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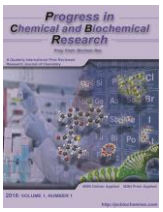

Synthetic methods and pharmacological potential of some cinnamic acid analogues particularly against convulsions

Mohammad Asif[1*], Mohd Imran[2]

[1]Department of Pharmacy, GRD(PG) Institute of Management & Technology, Dehradun, 248009, (Uttarakhand), India

[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Rafha 91911, PO Box 840, Saudi Arabia

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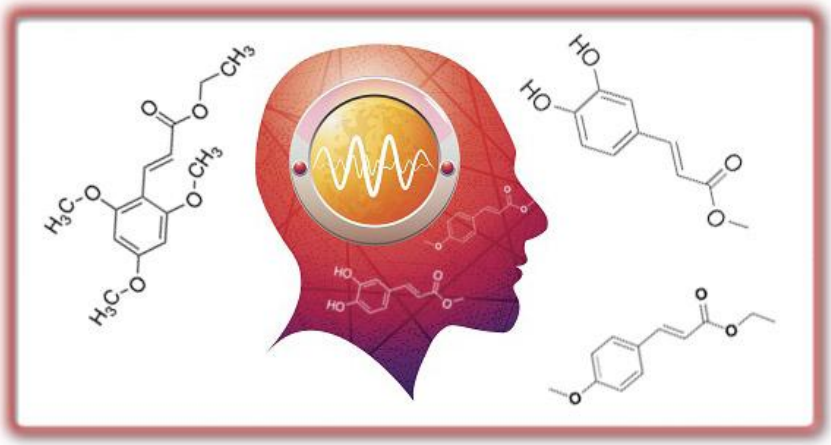
GRAPHICAL ABSTRACT



KEYWORDS

Cinnamic acid
Caffeic acid
Biological activities
Pharmaceutical products
Depression

ABSTRACT

Cinnamic acid analogues are naturally occurring compounds found in fruits, vegetables, and flowers. It is used as dietary phenolic compounds and play vital role in the preparation of essential intermediate compounds which are crucial for the making of various pharmaceutical components. Cinnamic acid and its analogues are studied for its various types of biological activities including antioxidant, anticancer, hepatoprotective, anticonvulsant, anxiolytic, antidepressants, insect repellents, antidiabetic and anticholesterolemic etc. Various substitutions on cinnamic acid moiety lead to different types of pharmacological activities such as m-hydroxy or p-methoxy group on cinnamic acid is significantly vital functional groups as an efficient insulin releasing compound while 3,4-Dihydroxycinnamic acid or caffeic acid showed hepatoprotective activity. Cinnamic acid analogues are showed variety of biological activities along with their milder to moderate adverse effects which are become obstacle for the clinical use of cinnamic acid analogues. So for the suitable use of cinnamic acid analogues, it is yet to investigate to decrease or terminate its adverse effects.

* Corresponding author: Asif, Mohammad
Tel number: +91-9897088910 E-mail: aasif321@gmail.com
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1. Introduction

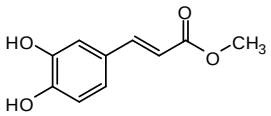
In biological chemistry, cinnamic acid is a main intermediate in shikimate and phenyl-propanoid pathways. Shikimic acid is a precursor of numerous alkaloids, aromatic amino acid dervatives, and indole derivatives. It is present in free form or in the form of esters (ethyl, cinnamyl, benzyl), in different essential oils, resins, balsams, cinnamon oil, Peru balsum and Tolu balsum etc. Cinnamic acid analogues are very essential intermediates in the biosynthetic pathway of the majority of the aromatic natural compounds and are widely distributed in the plants and possess extensive range of pharmacological activities [1].

In addition, cinnamic acids play vital role in the synthesis of other significant compounds such as cinnamic acid analogues can be converted into vastly essential compounds including styrenes and stilbenes through decarboxylation reaction. Cinnamic acid derivatives are known to exhibit a variety of pharmacological activities, like antimalarial [2], antifungal [3], antitubercular [4], anticancer [5, 6], muscle relaxant [7], local anesthetic [8] or tyrosinase inhibitor [9].

Moreover, anticonvulsant activity was also reported [10-12]. Interestingly, it was noticed that only *trans*-isomers of cinnamic acid showed antiepileptic activity while *cis*-isomers on the contrary caused marked stimulation of the central nervous system (CNS) manifested by tremors and convulsions [10]. The cinnamic acids are also used as precursor for the synthesis of various commercially important cinnamic esters.

Cinnamic esters are obtained from various plants and used in perfumery, cosmetic industries and pharmaceuticals like methyl caffeate (**1**) is found in plants *Gaillardin pulchella, Gochnatra rusbyana, Netopterygium incisum* and as 4-glycoside in the fruits of *Linum usitatissimum*. The methyl caffeate posses antitumour effect against Sarcoma 180 as well as antimicrobial effect [13].

Methoxy substituted cinnamate such as ethyl 3,4,5-trimethoxycinnamate (**2**) is present in *Piper longum* and acts as an essential role in controlling inflammatory diseases [14]. Long chain cinnamic ester like methoxy substituted octylcinnamates (**2**) are used in sunscreen agents and ideally suitable for cosmetic applications since they are non irritating to skin and provide lubricity to prevent drying effect of wind [15].



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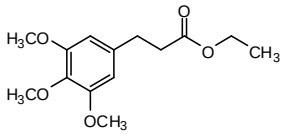

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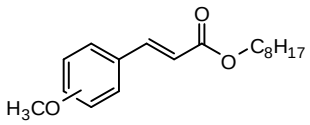


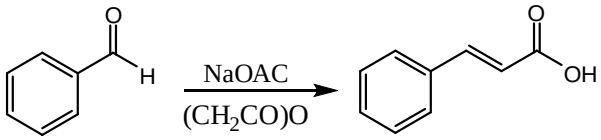
(3)

Fig. 1. Methyl caffeate (1), Ethyl-3,4,5-trimethoxycinnamate (2) Octylmethoxycinnamate (3)

2. General methods for the synthesis of cinnamic acid and its analogues are of following

2.1 Perkin reaction

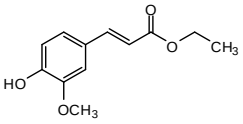
Cinnamic acid is easily formed by Perkin synthesis using benzaldehyde in acetic anhydride and anhydrous sodium acetate. This reaction is the most common method for the formation of the cinnamic acid (**4**) and its analogues but the main drawback of this reaction is aldehydes in the presence of base lead to development of unwanted side products formation.



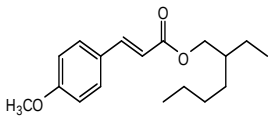
(**4**)

Fig 2. Cinnamic acid is formed by Perkin synthesis using benzaldehyde in acetic anhydride and anhydrous sodium acetate.

2.2 Enzymatic method: Synthesis of two derivatives by using enzymatic method by using Novozym 435 as a catalyst. These two derivatives of cinnamic acid are ethyl ferulate (**5**) from ferulic acid (4-hydroxy-3-methoxy cinnamic acid) and ethanol, and octylmethoxycinnamate (**6**) from *p*-methoxycinnamic acid and 2-ethyl hexanol. This methods is valuable than others methods reported as there is highest conversion of reactant to product take place and the enzyme can be reused time and again without any important loss of activity. The loss of enzyme activity is due to the use of ethanol which ultimate distort the water layer around the enzyme which is necessary for its activity [16].



(**5**)



(**6**)

Fig 3. Synthesis of two derivatives by using enzymatic method, Ethyl ferulate (Antioxidant) (**5**) and Octyl methoxycinnamate (sunscreen agent) (**6**)

2.3 Microwave irradiation methods (Knoevenagel condensation)

Being an intermediate in the synthesis of different organic compounds like segontin, cinnarizine etc. Various methods have been reported for the preparation of cinnamic acid and its analogues. Microwave irradiation of aryl aldehydes and malonic acid with polyphosphate ester as the mediator catalyst in solvent free condition produces cinnamic acid and its analogues [17, 18]. This method is appropriate for the synthesis of cinnamic acid which overcomes the disadvantage of Perkin reaction. Long reaction period is the main disadvantage of this method.

