



Synthesis of Fusidic Acid Derivative: A Novel Divinyl Ether with Potential Pharmaceutical Applications

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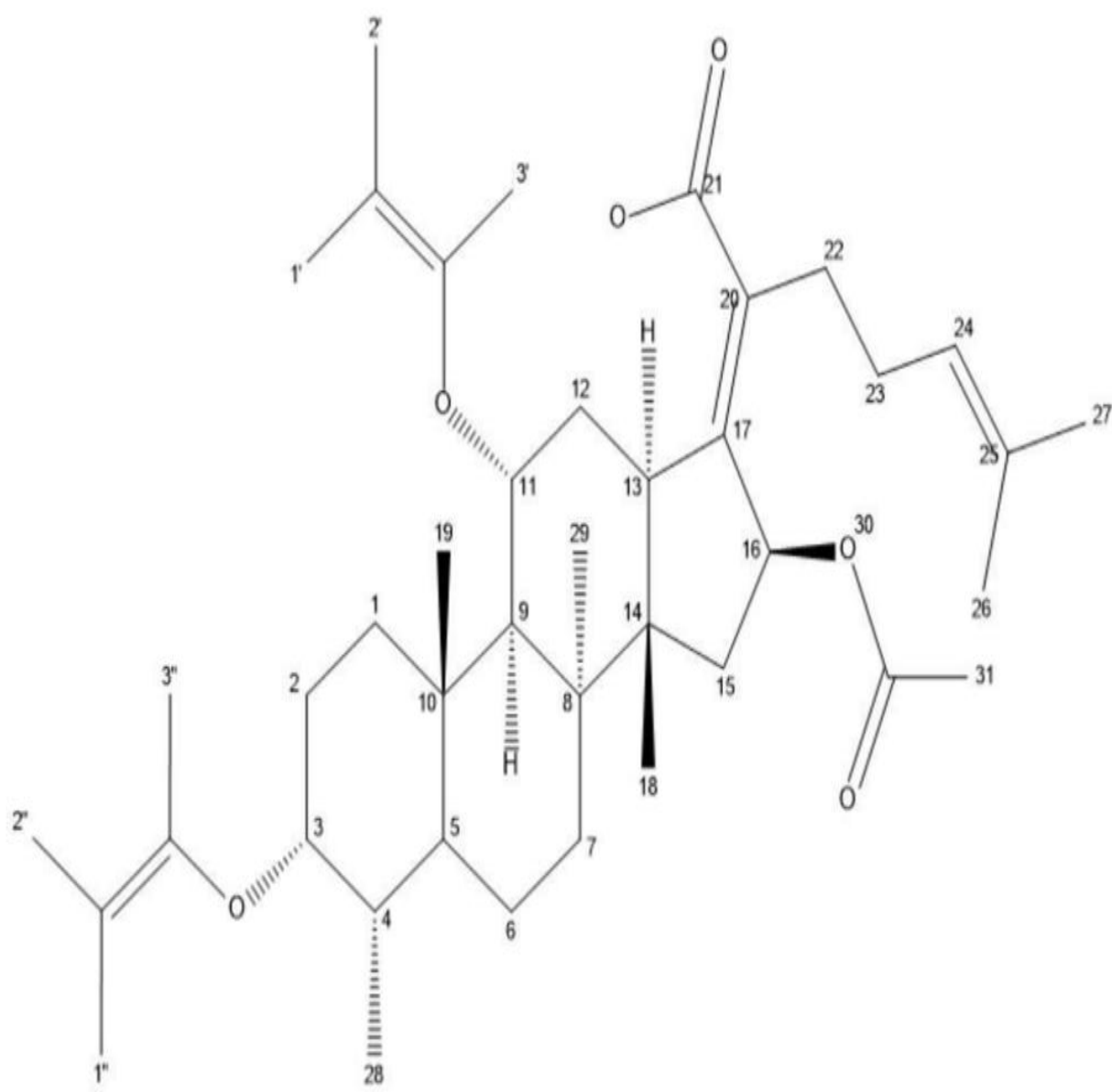
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Abstract

The primary objective of this research was to investigate the pharmaceutical potential of derivatives of triterpenoids, particularly Fusidic Acid (FA). FA, a naturally occurring tetracyclic triterpene from fungi like *Fusidium coccineum* and plants like *Corchorus aestuans*, exhibits broad pharmacological activities. This study focuses on synthesizing a novel Divinyl Ether derivative of FA. Characterization was performed using IR and ¹H-NMR spectroscopy. Antibacterial and antifungal activities were assessed, revealing insights into its potential applications.

