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PREPARATION OF TWO NEW DERIVATIVES OF ELLAGIC ACID AND *IN-SILICO* STUDIES OF THEIR DRUG LIKE PROPERTIES

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ABSTRACT: Till the nineteenth century, people worldwide were relying on herbal medicines for their health problems. Today, it is common knowledge that different parts of plants contain various phytochemicals. Phytochemicals exhibit variety of physiological activities and health benefits. Due to the side effects shown by synthetic medicines, there is increased interest in phytopharmaceuticals. There are many instances where natural chemicals have played important role in new drug discovery. Chemical modification of pharmacophore in naturally occurring drug has resulted into new drugs with better drug properties. Ellagic acid is a phytochemical belonging to polyphenol class. It shows many biological and medicinal activities including antioxidant, anti-inflammatory, anti-cancer, neuroprotective, anti-diabetic. Hepatoprotective, cardioprotective, skin protective effects. It contains lactone rings, aromatic rings in form of biphenyl unit and four phenolic hydroxy groups. The two new derivatives of ellagic acid are prepared. In the first one, benzoylation of all four phenolic hydroxy groupis carried out giving tetrabenzoyl ellagic acid. In the second, the lactone rings are opened by base hydrolysis forming aoctasodium salt of hydrolysed ellagic acid. The structures were confirmed by spectroscopy. *In-silico* study and comparison of drug like properties of ellagic acid with its two derivatives using ADMETlab showed that among the three molecules Ellagic acid and its hydroysis derivative are showing good physiochemical properties as well as medicinal properties. Among the three molecules, Hydrolysis derivative of Ellagic Acid shows the best absorption whereas Ellagic Acid shows best distribution. All the three molecules show moderate metabolism; excretion and toxicity profiles. On the basis of this analysis Ellagic Acid is having better drug like properties than its two derivatives.

INTRODUCTION: Till the end of nineteenth century, worldwide people were dependent on plant-based medicines for all type of health issues. Towards the end of nineteenth century, synthetic medicines came into the market. But soon people turned to herbal medicines as synthetic medicines showed many serious side effects.

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In recent times a new concept of phytopharmaceuticals has become popular. These are drugs containing active component which is plant based or isolated from plant. Caffeine, Digitonin, Quinine are the examples of phytopharmaceuticals [1].

Many phytochemicals isolated from plants show biological and pharmaceutical activities. E.g. 1) morphine which is an alkaloid is obtained from poppy seeds (*Papaver somniferum*) is used as, 2) *Streptomyces avermitilis* produces a macrocyclic lactone, avermectin which is used as a antiparasitic drug, 3) quinine is an alkaloid found in cinchona plant species and 4) artemisinin obtained from Artemisia annua, are used as antimalarials, 5)

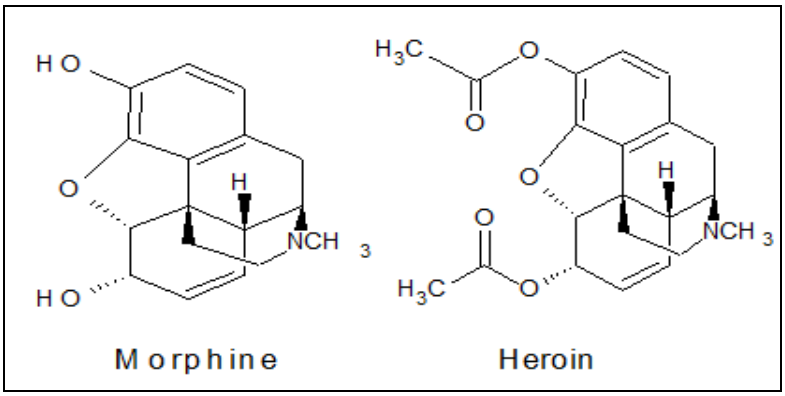
lovastatin, a lactone obtained from *Aspergillus terreus* that is useful in controlling lipids, 6) cyclosporine, a cyclic peptide and 7) rapamycin, a protein both obtained from fungi and are useful immunosuppressants especially in organ transplantation, 8) paclitaxel obtained from the bark of *Taxus brevifolia* and 9) irinotecan obtained from *Camptotheca acuminata* are useful as anticancer drugs [2, 3].

The therapeutic actions of drug molecules are due to a perticular structural unit present in the molecule known as pharmacophore. This can be established through structure activity relationship studies. One important strategy in developing new drugs is by making small structural changes in the pharmacohores of existing drug molecules [4, 5]. Such drugs are also known as designer drugs.

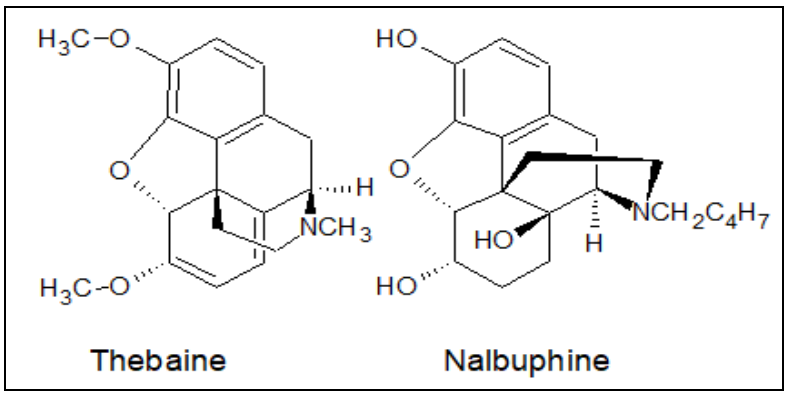
They are known as the structural analogs of the original drug. The original drug is named as precursor. The structural analogs may have similar or different pharmacological activity as the precursor.

If the structural analogs are having similar pharmacological activity as the precursor, then they are also known as the pharmacological or functional analogs. Thus, Heroin which is diacetyl morphine, is the structural and functional analog of morphine, whereas Fentanyl is only functional analog of morphine [6].

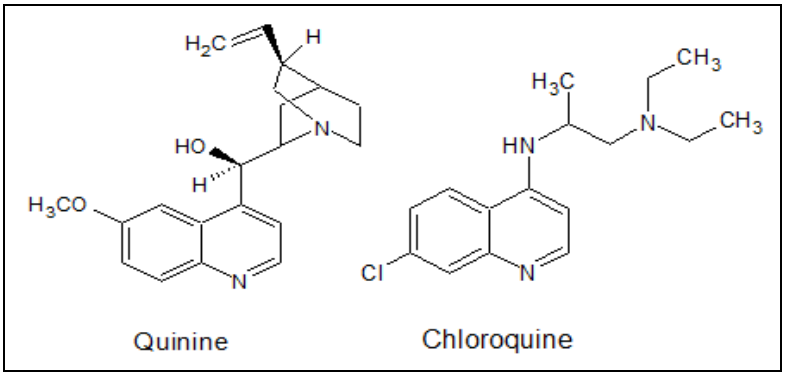
Heroine and morphine are analgesic drugs, but heroine is found to be more potent than morphine. Thus, structural analog is more potent than the precursor [7].