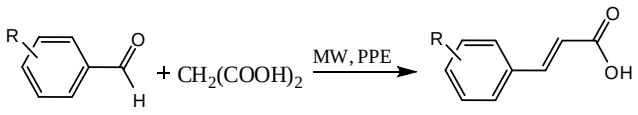


Fig 4. Microwave irradiation of aryl aldehydes and malonic acid with polyphosphate ester as the mediator catalyst in solvent free condition produces cinnamic acid and its analogues, R = 4-Br, 3,4(OCH_3)$_2$, 4-OH, 4-NO_2, 2,5(OCH_3)$_2$, OCH_3, 4-CH_3, 3-Cl, H.

Aromatic aldehydes or ketones and malonic acid in the presence of tetra butylammonium bromide and K_2CO_3 in microwave irradiation produce cinnamic acids [18].

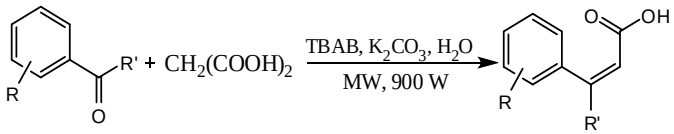


Fig 5. Producing cinnamic acids by Aromatic aldehydes or ketones and malonic acid, R/R'=H/H, 4-O CH_3/H, 4-NO_2/H, 3-Br/H, 2,4-Cl/H, 4-OH/H, H/ CH_3, 4-Br/ CH_3, 4-NO_2/ CH_3

2.4 Phosphorous oxychloride method

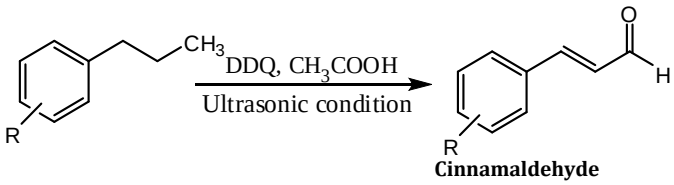
A series of cinnamic acid derivatives were most frequently synthesized by using Perkin reaction. In the presence of electron-donor substituent, the yield of the target product markedly decreases; in such systems the Perkin reaction is not employed for preparative purposes. For the electron donating groups, Knoevenagel and Debner modification reactions lead to the good yields of the final product but the main drawback is that reaction needs long duration of time. Phosphorus oxychloride (POC) act as acid catalyst, which activate both reaction components, since interaction of the aldehydes component with POC may produce the active carbocation [19].

2.5 Industrial preparations of cinnamic acid derivatives

There are numerous methods for the preparation of cinnamic acid analogues, but industrially it is prepared from 1,1,1,3- tatrachloro-3-*p*-phenylpropane by using CCl_4 as a solvent, which may be destroy the ozonosphere and is harmful to the human body. So this is the main drawback of this method.

2.6 Under ultrasonication method

Cinnamaldehyde having trans selectivity was formed from arylpropene under one pot two step synthesis by using DDQ (2,3-Dichloro-5,6-dicyno-1,4-benzoquinone), few drops of acetic acid and under ultrasonic condition [20].



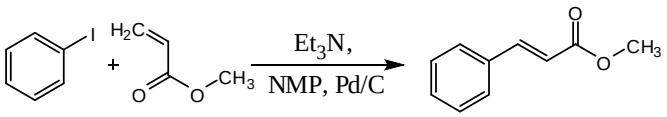
Cinnamaldehyde

Fig 6. Cinnamaldehyde having trans selectivity was formed from arylpropene under one pot two step synthesis by using 2,3-Dichloro-5,6-dicyno-1,4-benzoquinone

2.7 By using Heck coupling reaction

2.7.1 Using palladium on charcoal as a catalyst

Ambulgekar and co-worker synthesized the methyl ester of cinnamic acid rom iodobenzene and methyl acrylate in NMP (N-methyl pyrolidine) as a solvent and Pd/C as a catalyst under ultrasonic condition [21].



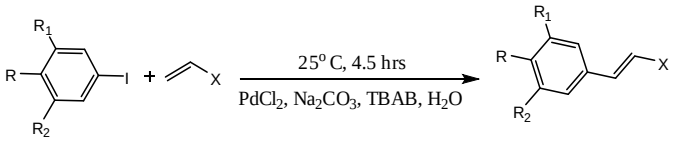
Iodobenzene Methyl acrylate **Methyl ester of cinnamic acid**

Fig 7. Using palladium on charcoal as a catalyst

2.7.2 Using palladium chloride as a catalyst

Cinnamic acid esters was prepared (when X= $COOCH_3$) from different aryl halides by using $PdCl_2$ as a catalyst under ultrasonic condition [22]. The role of TBAB (tetra butyl ammonium bromide) as phase transfer catalyst while Na_2CO_3 as a base. Commercial this reaction is very useful reaction as it was carried out under room

temperature condition and ultrasonic condition using water as a solvent.



Yield = 43-93 %

Fig 8. Using palladium chloride as a catalyst, R=H, O CH_3, Cl, Br, NHCO CH_3, or NO_2; R_1= I, CHO, H; R_2= I or H; X = CO_2 CH_3, COOH, CN or C_6H_5

2.7.3 Using Diatomite-Supported Pd Nanoparticles

Solid supported palladium, gold, nickel etc. play a very crucial role in the C-C bond formation reactions. Diatomite-supported palladium nanoparticles has been used for the synthesis of CADs. Aryl halides reacted with methyl acrylate to form various cinnamic acid derivatives using NMP (*N*-Methyl pyrolidine) as a solvent and triethylamine as a base produces good yield [23].

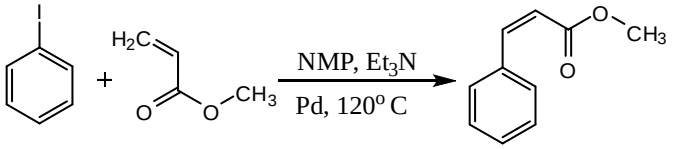


Fig 9. Using Diatomite-Supported Pd Nanoparticles

2.8 Claisen–Schmidt Condensations

A variety of (*E*)-cinnamic acid derivatives are prepared in high yields through the Claisen-Schmidt condensation in the presence of sodium metal and a catalytic amount of methanol with toluene employed as the co-solvent.

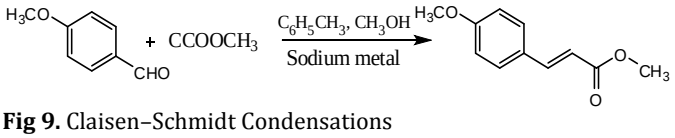


Fig 9. Claisen–Schmidt Condensations

Table 1. Various methods of synthesis of Cinnamic acid and their derivatives along with drawbacks of each method.

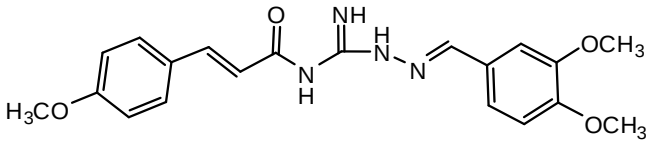
S.No.	Name of the reaction	Reactant involved	Disadvantages
1	Enzymatic method	Ferulic acid (4-hydroxy 3-methoxy cinnamic acid) and ethanol using Novozym 435 as a catalyst	Ethanol is responsible for the major loss of catalytic activity of enzyme
2	Perkin Reaction	Benzaldehyde in acetic anhydride and anhydrous sodium acetate	Not suitable for electron donor substituent as it leads to low yield.
3	Knoevenagel condensation	Aryl aldehydes and malonic acid with polyphosphate ester	Long time of reaction time and considerable amount of solvents are required
4	Phosphorous oxychloride method	Similar as used in Perkin and Knoevenagel condensation reaction	Low yield obtained except –OCH_3
5	Industrial Preparations	1,1,1,3-tatrachloro-3-p-phenyl propane and carbon tetrachloride	CCl_4 causes ozone layer depletion
6	Claisen–Schmidt Condensations	Aryl aldehydes in the presence of sodium metal and a catalytic amount of methanol with toluene	Problem of handling of sodium metal

3. Biological activities of cinnamic acid derivatives

The cinnamon acid analogues are extremely versatile and have featured in various drugs. The wide range of pharmacological profile shown by cinnamic acid derivatives can be classified into the following categories. Such as anti-TB, antidiabetic, antioxidant, antimicrobial, as a fragrance material, hepatoprotective, CNS depressant, anticholesterolemic, antifungal and fungitoxic, antihyperglycemic, antimalerial, antiviral, anxiolytic, cytotoxic, anti-inflammatory and UV rays absorbent.

