The Pharma Innovation Journal 2019; 8(5): 580-595

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(5): 580-595

www.thepharmajournal.com
Received: 25-03-2019
Accepted: 29-04-2019

Nitish Kumar
Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi, India

Amrita Parle
Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi, India

Correspondence
Nitish Kumar
Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi, India

Cinnamic acid derivatives: An ERA

Nitish Kumar and Amrita Parle

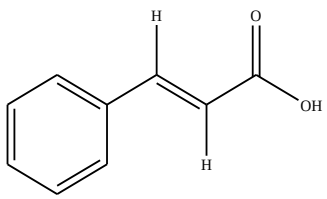
Abstract
Cinnamic acid and its derivatives are a class of unsaturated compounds containing carboxyl group. Cinnamic acids are present almost in all green plants even though in minute quantities. They are obtained from natural sources and some are synthesized chemically as well as enzymatically. Cinnamic acid and its derivatives possess pharmacological actions like: anti-oxidant, antiviral, anti-diabetic, CNS depressant, hepatoprotective etc. Currently they are attaining considerable importance for their anti-microbial activity. Current marketed preparations containing cinnamic acid as core moiety and ongoing clinical trials of cinnamic acid derivatives are also included in this review.

Keywords: Cinnamic acid, antimicrobial, anti-diabetic, marketed preparations, clinical trials

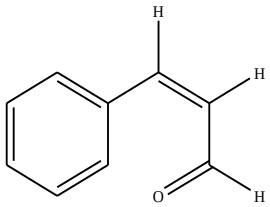
Introduction
Cinnamic acid is an unsaturated carboxylic acid having formula $C_6H_5CHCHCOOH$. Properties of cinnamic acid are described in Table 1.

Table 1: Properties of cinnamic acid.

S. No.	Cinnamic Acid	
1.	Physical state	Crystalline Compound
2.	Colour	White
3.	Odour	Honey like Odour
4.	Solubility	Slightly soluble in water, and freely soluble in many organic solvents [1].
5.	Melting Point	133ºC
6.	Boling Point	300ºC
7.	Acidity[pKa]	4.44
8.	Geometric Isomerism	It exists as both a *cis* and a *trans* isomer [2] in which *trans* isomer is more common [Figure 1].



rans-cinnamic acid



cis-cinnamic acid

Fig 1: Structure of cinnamic acid

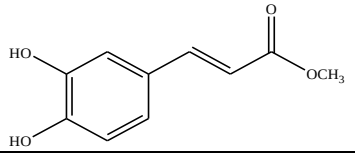
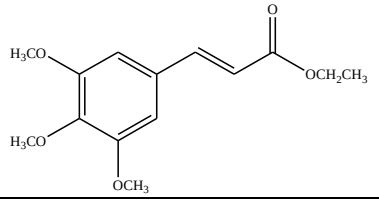
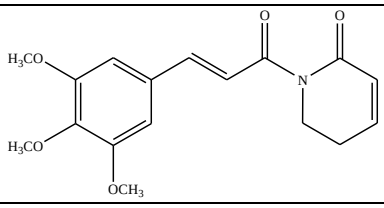
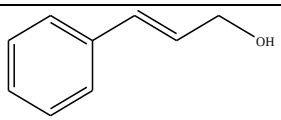
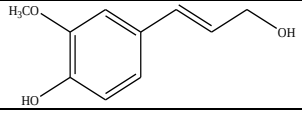
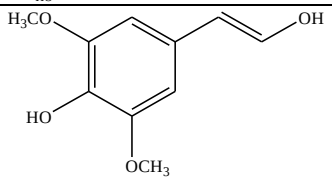
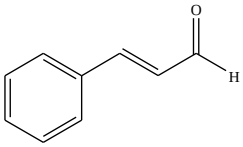
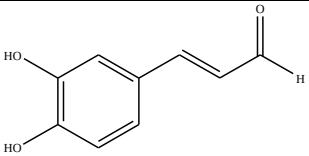
Sources of cinnamic acid and its derivatives
Cinnamic acid and its derivatives are found in natural sources or can be synthesized in laboratory.

Natural sources
Cinnamic acid is present almost in all green plants even though in minute quantities [3]. The term cinnamic is derived from the spice cinnamon [*Cinnamomum zeylanicum*] [4]. Cinnamic acid is found in free form or as an ester, amide, alcohol or aldehydic derivative. They are obtained from oil of Cinnamon, balsam of Peru, balsam of Tolu, Storax and Benzoin [5]. Some other plants like coffee beans, tea, mate, cocoa, apples and pears, berries, citrus, grape, brassicas vegetables, spinach, beetroot, artichoke, potato, tomato, celery, faba beans, and cereals also contain cinnamic acid and/or its derivatives [6].

In biological chemistry, Cinnamic acid is a key intermediate in biosynthetic pathways such as shikimate and phenyl-propanoid pathway in green plants, algae, fungi, and even in some prokaryotes and leads to the formation of secondary metabolites such as lignin, isoflavonoids, flavonoids, anthocyanins, coumarin etc. These secondary metabolites play significant roles in physiological change in plants [anthocyanins for pigmentation, flavonoids protect against UV photodamage] [7, 8].

Since ancient times they are used for flavouring the food preparations. Medicinally it is used as stimulant, carminative, antiseptic and insecticide [9]. Cinnamic acid derivatives found in plants, their structure, source and pharmacological actions are depicted in Table 2.

Table 2: Cinnamic acid derivatives found in plants.

S. No.	Cinnamic acid derivative	Structure	Source	Pharmalogical activity	Reference
Cinnamic Esters					
1.	Methyl caffeate		*Solanum torvum* Swartz.	Anti-diabetic activity against streptozotocin induced diabetic rats	[10].
2.	Ethyl 3,4,5-trimethoxy cinnamate		*Piper longum*	Anti-inflammatory	[11].
Cinnamic amide					
3.	Piplartine		*Piper longum*	Anticancer	[12].
Cinnamic alcohol					
4.	Cinnamyl alcohol		*Cinnamomum* species	Perfumes, tonics and other hair grooming aid	[13].
5.	Coniferyl alcohol		Gum Benzoin	fungal growth inhibitor	[14].
6.	Sinapyl alcohol		Bio-synthesized via pheyl-propanoid	Anti-inflammatory and anti-nociceptive effects	[15].
Cinnamic aldehyde					
7.	Cinnamaldehyde		Oil of Cinnamon	Flavouring agent, Attenuates pressure overload-induced cardiac hypertrophy, Anti-diabetic.	[16]. [17]. [18].
8.	Caffeic aldehyde		*Piper taiwanense,*	antitubercular	[19].

Synthesis of cinnamic acid and its derivatives

Different synthetic methods used for preparation of cinnamic acid and its derivatives are:

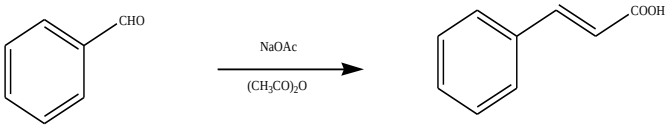
1. Perkin reaction

Perkin reaction is an organic reaction named after William Henry Perkin. It is a primary method for the synthesis of cinnamic acid and its derivatives.

Condensation of an aromatic aldehyde and acid anhydride takes place in this reaction, in the presence of an alkali salt [Sodium acetate] of the acid, which acts as a base catalyst and gives α, β-unsaturated aromatic acid [20]. Perkin reaction is not possible with simple aliphatic aldehyde or aromatic ketones.

Scheme 1a

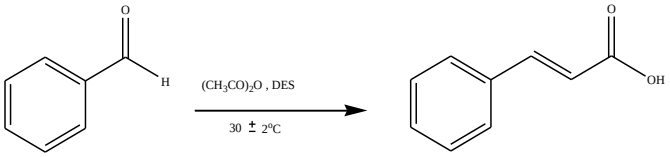
In presence of anhydrous sodium acetate, benzaldehyde and acetic anhydride is condensed to form cinnamic acid [21]. Aldehyde leads to the formation of unwanted side product like alcohols in presence of bases which is main disadvantage of this method.



Benzaldehyde Cinnamic acid

Scheme 1b

Benzaldehyde converts into cinnamic acid via perkin reaction in presence of acetic anhydride and biodegradable deep eutectic solvent [DES] based on choline chloride and urea, in 4 hours at 30±2ºC. The yield obtained is 92% yield [22].



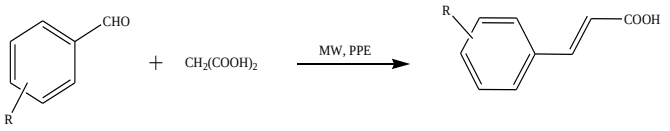
Benzaldehyde Cinnamic acid

2. Knoevenagel condensation

The Knoevenagel condensation reaction is an organic reaction developed by Emil Knoevenagel. Malonic acid undergoes knoevenagel condensation with almost every type of aldehyde and very reactive ketones. Methylenemalonic acids are usually obtained, if condensation [with malonic acid] is performed in ethanolic ammonia below 70ºC. If, however, basic solvents like pyridine and piperidine [Doebner modification] are used in place of ethanolic ammonia, decarboxylation normally takes place and acrylic or cinnamic acid is formed [23].

Scheme 2a

Aryl aldehyde reacts with malonic acid under microwave irradiation in presence of polyphosphate ester which acts as catalyst and reaction mediator gives cinnamic acid and its derivatives as the product [24]. There is advantage of this method over Perkin reaction is that electron donor substituent like 2, 6-dimethylbenzaldehyde can be used for synthesis of cinnamic acid. Long reaction time is disadvantage of this method.