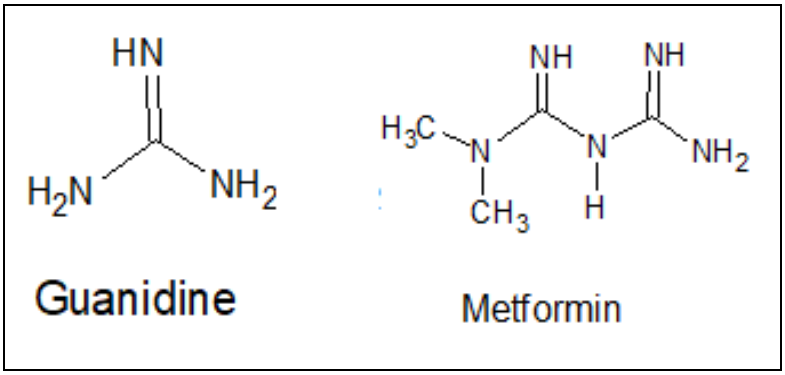


Another such example is alkaloid thebaine. Nalbuphine is a structural analog of thebaine obtained by adding a hydroxy group at C-14 and adding a cyclobutyl ring on the methyl group of tertiary amino group. Nalbuphine is anlgesic drug which is safer for use in children [8].

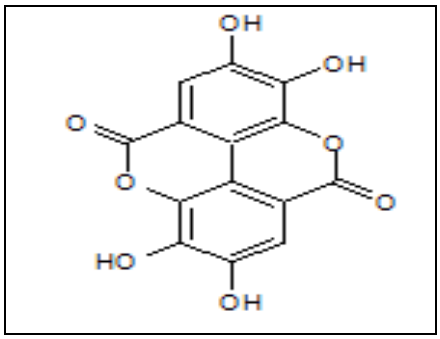


Quinine is an alkaloid present in the bark of cinchona species. It is an antimalarial drug which is precursor for the new antimalarial strucural homologs, Chloroquin. which is more potent than quinine [9]. Guanidine present in *Galega officinalis* shows blood sugar lowering action. But since it is very toxic to human beings it cannot be used in treatment of diabetes. Its structural analog dimethyl biguanide popular as metformin is a safe anti-hyperglycemic drug [10].





Hundreds of such examples are availble where the structural analogs are more potent and safer drug than the precursor. Ellagic acid is a polyphenol present in many plants either in free form or as a part of complex molecule that liberates ellagic acid. It shows many biological and medicinal activities including antioxidant, anti-inflammatory, anti-cancer, neuroprotective, anti-diabetic. hepatoprotective, cardioprotective, skin protective effects [11, 12, 13]. It is present in variety of plant parts especially fruits like berries, pomegranate etc. [14].



But it has very low solubility in water and low bioavailability. Even after increasing the intake for increasing the bioavailability, its human plasma concentration found to be very low (100 nM) [15]. So, an attempt is made to prepere a structural analog of ellagic acid for better drug properties. From the structure of ellagic acid, it can be observed that it is containing two lactone rings, a diphenyl nucleus and four phenolic OH groups. The O-alkylation and O-acylation of phenolic OH is easier due to presence of electron withdrawing lactone rings.

So, such O-alkylated and O-acylated structural analogs of ellagic acid have been prepared by some researchers. Heur *et al.*, synthesised 11 derivatives of ellagic acid as shown in **Table 1** [16].

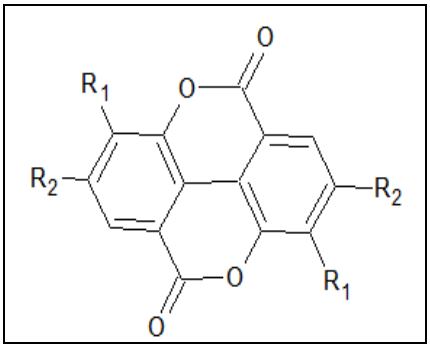


TABLE 1: ELLAGIC ACID ANALOGS SYNTHESISED BY HEUR *ET AL.*,

Name of the derivative	R1	R2
Ellagic acid	OH	OH
tetrahexanoyl ellagic acid	hexanoyloxy	hexanoyloxy
3,3 -dihexanoyloxydiphenic-2,2',6,6 -dilactone	hexanoyloxy	H

4,4'- dihexanoyloxydiphenic-2,2',6,6'-dilactone	H	hexanoyloxy
3,3'-di-p-D-glucopyranosylellagic acid diacetate	-0-tetra-0-acetyl-p-D-glucopyranosyl	Oac
3,3'-diacetylellagic acid	Oac	OH
3,3'-di-n-octyl-4,4'-dihexanoylellagic acid	-0-n-octyl	hexanoyloxy
4,4'-dihexanoylellagic acid	OH	hexanoyloxy
3,3'-dimethylellagic acid	OCH_3	OH
3,3'-dibenzylellagic acid	-0-Benzyl	OH
4,4'-dimethylellagic acid	OH	OCH_3

In another study, 3,3′-di-O-benzylellagic acid was synthesised [17].

Many research groups have isolated ellagic acid derivatives from different plants like Dipentodonsinicus [18], Anisophylleadichostyla [19], *Combretum yunnanensis* 1[7] and many more [20, 21, 22].

But very few attempts have been made to synthesise derivatives of ellagic acid. Here two new derivatives of ellagic acid are prepared by using simple methods. After purification, their structures were confirmed by IR, H1-NMR and C13 NMR spectras.

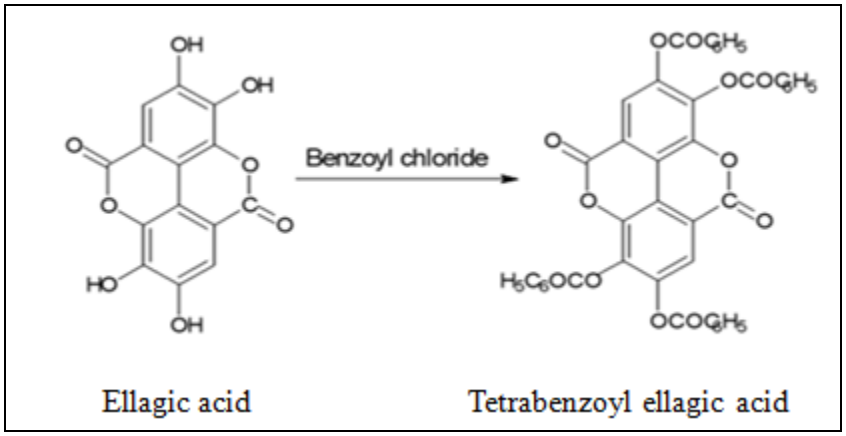
One of the important parts of new drug discovery is to determine drug likeliness and toxicity of the new molecule. Drug likeliness means the drug like properties which include structural, biochemical, physiochemical, pharmacokinetic studies. The results obtained by these studies decide whether the new molecule is likely to be good drug candidate or not. If the molecule shows some good drug properties but lack certain other drug like properties, then such properties can be optimised by making necessary structural changes. The drug likeliness involves many structural parameters study like molecular weight, hydrogen bonding possibilities, lipophilicity, topological polar surface area. The physiochemical parameters include solubility, permeability, enzyme and chemical stability. The biochemical parameters involved are metabolic stability, transportation, blood brain barrier, plasma stability. The safety and toxicity studies include drug-drug interactions, mutagen city, cytotoxicity, teratogenicity. Drug distribution, half-life, bioavailability are some parameters studied in pharmacokinetics [23]. The traditional methods of determining drug likeliness are time consuming and ineffective as only one property canbe determined at a time [24]. Hence, *in-silico* prediction of ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) has gained importance as it saves time required for determining pharmacokinetic properties at the early stage of drug discovery. Many softwares are available for prediction of ADMET of a drug which work on the basis of their database library. So, the database of a software plays very important role in accurate predictions of ADMET of a molecule [25]. ADMETlab is a software which has a database comprised of more than 2,88,000 entries. This web-based platform uses four function modules by which performing six types of drug-likeness analysis and predicting 31ADMET endpoints is easily possible.