3.1 Antitubercular activity

There are many drugs which are used against the *Mycobectrium tuberclosis*, but the main disadvantages of these drugs are that they develop resistance more abruptly. Cerulenin is an inhibitor of fatty acid and trans-cinnamic acid, which was recently shown to augment the activity of various antibiotic drugs against *M. avium* [24]. Cerulenin is a known inhibitor of fatty acid synthetase[25, 26] and has been reported to inhibit the biosynthesis of both unsaturated and saturated fatty acids as well as that of total phospholipids in *M. smegmatis*. Trans-cinnamic acid is a bacteriostatic even at concentrations as high as 200 µg/ml, whereas cerulenin was bacteriostatic until 50 µg/ml. Ethambutol resulted in synergistic activity in 12/30 drug combinations, as compared to 15/36 for cerulenin and 10/18 for trans-cinnamic acid while clofazimine, did not show any synergistic activity with ethambutol or cerulenin. Some phenylacrylamide derivatives incorporating cinnamic acids and guanylhydrazones by using microwave assisted synthesis and were evaluated using resazurin microtitre plate assay (REMA) against *M. tuberculosis* H37Rv. (2*E*)-*N*-((-2-(3,4-dimethoxybenzylidene) hydrazinyl) (imino) methyl)-3-(4-methoxyphenyl) acryl amide (**7**) showed MIC of 6.49 µM along with good safety profile of >50-fold in VERO cell line [27]. Cinnamic acid derivatives are not used as anti TB agent but they can only assist the action of various anti TB drugs. Clinically they are not used due to its toxicity problems.



(7)

Fig 10. (2*E*)-*N*-((-2-(3,4-dimethoxybenzylidene) hydrazinyl) (imino) methyl)-3-(4-methoxyphenyl) acryl amide

3.2 Antidiabetic activity

Insulin is a primary hormone that regulates glucose metabolism either by stimulating peripheral glucose uptake or by suppressing hepatic glucose production [28]. The *m*-hydroxy or *p*-methoxy residues of cinnamic acid were significantly important substituent as an effective insulin releasing agent in both in-vivo and in-vitro. The introduction of *p*-hydroxy and *m*-methoxy substituted groups in cinnamic acid (ferulic acid) structure displayed the most potent insulin secreting agent among those of cinnamic acid derivatives. Sulfonylurea based drugs are generally used against diabetes, but the main disadvantage of these are drugs are that they cause hypoglycemia and failure of insulin secretion. Ferulic acid is the most effective insulin-secreting agent among the cinnamic acid derivatives. *m- Hydroxy* or *p*-methoxy residues on cinnamic acid also shows good insulin releasing activity when Glibenclamide was used as a positive control in the experiment [29].

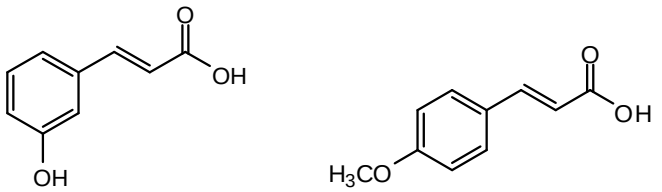


Fig 11. Chemical stracuture of m-hydroxy cinnamic acid and p-methoxy cinnamic acid

3.3 Antioxidant Activity

Cinnamic acid derivatives exhibit high antioxidant activity that is due to the presence of vinyl fragments. This property attracts attention to the study of these compounds as potential drugs for the treatment of pathologies related to the lipid peroxidation in cellular membranes. However, the reactive center (vinyl fragment) is significantly affected by substituent present in various positions of the benzene nucleus [30]. Caffeic acid and ferulic acid and their respective phenyl ethyl ester derivatives were showed antioxidant activity [31]. Derivatives of benzoic acid with the homologous cinnamic acid derivatives by using competition kinetic test and in vitro oxidative modification of human low-density lipoprotein (LDL) and showed the increased antioxidant activity in the following sequence *p*-hydroxy < *p*hydroxymethoxy < dihydroxy < *p*- hydroxydimethoxy. The four derivatives of benzoic acid used were *p*-hydroxybenzoic, protocatechuic, vanillic and syringic acid while cinnamic acid derivatives used were *p*-coumeric acid, caffeic acid, ferulic acid and sinapic acid [32].

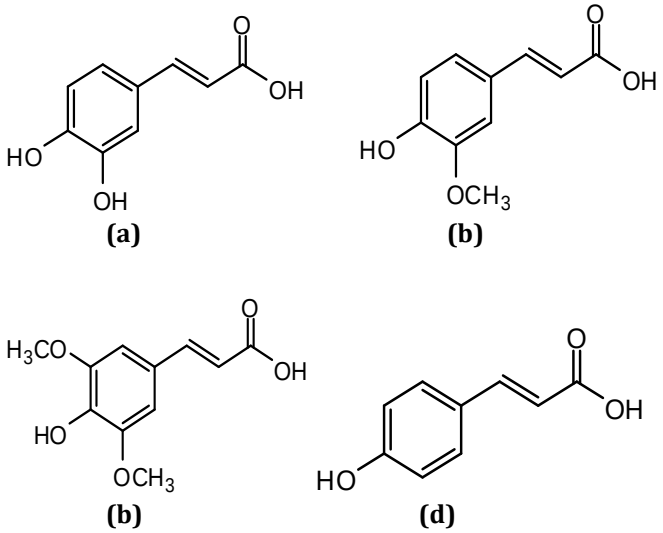


Fig 12. Chemical stracuture of Caffeic acid (a), Ferulic acid (b), Sinapic acid (c), p-coumaric acid (d)

3.4 Antimicrobial activity

Antimicrobial activity of CA derivatives is due to the presence ester and amide groups. The antibacterial activity against *Escherichia coli and Staphylococcus aureus, Bacillus subtilis* (Gram negative and Gram positive respectively) and antifungal activity against *Candida albicans* and *Aspergillus niger*. Isobutyl cinnamate and dibromo cinnamic acid exhibited strong antibacterial activity against Gram positive and Gram negative bacteria and good antifungal properties. Addition of halogens to the side chain caused remarkable increase in growth inhibitory effect of cinnamic acid whereas addition of hydroxy groups to the side chain double bond did not remarkably enhance the antimicrobial activity [33].

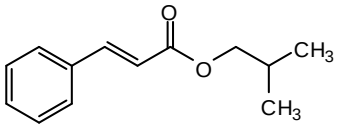


Fig 13. Chemical stracuture of Isobutyl cinnamate

3.5 In fragrance materials: The CA is a fragrance ingredient used in many fragrance compounds. It may be found in fragrances used in shampoos, fine fragrances, decorative cosmetics, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents. Its use worldwide is in the region of 1–10 metric tonnes per annum [34]. Although, cinnamic acid is not considered an important odorant, it serves as a precursor for derivatives such as the esters [35] which have pleasant long-lasting aromas. Methyl cinnamate used widely and is found in flavour and fragrance compositions created for products which include soaps and cosmetics as well as beverages, baked goods, and convenience foods. Reported applications for cinnamic acid and its derivatives also include: preparation of herbicidal compositions; as a raw material in the synthesis of heterocyclic color complexes. One of the most interesting uses for cinnamic acid in recent years has been as a raw material in the preparation of L-phenylalanine the key intermediate for the aspartame [36] (synthetic dipeptide sweetener). More than 95% of the consumption of cinnamaldehyde occurs in flavor applications where a spicy, cinnamon character is required. It is used in a wide range of products including bakery goods, confection, and beverages as well as in toothpastes, mouthwashes, and chewing gum. It is also used effectively in air fresheners. In electroplating processes, cinnamaldehyde is utilized as a brightener. In addition to these applications, it is used as an animal repellent, its use in compositions to attract insects. Cinnamaldehyde has been efficiently isolated in high purity by fractional distillation from cassia and cinnamon bark essential oils. This material has been utilized in several manufacturing protocols for the preparation of natural benzaldehyde through a retro-aldol process. The demand for natural flavors has increased dramatically. This demand has led to a corresponding requirement for a more extensive line of readily available natural aroma chemicals for flavor creation. Cinnamyl alcohol and its esters, especially cinnamyl acetate, are widely employed in perfumery because of their excellent sensory and fixative properties. They are also used in blossom compositions such as jasmine, lilac, lily of the valley, gardenia and hyacinth to impart balsamic and oriental notes to the fragrance. In addition, they are utilized as modifiers in berry, nut, and spice flavor systems. The value of cinnamyl alcohol has also been mentioned in a variety of applications which include the production of photosensitive polymers, the creation of inks for multicolor printing, the formulation of animal repellent compositions, and the development of effective insect attractants [37, 38].

