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SYNTHESIS OF ANTIMICROBIAL DERIVATIVES OF OLEANOLIC ACID

NABILA HASSAN,[1] ANJUM AYUB*,[1] NUZHAT ARSHAD,[1] SABIRA BEGUM,[2] SAIMA TAUSEEF[3]
NED University of Engineering & Technology, Karachi-75270, Pakistan
H.E.J. Research Institute of Chemistry, University of Karachi, International Center for Chemical and Biological Sciences, Karachi-75270, Pakistan.
Federal Urdu University of Arts, Science & Technology, Karachi-75300, Pakistan
E-mail: nabilahassan123@yahoo.com

ABSTRACT

Natural products from medicinal plants provide unlimited opportunities for new drug leads. Due to an increasing demand for seeking therapeutic drugs from natural products, we synthesized some compounds. Herbal preparations for medicinal usage contain various types of bioactive compounds. The focus of our study is on the methodologies, which include the derivatization and characterization.

Oleanolic acid (3*β*-hydroxy-olean-12-en-28-oic acid), a penta-cyclic triterpenoid comprising a wide range of pharmacological and biological activities. It consisting three active sites the hydroxyl group C_3, double bond in between C_{12} and C_{13} and carboxylic group at C_{28}. Converting the C_{28}- carboxyl group to ester group led to different derivatives that showed nematicidal activity. Twelve derivatives of oleanolic acid have been prepared by converting the C_{28}- carboxyl group to ester group respectively. These were characterized by ^{1}H-NMR, UV and IR spectroscopy. Some of the compounds are reported for the first time. Parent compound along with derivatives were evaluated for their antimicrobial activity. Most of the compounds were found to be active against various Gram positive and Gram negative bacteria.

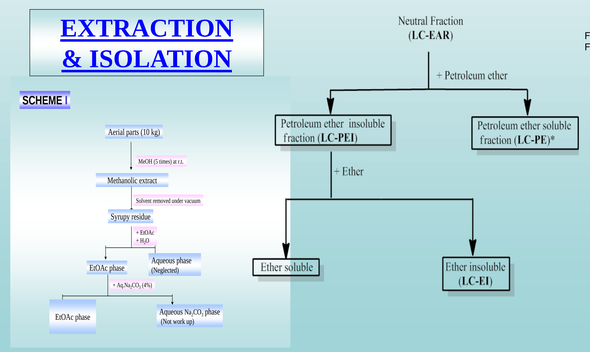
INTRODUCTION

Lantana camara Linn. (family: Verbenaceae) commonly known as lantana, is a large, evergreen, strong smelling hairy shrub, native to tropical America and cultivated elsewhere as an ornamental or hedge plant. Numerous varieties and types of *L. camara* are found.

The plant has been used in many parts of the world to treat a wide variety of human ailments such as itches, cuts, ulcers, swellings, bilious fever, catarrhal affection, eczema, tetanus, malaria, tumors, high blood pressure, cancers and rheumatism. Further, a number of pharmacological activities have been reported which include antibacterial, analgesic, anticonvulsant, antifungal, antihyperglycaemic, antihemorrhagic, antimalarial, CNS depressant, enzyme activity, hypertensive, hypotensive, immunosuppressant, insecticidal.[1-4] Phytochemical studies carried out by different groups of workers on different parts of the plant have resulted in the isolation of various terpenoids, steroids and flavonoids.[5,6]In the presnt studies two new and seven known natural products were isolated from methanolic extract of the aerial parts of the plant.

EXTRACTION & ISOLATION

SCHEME I



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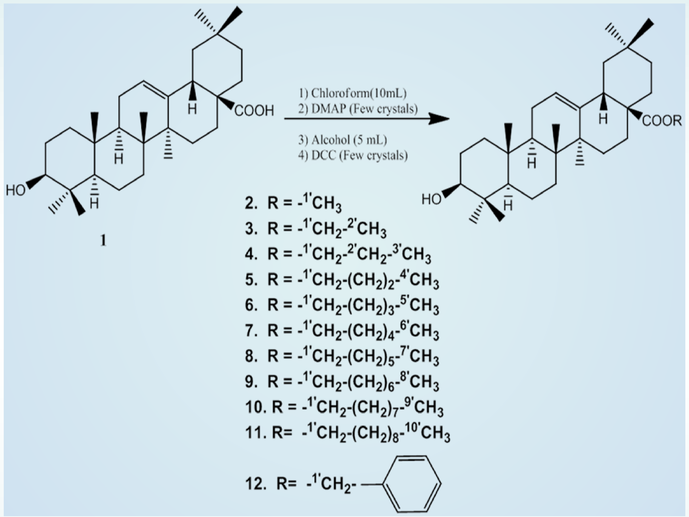

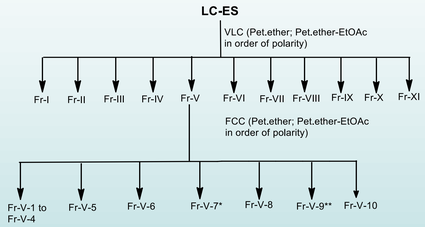

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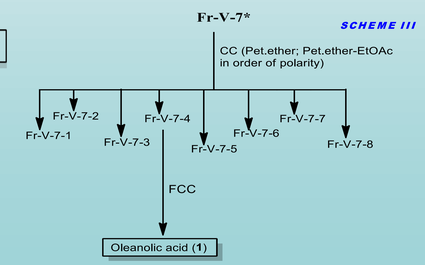