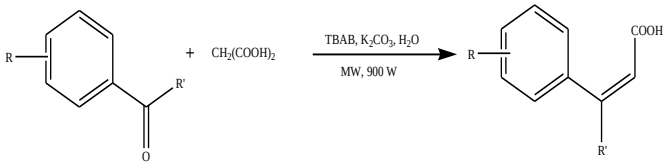


Benzeldehyde Cinnamic acid

R = 4-Br; 3, 4-di [OMe]; 4-OH; 4-NO_2; 2, 5-di [OMe]; OMe; 4-Me; 3-Cl; H.

Scheme 2b

Aromatic aldehye or ketone and malonic acid undergo Knoevenagel condensation in presence of tetra butyl ammoniumbromide [TBAB] and potassium carbonate [K_2CO_3] under microwave irradiation in presence of water to produce cinnamic acids [25]. It is simple and eco-friendly procedure for the synthesis of cinnamic acid. Excellent yield and high purity of product are obtained.

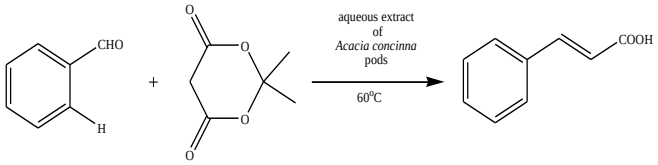


Ar aldehyde or ketones cinnamic acid derivative

R/R' = H/H; 4-OMe/H; 4-NO2/H; 3-Br/H; 2, 4-Cl/H; 4-OH/H; H/CH_3; 4-Br/CH_3; 4-NO_2/CH_3

Scheme 2c

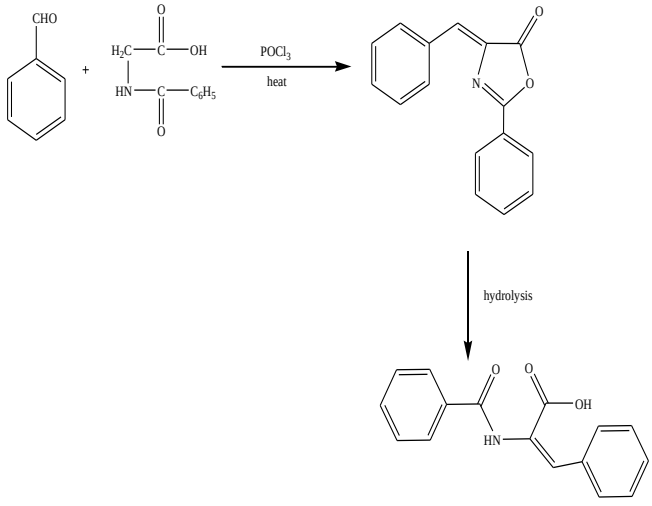
Under mild condition, aqueous extract of *Acacia concinna* pods catalyze the condensation of Meldrum's acid with aromatic aldehyde to yield cinnamic acids via Knoevenagel condensation [26]. Excellent yield[95%], eco-friendly, easy availability of catalyst and simple reaction procedure are the advantages of this method.



3. Phosphorous oxychloride method

Scheme 3a

Aromatic aldehydeis condensed with N-aroylglycine by heating in phosphorusoxychloride leads to 4-benzylideneoxazol-5-one derivative in high yield. On hydrolysis of 4-benzylideneoxazol-5-one derivative, α-benzoylaminocinnamic acid is formed [27]. This procedure is somewhat lengthy and energy consuming.

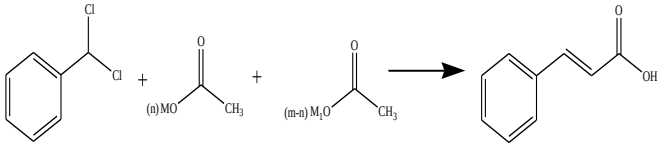


α-benzoylaminocinnamic acids

4. From benzal chloride

Scheme4a

Benzal chloride and anhydrous acetate is heated at 180° to 200° C for 10 hours to get the desired product cinnamic acid [28]. This procedure is also being used for commercial preparations. Benzal chloride used in this reaction is cheaper than benzaldehyde.



Benzal chloride

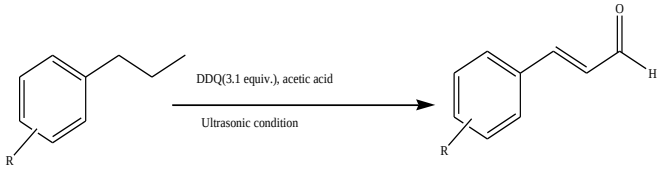
Wherein

- M and M1 are the same or different and are alkali metals.
- M and N are integers from 0-3.

5. Under ultrasonication method

Scheme 5a

Arylpropene is used to synthesize cinnamaldehyde[*trans*] by using DDQ [2, 3-Dichloro-5, 6-dicyno-1, 4-benzoquinone] and few drops of acetic acid [29]. Economical substrates, 100% [*E*]-selectivity of cinnamaldehyde and atom economy are merits of this process.



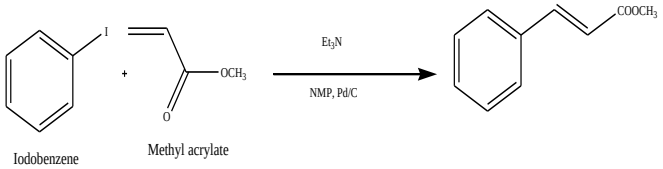
Cinnamaldehyde

6. Heck coupling reaction

When Aryl halide is coupled with alkene in presence of a base and palladium as catalyst, the reaction is referred as Heck coupling reaction. This process is also used to synthesize cinnamic acid using iodobenzene & methyl acrylate as reactant and palladium catalyst under different conditions.

Scheme 6a

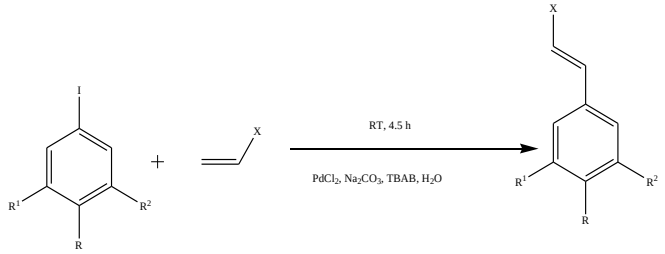
Ambulgekar and co-worker worked on synthesis of cinnamic acid, they synthesized methyl ester of cinnamic acid under ultrasonic condition from iodobenzene and methyl acrylateusing catalyst [Pd/C], NMP [N-methyl pyrolidine] as a solvent and triethyl-amine [30]. Triethyl-amine promotes the redeposition of palladium on charcoal.



Iodobenzene Methyl acrylate

Scheme 6b

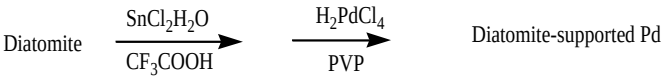
Different aryl halides can be used to prepare cinnamic acid esters [when X = COOMe] under ultrasonic condition in presence of a catalystpalladium chloride [$PdCl_2$], a phase transfer catalyst i.e. TBAB [tetra butyl ammonium bromide] and Na_2CO_3. Acceptable yield [i.e. 43-93%] of corresponding products can be obtained in aqueous solution at ambient temperature using this method [31]. It is also well accepted method for commercial preparations.



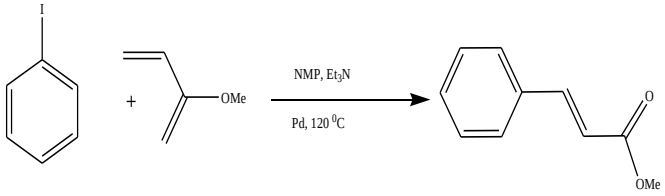
R = H, OMe, Cl, Br, NHCOMe, or NO_2
R^1= I, CHO, H
R^2= I or H
X = CO_2Me, COOH, CN or Ph

Scheme 6c

Diatomite-supported palladium nanoparticles have been prepared by following way



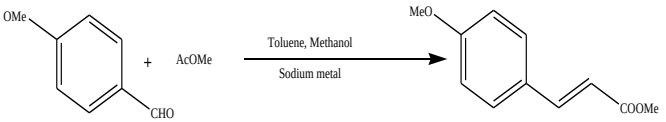
Prepared Pd-nanoparticle is used in the reaction of aryl halide and methyl acrylate which gives cinnamic acid derivatives as product in presence of a solvent NMP [*N*-Methyl pyrolidine] and a base i.e. triethylamine [32]. Excellent yield [i.e. 96%] is obtained within 25 minute.



7. Claisen–Schmidt condensations

Scheme 7a

By using this method, Cinnamic acid derivatives having [*E*]configuration are prepared by condensation reaction between aromatic aldehyde and methyl acetate in presence of sodium metal and methanol with toluene in a catalytic amount as co-solvent [33].



Patents [34] have been granted for this process for different reaction conditions which are covered in Table 3.

Table 3: Patents have been granted for this process.

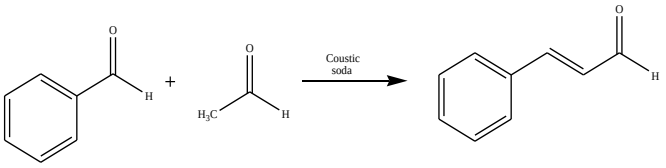
S. No.	Patent no.	Reactant used	Reaction condition	Final product	Disadvantage
1.	US – 6054607 A	Benzaldehyde and acetic acid ester	Reaction occurs in presence of a base	Cinnamic acid ester	2 step process
2.	German Patent DE709227	Benzaldehyde and ethyl or methyl acetate	Reaction occurs in presence of Sodium hydride as base	Ethyl cinnamate or methyl cinnamate	Sodium hydride is not easy to handle and is expensive
3.	Japanese Patent	Benzaldehyde and an	Reaction occurs in	Cinnamic acid ester and	This procedure requires specific

	Application Kokai Sho 61-7236	acetic acid ester.	presence of alcoholic solution of a metal alkoxide as a base	3-methoxy-3-phenylpropionic acid formed as by product.	purification step[distillation] to isolate cinnamic acid ester from reaction mixture and has low yield.
4.	U.S. Pat. No. 4618698	Optionally substituted benzaldehyde and optionally substituted acetic acid ester.	Reaction occurs in presence of alcoholate	Cinnamic acid ester	Long procedure followed by hydrolysis of reaction mixture and then esterification is done to obtain product.
5.	U.S. Pat. No. 5359122	Dialkyl acetal of an aromatic aldehyde and ketene	Reaction occurs in presence of a catalytic amount of a protic or Lewis acid	Cinnamic acid or ester	2 step process.