3.6 Hepatoprotective

The 3,4-Dihyhroxycinnamic acid (caffeic acid) is a natural product containing catechol with an α, β-unsaturated carboxylic acid chain that has hepatoprotective properties[38]. Alvarez and coworkers have determined the effects of the various substituents like 4-hydroxy, 3-hydroxy, 3,4-dihydroxy and the double bond moiety on the hepatoprotective activity in which the liver damage was produced by the CCl_4 [39].

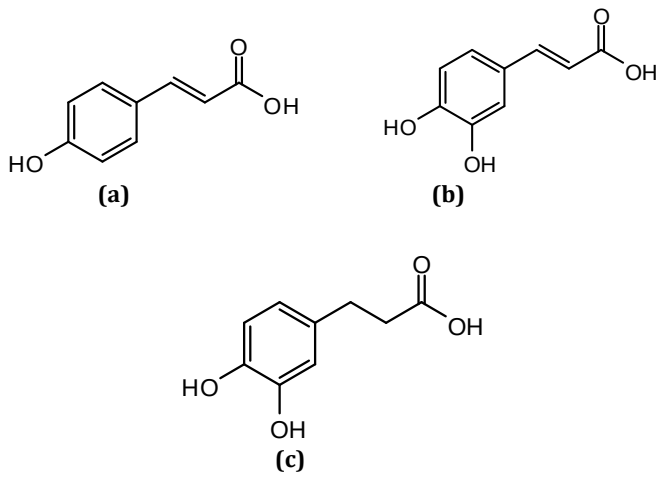


Fig 14. Chemical stracuture of 4-Hydrocinnamic acid (a), 3,4-dihydroxycinnamic acid(b), 3,4-dihyrdroxyhydrocinnamic acid (c)

No significantly difference between these two (3,4-dihydroxycinnamic acid and 3,4-dihyrdroxy hydrocinnamic acid) indicates a-b unsaturated carboxylic acid chain double bond has no effects on hepatoprotective activity. The hepatoprotective activity for 15 cinnamic acid derivatives in the CCl4 induced acute liver damage model (depend upon oxidative stress mechanism). Compounds with a methoxy group at position 3 or 4, or a 3,4-methylenedioxy moiety were the most active ones. They reported that bulkier the group, lesser will be the hepatoprotective activity [40].

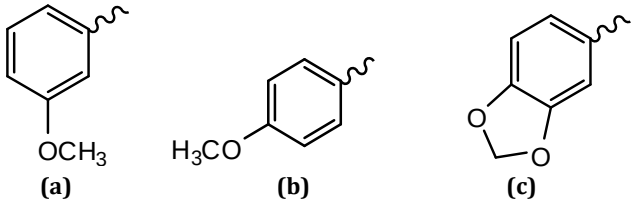


Fig 15. Chemical stracuture of 3-methoxy moiety (a), 4-methoxy moiety (b), 3,4-methylene dioxy moiety (c)

3.7 CNS depressant activity

Halogenated cinnamic acid derivatives showed the highest CNS depressant activity [41]. The effect of ferulic acid on the proliferation neural stem cell, oral administration of ferulic acid also increases the cAMP response element binding protein phosphorylation [42].

3.8 Anticholesterolemic activity

Hypercholesterolemia is considered to be a major cause of the diseases associated with atherosclerosis, and a number of hypercholesterolemic drugs have already been developed to improve the plasma lipid levels in patients. Lipid lowering efficacy (anticholesteremic) of two derivatives of 3, 4-dihydrocinnamate i, e. 3,4-dihydrophenylpropionic amide (L-serine methyl ester) and 3,4-dihydrophenylpropionic amide (L-aspartic acid) has been reported by Kim and co-workers using clofibrate as a positive control.

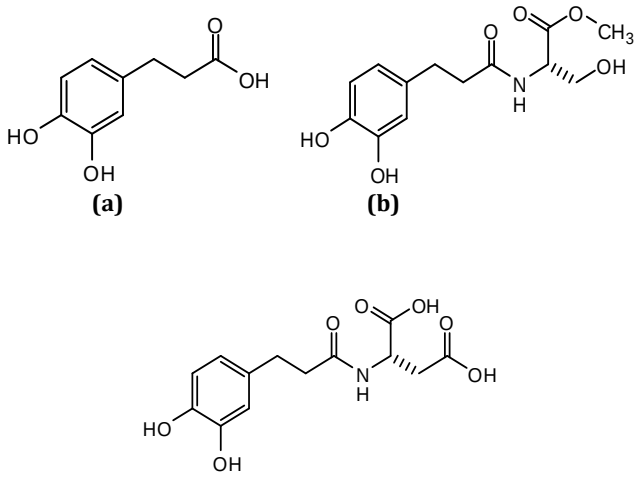


Fig 16. Chemical stracuture of 3,4-di(OH)-hydricinnamate(HC) ((L-serine methyl ester) amide (a), 3,4-di(OH)-phenylpropionic acid (L-aspartic acid) amide) (b), 3,4-di(OH)-phenyl propionic acid (c)

HC and its amide derivatives had lowered atherogenic index and increased the ratio of HDLcholesterol to the total plasma cholesterol in the same fashion as the clofibrate done. Author had also observed that hepatic cholesterol level was lowered in liver [43]. Two other derivatives of cinnamic acid [4-hydroxycinnamic acid (L-phenylalanine methyl ester) amide (**8**) and 3,4-dihydroxyhydrocinammic acid (L-aspartic acid dibenzyl ester) amide (**9**)] inhibit human acyl-CoA: cholesterol acyltransferase-1 and -2. So these two compounds a and b act as useful anti-atherosclerotic agent by inhibiting the cellular cholesterol storage, inhibiting the LDL-oxidation and HDL particle size rearrangement [44]. 3,4-di (OH)-cinnamate i, e. 3,4-Di (OH)-phenylpropionic acid (L-phenyl alanine methyl ester) amide (**10**) is also effective in lowering the plasma lipids and improving the antioxidant enzyme system [45]. Compound Allyl 3-(4-hydroxyphenyl) propanoate **11** and 1-naphthylmethyl 3-(4-hydroxy phenyl)propanoate **12** significantly lowered cholesterol and triglyceride levels in the plasma and liver with a simultaneous increase in the HDL-cholesterol concentration, whereas cinnamic acid only lowered the plasma cholesterol concentration. Cinnamic acid lowered hepatic HMG-CoA reductase activity in high cholesterol fed rats, however, its synthetic derivatives (**11** and **12**) did not affect HMG-CoA reductase activity compared to the control group [46].

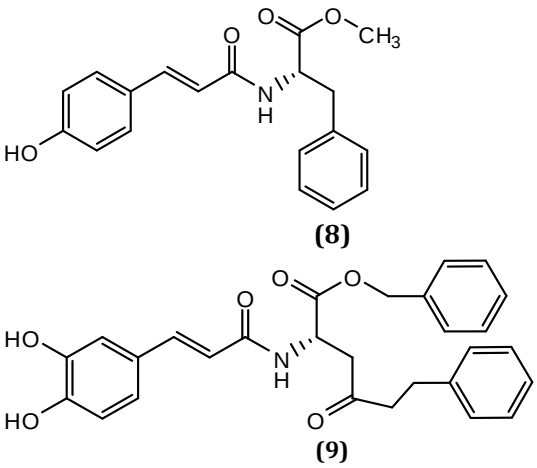


Fig 17. Chemical stracuture of Two other derivatives of cinnamic acid [4-hydroxycinnamic acid (L-phenylalanine methyl ester) amide (**8**) and 3,4-dihydroxyhydrocinammic acid (L-aspartic acid dibenzyl ester) amide (**9**)]

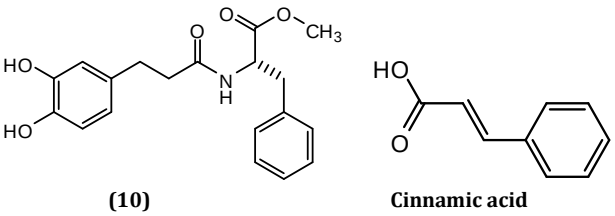


Fig 18. Chemical stracuture of 3,4-di (OH)-cinnamate i, e. 3,4-Di (OH)-phenylpropionic acid (L-phenyl alanine methyl ester) amide (**10**)