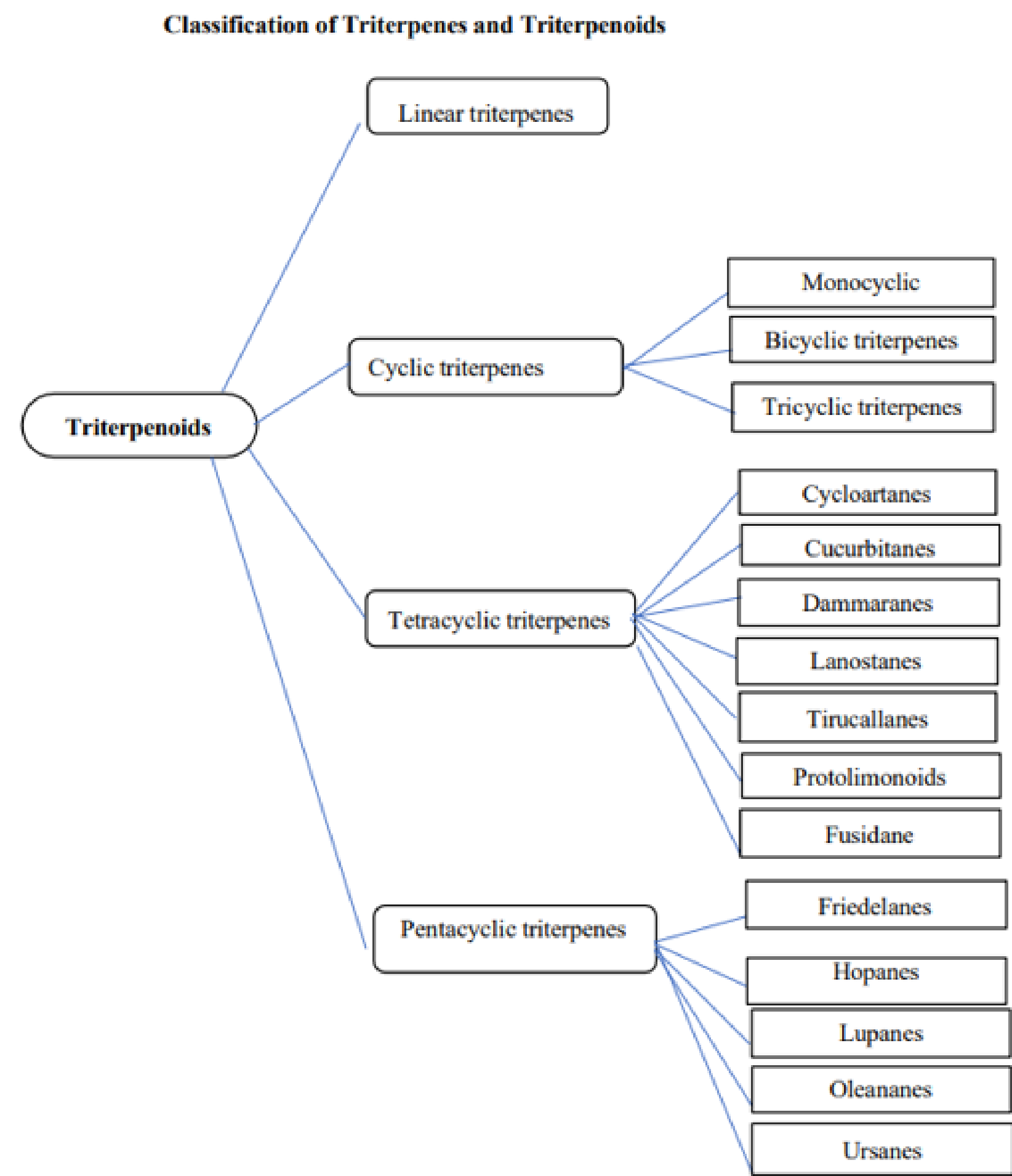
Key Outcomes: Successful synthesis of FA Divinyl Ether (C₄₁H₆₄O₆, MW: 652.94); Confirmed by spectral data; Potential for enhanced bioactivity.



