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A Brief Review on History, Synthesis, Structure Activity Relationship, Application, and Mechanism Action of P Methlycinnamic Acid

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ABSTRACT:

The p-methoxycinnamic acid (p-MCA) is one of the most studied phenylpropanoids with high Importance not only in the wide spectrum of therapeutic activities but also its potential application for the. Compound derived from plants exhibits a wide range food industry. This natural of biologically useful properties; therefore, during the last two decade it has been extensively tested for therapeutic and nutraceutical applications This study aimed to synthesize p-methoxy cinnamic acid through the Perkin reaction and to determine its activity as a photo protective and antibacterial agent against The PMCA compound was synthesized by reacting p-methoxy benzaldehyde with acetic anhydride using a sodium acetate catalyst in a sonicator at 500C for 60 minutes. The synthesized was a white precipitate with a % yield of 2.09% and a melting point of 172-1750C. ATR-FTIR identified this compound with several functional groups, C-O, OH carboxylic acid, para-substituted benzene, and C-C. Analysis by GC-MS showed a single peak at a retention time of 11.710 minutes with m/z 178. Characterization of this compound by 1H-NMR spectrometry showed several chemical shifts showing the presence of OH groups of carboxylic acids, C-C groups, aromatic benzene groups, and methoxy. The results of this characterization indicated that the synthesis product.

Keywords: P-methoxycinnamic acid, antibacterial activity, carboxylic acid , Solid state NMR, FT-IR

INTRODUCTION:

p-Methoxy cinnamic acid is a derivative of cinnamic acid, where a methoxy group is attached at the para position [1]. This compound is known to have various biological activities, including antibacterial [2-3], anti-inflammatory, anticancer [4], antioxidant, antidiabetic [5], hepatoprotective, Neuroprotective, and chemo preventive effects [1]. P-Methoxy cinnamic acid can be produced by hydrolyzing ethyl p-methoxycinnamate, which is isolated from natural sources such as aromatic ginger (Kaempferol galanga L.) [2], or through the Perkin reaction. The Perkin reaction is one of the most commonly used methods for synthesizing cinnamic acid derivatives [6].

The Perkin reaction offers the advantage of a simple process and easily accessible starting materials [7]. In the conventional method, p-methoxy cinnamic acid is synthesized by reacting p-methoxy benzaldehyde (an aldehyde) with acetic anhydride, using anhydrous sodium acetate as a catalyst. However, this process typically requires high temperatures, long reaction times, and often results in low yields [7]. Therefore, alternative approaches, such as the use of ultrasonic waves, are being explored.

Ultrasonic waves create a phenomenon called cavitation — the formation, growth, and collapse of bubbles — which can generate extremely high temperatures (around 5000 K) and pressures (up to 1000 atm), leading to the breaking of chemical bonds [8]. In recent years, so nochemical methods have gained popularity because they offer better control compared to traditional methods [9]. acid derivatives possess antibacterial activity against E. coli [3] and can also act as sunscreens [11–13]. Therefore, it is expected that p-methoxy cinnamic acid may show even better biological activities.

This research aims to synthesize p-methoxy cinnamic acid using a Perkin reaction assisted by ultrasonic waves and to evaluate its antioxidant, sunscreen, and antifungal activities against Candida albicans. The goal is to develop synthetic medicinal raw materials that can be used as photoprotective and antifungal agents.

Side effects

P-Methylcinnamic acid is a derivative of cinnamic acid with an ethyl group in the para position.It's mainly used in flavoring, fragrances, and sometimes studied in experimental pharmaceutical research.

- Toxicity and side effects data on p-ethylcinnamic acid specifically are very limited.
- Based on related cinnamic acid derivatives, potential side effects could include:
- Mild skin irritation (if used topically in concentrated forms)
- Allergic reactions (rare, but possible in sensitive individuals)
- Gastrointestinal irritation (if ingested in high amounts)
- **Adverse reactions**

- P-Methylcinnamic acid, a derivative of cinnamic acid with a para-substituted methyl group, has been investigated for various biological activities including antimicrobial and anti-inflammatory effects.

its toxicity and adverse reactions are limited. Some cinnamic acid derivatives have been associated with allergic reactions, skin sensitization, and mucosal irritation, particularly when used in cosmetic or fragrance formulations.

Further toxicological and clinical studies are necessary to comprehensively evaluate its safety profile, especially for therapeutic or cosmetic applications.

HISTORY:

Year/Period	Event / Discovery	Details
Early 20th Century	Initial synthesis and identification	p-Methylcinnamic acid synthesized as a derivative of cinnamic acid.
1930s–1950s	Use in fragrance industry	Found to have a pleasant odor, used in perfumery and as a flavoring agent.
1960s–1980s	Exploration in plant phenylpropanoid pathways	Identified as a secondary metabolite in some plant species.
1990s	Synthetic intermediate	Used in the synthesis of pharmaceuticals, agrochemicals, and polymers.
2000s	Studied for biological activity	Investigated for antimicrobial, antioxidant, and anti-inflammatory effects.
2010s–present	Increased interest in pharmacology	Examined as a potential scaffold for drug development.