8. Liquid-phase oxidation of cinnamic aldehyde

Scheme 8a

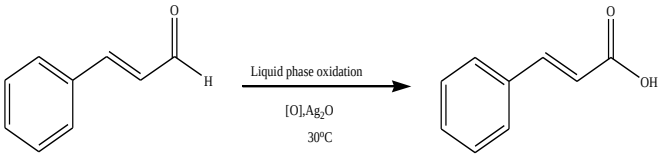
Cinnamic aldehyde is prepared by the condensation reaction of benzaldehyde with acetaldehyde in caustic soda solution.



Benzaldehyde Acetaldehyde Cinnamic aldehyde

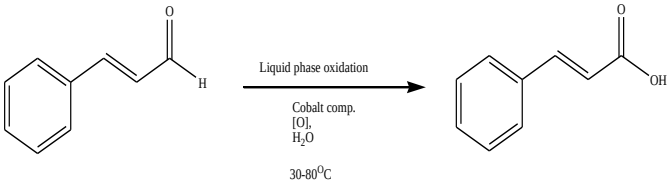
Scheme 8b

Cinnamic aldehdye is oxidized in the liquid phase using molecular oxygen in the presence of silver oxide as catalyst. This process publicly disclosed in U.S. Pat. No. 3162682 and in British Pat. No. 782430. Silver oxide which is used in this reaction is very expensive and requires the reaction temperature to be maintained at 30º C or lower because a silver mirror reaction occurs at higher temperature which is main disadvantage of this process.



Scheme 8c

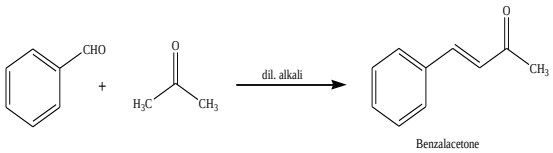
The above process was modified to overcome the drawbacks. In the modified method cinnamic aldehyde is dissolved in an aromatic hydrocarbon which is oxidized in the liquid phase with molecular oxygen at a temperature in the range of 30°-80° C, in presence of cobalt compound[e.g.-cobalt acetate, cobalt benzoate or cobalt stearate] and water, which leads to the formation of cinnamic acid [35].

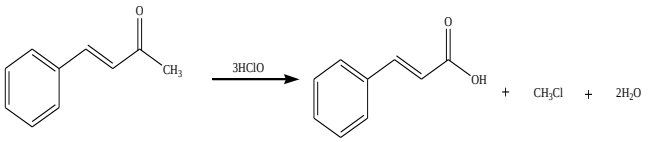


9. From benzaldehyde and acetone

Scheme 9a

Benzaldehyde and acetone are condensed in presence of dilute alkali to produce benzalacetone which is further oxidized by hypochlorous acid to give cinnamic acid.





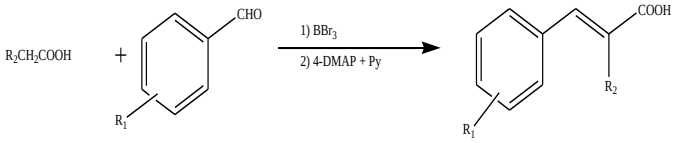
Benzalacetone cinnamic acid

This method is modified by Lewinshon to increase the yield [i.e. 88.2%]. He used sodium hypochlorite or hypobromite as oxidizing agent instead of hypochlorous acid to produce cinnamic acid [36].

10. Direct synthesis of cinnamic acids from aromatic aldehydes and aliphatic carboxylic acids

Scheme 10a

This is new direct synthetic method to synthesize cinnamic acids in high yield. The reaction occurs between aromatic aldehydes and aliphatic carboxylic acids, in the presence of boron tribromide as reagent, dimethylaminopyridine [4-DMAP] and pyridine [Py] as bases and N-methyl-2-pyrolidinone [NMP] as solvent, at reflux [180-190°C] for 8-12 hours. Yield up to 81% is obtained using this approach [37].

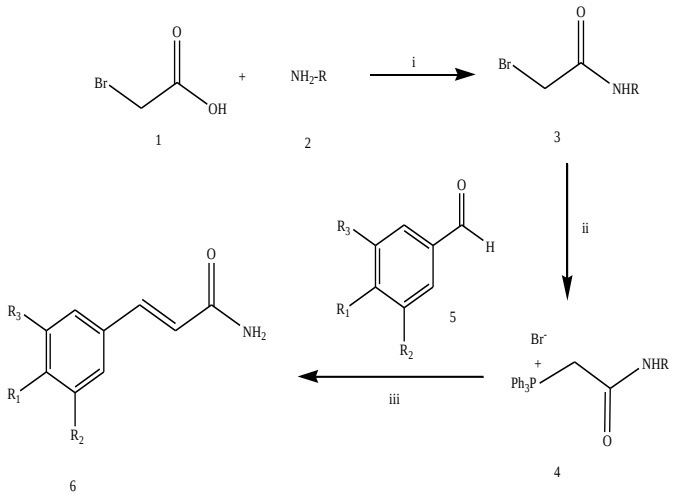


R_1/R_2 = *p*-Cl/H, *m*-Cl/H, *p*-H/H, *p*-CH_3O/H, *m*-NO_2/H, *m*-Cl/CH_3, *m*-NO_2/CH_3.

11. Microwave-accelerated synthesis of amides of substituted cinnamic acids by Wittig reaction

Scheme 11a

Initially bromoacetamides [3] are synthesized from the corresponding bromoacetic acid [1] and heptyl- or butylamines [2] using peptide methods then phosphonium salts are prepared from triphenyl-phosphonium [Ph_3P] and the corresponding amides of bromoacetic acid [38]. Then substituted cinnamic acid amides [6] were synthesized from general. Aromatic aldehydes with a free OH group in *p*-position react with phosphonium salts results in poor yield and a byproduct [triphenylphosphine oxide], separation of which is quite difficult [39].



Here in,

i] IBCF [isobutyl chloroformate]/ NMM [N-methyl morpholine], THF [tetra-hydrofuran], -15^{O}C.

ii] Ph_3P, C_6H_5-CH_3, RT.

iii] K_2CO_3, DMSO [dimethyl sulfoxide], microwave power-500W, T- 150^{o}C.

R = $[CH_2]_6CH_3$ or $[CH_2]_3CH_3$

R_1 = OH, OCH_3 or H.

R_2 = OH, OCH_3 or H.

R_3 = OH, OCH_3 or H.

12. By biological engineering

As cinnamic acids are present in plants in very low concentration[3], extraction of these products from plants is very difficult. It involves tedious process. An alternative method for the production of these aromatic acids is based on the use of microbial strains [*E. coli* strains] modified by metabolic engineering [40]. These biotechnological processes are usually based on the use of simple sugars like glucose as a raw material. The process is described in figure 2.

The phenylpropanoid pathway is a natural source for secondary metabolites like cinnamic acid [CA] and *p*-hydroxy cinnamic acid [pHCA].

The strategy is initiated as the microbial strains with the capacity to synthesize CA or pHCA is selected. A genetic modification is performed on it to increase the carbon flow to the L-phenylalanine [L-phe] or L-tyrosine [L-tyr]biosynthetic pathway. Phospho-enol-pyruvate [PEP] and erythrose-4-phosphate [E4P] condensation starts the common aromatic pathway in bacteria & plants and forms 3-deoxy-D-arabino-heptulosonate-7-phophate [DAHP]. In this PEP is produced via glycolysis process [41] and E4P is produced via condensation of glyceraldehyde-3-phosphate [G3P]& sedoheptulose-7-phosphate [S7P] and also via condensation of glyceraldehyde-3-phosphate [G3P]& fructose-6-phosphate [F6P]. DAHP [3-deoxy-D-arabino-heptulosonate-7-phophate] converts into chorismate [CHO] after seven enzymatic reactions. A frequent strategy is used an expression of feedback-inhibition-resistant [fbr] mutant version of enzyme DAHP synthase [DAHPS] to increase the carbon flow from central metabolism to the common aromatic pathway. Rate of chorismate synthesis is increased by this modification. Chorismate is a common precursor for L-phe, L-tyr and L-tryptophan [L-TRP]. An expression of feedback-inhibition-resistant version of enzyme CHO mutase-prephenate dehydratase [CM-PDT] employed to increase carbon flow from chorismate to L-phe biosynthesis and an expression of feedback-inhibition-resistant version of CHO mutase-prephenate dehydrogenase [CM-PDH] is employed for increasing L-Tyr synthesis from chorismate [CHO].

Production of L-Phe and L-Tyr can be improved by increasing availability of precursors, phospho-enol-pyruvate [PEP] and erythrose-4-phosphate [E4P]. Availability of phospho-enol-pyruvate [PEP] can be increased by generation of E.coli strains lacking the PEP: sugar phosphotransferase system [PTS] activity and further modified to display a high growth rate on glucose [PTS− glucose+ phenotype]. Transport by galactose permease [GalP] and ATP-dependent phosphorylation by glucokinase is necessary for growth of this type of mutant strains. During glucose import, PEP is not consumed, these PTS− glucose+ strains display a higher aromatics yield from glucose when compared to a wild type PTS+ strain.