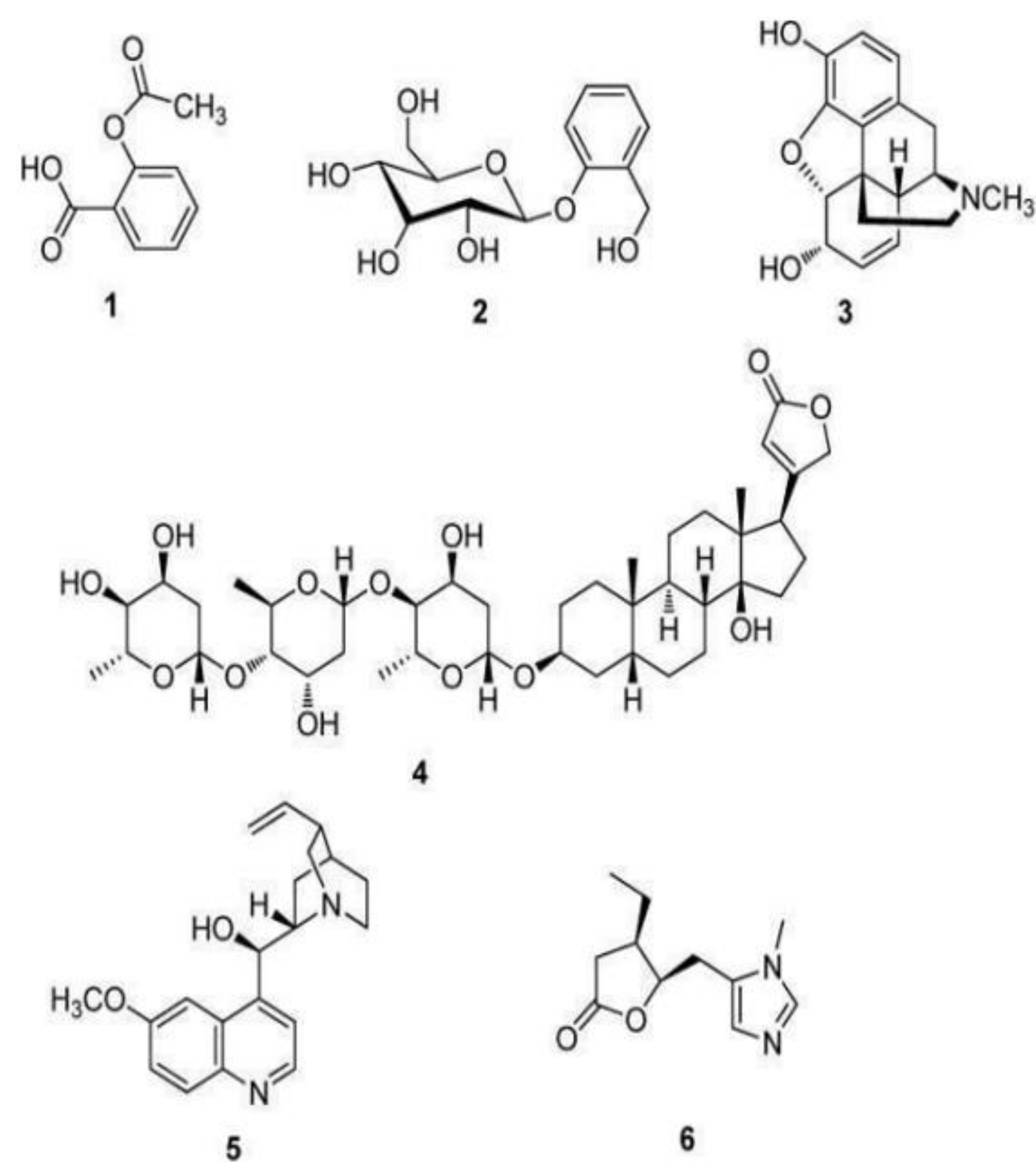
Structure of Fusidic Acid Divinyl Ether

Introduction/Background

- Natural Products & Triterpenoids:** Derived from plants/fungi (e.g., aspirin from willow bark, penicillin from fungi). Terpenoids (e.g., hemiterpenes to polyterpenes) have antimicrobial properties.
- Fusidic Acid (FA):** Tetracyclic fusidane triterpenoid (C₃₁H₄₈O₆); isolated in 1960 from *Fusidium coccineum*. Unique trans-syn-trans conformation; inhibits bacterial protein synthesis via EF-G binding.
- Structural Features:** Double bonds, carboxylic acid at side chain, acetate at C-16; OH groups at C-3 & C-11 modifiable.
- Significance:** Combats antibiotic resistance (e.g., MRSA); broad activities: antibacterial, anti-inflammatory, antimalarial, antiviral.
- Motivation:** >2M annual infections from resistant bacteria (CDC data); need for FA derivatives to enhance efficacy.



Classification of triterpenes and triterpenoids[1].