The six types of drug likeliness analysis include five rules and one prediction model. 31 endpoints include three basic properties, six absorption properties, three distribution properties, ten metabolism properties, two elimination properties and seven toxicity properties. (26) Many researchers have used ADMETlab for predicting preliminary drug likeliness of their research molecules. In one of the studies the ADMET of Salubrinal and its structural analogues which were containing a cinnamic acid residue or a quinoline ring was predicted using SwissADME, ADMETlab, admetSAR 2.0 [27]. In another study, the physicochemical and pharmacokinetic properties of the novel active drugs, pioglitazone and rosiglitazone was carried out by using ADMETlab 2.0 software [28]. Many other research groups have used ADMETlab in their study for predicting drug likeliness of their research molecules [29, 30, 31.] So, in the present study the drug likeliness of the ellagic acid derivatives is predicted using ADMETlab software.

MATERIAL AND METHODS:

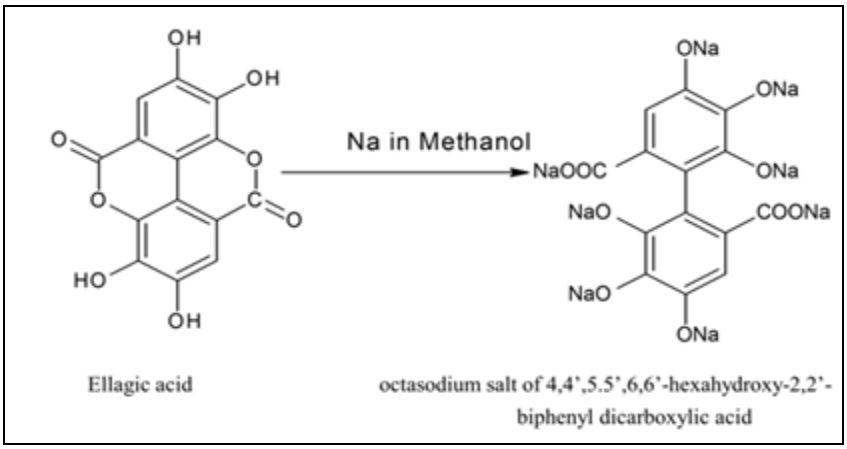
Tetrabenzoyl Derivative of Ellagic Acid (BEA): As the O-acylation of ellagic acid is easy due to presence of lactone ring, the first derivative of ellagic acid prepared is 3, 3', 4, 4'-tetrabenzoyl derivative of ellagic acid. Benzoylation reaction was not tried earlier by any researcher. The procedure followed for the synthesis is Vogel's Textbook of Practical Organic Chemistry.

Procedure: 1g of Ellagic acid was dissolved in 40cm 3 of 20% NaOH solution in a 250ml beaker. After shaking it for 1 hour on magnetic stirrer, the solution was filtered. The filtrate was collected in a 250ml conical flask. Then 4ml of benzoyl chloride was added to the conical flask. The flask was corked and content was shaken vigorously for 30 minutes. The content of the flask was poured in cold water. The product was filtered and washed with water. The reaction and the structure of the product obtained are shown below.



Octasodium Salt of Hydrolysis Derivative of Ellagic Acid (HEA): As the ellagic acid contains two 6-membered lactone rings, it can be hydrolysed when the lactone ring will open forming hydroxy carboxylic acid. Since, the hydroxy group and carboxylic acid groups, in the hydrolysed product, are present in closed proximity they immediately undergo reverse lactonization. Hence, it is difficult to open the lactone ring. The base catalysed hydrolysis of ellagic acid using sodium methoxide gives sodium salt of hydrolysed ellagic acid. This is the second derivative of ellagic acid prepared. The name of this derivative is octasodium salt of 4, 4'.5, 5', 6, 6'-hexahydroxy-2,2'-diphenyl dicarboxylic acid. This reaction was not tried earlier by any researcher.

Procedure: The procedure followed for the synthesis is as given in Vogel's Textbook of Practical Organic Chemistry 2g of dry sodium metal was refluxed with methanol in a dry round bottom flask, until sodium dissolves completely to get clear solution of sodium methoxide. This was filtered to remove insoluble impurities. To the filtrate 1g of ellagic acid was added pinch by pinch with constant stirring using magnetic stirrer. The product obtained was filtered and washed with methanol, this removes excess of sodium methoxide. It was then washed with DMSO to remove any unreacted ellagic acid. It was again washed with methanol and dried in the air.



***In-silico* Drug Likeliness and Toxicity Studies of Ellagic Acid and its Derivatives:** The physicochemical properties, drug likeliness and medicinal properties, absorption, distribution,

metabolism, excretion and toxicity predictions of Ellagic acid (EA), O, O, O.O-tetrabenzoyl ellagic acid (BEA) and octasodium salt of hydrolysed ellagic acid (HEA) were carried out using ADMETlab2.0.

RESULTS AND DISCUSSION:

BEA: The weight of the crude product is 1.8g. The compound is pinkish white in colour. The TLC was done by using hexane and ethyl acetate in ratio 2:8. The TLC plate is shown in **Fig. 1.**

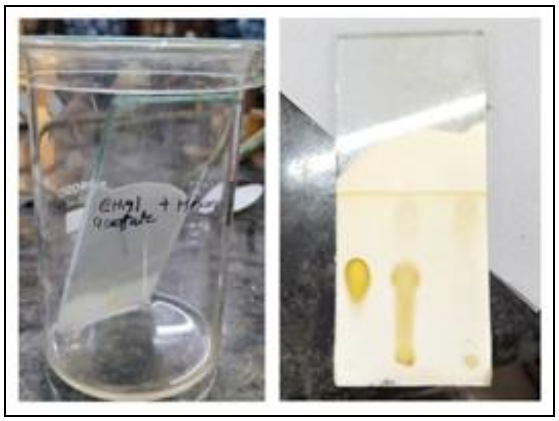


FIG. 1: TLC PLATE FOR PREPARATION OF TETRABENZOYL ELLAGIC ACID

The column was prepared by using silica gel in hexane. The column was loaded with the compound dissolved in hexane. Then it was eluted by using ethyl acetate and hexane mixture, slowly increasing the ethyl acetate volume till the fraction rich in benzoyl ellagic acid was obtained. The column chromatography purification and the purified compound are shown below in **Fig. 2**.

The melting point is 180°C and it is pinkish white in colour.

FIG. 2: COLUMN CHROMATOGRAPHY FOR PURIFICATION AND PURIFIED TETRABENZOYL ELLAGIC ACID

The purity of the product was also checked by Gas chromatography. The gas chromatogram was recorded at Shraddha analytical lab, Mumbai. An7820A GC system (Agilent Technologies, USA) equipped with a flame ionization detector (FID) was used for qualitative determination of BEA.