Deamination of L-Phe by phenylalanine ammonia-lyase [PAL] and deamination of L-Tyr by tyrosine ammonia-lyase [TAL] gives cinnamic acid and *p*-hydroxy cinnamic acid respectively.

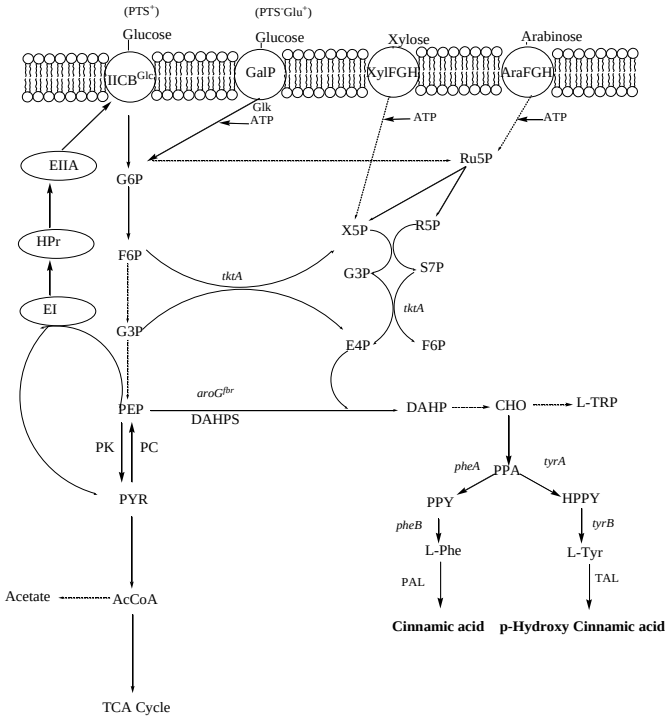


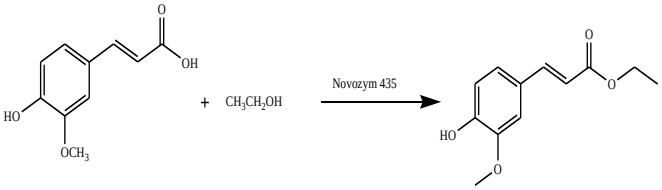
Fig 2: Central metabolism, sugar import routes and aromatics biosynthetic pathways: Dashed arrows indicate multiple enzyme reactions; EI- enzyme I; HPr- phosphohistidine carrier protein; EIIA-glucose-specific enzyme II; IICBGlc- integral membrane glucose permease; GalP-galactose permease; XylFGH- xylose transport proteins, AraFGH- arabinose transport proteins; G6P- glucose-6-phosphate; F6P- fructose-6-phosphate; G3P- glyceraldehyde-3-phosphate; PEP- phosphoenolpyruvate; R5P- ribose-5-phosphate; Ru5P- ribulose-5-phosphate; S7P- sedoheptulose-7-phosphate; X5P-xylulose-5-phosphate; PK- pyruvate kinase; PC- pyruvate carboxylase; PYR- pyruvate; AcCoA- acetyl-CoA; TCA-tricarboxylic acid; aroG fbr- gene encoding a feedback-inhibition-resistant version of 3-deoxy-D-arabino-heptulosonate-7-phosphate synthase [DAHPS]; tktA- transketolase; CHO- chorismate; PPA-prephenate; PPY- phenylpyruvate; HPPY- *p*-hydroxy phenylpyruvate; tyrB- tyrosine aminotransferase gene; PAL-phenylalanine ammonia lyase; TAL- tyrosine ammonia lyase.

13. Enzymatic method

Lee *et al*. has carried out synthesis of two derivatives of cinnamic acid by enzymatic method using Novozym 435 as a

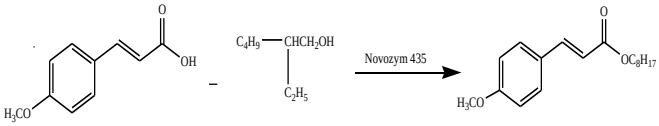
catalyst. Novozym 435 is *Candida antarctica* lipase B immobilized on acrylic resin and has a specific activity of 7 PLU [propyl laurate units]/mg based on ester synthesis. Two derivatives of cinnamic acid i.e. ethyl ferulate and octyl methoxy cinnamate are synthesized using Novozym 435 as a catalyst. In scheme 13a, ethyl ferulate [EF] is synthesized from ferulic acid [4-hydroxy 3-methoxy cinnamic acid] and ethanol while in scheme 13b, octyl methoxy cinnamate [OMC] is synthesized from *p*-methoxy cinnamic acid and 2-ethyl hexanol [42]. The yield obatained is 85%-90% which is higher as compared to other methods. Enzyme can be reused without any loss of activity. Ethanol distorts the water layer around enzyme which is necessary for its activity.

Scheme 13a



Ferulic Acid Ethanol Ethyl ferulate [Antioxidant]

Scheme 13b



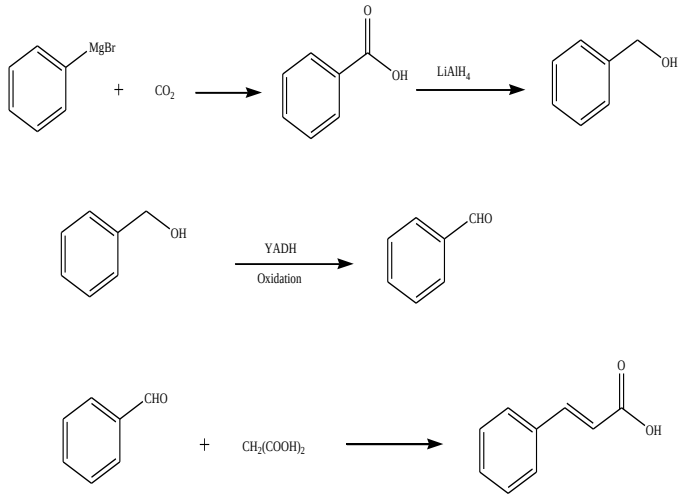
p-methoxycinnamic acid 2-ethyl hexanol Octyl methoxy cinnamate [Used as a sunscreen agent]

14. Combined chemical and enzymatic method

Scheme 14a

Radiolabeled cinnamic acid is synthesized using this method. Initially, radiolabeled [1-^{14}C] benzoic acid is prepared by carbonation of Grignard reagent with radiolabeled [^{14}C] carbon dioxide. Prepared benzoic acid is reduced in presence of lithium aluminium hydride [$LiAlH_4$] to give radiolabeled [1-^{14}C] benzyl alcohol. Benzyl alcohol is enzymatically oxidized using YADH [yeast alcohol dehydrogenase] to radiolabeled [1-^{14}C] benzaldehyde. Prepared bezaldehyde is immediately condensed with malonic acid to give radiolabeled [3-^{14}C] cinnamic acid [43].

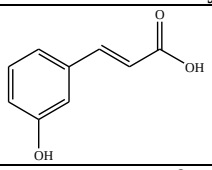
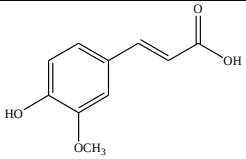
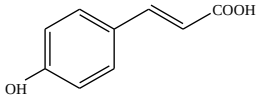
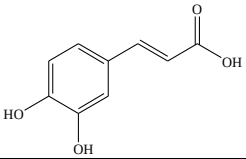
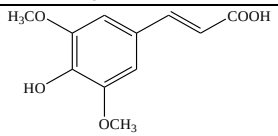
This combined chemical and enzymatic approach allows to obtain radiolabeled [3-^{14}C] cinnamic acid with radiochemical yield higher than 50% in respect to the starting alcohol.

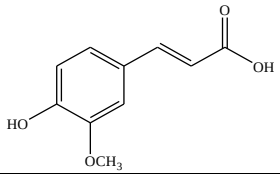
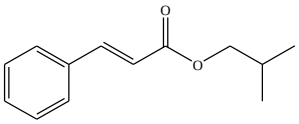
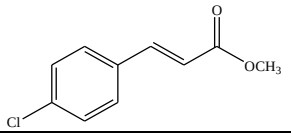
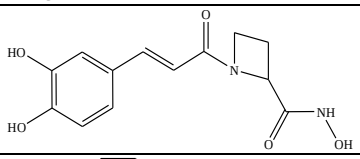
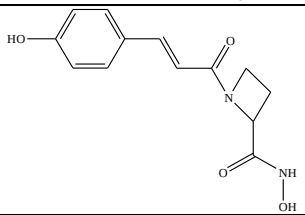
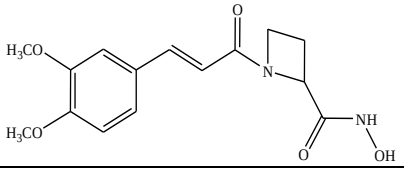
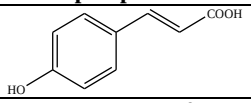
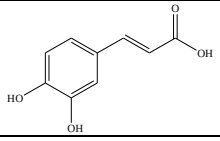
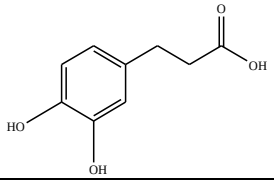
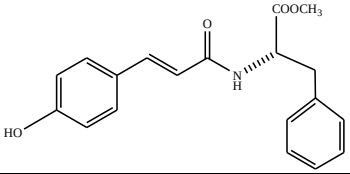
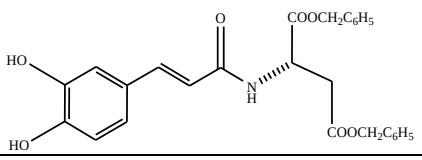
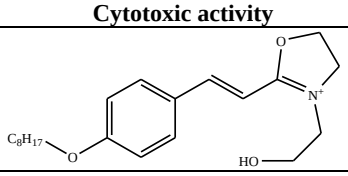