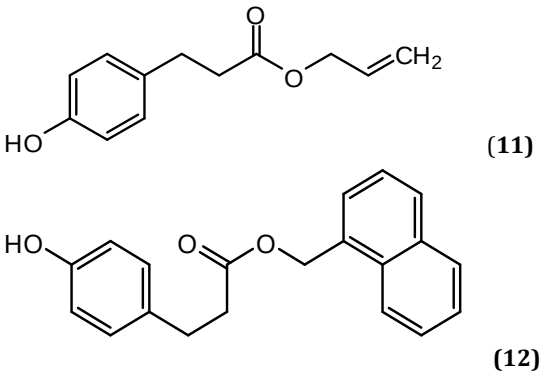


Fig 19. Chemical stracuture of Cinnamic acid synthetic derivatives

3.9 Antifungal activity

(*E*)-3-(4-Methoxy-3-(3-methylbut-2-enyl)phenyl)acrylic acid **13** exhibited highest antifungal activity against *A. niger*, comparable to that of miconazole and a significant antifungal effect against *A. flavus* and *A. terreus*, while caffeic acid was inactive to the antifungal activity [47]. The cinnamic acids were having more antifungal effects than coumaric acids [48]. Compound **14a, 14b** and **14c** showed the 40 % fungitoxic activity at 10 ppm, while Methyl 4-chloro cinnamate **14d** showed the highest activity.against *C. rolfsii.*

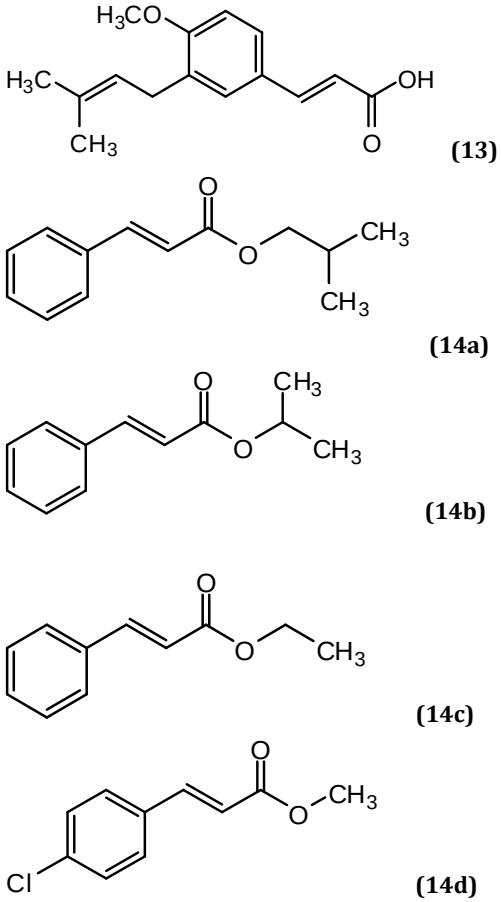


Fig 20. Chemical stracuture of (*E*)-3-(4-Methoxy-3-(3-methylbut-2-enyl)phenyl)acrylic acid (13) and its derivatives **(14)**

While in amide derivatives, 4-isopropylcinnamamide derivatives (**15a-c**) were showed the highest fungi toxic activity (40 % inhibition against *Pythium* sp. and 30 % against *C. rolfsi*) [49]. The N- isopropyl-4-chlorocinnamamide was showed highest fungitoxic activity (66 %).

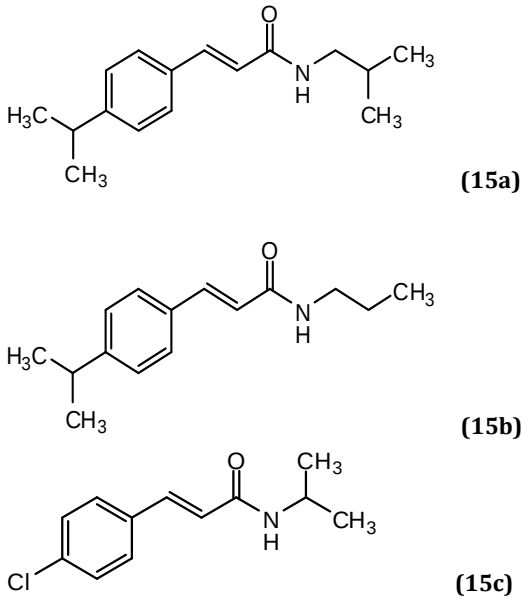


Fig 21. Chemical stracuture of 4-isopropylcinnamamide derivatives

3.10 Antihyperglycemic activity

A new series of thiazolidine-1,4-dione substituted α-phenyl cinnamic acid (**16**) with moderate PPARg agonist activity showing strong oral glucose lowering effects in animal model of type 2 diabetes. The presence of double bond and the geometry of cinnamic acid is a necessary for its PPAR agonistic activity. α-phenyl substituted cinnamic acid derivatives (**17**) possess a weak antihyperglycemic activity while its 2,4-thiazolidinedione analogues and related cinnamic and phenyl propionic acid and esters were having good activity [50]. Antihyperglycemic effects of p-methoxycinnamic acid (p-MCA) have reported [51].

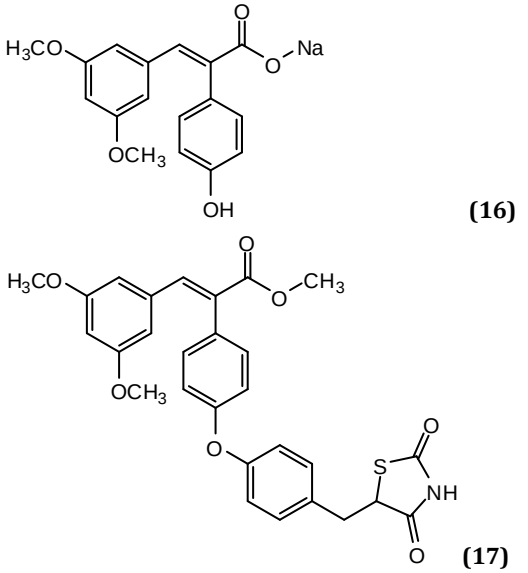


Fig 22. Chemical stracuture of Strong glucose lowering activity (**16**), Weak antihyperglycemic activity (**17**)

3.11 Antimalerial activity

Compound (**18**) has been proved as a novel class of anti-malarial agents. Replacement of the 3-phenylpropionyl moiety of the lead structure by a 4-propoxycinnamic acid residue resulted in a significant improvement in anti-malarial activity [52].

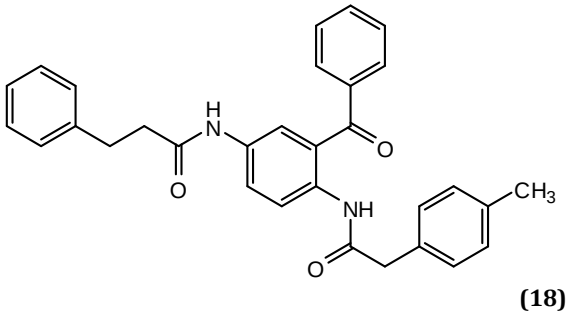


Fig 23. significant improvement in anti-malarial activity

Cinnamic acid derivatives (CADs) inhibit the transport of monocarboxylate across erythrocyte and mitochondrial membranes. They also inhibit parasite growth and that they are equally effective at the young (ring) and the mature (trophozoite) stages of parasite development. The alteration of parasite growth by CADs could be due to inhibition of lactate transport or of mitochondrial respiration. It must be emphasized that since cinnamic acid derivatives are also noxious to host cells, they could not be used as novel antimalarial drugs. They have been used as tools for the investigation of lactate disposal and for the detection of possible new targets for chemotherapeutic onslaught [53].

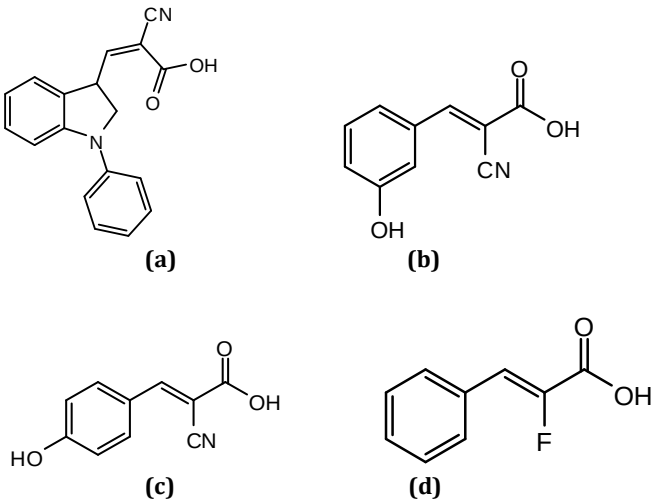


Fig 24. Chemical stracuture of α-Cyno-b-(1-phenylindol-3-yl)acrylicacid(a), α-Cyno-3-hydroxycinnamic acid (b), α -Cyno-4-hydroxycinnamic acid (c) and α –Fluorocinnamic acid (d).