The GC settings were as follows: Agilent 19091J-413 column (30 m x 320 µm x 0.25 µm) and ultrapure nitrogen (> 99.99%) as the carrier gas at a column flow rate of 1.1111 mL min^{-1}. Split mode of injection was employed and operated at 250 °C. The temperature program was 60 °C to 325 °C. The detector temperature was set at 280 °C. The chromatogram obtained is shown in **Fig. 3.**

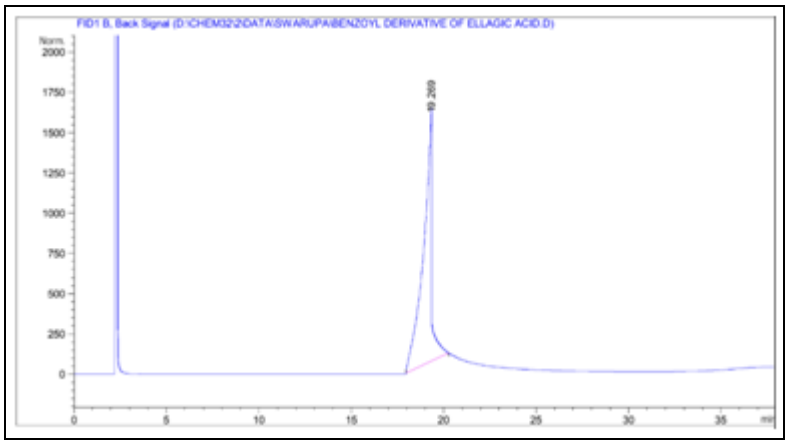


FIG. 3: GAS CHROMATOGRAM OF PURIFIED BEA

Since, only one peak was obtained the sample was concluded to be pure.

Characterization of BEA: The structure of the benzoyl derivative of ellagic acid was confirmed be

recording the IR spectrum, H^1- NMR spectrum and C^{13}-NMR spectrum.

1. IR Spectrum: It was recorded in Central Research Facility at Sathaye College, Mumbai. The FTIR spectrophotometer of Perkin Elmer and Spectrum 2 model (Serial number-120985) was used. Mid IR region with wavelength 4000 to 450 cm^{-1} was employed. The source of IR light was solid state silicon carbide laser whereas lithium tantanate detector was employed in the instrument. The spectrum was recorded in ATR diamond crystal mode. The software spectrum 10 is used. Few milligrams of pure sample was directly put on the diamond crystal previously cleaned with acetone. Then the probe was lowered till the pressure gauge was sufficient. Then the spectrum was recorded. The IR spectra of ellagic acid and BEA are shown in **Fig. 4** and **5** respectively.

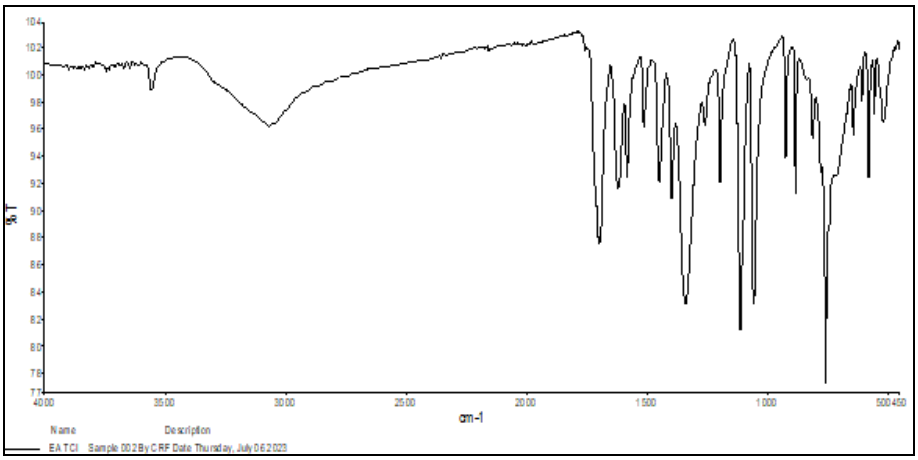


FIG. 4: IR SPECTRUM OF PURE ELLAGIC ACID

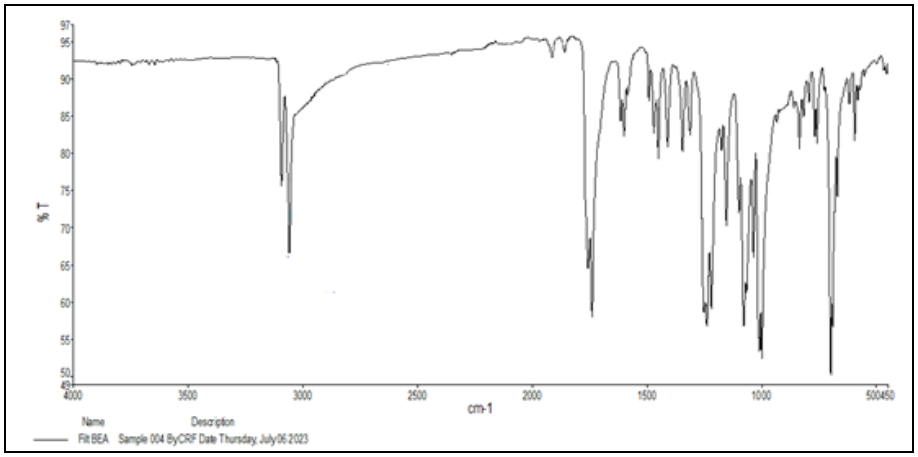


FIG. 5: IR SPECTRUM OF PURE BEA

The peaks in IR spectrum are explained in **Table 2** below.

TABLE 2: IR FREQUENCY CORRELATION TABLE FOR BEA

IR frequency in cm^{-1}	Description
3074	Aromatic C-H stretching
3063	Aromatic C-H stretching
1958	Weak overtones of benzene
1912	Weak overtones of benzene
1756	Saturated 6 membered lactone
1739	Esters of aromatic acids
1614	Aromatic C-C stretching
1599	Aromatic C-C stretching
1491	Aromatic C-C stretching
1251	ester, C-O stretching
1096	ester C-O stretching

834	polysubstituted benzene
817	polysubstituted benzene
792	monosubstituted benzene
767	monosubstituted benzene
757	polysubstituted benzene
692	polysubstituted benzene
690	polysubstituted benzene

H^1 NMR Spectrum: This was recorded at TIFR, Mumbai. The 600MHz NMR instrument by Agilent Technologies, USA, Direct Drive Console was used for recording this spectrum.

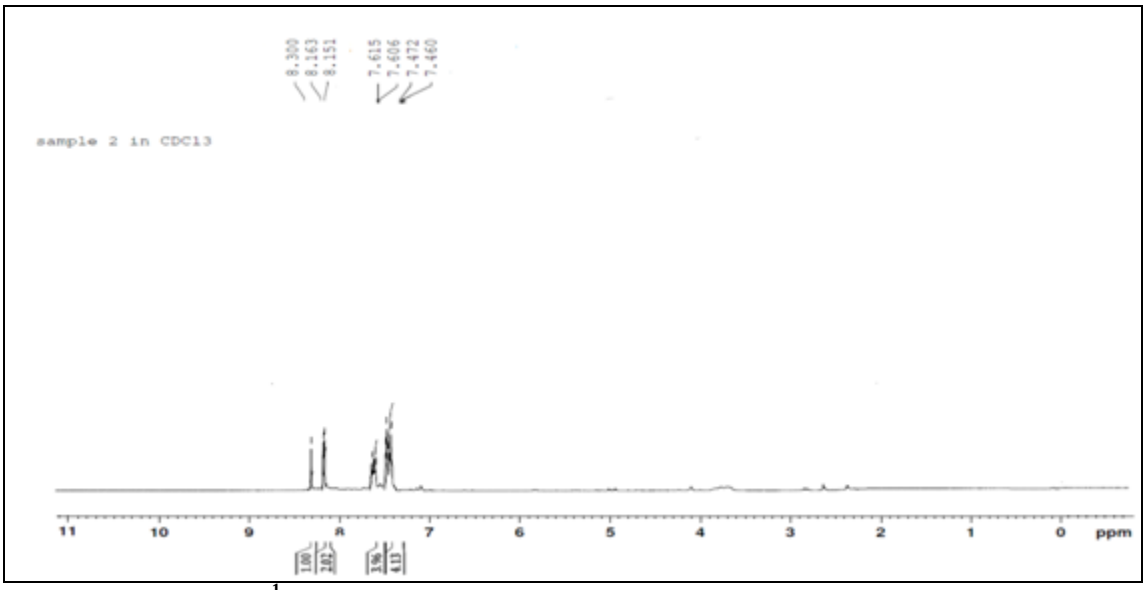


FIG. 6: H^1 NMR SPECTRUM OF TETRABENZOYL ELLAGIC ACID

The magnetic field of 14.1 Tesla, with standard bore (54mm) was applied. Computer was Dell T3500 precision with Intel dual core CPU was used. 5mm $^1H/^{13}C/^{15}N$ TXI probe with 30G/cm gradient along Z axis was used. CryoQ–probe (S/N ratio ~ 3000:1) with closed cycle cryogenic system was employed. $CDCl_3$ was used as the solvent.