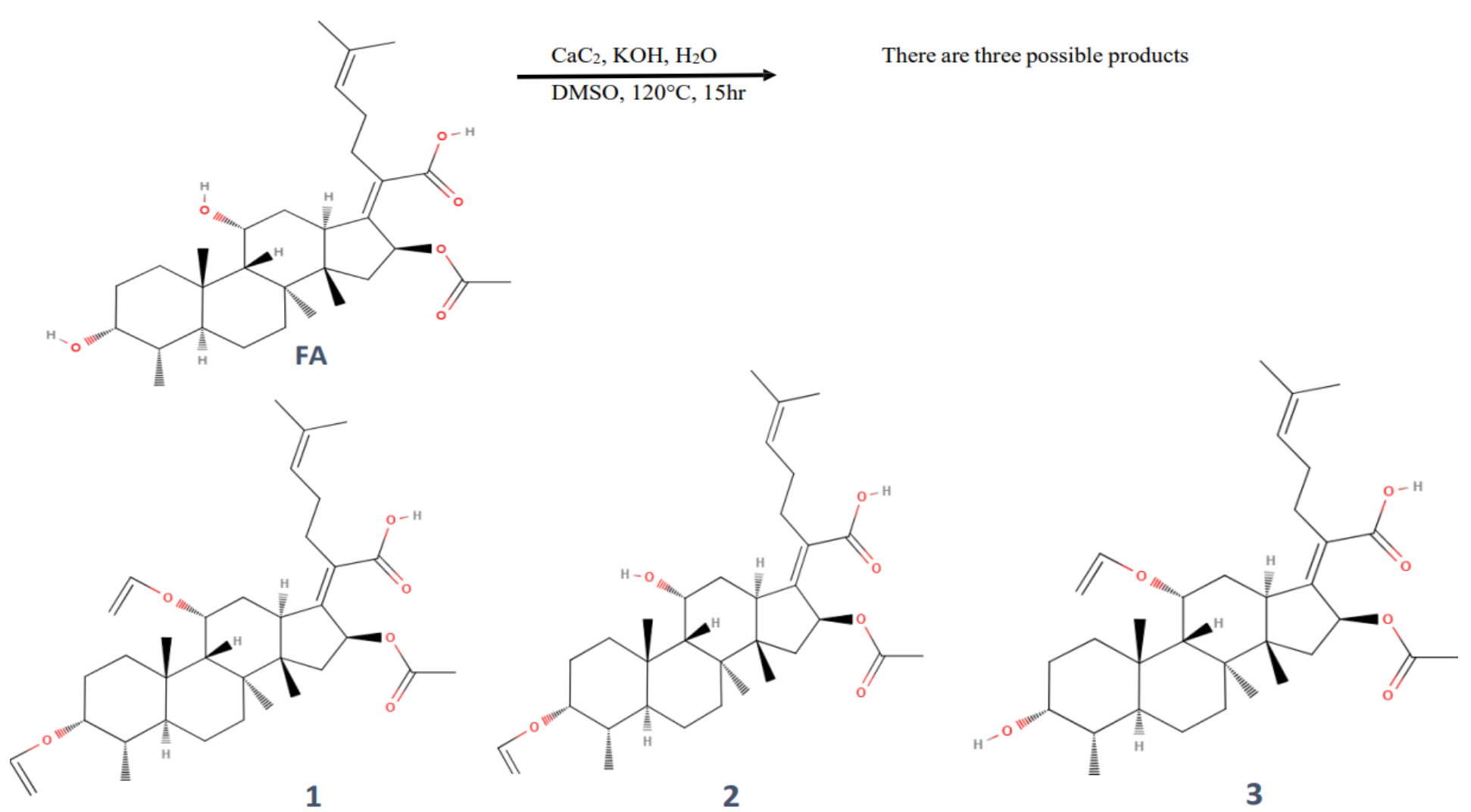
Pilocarpine

Aims & Objectives

- Investigate pharmaceutical potential of FA derivatives.
- Synthesize novel divinyl ether derivative at C-3 & C-11.
- Characterize using IR & ¹H-NMR spectroscopy.
- Assess antibacterial/antifungal activities for insights into applications.
- Develop/evaluate efficacy against resistant microbes.

Methods/Experimental

- Reagents: FA (44 mg), KOH (3 mg), DMSO (1 mL), CaC₂ (13.5 mg), H₂O (5.5 mL), chloroform, hexane, ethyl acetate (Table 2).
- Instruments: Glass column, NMR (Bruker Avance 500 MHz), IR (JASCO A-302), TLC (Kieselgel 60 F254).
- Procedure (Favorskii-Reppe Reaction): Mix FA, KOH, H₂O in DMSO; stir 30 min at RT. Add CaC₂; heat to 120°C with condenser; stir 15 hr. Filter, wash (hexane:ethyl acetate 4:1); evaporate solvent. Purify via column chromatography (increasing polarity). Monitor via TLC.
- General Mechanism:* Alcohol → Vinyl ether using CaC₂ as acetylene source; avoids high-pressure equipment.
- Safety:* Conducted per GLP; glassware sterilized at 101°C.