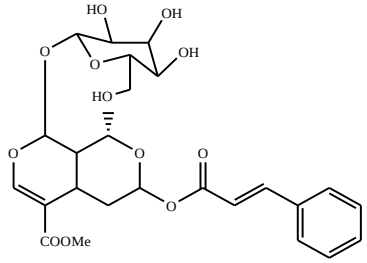
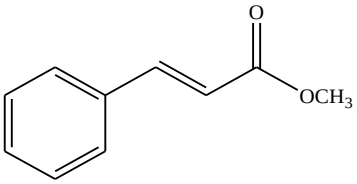
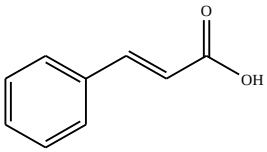
Pharmacological action

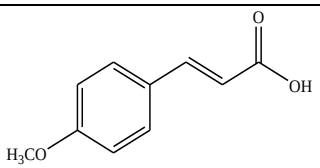
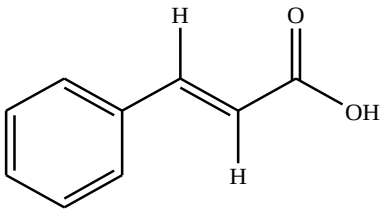
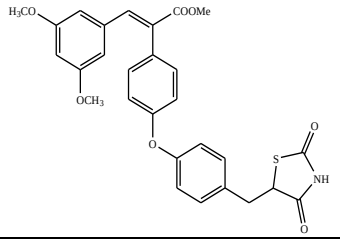
Cinnamic acid and its derivatives are extremely versatile and exhibit wide range of pharmacological activity.

Table 4: Pharmacological activity of cinnamic acid derivatives

S. No.	Cinnamic acid derivatives	Structure	Mechanism of action	Reference
		Antidiabetic activity		
1.	*m*-Hydroxy cinnamic acid		Stimulating peripheral glucose uptake	[44].
2.	Ferulic acid [4-hydroxy-3-methoxy cinnamic acid]		PPAR agonistic activity	[44].
		Antioxidant		
3.	*p*-Coumaric acid [4-hydroxycinnamic acid]		Inhibits LDL- oxidation	[45].
4.	Caffeic acid [3,4-dihydroxy cinnamic acid]		Inhibits, membrane lipid peroxidation	[46].
5.	Sinapic acid [3,5-dimethoxy-4-hydroxy cinnamic acid]		GABA receptors and potentiating Cl^- currents	[47].

6.	Ferulic acid [4-hydroxy- 3-methoxy cinnamic acid]		Inhibits LDL- oxidation	[48].
Antimicrobial				
7.	Isobutyl cinnamate		Interaction on protein thiol groups [Related to the hydrophobic character of the molecule]	[49].
8.	Methyl-4-chlorocinnamate [Antifungal]		Alteration in permeability of fungal cell membrane	[50].
9.	N-hydroxy-1-[[2E]-3-[3,4-dihydroxyphenyl]prop-2-enoyl]azetidine-2-carboxamide		Inhibition of NDM-1	[51].
10.	*N*-hydroxy-1-[[2E]-3-[4-hydroxyphenyl]prop-2-enoyl]azetidine-2-carboxamide		Inhibition of NDM-1	[51].
11.	*N*-hydroxy-1-[[2E]-3-[3,4-dimethoxyphenyl]prop-2-enoyl]azetidine-2-carboxamide		Inhibition of NDM-1	[51].
Hepatoprotective				
12.	4-hydroxy cinnamic acid		5-lipoxygenase inhibition Activity	[52].
13.	Caffeic acid [3,4-dihydroxy-cinnamic acid]		Not Defined	
Anticholestrolemic				
14.	3, 4-Di[OH]-hydrocinnamate		Hepatic HMG-CoA reductase activity	[53, 54].
15.	4-Hydroxy cinnamic acid [L-phenylalanine methyl ester] Amide		Inhibit human acyl-CoA: cholesterol acyltransferase-1 and -2	[53, 54].
16.	3,4-Dihydroxyhydro cinammic acid [L-aspartic acid dibenzyl ester] amide		Inhibit human acyl-CoA: cholesterol acyltransferase-1 and -2	[53, 54].
Cytotoxic activity				
17.	Cinnamic acid derived oxazolinium ions		Act as alkylating agents	[55].

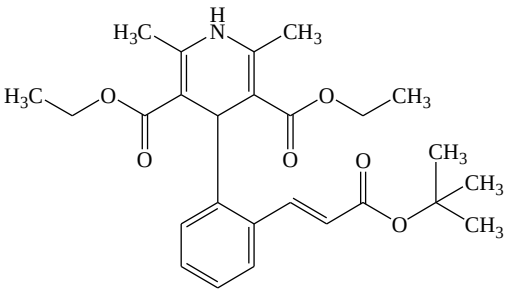
Anti-inflammatory				
18.	7-*O*-cinnamoyl Morronniside		Inhibitor of TNF-α-induced E-selectin expression	[56].
Cosmetology & flavouring agent				
20.	Methyl cinnamate		-	[57].
20.	Cinnamaldehyde		-	[58].

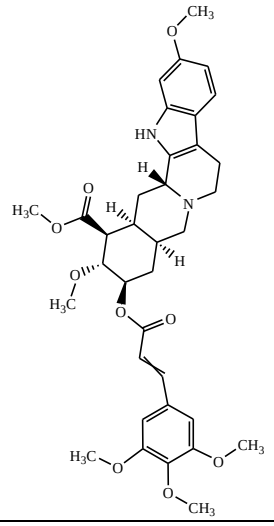
Miscellaneous					
S. No.	**Cinnamic acid derivatives**	**Structure**	**Pharmacological activity**	**Mechanism of action**	**Reference**
1.	*p*-Methoxy cinnamic acid		Antidiabetic, Hepatoprotective, Sunscreen agent	PPAR agonistic activity	[59].
2.	*Trans*-Cinnamic acid		Anti TB, Antiviral	I] Inhibits the transfer of mycolic acid II] Inhibited the viral replication cycle	[60].
3.	Thiazolidine1,4 - dione substituted - phenyl cinnamic acid derivatives		Anti-hyperglycemic Activity	PPAR-agonist activity	[59].

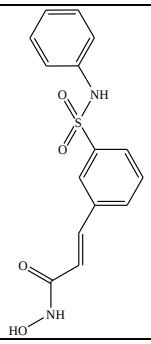
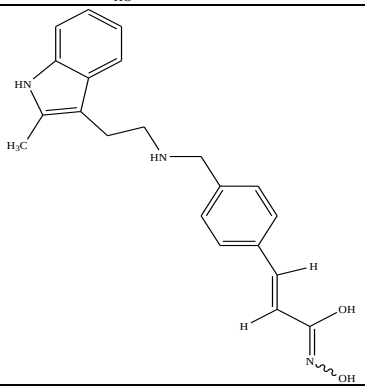
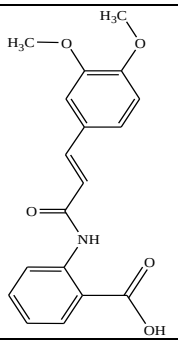
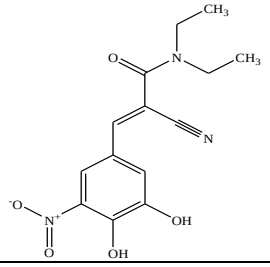
Currently marketed cinnamic acid derivatives

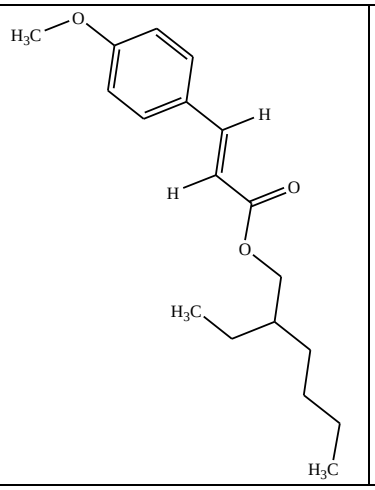
Table 5 summarizes the currently available marketed preparations with their name, structure, pharmacological activity, mechanism of action and manufacturer.

Table 5: Current marketed preparations of cinnamic acid derivatives

S. No.	Drug	Structure	Pharmacological Activity	Mechanism of Action	Company	Reference
1.	Lacidipine		Antihypertensive	Calcium channel blocker	Sunpharma, GSK	[61].

2.	Rescinnamine		Antihypertensive	Angiotensin-converting enzyme inhibitor	Pfizer	[62].

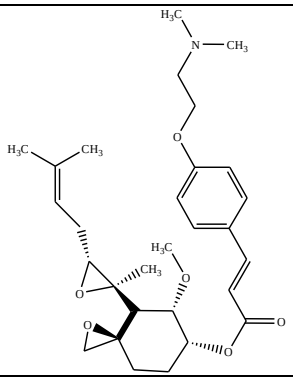
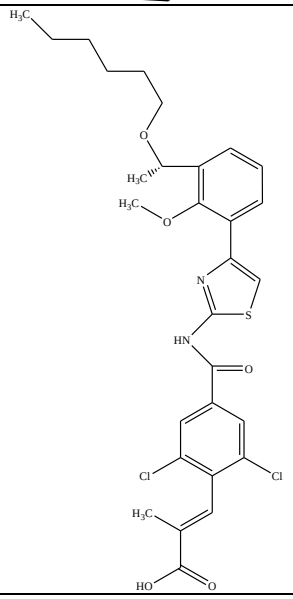
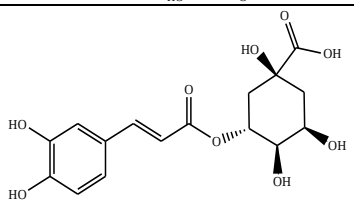
3.	Belinostat		Developed as orphan drug to target hematological malignancies and solid tumors by Topo Target and it is used as therapeutic agent for refractory peripheral T-cell lymphoma.	It inhibits the enzyme histone deacetylase [HDAC]	Ikris Pharma	[63].
4.	Panobinostat		Used in the treatment of multiple myeloma.	Oral deacetylase [DAC] inhibitor	Novartis	[64].
5.	Tranilast		Antiallergic.	Selective target of hematopoietic prostaglandin D synthase	Kissei Pharmaceutical	[65, 66].
6.	Entacapone		Used for the treatment of parkinson's disease.	Selective, reversible catechol-O-methyl transferase[COMT] inhibitor	Novartis	[67].