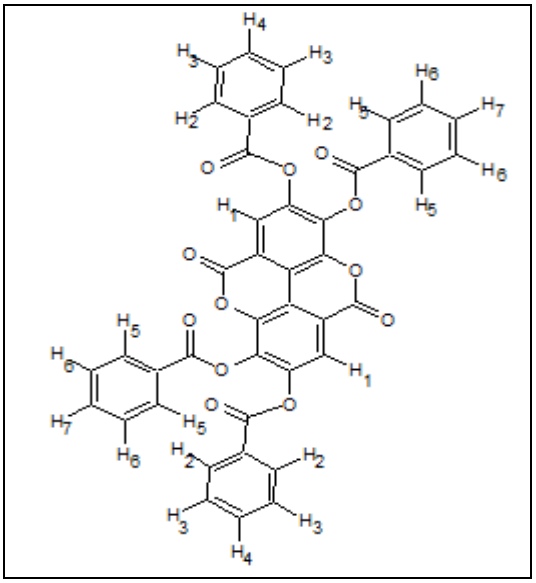


TABLE 3: H^1 NMR SPECTRUM CHEMICAL SHIFT CORRELATION TABLE FOR BEA

δ in ppm	Area	Explanation
7.460	4.13 Corresponds	Due to four H_3 protons
7.472	to 8 protons	Due to four H_6 protons
7.606	3.96 Corresponds	Due to four H_3 protons
7.615	to 8 protons	Due to four H_5 protons
8.151	2.021 Corresponds	Due to two H_2 protons
8.163	to 4 protons	Due to two H_7 protons
8.300	1.00 Corresponds	Due to two H_1 protons
	to 2 protons	

C^{13} NMR Spectrum: This was recorded at TIFR, Mumbai. The 800MHz NMR instrument by BrükerBiospin, Switzerland, Avance AV 800 was used for recording this spectrum. The magnetic field of 18.89 Tesla, 20K pumped magnet, Standard bore (51mm) was applied. Computer was HP make HPXW4200 workstation, PIV 3.0GHz 120Gb hard disk, 1Gb RAM, DVD-RW, 20inch LCD monitor was used. 5mm $^1H/^{13}C/^{15}N$ triple resonance *probe* fitted with gradient coil along Z axis and automated tuning / matching ATM unit was used. $CHCl_3$ was used as the solvent.

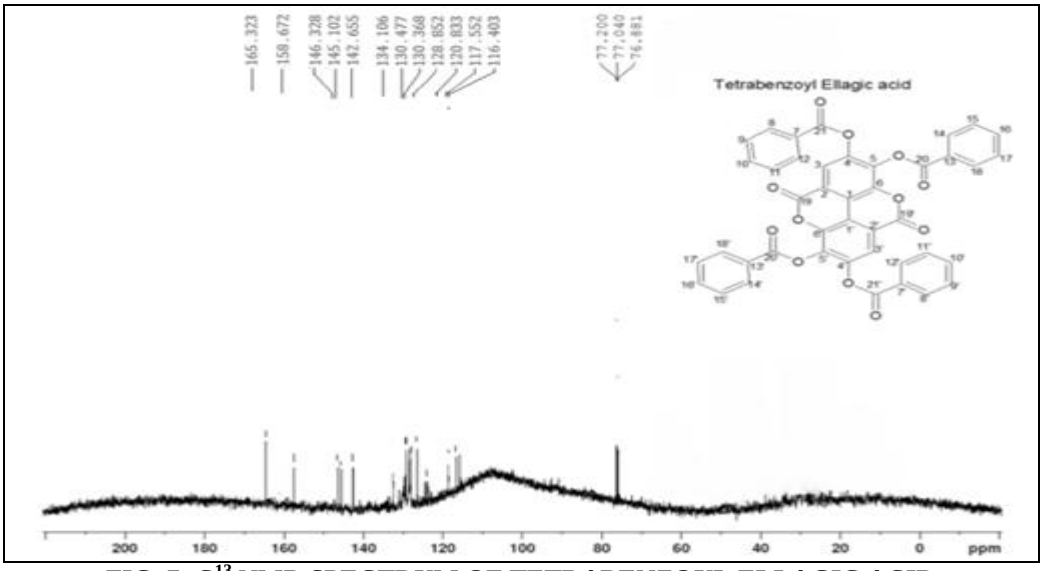


FIG. 7: C^{13} NMR SPECTRUM OF TETRABENZOYL ELLAGIC ACID

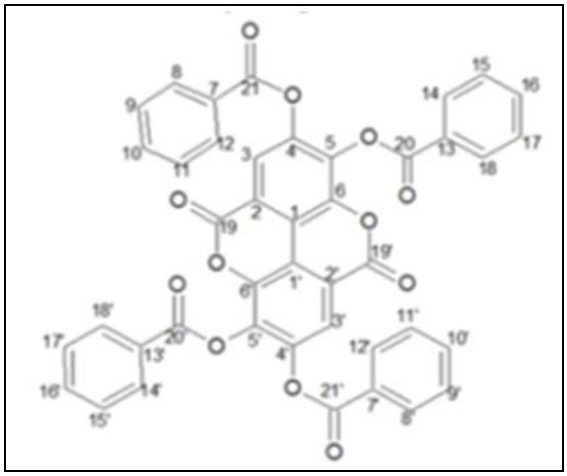


TABLE 4: C^{13} NMR SPECTRUM CHEMICAL SHIFT CORRELATION FOR TETRABENZOYL ELLAGIC ACID

δ in ppm	Type of C	Explanation
116.403	Aromatic ring C	Due to C3, C3’
117.552		Due to C2, C2’
120.833		Due to C1, C1’
128.852		Due to C9, C11, C17, C15, C9’, C11’, C17’, C15’
130.368		Due to C7, C13, C7’, C13’
130.477		Due to C8, C12, C14, C18, C8’, C12’, C14’, C18’
134.106		Due to C10, C16, C10’, C16’
142.655		Due to C6, C6’
145.102		Due to C4, C4’
146.328		Due to C5, C5’
158.672	C=O in lactone	Due to C19, C19’
165.323	C=O in ester	Due to C20, C21, C20’, C21’

HEA: The melting point is 257 to 265°C and it is dark chocolate brown in colour as shown in **Fig. 8.** It is easily soluble in water and practically insoluble in all other solvents. The weight of the product obtained is 0.684g.

