh) as adsorbent and benzene as eluent or repeated recrystallization from ethanol or methanol. The starting material **12a-c** was prepared in high yield by Freidal craft acylation. The chalcone intermediate of 15a-c was then converted into nanoparticle by first treating with polymer PEG which was characterized by transmission electron



a) *NaOH, C_2H_5OH-H_2O,rt, CH_2Cl_2,Zn-Cu couple, ether, Anhydrous $SnCl_2$,dry $C_6H_5NO_2$, Ac_2O,*
b) $NaBH_4$, methanol,HBr,CH_3CN,amino acid, BU_4NI, Et_3N,THF

Scheme1. microscopy and the biological activities was studied for synthesized nanoparticle.

General procedure for the synthesis: commercial available acetophenone 12a-c (6.2mmol) on claisen condensation with 3,4,5-trimethoxy benzaldehyde (6.2mmol) give the yellow crystalline chalcone 13a-c (5g, 0.0196 mole), which on reaction with dichlorobenzene in Zn-Cu(0.005mole) couple using ether as solvent(20mL) followed by usual work up yield a dark brown colour semi solid14a-c.The obtained compound which on reaction with Lewis acid i.e stannic chloride(3.826g, 0.0146 mole) using acetic anhydride(2.98g, 0.0292mole) in nitrobenzene(50mL) followed by work yield compound15a-c which on reduction with $NaBH_4$ followed by brominating yield dark grey color product. The obtained product was reacted with alanine (2-aminopropanoic acid) which gives the precipitate15a-c. The precipitate was then filtered of, washed thoroughly with water and dried to yield 16a-c.

***(2E)-1-(3,4-dimethylphenyl)-3-(3,4,5-trimetho-xyphenyl)prop-2-en-1-(2-aminopropanoic acid)16a*:** *80% (1.22 g)* yield, m.p.= 86^0C, IR (KBr): 1600 (C=C),1605,1657 (CO) *cm^{-1}:* ^{1}H NMR ($CDC1_3$): δ 2.25 (s, 6H, CH_3),3.90 (s**,**6H, -OCH_3),6.80 (bd, 2H, - HC=CH-), 7.0-7.20 (m, SH, Ar-H), 7.20-7.30 (d, lH, Ar-H), 7.50-7.65 (bd, 2H, k-H);
Anal. Calcd. For $C_{23}H_{29}N0_5$ C, 80.92; H, 6.40%: Found C, 80.86; H, 6.42%.

(2E)-1-(3,4-dimethoxyphenyl)-3-(3,4,5-trimetho-xyphenyl)prop-2-en-1-(2-aminopropanoic acid)16b: *yellow crystalline* compound in 78% (1.22 g) yield, m.p. = 82^0C, IR (KBr): 1600 (C=C), 1605, 1657 (CO) *cm^{-1}***;** ^{1}H NMR ($CDC1_3$): δ 3.90 (s**,**6H, -OCH_3), 6.80 (bd, 2H, - HC=CH-), 7.0-7.20

(m, SH, Ar-H), 7.20-7.30 (d, lH, Ar-H), 7.50-7.65 (bd, 2H, k-H);

Anal. Calcd. For $C_{23}H_{29}N0_7$ C, 80.92; H, 6.40%: Found C, 80.86; H, 6.42%.

(2*E*)-1-(3,4-dihydroxyphenyl)-3-(3,4,5-trimetho-xyphenyl)prop-2-en-1-(2-aminopropanoic acid) 16c:

Orange colour precipitate compound in 68% yield, m.p=82^{0}C, IR(KBr): 1600 (C=C), 1605, 1657 (CO)cm^{-1} ;^{1}HNMR ($CDC1_3$): δ 3.90**(s,**3H, OH),3.90(**s,**3H, OH)6.80 (bd, 2H, - HC=CH-), 7.0-7.20 (m, SH, Ar-H), 7.20-7.30 (d, lH, Ar-H), 7.50-7.65 (bd, 2H, k-H);

Anal. Calcd. For $C_{21}H_{25}N0_7$ C, 80.92; H, 6.40%: Found C, 80.86; H, 6.42%.

3. RESULTS AND DISCUSSION

In this context, we have chosen chalcone route with some changes in the experimental procedure and reagents to synthesize tetralin intermediates.The synthesized compound was converted into nanoparticle which shows that we can convert the aryl tetralin derivatives into a nanoparticle. The activities showed that we can use nanoparticle of aryl tetralin as an antitumor agent and antifungal agent. The synthesized nanoparticle activities was very effective against viral infection which is given in the table1.the characterization of the nanoparticle is done by electron microscopy (TEM, SEM) which is given in the figure3. Values are the mean (S.D) of a quadruplicate culture from experiment.

Table1. Antiviral effect of ACV (acyclovir), aryl tetralin analogues 16a-c on the growth of HSV-1 strain in the plaque reduction assay

compound	EC_{50}(μM)
16a	0.789(±0.10)
16b	0.64 (±0.15)
16c	0.54(±0.095)

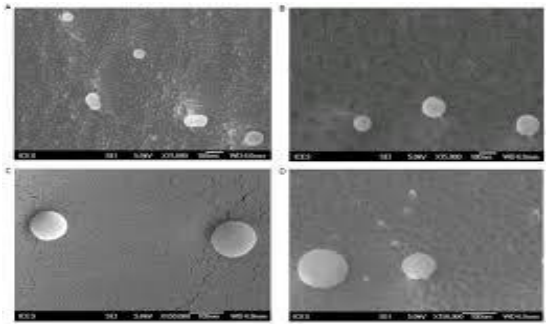


Figure3: TEM image of Podophyllotoxin analogs intermediate.

4. CONCLUSION

We have successfully synthesized new nanoparticles of analogues of tetralins. All compounds were characterized by standard spectroscopic techniques. The evaluation of the antiviral activity of all the new compounds was carried out against virus and proved significant to moderate activity.

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