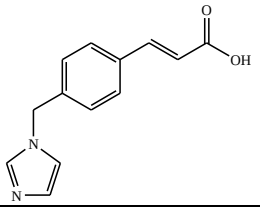
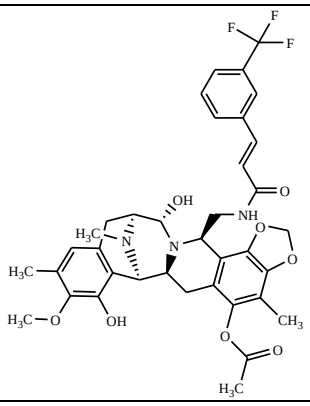
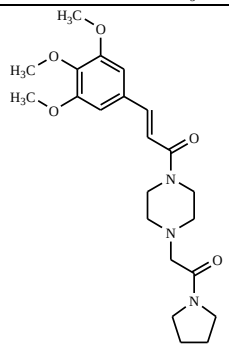
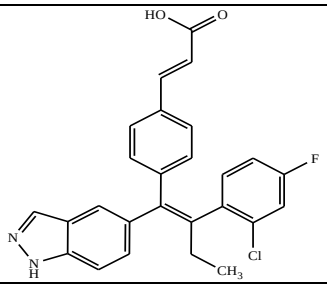
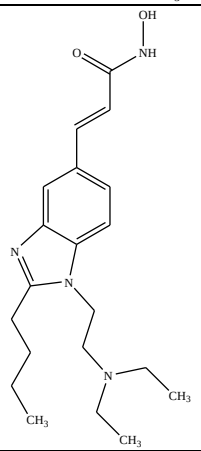
7.	Octinoxate		Used in skin care products to minimize DNA photodamage.	It absorbs UV rays from sun	Palsons, Cipla, Fulford, Wockhardt, Glenmark	[68].

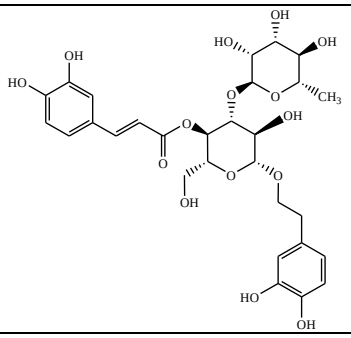
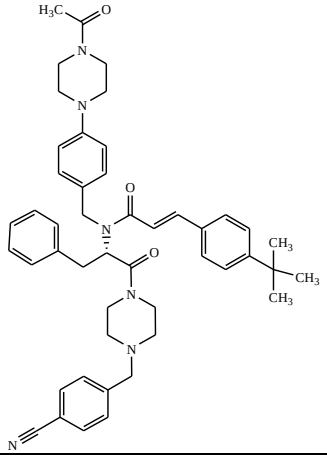
Cinnamic acid derivatives undergoing clinical trial studies:

Table 6 covers the ongoing clinical trials of cinnamic acid derivatives with their name, structure, study, phase status and mechanism of action

Table 6: Ongoing clinical trials of cinnamic acid

S. No.	Drug	Structure	Study	Status	Mechanism of Action	Reference
1.	Beloranid		Obesity	Clinical trial Phase II [completed]	Inhibitor of the enzyme METAP2 [73]	[69].
			Obesity + Anti-diabetic	Phase II [Terminated]		[70].
			Obesity + Prader-Willi Syndrome	Phase III [Terminated]		[71].
			Obesity + Hypothalamic Injury + Craniopharyngioma	Phase II [completed]		[72].
2.	Lusutrombopag		Thrombo-cytopenias in patients with chronic liver disease	Clinical Trail Phase III	It acts selectively on the human TPO receptor and activates signal transduction pathways [75]	[74].
3.	Chlorogenic Acid		Glioblastoma	Clinical Trail Phase I	-	[76].
			Advanced Cancer			[77].
			Impaired Glucose Tolerance	Phase II		[78].

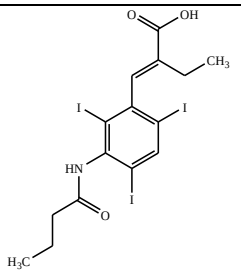
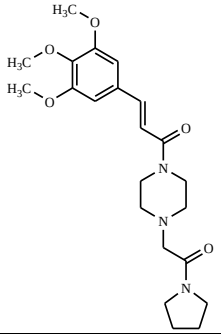
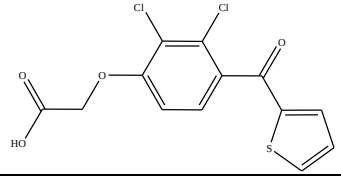
4.	Ozagrel		Acute ischemic stroke	Clinical Trail Phase IV [completed]	Thromboxane A2 synthesis inhibition [80]	[79].
5.	Zalypsis		Uterine Cervical Cancer + Endometrial Cancer	Clinical trial Phase II [Terminated]	Alkylating agent [84]	[81].
			Ewing's Sarcoma + Primitive Neuro-ectodermal Tumor [PNET]	Clinical trial Phase II [Completed]		[82].
			Solid Tumors + Lymphoma	Clinical trial Phase I [Terminated]		[83].
6.	Cinepazide		Treatment of Ischemic Stroke	Clinical trial Phase II	Neuro-protective [86]	[85].
7.	GDC-0810		Treatment of Breast Cancer	Clinical trial Phase II	Antagonism of ERα [88]	[87].
8.	Pracinostat		Acute Myeloid Leukemia	Clinical trial Phase III	HDAC Inhibitor [90]	[89].
9.	Acteoside		Treatment of IgA Nephropathy	Clinical trial Phase II & Phase III	-	[91].

						
10.	ACT-451840		Antimalarial	Clinical trial Phase I [Completed]	Blocks transmission [93].	[92].

Cinnamic acid derivative withdrawn from the market

Table 7 covers the cinnamic acid derivative that are withdrawn from the market with its name, structure, pharmacological activity, cause of withdrawal and markets from where it is withdrawn.

Table 7: Cinnamic acid derivative that are withdrawn from the market

S. No.	Drug	Structure	Pharmacological activity	Cause	Status	Reference
1.	Bunamiodyl		Used in the examination of the biliary tract	Due to nephropathy	Withdrawn from Canadian, US and UK markets in 1963 & Worldwide in 1984	[94].
2.	Cinepazide		Vasodilator	Agranulocytosis	Withdrawn from Spain in 1988	[95, 96].
3.	Ticrynafen		Uricosuric diuretic	Liver toxicity	Withdrawn from Germany, France, UK and US markets in 1980	[97, 98].

Conclusion

Cinnamic acid & its derivatives are important class of drugs with wide range of pharmacological activity. The review covers various methods of their synthesis, Perkin reaction being one of the simplest and commonest method of synthesis while biological engineering is modern tool for their preparation. Preparation via Knoevenagel condensation of Meldrum's acid with aromatic aldehyde using aqueous extract

of *Acacia concinna* pods as catalyst under mild condition, have least drawbacks and it has better future scope.

The review has concisely depicted in tabular form, plant derivaitves, pharmacological activity, currently marketed preparations, ongoing clinical trials, withdrawn preparation of cinnamic acid derivatives for use of researchers working in this field.