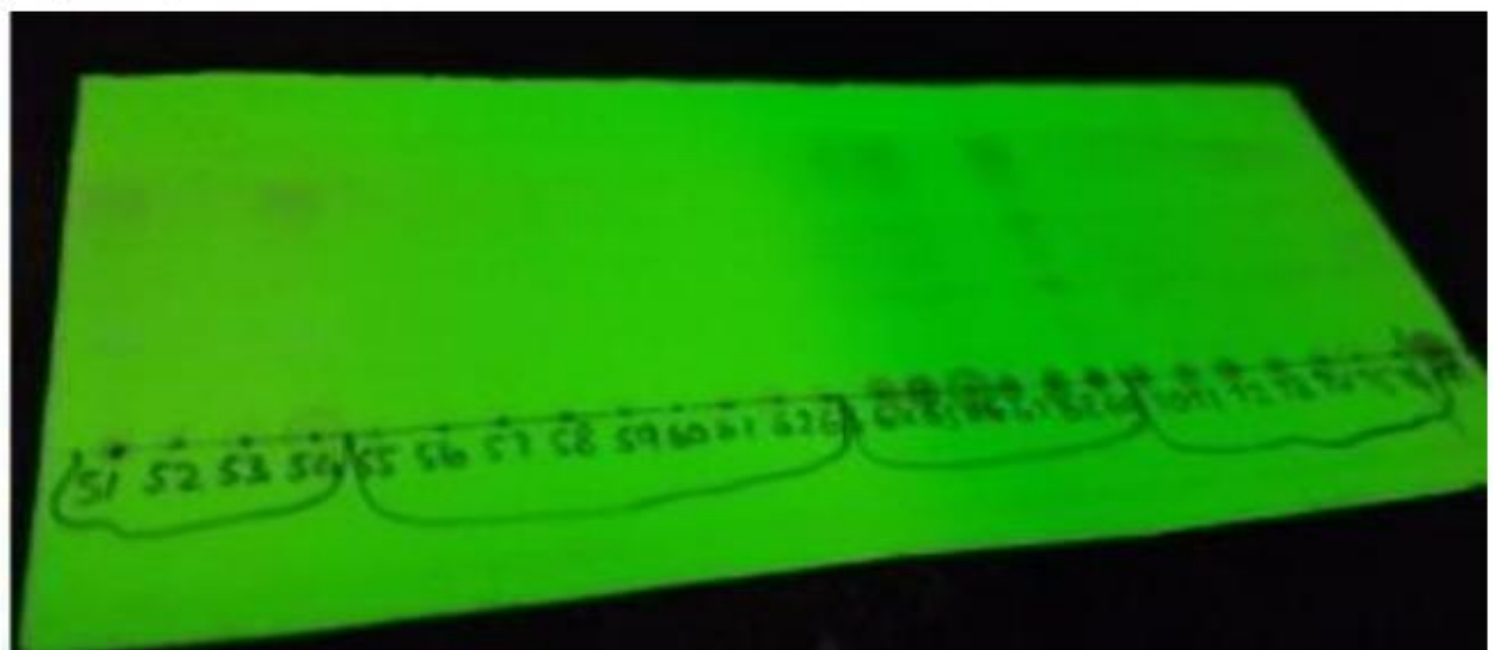


References

- [1] Prihoda et al. (2021) Nat Prod Rep 38(6):1100-8.
- [2] Masyita et al. (2022) Food Chem X 13:100217.
- [3] Adefegha et al. (2022) Studies Nat Prod Chem 72:391-421.
- [4] Zheng et al. (2023) Front Chem 10:1094841.

Naturally Occurring Fusidane Triterpens			
There are some naturally occurring fusidanes with antibiotic activity.			
No.	Name	Source	References
01	Fusidic acid C ₃₁ H ₄₈ O ₆	It is derived from various fungal sources, including <i>Acremonium fusidioides</i> , <i>Fusidium coccineum</i> , <i>Cephalosporium lamellatoide</i> , <i>Epidermophyton floccosum</i> , and <i>C. acremonium</i> . These fungi produce fusidic acid as a secondary metabolite.	[73]
02	3-Ketofusidic acid C ₃₁ H ₄₆ O ₆	3-Ketofusidic acid, also known as fusidic acid-3-ketone. It is derived from fungal sources such as <i>Epidermophyton floccosum</i> and <i>Fusidium coccineum</i>	[73]
03	Cephalosporin P1 C ₃₁ H ₄₈ O ₆	It is derived from the fungal species <i>Cephalosporium acremonium</i> and <i>Cladosporium sp.</i>	[73]
04	Viridomicic acid A C ₃₁ H ₄₈ O ₆	It is derived from the fungal species <i>Cladosporium sp.</i>	[73]
05	Helvolic acid C ₃₁ H ₄₈ O ₆	It is primarily sourced from various fungal species, including <i>Pichia guilliermondii</i> , and <i>Sarcocladium oryzae</i> .	[73]