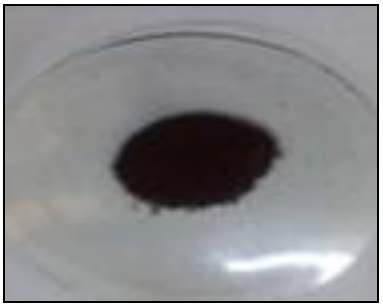


FIG. 8: HYDROLYSIS DERIVATIVE OF ELLAGIC ACID

Characterization of Octasodium Salt of Hydrolysis Derivative of Ellagic Acid (HEA): The structure of the benzoyl derivative of ellagic acid was confirmed be recording the IR spectrum, H^1- NMR spectrum and C^{13}-NMR spectrum.

IR spectrum: It was recorded in Central Research Facility at Sathaye College, Mumbai. The FTIR spectrophotometer of Perkin Elmer and Spectrum 2 model (Serial number-120985) was used. Mid IR region with wavelength 4000 to 450 cm^{-1} was employed. The source of IR light was solid state silicon carbide laser whereas lithium tantanate detector was employed in the instrument. The spectrum was recorded in ATR diamond crystal mode. The software spectrum 10 is used. Few milligrams of pure sample was directly put on the diamond crystal previously cleaned with acetone. Then the probe was lowered till the pressure gauge was sufficient. Then the spectrum was recorded.

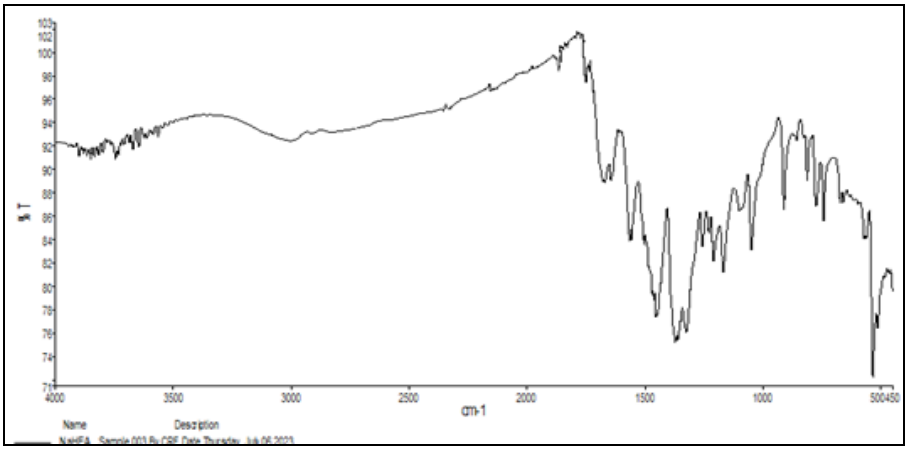


FIG. 9: IR SPECTRUM OF HEA

The IR spectra of octasodium salt of hydrolysed ellagic acid and tetrabenzoyl ellagic acid are shown in **Fig. 9.**

TABLE 5: IR FREQUENCY CORRELATION TABLE FOR HEA

IR frequency in cm^{-1}	Description
3008	Due to aromatic C-H stretching
1922	weak overtone of benzene
1820	weak overtone of benzene
1695	Aromatic carboxylic acid C=O stretching
1564	Aromatic C-C stretching
1454	Aromatic C-C stretching
1372	phenolic C-O stretching
1325	phenolic C-O stretching
1168	phenolic C-O stretching
1099	C-O stretching in acid
911	Polysubstituted benzene
813	Polysubstituted benzene
774	Polysubstituted benzene
742	Polysubstituted benzene

H^1 NMR Spectrum: This was recorded at TIFR, Mumbai. The 600MHz NMR instrument by Agilent Technologies, USA, Direct Drive Console Was used for recording this spectrum.

The magnetic field of 14.1 Tesla, with standard bore (54mm) was applied. Computer was Dell T3500 precision with Intel dual core CPU was used. 5mm $^{1}H/^{13}C/^{15}N$ TXI probe with 30G/cm gradient along Z axis was used.

CryoQ–probe (S/N ratio ~ 3000:1) with closed cycle cryogenic system was employed. D_2O was used as the solvent and TSPA which is 3-(Trimethylsilyl) propionic-2,2,3,3-d_4 acid d, containing nine equivalent protons as standard.

The H^1 NMR spectrum of HEA is shown in **Fig. 10.**

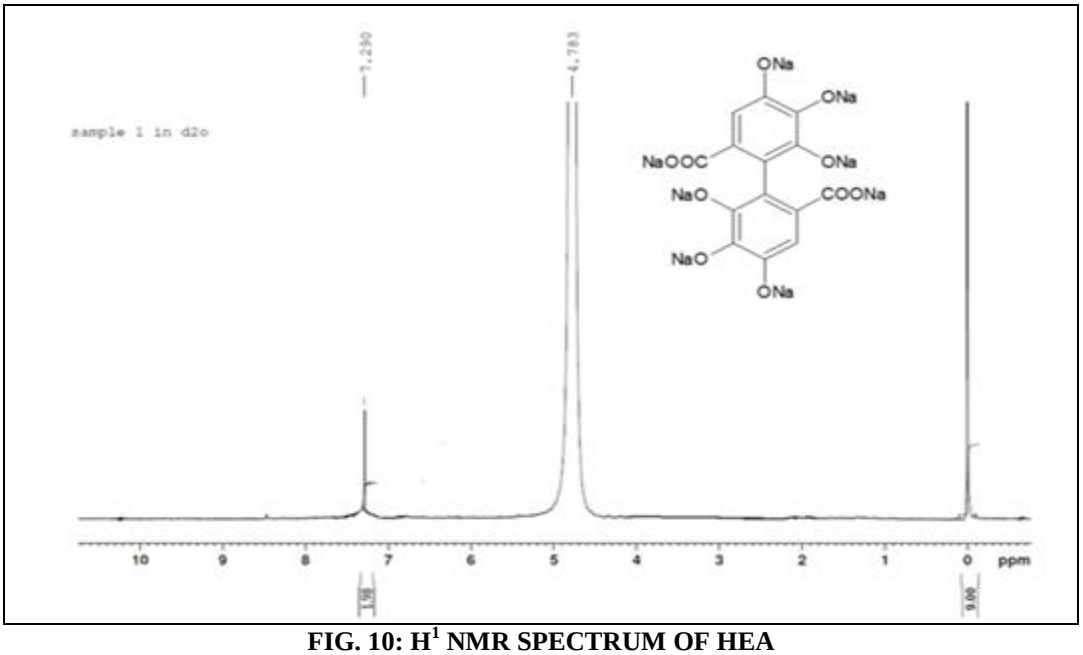
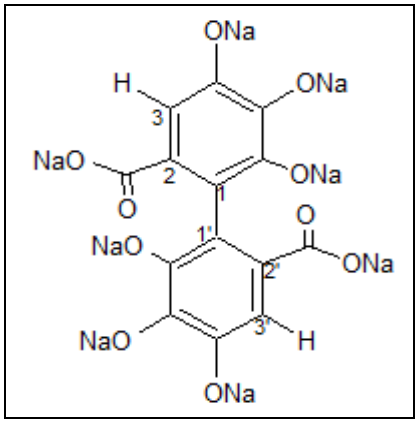


FIG. 10: H^1 NMR SPECTRUM OF HEA



As it can be seen from above structure that HEA contains only two protons at position 3 and 3'. Both these protons are equivalent. Hence, only one peak is observed at δ= 7.29, due to these two aromatic protons.