SCHEME IV

Table 1 Antibacterial Activity of OA Esters

BACTERIA TESTED	1	2	3	4	5	6	7	8	9	10	11	12
GRAM POSITIVE												
Bacillus cereus	10	12	12	11	10	10	11	13	13	11	12	10
Bacillus subtilus	10	11	12	12	10	11	11	11	14	12	10	11
Bacillus thuringiensis	8	10	11	10	8	9	8	8	9	9	8	8
Corynebacterium diptheriae	9	8	10	11	10	9	10	11	9	11	10	10
Corynebacterium hoffmanii	8	8	9	10	8	10	8	8	9	9	8	8
Corynebacterium xerosis	8	10	8	9	9	8	9	9	10	10	9	8
Micrococcus luteus	9	9	10	11	10	11	8	11	8	10	10	9
Staphylococcus aureus	8	10	8	9	9	8	9	9	10	11	9	8
Staphylococcus aureus AB, 188	9	8	10	9	10	9	11	11	12	10	9	10
Staphylococcus epidermidis	8	9	10	11	8	9	8	8	9	9	8	8
Staphylococcus faecalis	8	8	9	10	8	10	8	8	9	9	8	8
Staphylococcus saprophyticus	9	9	10	8	9	8	9	10	11	10	8	9
GRAM NEGATIVE												
Escherichia coli	9	8	10	10	9	9	10	8	10	9	10	9
Escherichia coli ATCC 8739	11	13	12	11	10	10	12	12	13	12	13	11
Escherichia coli Multi drug resistant	13	13	13	11	12	11	10	10	13	11	11	12
Klebsiella pneumonia	0	11	10	11	8	11	10	12	8	11	10	10
Proteus mirabilis	9	8	7	9	10	9	8	8	9	9	10	11
Pseudomonas aeroginosa	0	0	0	0	0	0	0	0	0	0	0	0
Pseudomonas aeroginosa ATCC 9027	0	0	0	0	0	0	0	0	0	0	0	0
Salmonella paratyphi A	0	0	0	0	0	0	0	0	0	0	0	0
Salmonella paratyphi B	0	0	0	0	0	0	0	0	0	0	0	0
Salmonella typhi	0	0	0	0	0	0	0	0	0	0	0	0
Shigella dysenteriae	0	0	0	0	0	0	0	0	0	0	0	0

Table 2 Antifungal Activity of OA Esters

FUNGI TESTED	1	2	3	4	5	6	7	8	9	10	11	12
FILAMENTOUS												
Aspergillus flavus	0	7	0	0	0	0	0	0	0	0	0	0
Aspergillus terreus	0	0	0	0	0	0	0	0	7	0	0	
Rhizopus sp.	0	0	0	0	7	0	0	0	0	0	0	
Penicillium sp.	0	0	0	0	0	0	0	7	0	0	0	0
DERMATOPHYTES												
Trichophyton rubrum	0	7	0	0	0	7	0	0	0	7	0	0
Trichophyton mentagrophytes	0	0	7	0	0	0	0	0	0	0	0	0
Trichophyton tonsurans	0	0	7	0	0	0	0	0	0	0	0	0
Microsporum canis	0	0	0	0	0	0	0	7	0	0	0	0
Microsporum gypseum	0	0	0	0	0	7	0	0	0	0	0	0
Fusarium sp.	0	7	0	0	0	0	7	0	0	0	7	0
OTHER FUNGI												
Candida albicans	0	0	0	0	0	0	0	0	0	0	0	0
Candida albicans ATCC 0383	8	9	7	7	9	8	8	8	7	9	8	7
Saccharomyces cerevisiae	9	12	11	11	10	10	9	12	11	9	11	10
Helimanthosporum sp.	0	0	0	0	0	0	0	0	0	0	0	0

Antibacterial Activity

Antibacterial activity of oleanolic acid and its derivatives was studied against various Gram-positive and Gram-negative bacteria. These were found effective against 2 out of 12 Gram-positive and 2 out of 11 Gram-negative bacteria tested at 500 μg/disc concentration (Table 1).

Antifungal Activity

The *in vitro* antifungal activity of oleanolic acid and its derivatives was also determined against four filamentous fungi (*Aspergillus flavus*, *Aspergillus terreus*, *Rhizopus* sp., *Penicillium* sp.), six dermatophytes, (*Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans*, *Microsporum canis*, *M. gypseum*, *Fusarium* sp.) and four other fungi (*Candida albicans*, *Candida albicans* ATCC 0383, *Saccharomyces cerevisiae* and *Helimanthosporum* sp.). All the fungi tested showed resistance against these samples except *Saccharomyces cerevisiae* which was inhibited by almost all fractions (Table 2).

CONCLUSION

Antibacterial Activity

Oleanolic acid and its derivatives were tested for their possible antibacterial activity against 6 gram positive and 9 gram negative bacteria. It could be observed from the results that compounds showed inhibition against Staphylococcus epidermidis and Staphylococcus saprophyticus which were comparable with that of parent compound. Parent compound and all the ester derivatives showed no significant zone of inhibition against all the gram negative bacteria tested. All these compounds showed no significant zone of inhibition against the bacteria tested.

Antifungal Activity

Oleanolic acid and their ester derivatives were also screened for their antifungal activity. Compounds showed weak activity against Aspergillus flavus, Candida albicans and Candida tropica ATCC 0383 at 500 µg/disc concentration. Rest of the compounds was found to be inactive against all the fungi tested.

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