References

1. Chafer A, Fornari T, Stateva RP, Berna A. Trans-Cinnamic Acid Solubility Enhancement in the Presence of Ethanol As a Supercritical CO2 Cosolvent. J Chem. Eng. Data. 2009; 54:2263-2268.
2. Cinnamic Acid. Ullmann's Encyclopedia of Industrial Chemistry [Online]; Dorothea Garbe, Posted, 2000.
3. Lichtenthaler HK, Schweiger J. Cell wall bound ferulic acid, the major substance of the blue-green fluorescence emission of plants. J. Plant Physiol. 1998; 152:272-282.
4. Koktate CK, Purohit AP, Gokhale SB. Terpenoids. *Pharmacognosy*, 46th; Nirali Prakashan: Pune. 2010; 2(1):46.
5. Koktate CK, Purohit AP, Gokhale SB. Terpenoids. *Pharmacognosy*, 46th; Nirali Prakashan: Pune. 2010; 2(1):126-139.
6. Clifford MN. Chlorogenic acids and other cinnamates-nature, occurrence and dietary burden. J Sci. Food Agric. 1999; 79:362-372.
7. Vogt T. Phenylpropanoid biosynthesis. Mol. Plant. 2010; 3:2-20.
8. Ferrer J-L, Austin MB, Stewart C, Jr Noel JP. Structure and function of enzymes involved in the biosynthesis of phenylpropanoids. Plant Physiol. Bio chem. 2008; 46(3):356-370.
9. Pittman S. Cinnamon: It's not just for making cinnamon rolls. Ethnobot. Leafl. 2011, 2000, 11.
10. Gandhi RG, Ignacimuthu S, Paulraj MG, Sasikumar, P. Antihyperglycemic activity and antidiabetic effect of methyl caffeate isolated from Solanum torvum Swartz. fruit in streptozotocin induced diabetic rats. Eur. J Pharmacol. 2011; 670(2-3):623-631.
11. Kumar S, Arya P, Mukherjee C, Singh BK, Singh N, Parmar VS *et al*. Novel aromatic ester from Piper longum and its analogues inhibit expression of cell adhesion molecules on endothelial cells. Biochemistry. 2005; 44(48):15944-52.
12. Bezerra DP, Pessoa C, de Moraes MO, Saker-Neto N, Silveira ER, Costa-Lotufo LV. Overview of the therapeutic potential of Piplartine (Piperlongumine). Eur. J Pharm. Sci. 2013; 48(3):453-63.
13. Letizia CS, Cocchiara J, Lalko J, Lapczynski A, Api AM. Fragrance material review on cinnamyl alcohol. Food. Chem. Toxicol. 2005; 43(6):837-866.
14. König S, Feussner K, Kaever A, Landesfeind M, Thurow C, Karlovsky P *et al*. Soluble phenylpropanoids are involved in the defense response of Arabidopsis against Verticillium longisporum. New Phytol. 2014; 202(3):823-37.
15. Choi J, Shin KM, Park HJ, Jung HJ, Kim HJ, Lee YS, *et al*. Anti-inflammatory and antinociceptive effects of sinapyl alcohol and its glucoside syringing. Planta med. 2004; 70(11):1027-32.
16. Wang R, Wang R, Yang B. Extraction of essential oils from five cinnamon leaves and identification of their volatile compound compositions. Innov. Food Sci. Emerg. Technol. 2009; 10:289-292.
17. Yang L, Wu QQ, Liu Y, Fu Hu ZH, Bian ZY, Tang QZ. Cinnamaldehyde attenuates pressure overload-induced cardiac hypertrophy. Int. J Clin. Exp. Pathol. 2015; 8(11):14345-14354.
18. Zhu R, Liu H, Liu C, Wang L, Ma R, Chen B *et al*. Cinnamaldehyde in diabetes: A review of pharmacology, pharmacokinetics and safety. Pharmacol. Res. 2017; 122:78-89.
19. Chen S, Huang HY, Cheng MJ, Wu CC, Ishikawa T, Peng CF *et al*. Neolignans and phenylpropanoids from the roots of Piper taiwanense and their antiplatelet and antitubercular activities. Phytochemistry. 2013; 93:203-209.
20. Perkin WH. On the hydride of Aceto-Salicly. J Chem. Soc. 1868; 21:181-186.
21. Rosen T. The Perkin reaction. In *Comprehensive Organic Synthesis* (Online); Trost, BM and Fleming I: Pergamon Press: Oxford, New York, Seoul, Tokyo. 1991; 2:399-400.
22. Pawar PM, Jarag KJ, Shankarling GS. Environmentally benign and energy efficient methodology for condensation: an interesting facet to the classical Perkin reaction. Green Chem. 2011; 13:2130-2134.
23. Tietza LF, Beifuss U. The Knoevenagel Reaction. In *Comprehensive organic synthesis* [Online]; Trost, B. M.; Fleming, I.; Pergamon Press: Oxford, New York, Seoul, Tokyo. 1991; 2:356-257.
24. Mobinikhaledi N, Foroughifar N, Fathinejad JH. Microwave-Assisted Synthesis of Cinnamic Acid Derivatives in the Presence of PPE and under Solvent-Free Conditions. Synth. React. Inorg. M. 2008; 38:428-430.
25. Gupta M, Wakhloo BP. Tetrabutylammonium Bromide Mediated Knoevenagel Condensation in Water: Synthesis of Cinnamic Acids. Arkivoc. 2007; 15:94-98.
26. Chavan HV, Bandgar BP. Aqueous Extract of Acacia concinna Pods: An Efficient Surfactant Type Catalyst for Synthesis of 3-Carboxycoumarins and Cinnamic Acids via Knoevenagel Condensation. ACS Sustainable Chem. Eng. 2013; 1(8):929-936.
27. Avanesyan AA, Simonyan AV, Simonyan MA. Phosphorus Oxychloride in Organic Synthesis. Part 3: Synthesis of α-Benzoylaminocinnamic Acids. Pharm. Chem. J. 2005; 39:379-380.
28. Telschow JE. Preparation of cinnamic acid. Patent US4571432 A, February 18, 1986.
29. Joshi BP, Sharma A, Sinha AK. Efficient one-pot, two-step synthesis of (E)-cinnmaldehydes by dehydrogenation–oxidation of arylpropanes using DDQ under ultrasonic irradiation. Tetrahedron. 2006; 62:2590-2593.
30. Ambulgekar GV, Bhanage BM, Samant SD. Low temperature recyclable catalyst for Heck reactions using ultrasound. Tetrahedron Lett. 2005; 46:2483-2485.
31. Zhang Z, Zha Z, Gan C, Pan C, Zhou Y, Wang Z *et al*. Catalysis and Regioselectivity of the Aqueous Heck Reaction by Pd(0) Nanoparticles under Ultrasonic Irradiation. J. Org. Chem. 2006; 71:4339-4342.
32. Zhang Z, Wang Z. Diatomite-Supported Pd Nanoparticles: An Efficient Catalyst for Heck and Suzuki Reactions. J Org. Chem. 2006; 71:7485-7487.
33. Hatsuda M, Kuroda T, Seki M. An Improved Synthesis of [E]-Cinnamic Acid Derivatives via the Claisen–

Schmidt Condensation; Synth. Commun. 2003; 33:427-434.
34. Okui H, Tsukamoto Y, Mio S. Process for the preparation of cinnamic acid esters. Patent US6054607 A, April 25, 2000.
35. Harada H. Process for the production of cinnamic acid. Patent US4778924 A, 1998.
36. Su F, Chen WC. Synthesis of Cinnamic Acid from Benzaldehyde and Acetone. J Chin. Chem. Soc. 1956; 3:87-91.
37. Chiriac C, Tanasa F, Onciu M. A Novel Approach in Cinnamic Acid Synthesis: Direct Synthesis of Cinnamic Acids from Aromatic Aldehydes and Aliphatic Carboxylic Acids in the Presence of Boron Tribromide. Molecules. 2005; 10(2):481-487.
38. Considine WJ. Triphenyl carbethoxymethyl phosphonium Chloride Dihydrate. J Org. Chem. 1962; 27:647-649.
39. Spasova MG, Ivanova GI, Weber H, Ranz A, Lankmayr E, Milkova TS. Microwave-accelerated synthesis of amides of substituted cinnamic acids by Wittig reaction. Bulg. Chem. Commun. 2006; 38:27-30.
40. Vargas-Tah A, Martínez LM, Hernández-Chávez G, Rocha M, Martínez A, Bolívar F *et al*. Production of cinnamic and p-hydroxycinnamic acid from sugar mixtures with engineered Escherichia coli. Microb. Cell Fact. 2015; 14:6.
41. Akram M. Mini-review on glycolysis and cancer. J Cancer Educ. 2013; 28(3):454-457.
42. Lee GS, Widjaja A, Ju YH. Enzymatic synthesis of cinnamic acid derivatives. Biotechnol Lett. 2006; 28(8):581-585.
43. Bukowski J, Szul R, Kański M. Kańska. Enzymatic Synthesis of [3-14C] Cinnamic Acid. J Radioanal. Nucl. Chem. 2000; 243(3):635-638.
44. Adisakwattana S, Moonsan P, Yibchok-Anun S. Insulin-releasing properties of a series of cinnamic acid derivatives in vitro and *in vivo.* J Agric. Food Chem. 2008; 56:7838-7844.
45. Kiliç I, Yeşiloğlu Y. Spectroscopic studies on the antioxidant activity of p-coumaric acid. Spectrochim. Acta. A. Mol. Biomol. Spectrosc. 2013; 115:719-724.
46. Thiago CGM, Ângelo QM, Daniel R, Antonio A, Marcelo HL. Antioxidant Activity of Caffeic Acid against Iron-Induced Free Radical Generation-A Chemical Approach; Plos One. 2015; 10(11):e0142402.
47. Chen C. Sinapic Acid and Its Derivatives as Medicine in Oxidative Stress-Induced Diseases and Aging. Oxid. Med. Cell Longev. 2016; 2016:1-10.
48. Kikuzaki H, Hisamoto M, Hirose K, Akiyama K, Taniguchi H. Antioxidant Properties of Ferulic Acid and Its Related Compounds. J Agric. Food Chem. 2002; 50(7):2161-2168.
49. Narasimhan B, Belsare D, Pharande D, Mourya V, Dhake A. Esters, amides and substituted derivatives of cinnamic acid: synthesis, antimicrobial activity and QSAR investigations. Eur. J Med. Chem. 2004; 39:827-834.
50. Zhu J, Zhu H, Kobamoto N, Yasuda M, Tawata S. Fungitoxic and phytotoxic activities of cinnamic acid esters and amides. J Pesticide Sci. 2000; 25:263-266.
51. Parle A, Arora T. Docking, synthesis and NDM-1 inhibitory activity of some novel cinnamic acid derivatives. Pharma Innovation. 2017; 6(6):119-123.
52. Perez-Alvarez V, Bobadilla RA, Muriel P. Structure–hepatoprotective activity relationship of 3,4-dihydroxycinnamic acid (caffeic acid) derivatives. J. Appl. Toxicol. 2001; 21:527-531.
53. Lee S, Han JM, Kim H, Kim E, Jeong TS, Lee WS *et al*. Synthesis of cinnamic acid derivatives and their inhibitory effects on LDL-oxidation, acyl-CoA: cholesterol acyltransferase-1 and -2 activity, and decrease of HDL-particle size Bioorganic Med. Chem. Let. 2004; 14:4677-4681.
54. Park EJ, Lee S, Jeong TS, Bok SH, Lee MK, Park YB *et al*. Effect of 3,4-di(OH)-cinnamate synthetic derivative on plasma and hepatic cholesterol level and antioxidant enzyme activities in high cholesterol-fed rats. J Bio chem. Mol. Toxicol. 2004; 18:279-287.
55. Takeda Y, Tanigawa N, Sunghwa F, Ninomiya M, Hagiwara M, Matsushita K *et al*. Morroniside cinnamic acid conjugate as an anti-inflammatory agent. Bioorganic Med. Chem. Let. 2010; 20:4855-4857.
56. Sun W, He Q, Luo Y. Synthesis and properties of cinnamic acid series organic UV ray absorbents–interleaved layered double hydroxides. Mater. Let. 2007; 61:1881-1884.
57. Batista-Lima FJ, Cosker F, de Brito TS, Magalhaes PJC. Antispasmodic and myorelaxant effects of the flavoring agent methyl cinnamate in gut: Potential inhibition of tyrosine kinase. Eur. J Pharmacol. 2014; 740:192-199.
58. Rui W, Ruijiang W, Bao Y. Extraction of essential oils from five cinnamon leaves and identification of their volatile compound compositions. Innov. Food Sci. Emerg. Technol. 2009; 10:289-292.
59. Adisakwattana S, Roenqsamran P, Hsu WH, Yibchok-anun S. Mechanisms of antihyperglycemic effect of p-methoxycinnamic acid in normal and streptozotocin-induced diabetic rats. Life Sci. 2005; 78:406-412.
60. De P, Belvala FB, Bacquéa CV, Baltas M. Cinnamic Acid Derivatives in Tuberculosis, Malaria and Cardiovascular Diseases -A Review. Curr. Org. Chem. 2012; 16:747-768.
61. McCormack PL, Wagstaff AJ. Lacidipine: a review of its use in the management of hypertension. Drugs. 2003; 63(21):2327-2356.
62. Fife R, Maclaurin JC, Wright JH. Rescinnamine In Treatment Of Hypertension In Hospital Clinic And In General Practice; Br. Med. J. 1960; 2:1848-1850.
63. Hood K, Shah A. Belinostat for Relapsed or Refractory Peripheral T-Cell Lymphoma. J Adv. Pract. Oncol. 2016; 7(2):209-218.
64. Greig SL. Panobinostat: A Review in Relapsed or Refractory Multiple Myeloma. Target Oncol. 2016; 11(1):107-114.
65. Shiota N, Kovanen PT, Eklund KK, Shibata N, Shimoura K, Niibayashi T *et al*. The anti-allergic compound tranilast attenuates inflammation and inhibits bone destruction in collagen-induced arthritis in mice. Br. J Pharmacol. 2010; 159(3):626-635.
66. Darakhshan S, Pour AB. Tranilast: a review of its therapeutic applications. Pharmacol. Res. 2015; 91:15-28.
67. Alagar RM, Chaudhary S, Banji D, Rao KNV, Selva, KD. Analytical method development and validation for simultaneous estimation of carbidopa, levodopa and entacapone in its bulk and tablet dosage form by UPLC. Int. Res. J Pharm. 2013; 4(11):53-56.
68. Banker T, Kale P, Peepliwal A. Method development and validation for simultaneous estimation of oxybenzone