3.12 Antiviral activity

The antiviral for *trans*-cinnamic acid. *Trans*-cinnamic acid did not show virucidal activity but inhibited the viral replication cycle. In addition to this author has also reported the antiviral activity for quercetin and morin against *equid herpesvirus 1* (EHV-1) [54].

3.13 Anxiolytic activity

Sinapic acid shows anti-anxiety action by using elevated plus-maze apparatus (EPM) test and diazepam as a positive control. Anxiolytic like effects of Sinapic acid is mediated via GABAA receptors and potentiating Cl- currents. It is unlikely that it has side-effects that are severe enough to prevent its pharmacological activities alone or in combination with other agents. Moreover, sinapic acid may be viewed as a lead compound for the development of more selective anxiolytic agents [55].

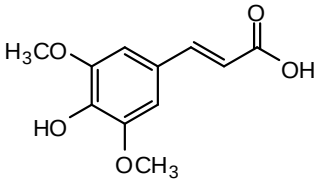


Fig 25. Chemical stracuture of Sinnapic acid

3.14 Cytotoxic activity

Cinnamoyl chloride, when converted into (2-hydroxyethyl)-oxazolinium chlorides (**19a**), *N, N*-bis- (2-chloroethyl) amides (19b) and (2-chloroethyl)-oxazolinium chlorides (**19c**), show the cytotoxic Activity [56].

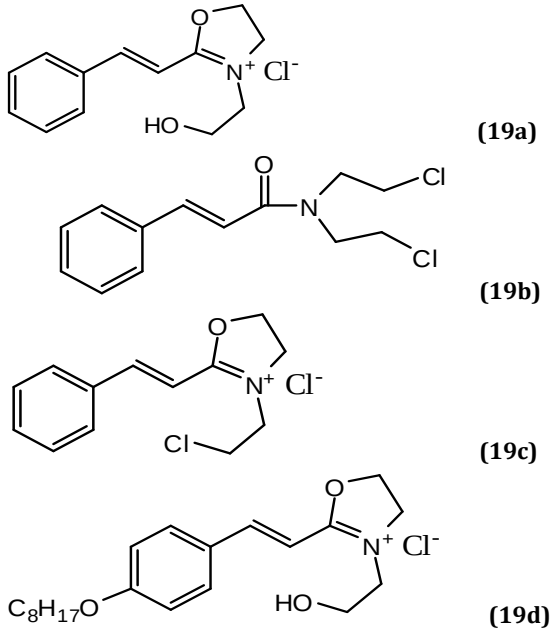


Fig 26. Chemical stracuture of(2-hydroxyethyl)-oxazolinium chlorides (**19a**), *N, N*-bis- (2-chloroethyl) amides (19b) and (2-chloroethyl)-oxazolinium chlorides (**19c**),

Substitution at phenyl ring with electron donating group (methyl, methoxy) is having more potent than substitution with electron withdrawing group (chloro, nitro etc.). Compound with 4-octyloxy-phenyl-substituent(most potent) as it is more lipophilic.

3.15 Anti-inflammatory activity

Morroniside cinnamic acid conjugate showed the anti-inflammatory activity on E-selectin mediated cell–cell adhesion. Compound 7-*O*-Cinnamoylmorroniside **20** exhibited excellent anti-inflammatory activity and was observed to be a potent inhibitor of TNF-α-induced E-selectin expression [57].

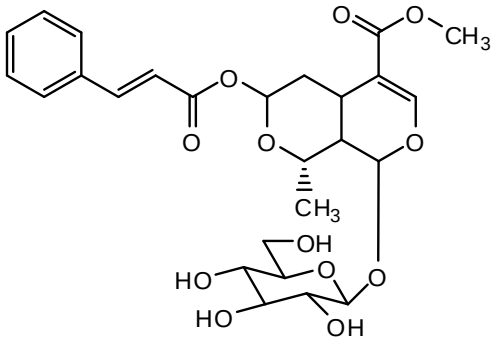


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Fig 27. Chemical stracuture of 7-*O*-Cinnamoylmorroniside

3.16 UV rays absorbent

When cinnamic acid and *p*-methoxycinnamic acid intercalated into ZnAl layered double hydroxide by co-precipitation reaction, then it show UV rays absorption property. In addition to this methoxy substituted octyl - cinnamates is having excellent property of UV absorption that is why these are used in sunscreen composition.

4. Anticonvulsant activities

Epilepsy, with its prevalence of 1% of world human population, belongs to most common disorders of brain function. The main objective of pharmacotherapy of epilepsy is to control the seizures, which could mean either total elimination or at least limitation of their number or severity. Despite the large number of antiepileptic drugs (AEDs) available in the pharmaceutical market, there are still approximately one third of epilepsy patients that are inadequately treated. Moreover, the use of antiepileptic drugs is associated with multiple and often serious adverse effects. Considering those facts, epilepsy constitutes a great challenge both in the field of clinical neurology as well as medicinal chemistry [58-60].

Table 2. Different derivatives of cinnamic acid along with different pharmacological activities and mechanism of action.

No.	Cinnamic acid derivatives	Pharmacological activity	Mechanism of Action
1	*Trans*-cinnamic acid with cerulin	Anti TB, Antiviral	i) inhibits the transfer of mycolic acid ii) inhibited the viral replication cycle
2	*m*- hydroxy cinnamic acid	Antidiabetic	stimulating peripheral glucose uptake
3	*p*-methoxy cinnamic acid	Antidiabetic, hepatoprotective, antihyperglycemic, sunscreen	PPAR agonistic activity, UV absorption property
4	Methyl Cinnmate	As a flavoring agent and used in composition of soap.	-
5	4- Hydroxy cinnamic acid	Hepatoprotective	5-lipoxygenase inhibition activity
6	Ferulic acid	Antioxidant, antidiabetic	inhibit LDL –oxidation, PPAR agonistic activity
7	Methyl-4-Chlorocinnamate	Antifungal activity	Alteration in permeability of fungal cell membrane
8	Cinnamic acid derived oxazol-inium ions	Cytotoxic activity	Act as alkylating agents
9	7-*O*-cinnamoyl Morronniside	Anti-inflammatory activity	inhibitor of TNF-α-induced E-selectin expression
10	Caffeic acid	Antioxidant, Hepatoprotective	--
11	4-isopropyl cinna-mates	Fungitoxic activity	--
12	Cinnamaldehye	Widely used as flavoring agent	-
13	*p*- coumaric acid	Antioxidant	inhibit LDL –oxidation
14	3, 4-dihydroxy cinnamic acid	Hepatoprotective	--
15	3, 4-di(OH)-Hydrocinnamate	Anticholestrolemic Activity	hepatic HMG-CoA reductase activity
16	Sinapic acid	Anxiolytic and antioxidant	GABAA receptors and potentiating Cl– currents
17	Isobutyl cinnamate	Antimicrobial	Interaction (related to hydro-phobic character of molecule) on protein thiol groups.
18	Thiazolidine1,4-di-one substituted a- phenyl cinnamic acids	Antihyperglycemic	PPARg agonist activity

The seizures of epilepsy often caused excessive calcium influx by measuring intracellular calcium concentration of epilepsy patients [61]. Calcium channel blockers are a class of drugs and natural substances which disrupt the conduction of calcium channels. Because they have effects on many excitable cells of the body, such as cardiac muscle, i.e. heart, smooth muscles of blood vessels, or neurons, so calcium channel blockers are mainly used to decrease blood pressure clinical and also used to other diseases, i.e. migraine.