C^{13} NMR Spectrum: This was recorded at TIFR, Mumbai. The 800MHz NMR instrument by BrükerBiospin, Switzerland, Avance AV 800 was used for recording this spectrum. The magnetic field of 18.89 Tesla, 20K pumped magnet, Standard bore (51mm) was applied. Computer was HP make HPXW4200 workstation, PIV 3.0GHz 120Gb hard disk, 1Gb RAM, DVD-RW, 20inch LCD monitor was used. 5mm $^{1}H/^{13}C/^{15}N$ triple resonance *probe* fitted with gradient coil along Z axis and automated tuning / matching ATM unitwas used. D_2O was used as the solvent.

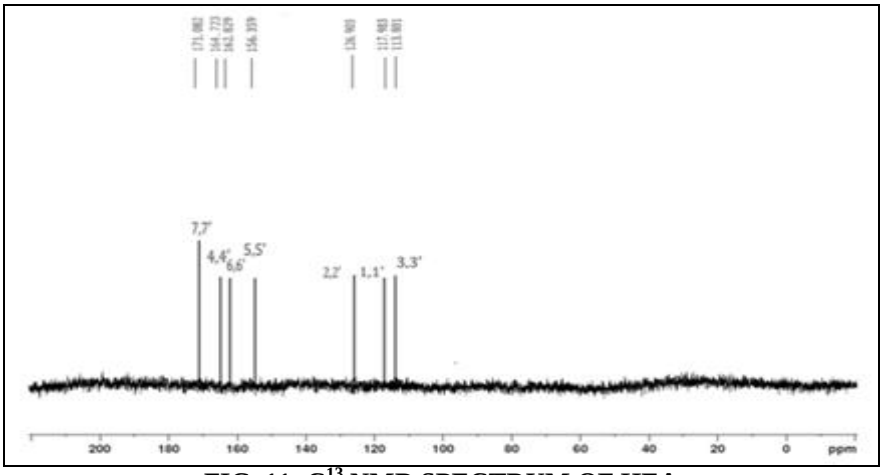


FIG. 11: C^{13} NMR SPECTRUM OF HEA

The analysis of the spectrum is given below:

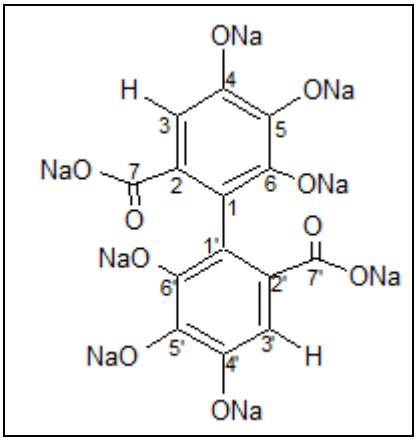


TABLE 6: C^{13} NMR SPECTRUM CHEMICAL SHIFT CORRELATION TABLE OF HEA

δ in ppm	Type of C	Explanation
113.801	Aromatic ring C	Due to C3, C3'
117.983		Due to C1, C1'
126.903		Due to C2, C2'
156.359		Due to C5, C5'
162.829		Due to C6, C6'

164.173		Due to C4, C4’
171.082	C=O in carboxylic acid	Due to C7, C7’

Results of ADMETlab Analysis for Different Parameters:

Physiochemical Properties: The physicochemical properties of include different parameters. The values of these parameters are important in predicting overall solubility and absorption of drug in gastrointestinal tract [32]. The predicted value of different parameters for EA, BEA and HEA are tabulated in **Table 7.**

TABLE 7: PHYSIOCHEMICAL PROPERTIES PREDICTIONS FOR EA, BEA, HEA

Property	Value			Comment
	EA	BEA	HEA	
Molecular Weight	302.01	784.19	513.88	Contain hydrogen atoms. Optimal:100~600
Volume	265.705	795.173	634.465	Van der Waals volume
Density	1.137	0.986	0.81	Density = MW / Volume
nHA	8	11	10	Number of hydrogen bond acceptors. Optimal:0~12
nHD	4	0	0	Number of hydrogen bond donors. Optimal:0~7
nRot	0	12	11	Number of rotatable bonds. Optimal:0~11
nRing	4	9	2	Number of rings. Optimal:0~6
MaxRing	14	14	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	8	11	18	Number of heteroatoms. Optimal:1~15
fChar	0	0	0	Formal charge. Optimal:-4 ~4
nRig	4	55	14	Number of rigid bonds. Optimal:0~30
Flexibility	0.0	0.218	0.786	Flexibility = nRot /nRig
Stereo centres	0	0	0	Optimal: ≤ 2
TPSA	141.34	148.55	107.98	Topological Polar Surface Area. Optimal:0~140
logS	-4.027	-5.415	-5.275	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	0.796	8.752	3.655	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	0.276	5.263	1.781	logP at physiological pH 7.4. Optimal: 1~3

Medicinal Chemistry: The parameters included here are important in predicting drug likeliness of the compounds using different rules for oral administration. Some of them are helpful in predicting the synthetic ease, natural product score [33]. Predicted values for the medicinal chemistry parameters are tabulated in **Table 8.**

TABLE 8: MEDICINAL CHEMISTRY PREDICTIONS FOR EA, BEA, HEA

Property	Value			Comment
	EA	BEA	HEA	
QED	0.216	0.045	0.372	A measure of drug-likeness based on the concept of desirability; Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
Sascore	2.98	3.327	5.915	Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. Sascore≥ 6, difficult to synthesize; Sascore<6,easy to synthesize Fsp3 0.0 l. The number of sp3
Fsp3	0.0	0.104	0.0	The number of sp3 hybridized carbons / totalcarbon count, correlating with melting point andsolubility. Fsp3≥ 0.42 is considered a suitable value.
MCE-18	24.0	105.057	18.0	MCE-18 stands for medicinal chemistry evolution. MCE-18 ≥45 is considered a suitable value.
Npscore	1.071	0.337	0.119	Natural product-likeness score. This score is typically in the range from -5 to 5. The higher the score is, the higher the probability isthat the molecule is a NP.
Lipinski Rule	Accepted	Rejected	Accepted	MW ≤ 500; logP≤ 5; Hacc≤ 10; Hdon≤ 5. If two properties are out of range, a poor, absorption or permeability is possible, one isacceptable.
Pfizer Rule	Accepted	Accepted	Accepted	logP> 3; TPSA < 75, Compounds with a high log P (>3) and low TPSA(<75) are likely to be toxic.
GSK Rule	Accepted	Rejected	Rejected	MW ≤ 400; logP≤ 4, Compounds satisfying the GSK rule may have amore favourable ADMET profile
Golden	Accepted	Rejected	Rejected	MW ≤ 400; logP≤ 4, Compounds satisfying the GSK rule may have a

Triangle				more favourable ADMET profile
PAINS	1 alert	0	0	200 ≤ MW ≤ 50; -2 ≤logD≤ 5, Compounds satisfying the Golden Triangle rulemay have a 3 alertsmore favorable ADMET profile.
ALARM NMR	3 alerts	2	2	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
BMS	1 alert	1	0	Undesirable, reactive compounds.
Chelator Rule	1 alert	0	0	Chelating compounds

Absorption: Here different parameters are used for predicting absorption of drug in intestine after oral administration. Colon adenocarcinoma (Caco-2) and Madin–Darby canine kidney (MDCK) permeability, P-glycoprotein transport are important parameters in predicting the absorption of drug in the intestine epithelial cells [34]. The predictions of values for different absorption parameters are tabulated in **Table 9.**