octinoxate and avobenzone in sunscreen lotion by reversed phase high performance liquid chromatography. Int. J Biomed. Adv. Res. 2011; 2:92-102.
69. Marjason JK. An Efficacy, Safety and Pharmacokinetics Study of Beloranib (ZGN-440 for Injectable Suspension) in Obese Subjects. https://clinicaltrials.gov/ct2/show/NCT01666691 (accessed July 14, 2016).
70. Kim D. An Efficacy and Safety Study of Beloranib in Obese Subjects With Type 2 Diabetes Mellitus. https://clinicaltrials.gov/ct2/show/NCT02324491 (accessed January 6, 2016).
71. Kim D. Double-Blind, Placebo Controlled, Phase 3 Trial of ZGN-440 (Beloranib) in Obese Subjects with Prader-Willi Syndrome (best PWS). https://clinicaltrials.gov/ct2/show/NCT02179151 (accessed January 26, 2017).
72. An Efficacy, Safety, and Pharmacokinetics Study of Beloranib in Obese Subjects with Hypothalamic Injury. https://clinicaltrials.gov/ct2/show/NCT02063295 (accessed July 18, 2016).
73. Kim DD, Krishnarajah J, Lillioja S, de Looze F, Marjason J, Proietto J *et al*. Efficacy and safety of beloranib for weight loss in obese adults: a randomized controlled trial. Diabetes Obes. Metab. 2015; 17:566-572.
74. Safety and Efficacy Study of Lusutrombopag for Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS 2). https://clinicaltrials.gov/ct2/show/NCT02389621 (accessed May 2, 2017).
75. Sakamaki A, Watanabe T, Abe S, Kamimura K, Tsuchiya A, Takamura M *et al*. Lusutrombopag increases hematocytes in a compensated liver cirrhosis patient. Clin. J Gastroenterol. 2017; 10(3):261-264.
76. Li W. Tolerance and Pharmacokinetic Study of Chlorogenic Acid to Advanced Glioblastoma. https://clinicaltrials.gov/ct2/show/NCT02728349 (accessed October 14, 2016).
77. Shen L. Tolerance and Pharmacokinetic Study of Chlorogenic Acid to Advanced Cancer. https://clinicaltrials.gov/ct2/show/NCT02245204 (accessed October 20, 2015).
78. Martínez E. Effect of Chlorogenic Acid on Patients with Impaired Glucose Tolerance. https://clinicaltrials.gov/ct2/show/NCT02621060 (accessed March 29, 2016).
79. Shinohara Y. Edaravone-Sodium Ozagrel Comparative Post-Marketing Study on Acute Ischemic Stroke. https://clinicaltrials.gov/ct2/show/NCT00200356 (accessed January 15, 2013).
80. Zhang J, Yang J, Chang X, Zhang C, Zhou H, Liu M. Ozagrel for acute ischemic stroke: A meta-analysis of data from randomized controlled trials. Neurol. Res. 2012; 34:346-353.
81. Clinical Trial of PM00104 (Zalypsis®) in Patients With Advanced and/or Metastatic Endometrial or Cervical Cancer Previously Treated With One Line of Systemic Chemotherapy. https://clinicaltrials.gov/ct2/show/NCT00900562 (accessed January 15, 2013).
82. Navid F, Chawla SP, Blay JY, Ferrari S, Santoro A, Casali P *et al*. Study of Zalypsis® (PM00104) in Patients With Unresectable Locally Advanced and/or Metastatic Ewing Family of Tumors (EFT) Progressing After at Least One Prior Line of Chemotherapy. https://clinicaltrials.gov/ct2/show/NCT01222767 (accessed June 5, 2012).
83. Lewis N. A Phase I Study of Zalypsis (PM00104) in Subjects With Advanced Malignant Solid Tumors or Lymphoma. https://clinicaltrials.gov/ct2/show/NCT00359294 (accessed April 21, 2009).
84. Petek BJ, Jones RL. PM00104 [Zalypsis®]: A Marine Derived Alkylating Agent. Molecules. 2014; 19(8):12328-12335.
85. Zhao G, Zhang GY, Zhu Y. Mildronate for Acute Ischemic Stroke. https://clinicaltrials.gov/ct2/show/NCT01831011 (accessed April 12, 2013).
86. Zheng PU, Xiao-rong W, Jing GAN, Chen QI. Effect of cinepazide maleate preconditioning on rat models of cerebral ischemia. J. Shanghai Jiaotong Univ. 2013; 08.
87. A Study of GDC-0810 Single Agent or in Combination With Palbociclib and/or a Luteinizing Hormone-releasing Hormone (LHRH) Agonist in Women With Locally Advanced or Metastatic Estrogen Receptor Positive Breast Cancer. https://clinicaltrials.gov/ct2/show/NCT01823835 (accessed November 17, 2017).
88. Joseph JD, Darimont B, Zhou W, Arrazate A, Young A, Ingalla E *et al*. The selective estrogen receptor downregulator GDC-0810 is efficacious in diverse models of ER+ breast cancer. eLife. 2016; 5:e15828.
89. Search of: Pracinostat – List Results - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/results?cond=&term=Pracinostat&cntry1=&state1=&Search=Search.
90. Novotny-Diermayr V, Hart S, Goh KC, Cheong A, Ong LC, Hentze H, *et al*. The oral HDAC inhibitor pracinostat (SB939) is efficacious and synergistic with the JAK2 inhibitor pacritinib (SB1518) in preclinical models of AML. Blood Cancer J. 2012; 2:e69.
91. Jiang Z. Validity and Security of Reh-acteoside Therapy for Patients of IgA Nephropathy. https://clinicaltrials.gov/ct2/show/NCT02662283 (accessed February 2, 2016).
92. Effect of ACT-451840 against Early Plasmodium Falciparum Blood Stage Infection in Healthy Subjects. https://clinicaltrials.gov/ct2/show/NCT02223871 (accessed January 12, 2017).
93. Dr. Boss C, Dr. Aissaoui H, Amaral N, Bauer A, Bazire S, Dr. Binkert C *et al*. Back Cover: Discovery and Characterization of ACT-451840: an Antimalarial Drug with a Novel Mechanism of Action. Chem med chem. 2016; 11:2096.
94. Abraham Geffen MD. An Evaluation of Orabilex (Bunamiodyl), a New Medium for Cholecystography. Radiology, 1959; 72:839.
95. Fracchia GN. European Medicine Research: Perspective in Pharmacology and Pharmacovigilance (Online). IOS press, Amsterdam Oxford, Washington, Tokyo, 1994, 376.
96. Lui H, Qi F, Hao Y, Dong S, Meng Q. Photoisomerism of a vasodilator cinepazide maleate. Med. Chem. Res. 2011; 20:1154-1157.
97. Manier JW, Chang WWL, Kirchner JP, Beltaos E. Hepatotoxicity associated with Ticrynafen - A uricosuric diuretic. Am. J Gastroenterol. 1982; 77(6):401-404.
98. Neuberger J, Williams R. Immune mechanisms in tienilic acid associated hepatotoxicity. Gut. 1989; 30(4):515-519.