The preliminary evaluation of anticonvulsant activity and neurotoxicity of a series of aminoalkanol (**21-24**) and amino acid (**25-28**) derivatives of *trans*-cinnamic acid as well as aminoalkanol derivatives of α-phenylcinnamic acid (**29-30**). Compound **22** was formerly identified in *Oxytropis pseudoglandulosa* [62] and its anticancer *in vitro* activity was reported [63]. The flunarizine can protect rats and mice in controlling the seizure induced by MES test [64]. The refractory epilepsy using additional flunarizine showed 71% reduction in the number of patients with seizures [65]. The double blind placebo-controlled trial of flunarizine as add-on therapy in refractory childhood epilepsy [66], flunarizine is a difluorinated derivative of cinnarizine. It showed anticonvulsant activity [67, 68]. Recently, the side effects of flunarizine were reported such as depression and parkinsonism [69]. To find better anticonvulsant compound and explain the structure-activity relationship, some flunarizine analogues were prepared and evaluated for their anticonvulsant activity. A series of cinnamic acid derivatives were evaluated for anticonvulsant activity. These compounds were tested by maximal electroshock (MES) and subcutaneous pentetrazole (scPTZ) induced seizures as well as neurotoxicity assessment by rotarod test. Some compounds showed protection in MES at 100 mg/kg b.w. and one at 300 mg/kg b.w. For selected derivatives evaluation in scPTZ test and pilocarpine-induced status in rats were performed. The results are

quite encouraging and further modification of the structures might lead to discovering new potential anticonvulsants [70-72]. All compounds were subjected to Phase 1 of the anticonvulsant activity screening (mice, *i.p*). Additional evaluations were performed for the selected substances. Compound **28** was selected to anticonvulsant evaluation in ScMet test in rats after *per os* administration, **5** and **6** were evaluated in 6-Hz test in mice, **21** and **26** in pilocarpine induced status in rats. The protective activity in MES test was found for compounds **23**, **24**, **26**, **27**, **28**, **29,** and **30**. Six of them showed protection at 100 mg/kg b.w. and one at 300 mg/kg b.w. Considering ScMet evaluation, compounds **24** and **28** showed some activity at the dose of 100 and 300 mg/kg b.w, respectively. While testing compd. **28** myoclonic jerks were observed (0.5h, 300 mg/kg b.w.).

Compounds **23**, **26**, **27** and **28** showed no neurotoxicity at all tested doses while anticonvulsant properties of α-phenylcinnamic acid derivatives (**29** and **30**) were accompanied by neurological toxicity (at the dose of 100 mg/kg b.w, rotarod). Considering results of *p.o*. evaluation in rats, compound **28** exhibited no activity at the dose of 50 mg/kg b.w. in ScMet test. Anticonvulsant evaluation in psychomotor seizure test (6 Hz) after *i.p*. injection in mice did not prove any activity of compound **25** but compound **26** showed partial protection after 0.5 (one of four mice was protected) and 1.0 h (two of four mice were protected). Nevertheless, most promising results were related with pilocarpine-induced status epilepticus. Compound **21** showed protection in five of eight tested rats at the dose of 450 mg/kg b.w. (0 h), while in the option of postponed administration of pilocarpine (0.5 h) three of seven used rats were protected at the dose of 450 mg/kg b.w. Compound **6** did not display any activity [73-78].

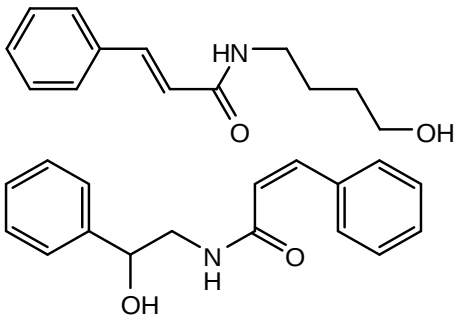

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Fig 27. Preliminary evaluation of anticonvulsant activity and neurotoxicity of a series of aminoalkanol (**21-22**).

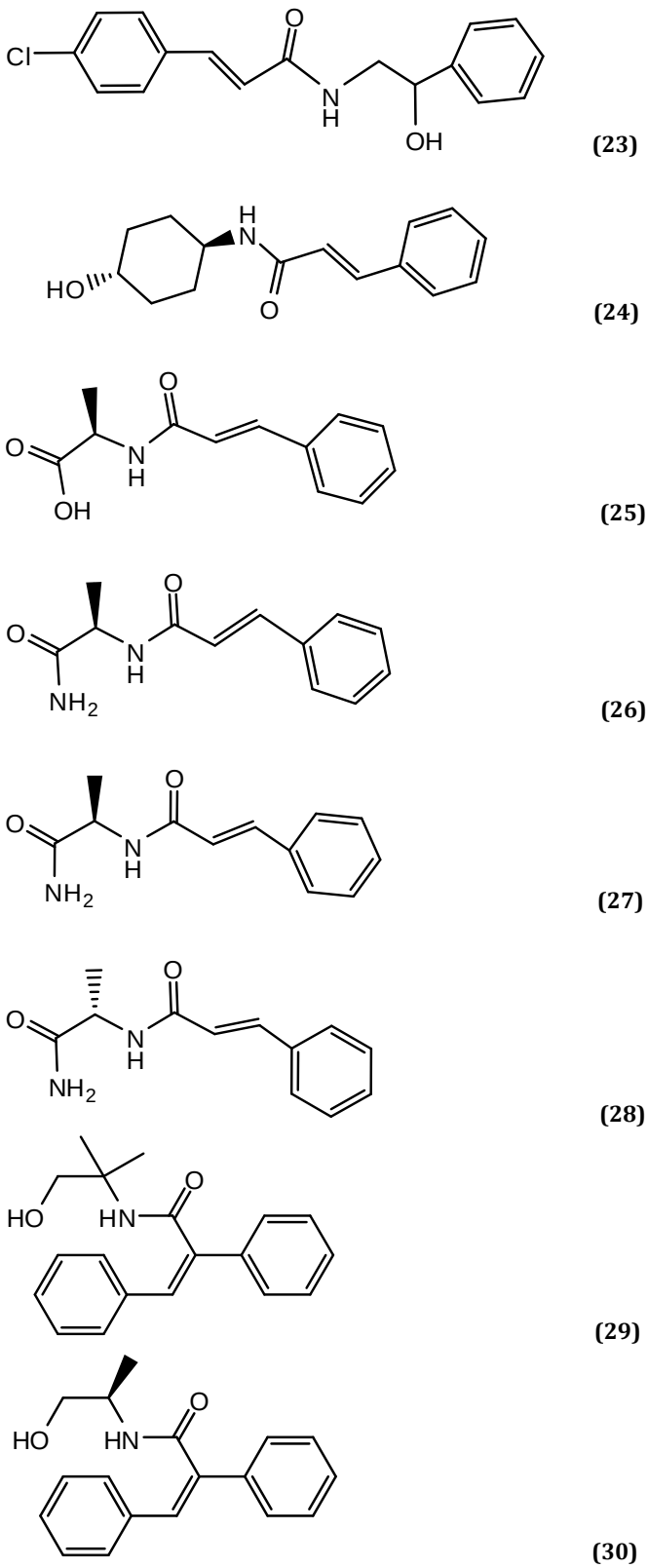

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Fig 28. Preliminary evaluation of anticonvulsant activity and neurotoxicity of a series of aminoalkanol (**23-24**) and amino acid (**25-28**) derivatives of *trans*-cinnamic acid as well as aminoalkanol derivatives of α-phenylcinnamic acid (**29-30**).

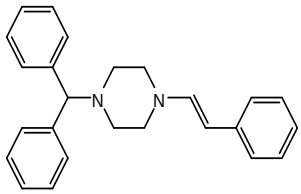
The results indicate beneficial role of chlorine atom observed in case of **23** when compared to **22**. Introduction of chlorine atom caused noticeable increase of activity and at the same time compound **3** remained non-neurotoxic. Some relationship of activity with the stereoisomerism was seen in the tested series. In case of compounds **26**, **27** and **28** only isomer *S*(+) showed some activity in ScMet test while the other two were inactive. The activity in MES test of those three substances was similar. Compound **24** showed some interesting results. It was active after 0.5 h both in MES and ScMet tests but it was also neurotoxic. Interestingly, after 4.0 h the neurotoxicity was reduced and anticonvulsant activity increased. This could suggest some favorable metabolism. It is worth to take into account values of calculated partition coefficient as an important factor influencing the possibility of crossing of blood-brain barrier[70]. In this small series the anticonvulsant activity was observed both for compounds with low (**26**, **28**) as well as high (**23**, **29**, **30**) values of logP so actually the values do not correspond with the anticonvulsant activity of the tested compounds. One conclusion could be made that increased lipophilicity may be partially responsible for neurotoxicity of **29** and **30** (but not in case of compound **23**). Compounds with lower values of partition coefficient: **21**, **25**, **26**, **27** and **28** did not show any neurotoxicity. Compound **1** was active in pilocarpine-induced status test although it did not show any anticonvulsant activity on both MES and ScMet induced seizures.