TABLE 9: ABSORPTION PREDICTIONS FOR EA, BEA, HEA

Property	Value			Comment
	EA	BEA	HEA	
Caco-2 Permeability	-5.394	-5.09	-4.919	Optimal: higher than -5.15 Log unit
MDCK Permeability	1.1 e-05	2.5 e-05	2.7 e-05	low permeability: < 2 × 10-6 cm/s medium permeability: 2–20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
Pgp-inhibitor	0.003	1.0	1.0	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.276	0.002	0.0	Category 1: substrate; Category 0: Non-substrate; The output value is the probability of being Pgp-substrate
HIA	0.364	0.012	0.341	Human Intestinal Absorption Category 1: HIA+(HIA >30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
F20%	0.13	0.945	0.627	20% Bioavailability Category 1: F20%+ (bioavailability < 20%); Category 0: F20%- (bioavailability ≥ 20%); The output value is the probability of being F20%+
F30%	0.998	0.147	0.106	30% Bioavailability Category 1: F30%+ (bioavailability < 30%); Category 0: F30%- (bioavailability ≥ 30%); The output value is the probability of being F30%+

Distribution: Blood brain barrier and other biological barriers, protein binding play important role in distribution of the drug [35]. Such parameters are predicted for EA, BEA and HEA in **Table 10.**

TABLE 10: DRUG DISTRIBUTION VALUE PREDICTIONS FOR EA, BEA, HEA

Property	Value			Comment
	EA	BEA	HEA	
PPB	83.86%	115.4%	64.18%	Plasma Protein Binding, Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.693	0.221	1.071	Volume Distribution Optimal: 0.04-20L/kg
BBB penetration	0.014	0.001	0.001	Blood-Brain Barrier Penetration Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	23.55%	0.851%	10.66%	The fraction unbound in plasms Low: <5%; Middle: 5~20%; High: > 20%

Metabolism: Here, the metabolism of drug is predicted on the basis of inhibition of Cytochrome P(CYP) or metabolism of drug by CYP isoforms [36]. The prediction of metabolic behaviour of EA, BEA, HEA is shown in **Table 11.**

TABLE 11: METABOLISM OF EA, BEA, HEA

Property	Value			Comment
	EA	BEA	HEA	
CYP1A2 inhibitor	0.922	0.129	0.93	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP1A2 substrate	0.156	0.04	0.094	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP2C19 inhibitor	0.016	0.485	0.978	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP2C19 substrate	0.05	0.043	0.069	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP2C9 inhibitor	0.47	0.627	0.965	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP2C9 substrate	0.473	0.75	0.969	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP2D6 inhibitor	0.013	0.0	0.003	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP2D6 substrate	0.146	0.023	0.733	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP3A4 inhibitor	0.079	0.018	0.57	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP3A4 substrate	0.014	0.019	0.51	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate

Excretion: Excretion of drug is measure of removal of drug from the body. It is expressed in terms of clearance which is part of drug eliminated from the total distributed drug [37]. The predictions about excretion of EA, BEA and HEA are tabulated in **Table 12.**

TABLE 12: EXCRETION OF EA, BEA, HEA

Property	Value			Comment
	EA	BEA	HEA	
CL	3.724	1.394	1.473	Clearance, High: >15 mL/min/kg; moderate: 5-15 mL/min/kg;low: <5 mL/min/kg
$T_{1/2}$	0.886	0.129	0.07	Category 1: long half-life ; Category 0: short, half-life; long half-life: >3h; short half-life: <3h. The output value is the probability of having long half-life.

Toxicity: Along with determining drug likeliness, bioavailability, metabolism, distribution, it is equally important to determine the toxicity of drug to various body systems. This includes toxicity to heart, kidney, liver, mouth, eyes, skin, respiratory system. This also includes mutagenicity, carcinogenicity studies of drug [38]. The toxicity predictions of EA, BEA, HEA for different parameters is tabulated in **Table 13.**

TABLE 13: TOXICITY OF EA, BEA, HEA

Property	Value			Comment
	EA	BEA	HEA	
hERG Blockers	0.015	0.001	0.012	Category 1: active; Category 0: inactive; The output value is the probability of being active.
H-HT	0.845	0.023	0.024	Human Hepatotoxicity Category 1: H-HT positive(+); Category 0: H-HTnegative(-); The output value is the probability of being toxic.
DILI	0.994	0.989	0.848	Drug Induced Liver Injury. Category 1: drugs with a high risk of DILI; Category0: drugs with no risk of DILI. The output value is theprobability of being toxic.
AMES Toxicity	0.189	0.014	0.513	Category 1: Ames positive(+); Category 0: Amesnegative(-); The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.039	0.187	0.992	Category 0: low-toxicity; Category 1: high-toxicity; The output value is the probability of being highlytoxic.
FDAMDD	0.697	0.91	0.878	Maximum Recommended Daily Dose

				Category 1: FDAMDD (+); Category 0: FDAMDD(-) The output value is the probability of being positive.
Skin Sensitization	0.904	0.97	0.967	Category 1: Sensitizer; Category 0: Non-sensitizer; The output value is the probability of beingsensitizer.
Carcinogen city	0.067	0.583	0.443	Category 1: carcinogens; Category 0: non-carcinogens; The output value is the probability of being toxic.
Eye Corrosion	0.121	0.003	0.106	Category 1: corrosives; Category 0: non-corrosives The output value is the probability of beingcorrosives.
Eye Irritation	0.894	0.711	0.944	Category 1: irritants; Category 0: non-irritants The output value is the probability of being irritants.
Respiratory toxicity	0.041	0.043	0.332	Category 1: respiratory toxicants; Category 0:respiratory non-toxicants The output value is the probability of being toxic.

In all above tables colours used indicate- green: excellent, orange: medium, red: poor

CONCLUSION: For the preparation of tetrabenzoyl ellagic acid (BEA) from ellagic acid, very commonly used and simple method for O-benzoylation of phenol was employed. The conversion was verified by TLC and mixture of Hexane and ethyl acetate (8:2) was used. Good yield of pinkish white product was obtained. It has better solubility in methanol, chloroform, hexane. The product was purified by column chromatography by using silica gel in hexane and eluting it with the mixture of hexane and ellagic acid. The purity of product was checked with gas chromatography which gave a single peak, indicating absence of any impurity in the product. From the comparison of the IR spectrum of ellagic acid and benzoyl ellagic acid, the peak for phenolic -OH in ellagic acid disappeared in benzoyl ellagic acid. This confirms the structure of product. The structure of the product was further confirmed by H^1 and C^{13} NMR spectras. For the preparation of octasodium salt of hydrolysis of ellagic acid (HEA) from ellagic acid, very commonly used and simple method for base catalysed hydrolysis of lactones was employed. Good yield of dark brown product was obtained. It has solubility only in water. From the comparison of the IR spectrum of ellagic acid and sodium salt of hydrolysis of ellagic acid, the peak for lactone in ellagic acid disappeared in sodium salt of hydrolysis of ellagic acid. This confirms the structure of product. The structure of the product was further confirmed by H^1 and C^{13} NMR spectras. The *in-silico* study of drug like properties of EA, BEA, HEA was carried out using ADMETLab2 online platform. The predictions about the physiochemical properties, medicinal properties, absorption, distribution, metabolism, excretion, toxicity were carried out using the structure of these molecules. From these predictions it can be seen that among the three molecules EA and HEA are showing good physiochemical properties as well as medicinal properties. Among the three molecules, HEA shows the best absorption whereas EA shows best distribution. All the three molecules show moderate metabolism; excretion and toxicity profiles. On the basis of this analysis EA is having best drug like properties than HEA and BEA.

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CONFLICTS OF INTEREST: Nil

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