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A brief review on History, Synthesis, Structure activity Relationship, application, and Mechanism action of Pmethlycinnamic acid

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ABSTRACT:

p-Methoxy cinnamic acid (p-MCA) is one of the most extensively studied phenylpropanoids, known not only for its broad spectrum of therapeutic properties but also for its potential applications in the food and pharmaceutical industries. As a naturally derived compound from plants, p-MCA has attracted significant attention over the past two decades due to its wide range of biologically beneficial activities. These include antioxidant, antibacterial, anti-inflammatory, and photoprotective effects, making it a valuable candidate for both therapeutic and nutraceutical development. In the present study, p-MCA was synthesized via the Perkin reaction, a well-established method for producing cinnamic acid derivatives. The synthesis involved the reaction of p-methoxybenzaldehyde with acetic anhydride in the presence of sodium acetate as a catalyst. The reaction was carried out under ultrasonic irradiation at 50°C for 60 minutes. The resulting product was obtained as a white precipitate with a percentage yield of 2.09% and a melting point in the range of 172–175°C.The structural characterization of the synthesized compound confirmed the successful formation of p-MCA. ATR-FTIR analysis revealed the presence of characteristic functional groups, including hydroxyl (OH) of carboxylic acids, C–O bonds, para-substituted aromatic benzene rings, and carbon-carbon double bonds (C=C).

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

INTRODUCTION:

p-Methoxy cinnamic acid is an important derivative of cinnamic acid, characterized by the presence of a methoxy (-OCH_3) group at the para position of the aromatic ring. This subtle structural modification significantly enhances the compound's biological activity, making it a molecule of great interest in the pharmaceutical and cosmeceutical industries. Numerous studies have demonstrated that p-methoxy cinnamic acid exhibits a wide range of pharmacological properties. Among these are antibacterial, anti-inflammatory, antioxidant, antidiabetic, anticancer, hepatoprotective, neuroprotective, and chemo preventive effects. These multifunctional biological activities make it a promising candidate for therapeutic applications, particularly as a photoprotective and antifungal agent.

Traditionally, p-methoxy cinnamic acid is synthesized through the hydrolysis of ethyl p-methoxycinnamate, a compound that can be extracted from natural sources such as aromatic ginger (Kaempferia galanga). However, chemical synthesis remains the preferred approach due to its scalability and reproducibility. One of the most established synthetic methods for producing cinnamic acid derivatives, including p-methoxy cinnamic acid, is the Perkin reaction. The Perkin reaction involves the condensation of an aromatic aldehyde with an acid anhydride in the presence of a base, typically anhydrous sodium acetate. In this case, p-methoxybenzaldehyde is reacted with acetic anhydride under heating conditions, forming the desired α, β-unsaturated carboxylic acid.

Although effective, the conventional Perkin reaction comes with several drawbacks. It often necessitates prolonged heating at high temperatures, which not only consumes significant energy but can also lead to undesirable side reactions and reduced yields. In response to these challenges, researchers have explored innovative approaches to improve the efficiency and sustainability of the reaction. One such method is the use of ultrasonic waves, a technique that has gained popularity in recent years due to its ability to enhance reaction rates and yields under milder conditions.

Ultrasound-assisted synthesis leverages the phenomenon of acoustic cavitation—the formation, growth, and implosive collapse of microbubbles in a liquid medium. This process generates localized hot spots with extreme temperatures (up to 5000 K) and pressures (approximately 1000 atm), creating an environment conducive to bond breaking and chemical transformation.

In addition to synthetic advantages, compounds like p-methoxy cinnamic acid also possess promising applications in the field of dermatology and infectious disease treatment. The molecule has been shown to exhibit antibacterial activity, particularly against Escherichia coli, and it demonstrates effective UV-absorbing properties, making it a potential candidate for use in sunscreen formulations. Its structural features—particularly the conjugated double bond system and electron-donating methoxy group—contribute to both its antioxidant capacity and its photostability, further supporting its application as a photoprotective agent.

Given its multifaceted biological profile, this research aims to synthesize p-methoxy cinnamic acid using an ultrasound-assisted Perkin reaction and subsequently evaluate its antioxidant, antifungal, and sunscreen properties. The goal is to establish a more efficient synthetic pathway that could yield high-purity products suitable for use as medicinal raw materials. These materials could serve as effective agents in photoprotection and antifungal treatments, aligning with current trends in green chemistry and sustainable drug development. The outcome of this study may contribute to the development of new therapeutic strategies that harness the potential of natural product derivatives in modern medicine.