naturally occurring fusidane triterpens



Column



Experimental Setup

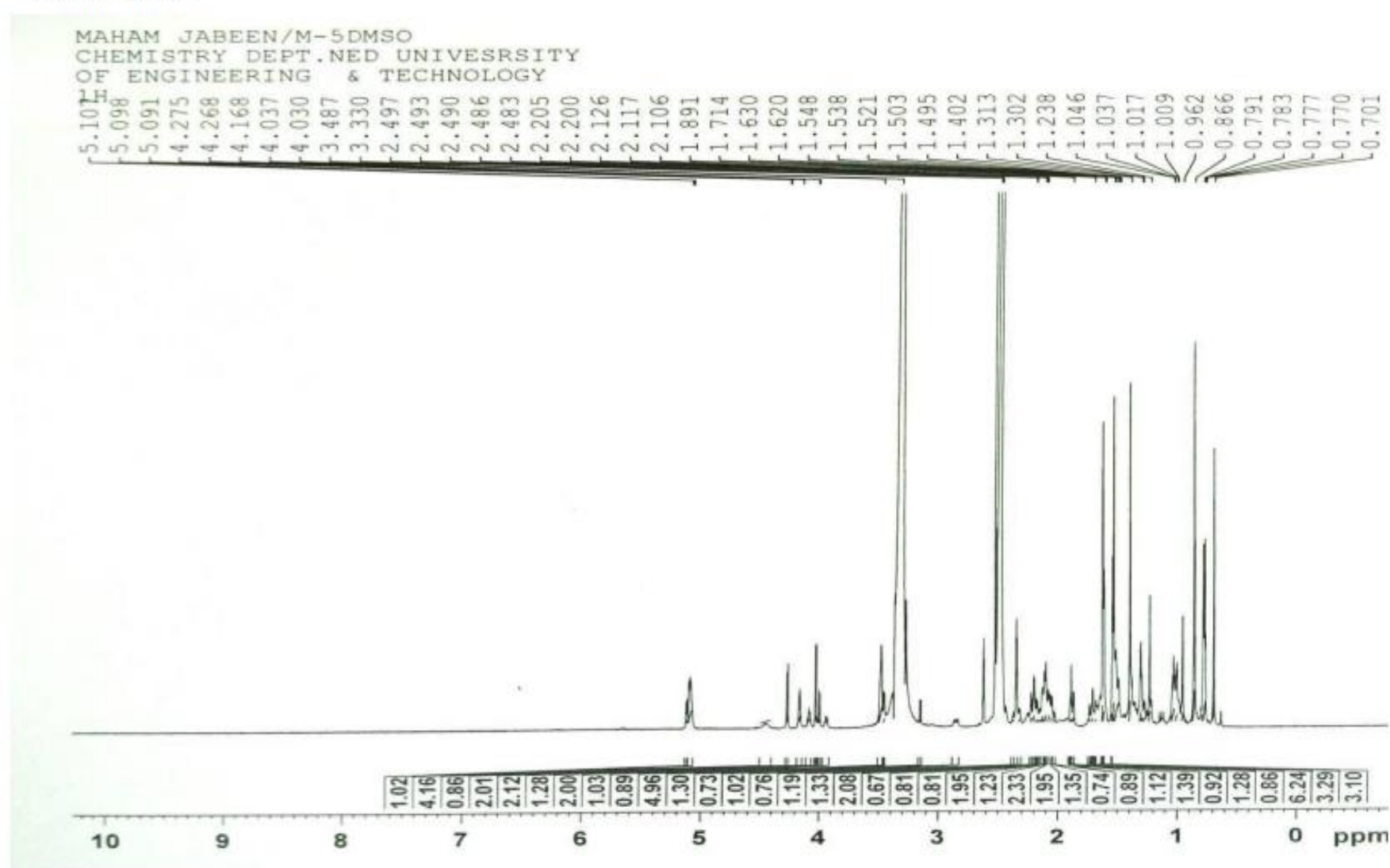


Experimental Setup

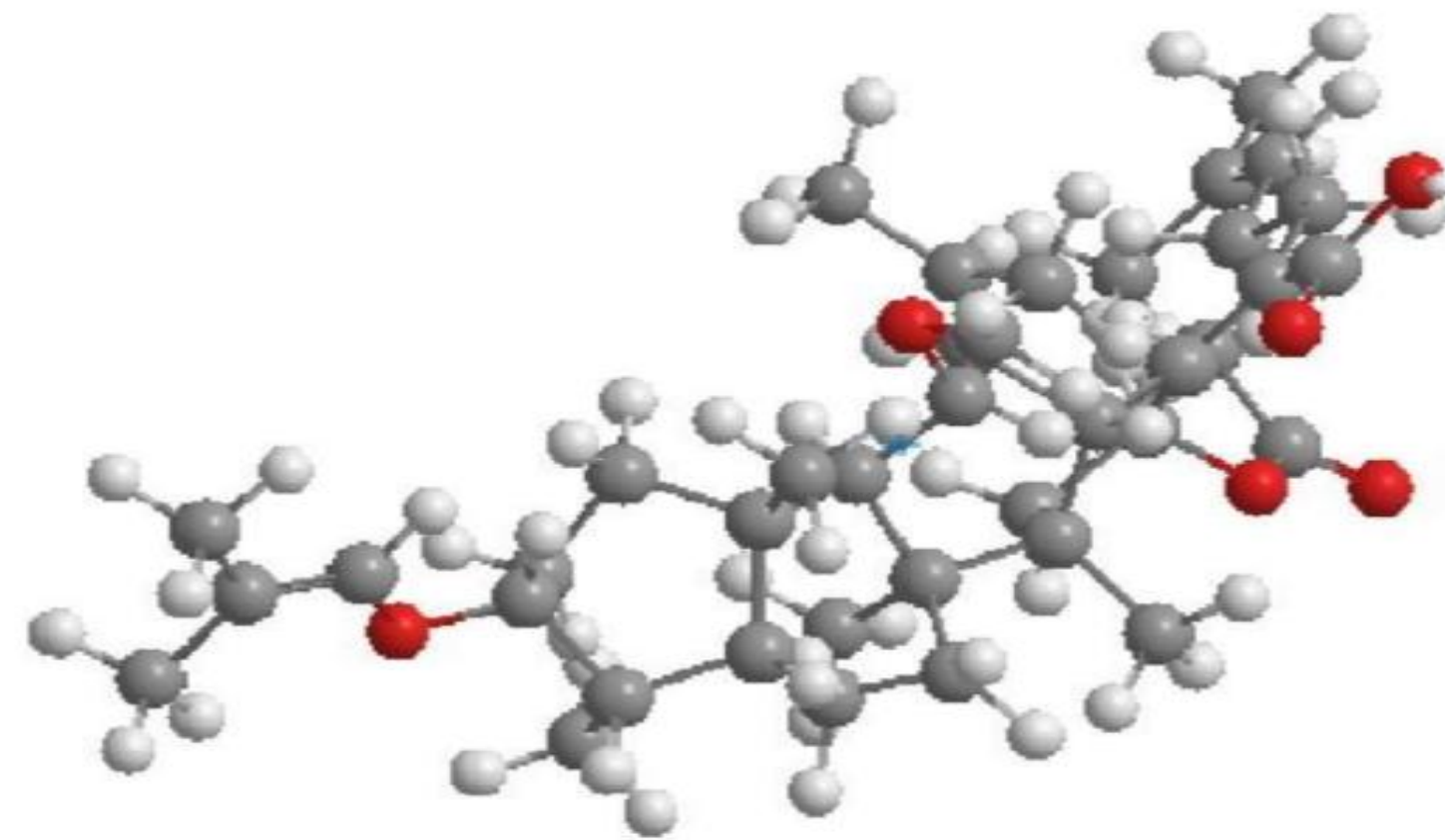
Results

- Synthesis Outcome:** FA divinyl ether derivative synthesized (white powder; stable).
- Structure:* (E)-2-((3R,4S,8S,9R,10S,11R,13R,14S,16S)-16-acetoxy-4,8,10,14-tetramethyl-3,11-bis((3-methylbut-2-en-2-yl)oxy)dodecahydro-1H-cyclopenta[a]phenanthren-17(2H,10H,14H)-ylidene)-6-methylhept-5-enoic acid.
- IR Spectrum:** 3083-3015 cm⁻¹ (alkene C-H), 2956-2863 cm⁻¹ (alkane C-H), 2800 cm⁻¹ (COOH O-H), 1740 cm⁻¹ (ester C=O), 1644-1632 cm⁻¹ (C=C).
- ¹H-NMR Spectrum (500 MHz, DMSO):*** Key signals:
 - δ 5.12 (1H, d, J=2.25 Hz, H-3'), 5.102 (1H, d, J=2.25 Hz, H-3'') → Vinyl groups.
 - δ 4.272 (1H, d, J=1.75 Hz, H-2'), 4.033 (2H, d, J=1.75 Hz, H-1'/H-2'') → Confirm divinyl ether.
- Methyls:** δ 1.620 (acetyl), 1.402 (H-29), 0.866 (H-18), etc.
- Evidence of Formation:** OH groups at C-3/C-11 replaced by vinyl ethers; spectral data matches proposed structure.

¹H-NMR Spectra



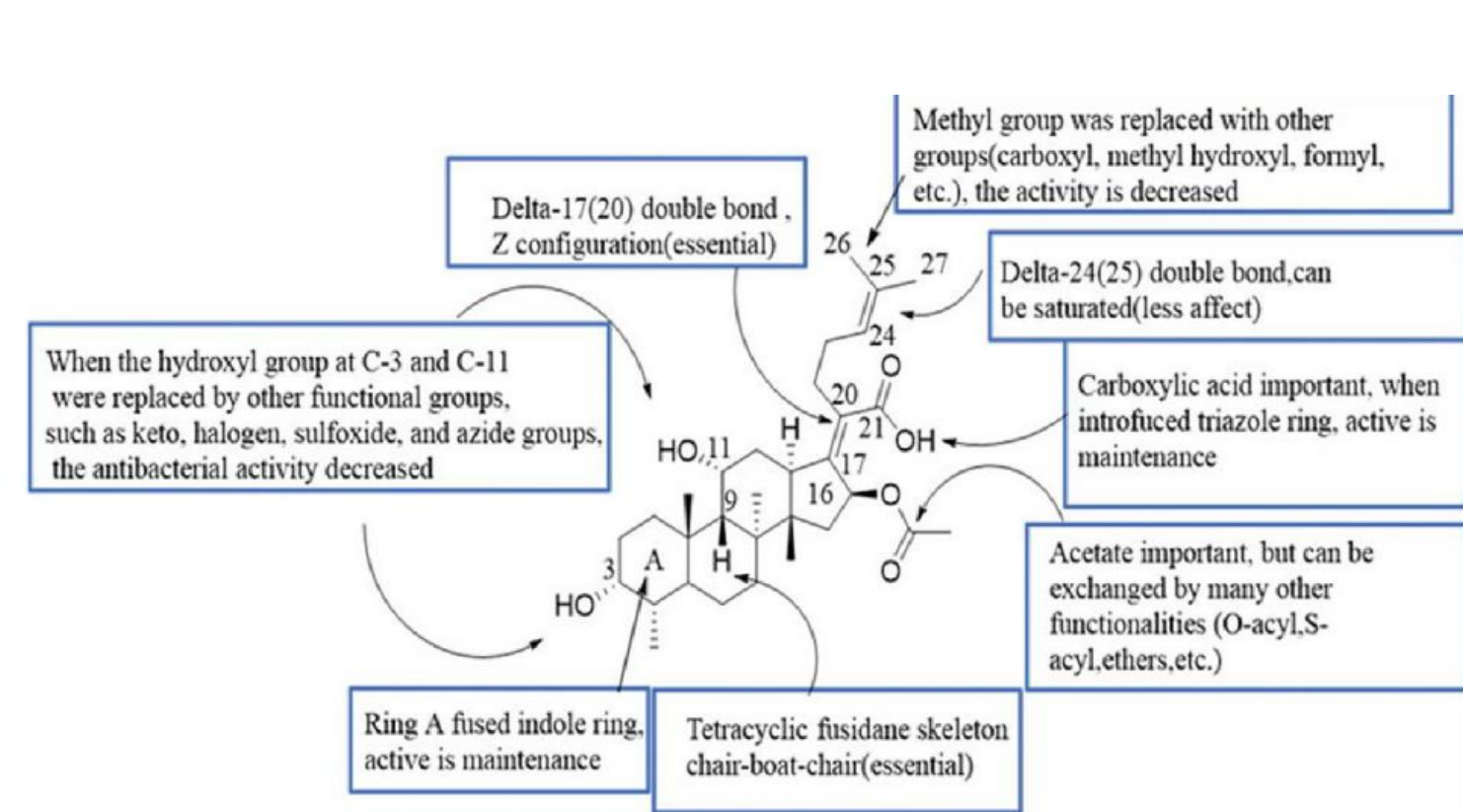
IUPAC Name: (E)-2-((3R,4S,8S,9R,10S,11R,13R,14S,16S)-16-acetoxy-4,8,10,14-tetramethyl-3,11-bis((3-methylbut-2-en-2-yl)oxy)dodecahydro-1H-cyclopenta[a]phenanthren-17(2H,10H,14H)-ylidene)-6-methylhept-5-enoic acid