On the other hand, compound **26** which showed some activity in Phase 1 was not active in pilocarpineinduced status. Lipophilicity is definitely one of the important factors responsible for possible activity in CNS but not the only one. Some other favorable structure elements must be present [70, 79-85]. All compounds **31a-31n** exhibited different anticonvulsant activity, among the fourteen compounds **31a-31n: 31f, 31g, 31k, 31l** and **31n**, five compounds hardly exhibited anticonvulsant activity at the dose of 300mg/kg; **31b-31e**, **31h** and **31j**, six compounds exhibited weak anticonvulsant activity at the dose of 300mg/kg; (E)-1-benzhydryl-4-styrylpiperazine dihydrochloride (**31a**) and (E)-1-((2-methoxyphenyl)(4-methoxyphenyl) methyl)-4-styrylpiperazine dihydrochloride (**31m**), two compounds exhibited median anticonvulsant activity at the dose of 100mg/kg; and only one compound **31i** exhibited more stronger anticonvulsant activity at the dose of 30mg/kg, being flunarizine.

As a result of preliminary screening, compound **31i** was considered for phase II trials. This provides an evaluation of the median effective dose and median toxic dose. The slope of the regression line and the SE of the alope were then calculated. Compound **31i** was the most active compound with ED_{50} of 38.1 mg/kg, TD_{50} of 164.3 mg/kg and PI of 4.3 through i.p. administration, and with ED50 of 56.8 mg/kg, TD_{50} of 456.3 mg/kg and PI of 8.0 through oral administration.

In conclusion, 14 flunarizine analogs were synthesized, but no one exhibited better anticonvulsant activity than flunarizine. The initiation of epileptogenic activity in the neuron is thought to be connected with the phenomenon known as “intrinsic burst firing”, which is activated by an inward Ca^{2+} current. The Ca^{2+} is described as the primary mediator of “excitotoxic” neuronal damage. Both necrotic and apoptotic cell death are associated with Ca^{2+} entry into the cells during status epilepticus. The Ca^{2+} channel blockers depressed epileptic depolarizations of neurons and inhibited the spread of epilepsy [86, 87]. In this study, the results of pharmacology test show that flunarizine and some of its analogs possess anticonvulsant effects thus further confirming the anticonvulsant activity of calcium channel blockers. Those compounds might exhibit the anticonvulsant activity via blocking the Ca^{2+} inward flow [88-90].

All compounds were evaluated for anticonvulsant activities in mice. Among all the flunarizine analogues, no one exhibited better anticonvulsant activity than flunarizine. Flunarizine (**31i**) exhibited anticonvulsant activity with ED_{50} of 38.1 mg/kg, TD50 of 164.3 mg/kg and PI of 4.3 through administration i.p, and with ED_{50} of 56.8 mg/kg, TD50 of 456.3 mg/kg and PI of 8.0 through oral administration [71]. In conclusion, a series of aminoalkanol and amino acid derivatives of cinnamic acids were tested for anticonvulsant activity and they were only moderately active. In case of searching for new antiepileptic drugs rational design is very limited. It is related with the nature of epilepsy which is a heterogeneous disorder with unclear pathophysiology. The strategies of searching for novel antiepileptic drugs include chemical and/or structural modifications of currently available AEDs, screening of many chemical substances in experimental models of epilepsy or creation of new AEDs in association with pathophysiological mechanism of seizures. Our research was based both on those strategies and also on literature data mentioned above. The results of ten tested substances are quite encouraging and further modification of the structures might lead to discovering new potential anticonvulsants [85-90].



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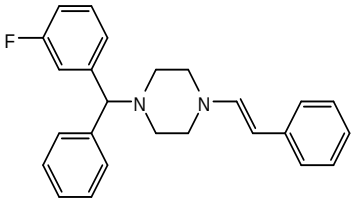

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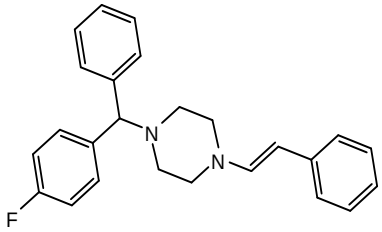

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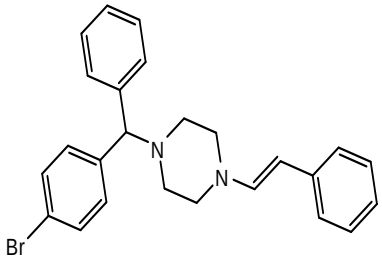

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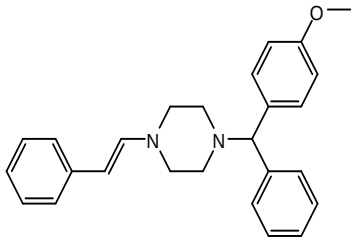

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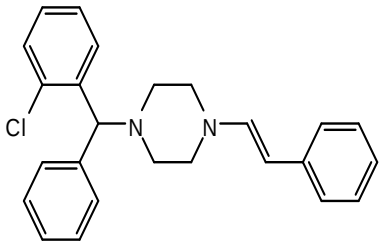
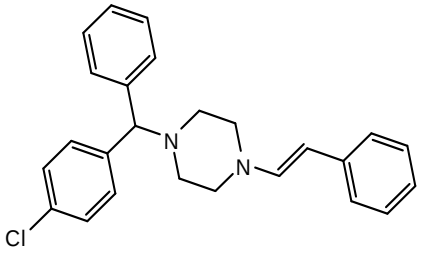
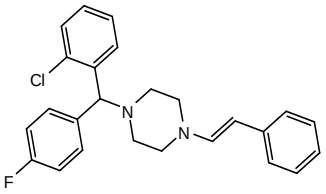


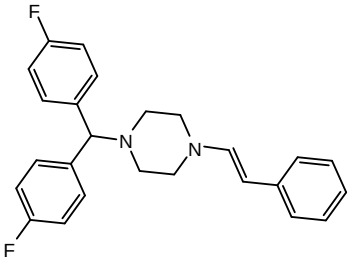
(31f)



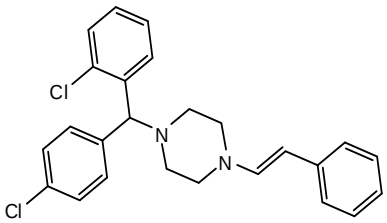
(31g)



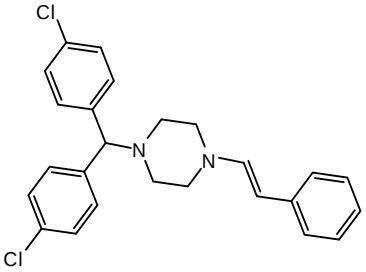
(31h)



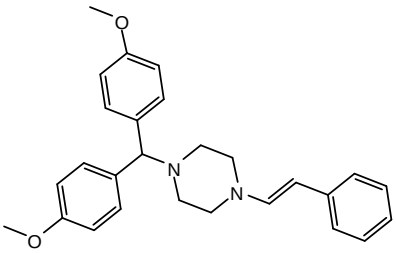
(31i)



(31k)



(31l)



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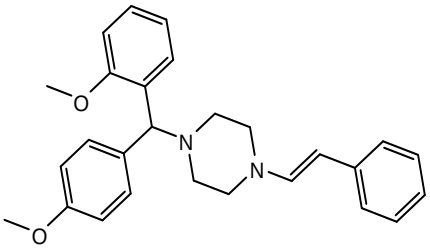

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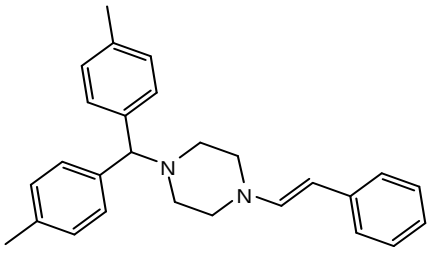

(31o)

Fig 29. Evaluation of anticonvulsant activity and neurotoxicity

4. Conclusion

Although Cinnamic acid derivatives has been prepared by various methods starting from Perkin reaction, but each mehods have its own loopholes like low yield, tedious synthetic procedure, long duration of reaction time etc. It is cleared from the chemistry part of this review that modern Heck reaction using various novel supported catalysts is important for the synthesis of CADs. The various positions of cinnamic acid derivatives are needed to be explored to achieve the clinically used drugs. In this context, tabular depiction of various methods of synthesis and their pharmacological activities of CADs make the information simpler and give the ultimate blend of chemistry with the pharmacological activities.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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