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)

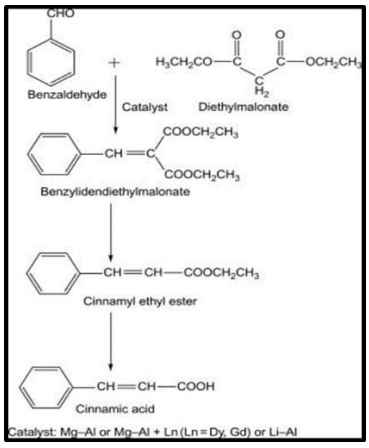
Adverse reactions

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:

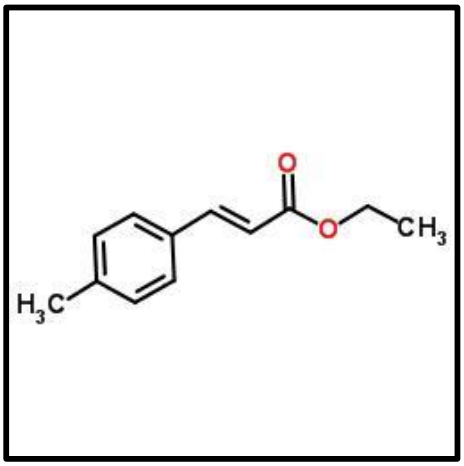
Year/Period	Event / Discovery	Details
Early 20th Century	**Initial synthesis and identification**	**p-Methylcinnamic acid synthesized as a derivative of cinnamic acid.**
1930s–1950s	**Use in fragrance industry**	**Found to have a pleasant odor, used in perfumery and as a flavoring agent.**
1960s–1980s	**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.**



SYNTHESIS:

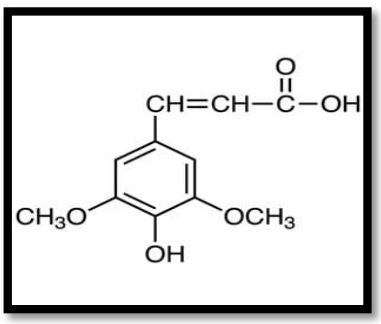
STRUCTURE:



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

Chemistry:

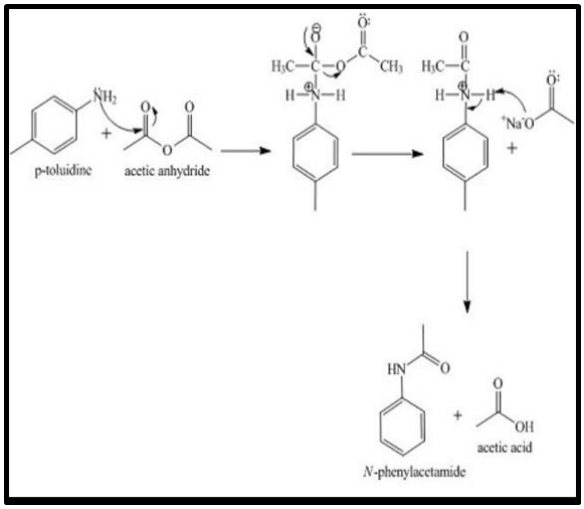


p methlycinnamic acid

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:

Medicinal chemistry aims to develop new antimicrobial agents. Research on p-methylcinnamic acid derivatives is promising, with potential applications in organic chemistry and drug discovery. These compounds can be synthesized efficiently using various methods, including the Perkin reaction with ultrasonic waves. Characterization techniques like FT-IR, 1H-NMR, and mass spectroscopy provide valuable information on their molecular structure and purity. The compound's properties make it a potential lead for developing multifunctional therapeutic agents. Its dual antibacterial and anti-inflammatory properties are particularly noteworthy. Further research is needed to validate its efficacy and safety profiles through in-depth pharmacokinetic studies and clinical evaluations.

Overall, p-methylcinnamic acid derivatives hold promise for advancing medicinal chemistry and drug discovery. Continued research in this area may lead to the development of new therapeutic agents with improved efficacy and safety profiles. With its potential applications and benefits, this area of research is worth exploring further.

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