Activity	Details / Mechanism
Antimicrobial	Inhibits growth of certain bacteria and fungi; possible membrane disruption.
Antioxidant	Scavenges free radicals; protects against oxidative stress.
Anti-inflammatory	Reduces pro-inflammatory cytokine production in vitro and in vivo.
Anticancer (potential)	Studied for cytotoxicity against cancer cell lines; mechanism under study.
Enzyme inhibition	Inhibits certain enzymes involved in inflammation and metabolism.

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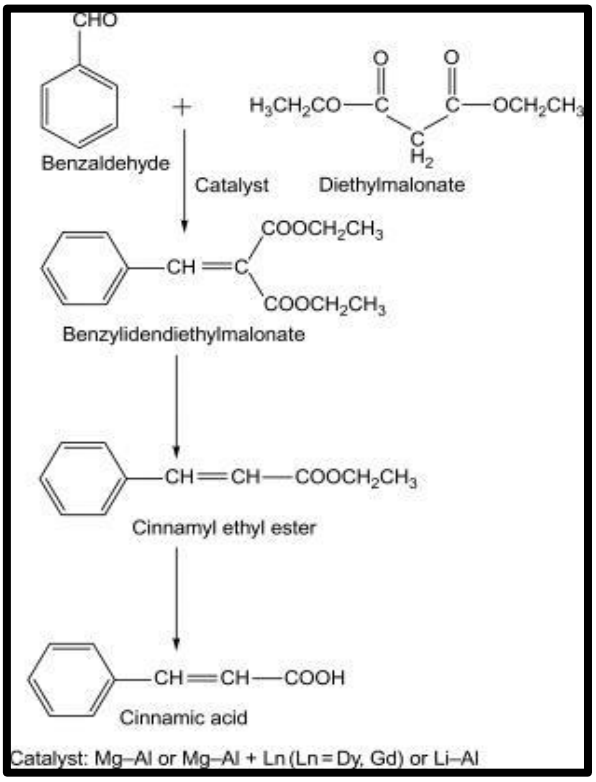
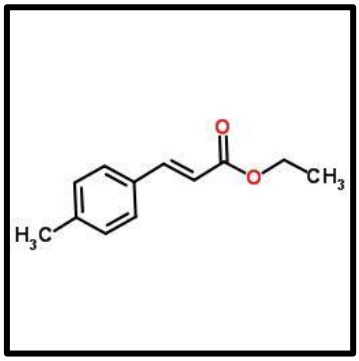
SYNTHESIS:



STRUCTURE:



PHYSICAL AND CHEMICAL PROPERTE

IUPAC Name	3-(4-Methylphenyl)prop-2-enoic acid
Molecular formula	C10H10O2
Molecular mass	162.19 g/mol
Melting point:	173-175°C
Form:	White crystalline form
Pka	≈ 4.5 4.8 (at 25°c)
Color	White to off-white crystalline solid
Water solubility	Sparingly soluble
Vapor pressure	0.000494 (mmHg)
Stability	Light and Air Sensitivity of UV
PH	4.6- 4.8
category	Antimicrobial ,Anti- inflammatory

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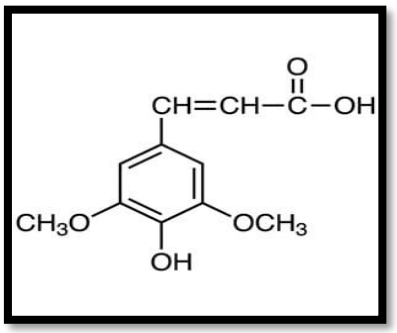
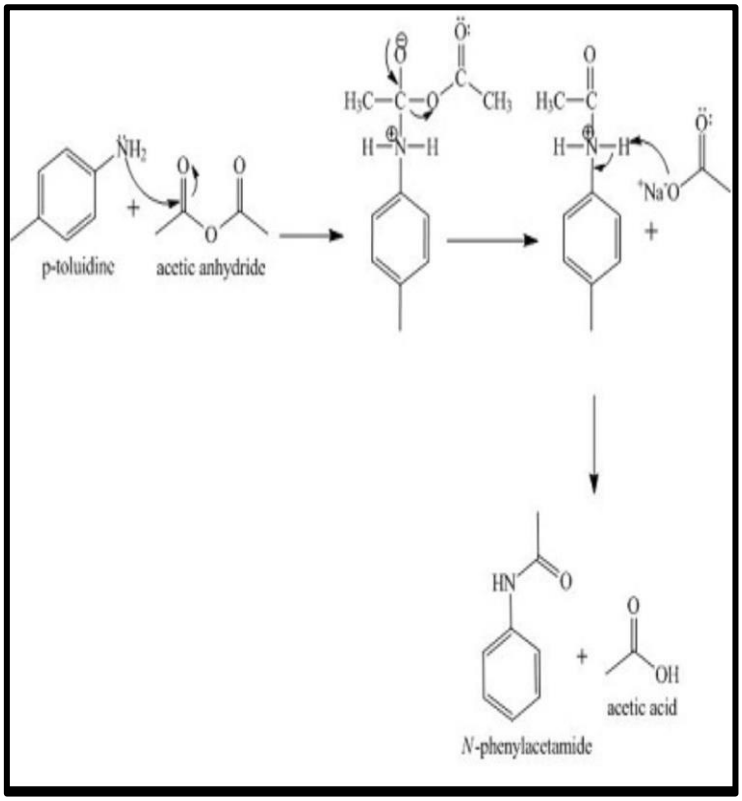
Chemistry:



p methlycinnamic acid

p-Methylcinnamic acid (4-methylcinnamic acid) is a derivative of cinnamic acid characterized by a para-substituted methyl group on the aromatic ring. It possesses the molecular formula C10H10O2 and exists predominantly in the trans € configuration due to the thermodynamic stability conferred by the extended conjugation. The carboxylic acid functional group imparts weak acidity (pKa ~4.4), enabling the compound to participate in acid-base reactions and esterification. The conjugated alkene system is reactive toward hydrogenation and Michael addition, while the aromatic ring, activated by the electron-donating methyl substituent, is susceptible to electrophilic aromatic substitution at the ortho and para positions. Synthetically, p-methylcinnamic acid is commonly prepared via Knoevenagel condensation of p-tolualdehyde with malonic acid under basic conditions. Its solubility profile includes moderate solvents and limite ility in organic aqueous solubility, making it suitable for various organic transformations and formulation studies.

STRUCTURE ACTIVITY RELATIONSHIP



1.Derivative of cinnamic acid with a methyl group at the para (4-position of the phenyl ring.

2. Electronic Effects Para-methyl group is an electron-donating group (+l effect), which increases electron density on the aromatic ring. Enhances interaction with certain enzyme active sites and receptors.

3. Steric Effects Small size of the methyl group provides minimal steric hindrance, preserving the molecule's binding capacity. Does not significantly distort the planar geometry of cinnamic acid.

4.Lipophilicity Methyl substitution increases hydrophobicity, potentially enhancing membrane permeability and bioavailability. Improves passive diffusion through lipid membranes.

5.Antimicrobial Activity Enhanced activity compared unsubstituted cinnamic acid in some microbial assays. Lipophilic nature may disrupt microbial membranes more.

Antioxidant Properties Electron-donating methyl group may stabilize phenyl radicals, enhancing antioxidant potential's Compared to hydroxyl or methoxy Derivatives, methyl group provides moderate antioxidant effect.

7.Anti-inflammatory Activity Shows inhibition Pro-inflammatory mediators in Preliminary studies. Activity influenced by substitution Pattern on aromatic ring.

8. Structure Modifiability The p-methyl group serves as a keySite for further detribalization to Synthesize esters, amides, or hybrid Molecules with improved Pharmacologic profiles.

APPLICATION :

Antibacterial effect:
Several studies have highlighted the antibacterial potential of p-methylcinnamic acid against both Gram-positive and Gram-negative bacteria. The compound is believed to exert its antimicrobial effect through disruption of bacterial cell membrane integrity, inhibition of enzymatic systems, and interference with nucleic acid synthesis. Notably, p-methylcinnamic acid has demonstrated inhibitory activity against Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, with MIC values suggesting moderate to high potency. This makes it a potential candidate for incorporation into antimicrobial formulations, especially as resistance to conventional antibiotics rises.[Baraa G. Alani Et.al. 2024].

Anti- inflammatory:
The anti-inflammatory properties of p-methylcinnamic acid are attributed to its ability to inhibit the production of pro-inflammatory cytokines, such as TNF-α and IL-6, and down regulate COX-2 expression. Mechanistic studies indicate that the compound can modulate NF-κB and MAPK signaling pathways, leading to reduced expression of inflammatory mediators. In vivo models of inflammation, such as carrageenan-induced paw edema in rats, have demonstrated the compound's potential in reducing edema and tissue inflammation, comparable to standard anti-inflammatory agents like indomethacin.[Baraa G. Alani Et.al. 2024].

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CONCLUSION:

The compound p-methoxy cinnamic acid (PMCA) can be synthesized by The Perkin reaction with assisted ultrasonic waves. This method requires a longer time for PMCA synthesis. Simple GIAO calculations allow to rationalize the Splatting's observed for ortho and meta carbons of cinnamic acids in the solid state. In solution, the free rotation about the single bonds linking the phenyl ring to CH-CH-CO, R and X substituents suppresses the splitting averaging the signals. Moreover, the calculations allow an assignment of the spitted signals, thus offering an alternative to a problem of great experimental difficulty since it requires very Given its dual antibacterial and anti-inflammatory properties, p-methylcinnamic acid holds potential as a lead compound in the development of multifunctional therapeutic agents. Further in-depth pharmacokinetic studies and clinical evaluations are warranted to validate its efficacy and safety profiles.

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Conflict of Interest Statement: All authors have nothing else to disclose.