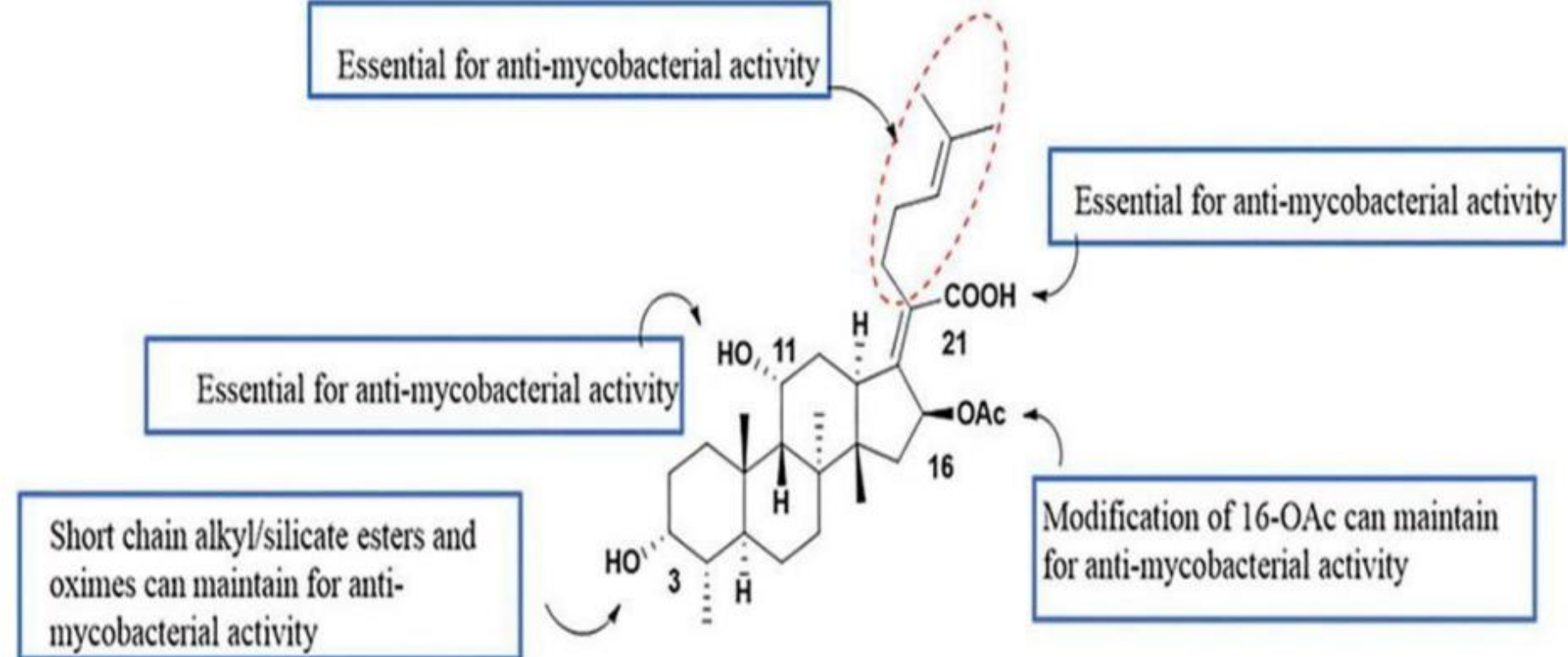
(Figure 21). 3D Structure of Fusidic Acid Divinyl Ether

Discussion

- Spectral Confirmation:** IR shows new alkene/ester peaks; ¹H-NMR vinyl signals (δ 5.12-4.001) validate C-3/C-11 modification. Matches SAR from literature (e.g., side chain orientation crucial for activity).
- Comparison to Literature:*** Builds on Wu et al. (2018) hydrogenation derivatives; enhances FA's antimicrobial potential (e.g., against MRSA, TB).
- Biological Insights:** Potential for improved anti-inflammatory (TNF-α inhibition), antibacterial (EF-G targeting), antiviral (HIV/JCV) activities; addresses resistance (e.g., >2M cases/year).
- Limitations:** In vitro focus; needs in vivo testing. Grey areas in fusidane SAR persist.
- Implications:** Vinyl ether enhances bioavailability; could lead to new drugs for infections/malaria.



(Figure 10). FA Structure-Activity-Relationship as Antimicrobial Activity



(Figure 7) FA (SAR) of Antituberculosis Activity

Conclusion

- Successful synthesis and characterization of FA divinyl ether derivative.
- Spectral data confirms structure; OH → Vinyl ether modification enhances potential.
- Promising for antibacterial/antifungal applications; combats resistance.
- Future: Extend to in vivo studies, other derivatives, morphological evaluations.