Chemistry and Pharmacology of Natural Products

Lignans

Chemical, biological and clinical properties

CHEMISTRY AND PHARMACOLOGY OF NATURAL PRODUCTS

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Chemical, biological and clinical properties

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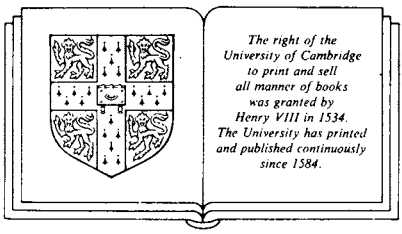

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Contents

To students and colleagues in Westfield College,
1965–1984.

Preface

The first systematic review of the naturally occurring lignans was presented by Professor R.D. Haworth in his Tilden lecture of 1942. There have been a number of subsequent review articles, notably that by W.M. Hearon and W.S. MacGregor in 1955. Their chemistry was covered in a collection of learned reviews published in honour of Professor L.R. Row by Andhra University Press in 1978. The present work is the first to cover the whole field of lignan chemistry including the application and promise of lignans as pharmaceutical agents. It is anticipated that expansion will continue through the application of modern methods of chromatography including HPLC, combined with the use of 2D-NMR and NOE for structure evaluation. These techniques are of especial relevance to the study of oligomeric lignans which are touched upon in the text.

The principal classes are defined in Chapter 1 with an explanation of the system of nomenclature that has been adopted. The contribution of Dr G.P. Moss who took on the considerable task of rationalising the often conflicting systems is gratefully acknowledged. It is hoped that readers who find that we have diverged from their own preference will accept that changes had to be made in order to be self-consistent. The system used throughout the book evolved with the help of some twenty active researchers who kindly responded to our requests for criticism of draft proposals.

Chapter 2 is a registry of lignans described up to April 1988 and includes at least one leading literature reference and plant source for each entry. A comprehensive review of the sources of lignans and neolignans has recently been published (p. 84) and Professor Richard Gottlieb is thanked for his help in making the manuscript available before publication. The senior author (DCA) would be particularly grateful if any sins of commission or omission in the registry are brought to his attention.

Chapter 3 (DCA and JDL) describes the general aspects of the pharmacology of lignans. The fourth chapter (JDL) describes the development of the clinically effective podophyllotoxin derivatives, Etoposide and Teniposide. Moreover, this chapter describes the current understanding of the

mechanism of action of these drugs. Subsequent chapters (DCA) deal with the isolation, characterisation and synthesis of lignans; here the volume of material necessitated a selective approach and this has been based on examples of general application largely chosen from the more recent literature. Dr Paul Dewick offered valuable criticism of the section on biosynthesis and the lignin scheme which appears in it was published with the approval of the American Chemical Society.

The infrared spectrum of wuweizisu C was provided by Professor H. Taguchi and material for the SFORD Scheme 6.14 by Professor D.N. Kirk, who also read part of the manuscript. Acknowledgement is also made to the Royal Society of Chemistry for the data in Scheme 6.32, to the Editor of the *Journal of Natural Products* for Scheme 6.33 and to the Editor of *Tetrahedron* for Scheme 6.34. Permission to publish Scheme 6.39 was given by the Pharmaceutical Society of Japan and material for figures 6.36 and 6.37 was kindly provided by Dr Peter B. Hulbert. We also wish to thank those authors who approved of the use of their material and to numerous others who responded to chemical queries which arose during the preparation of the manuscript.

The support of the Chemistry Department in Queen Mary College is gratefully acknowledged and Professor B. J. Aylett and Mr G. Coumbarides are thanked for help with computing.

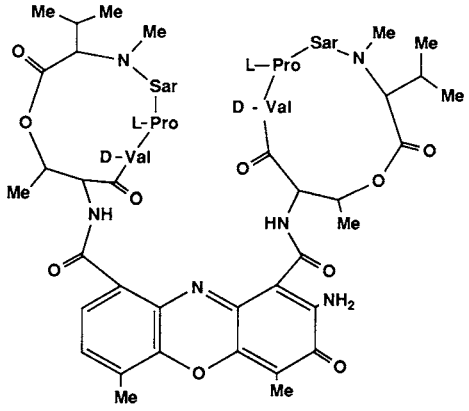
The production of the text owes much to the services of the library of the Royal Society of Chemistry, to the staff of the Cambridge University Press and to Editorial colleagues Professor J. David Phillipson and Mr Herbert Baxter.

London	D.C. Ayres	January 1990
New York	J.D. Loike	

Glossary for lignans

ACTINOMYCIN D (structure as given)

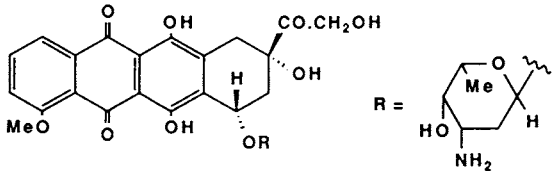
Actinomycin D



ADENOCARCINOMA Malignant cancer of epithelial cell origin, derived from any of the three germ layers with a glandular growth pattern.

ADRIAMYCIN (structure as given)

Adriamycin

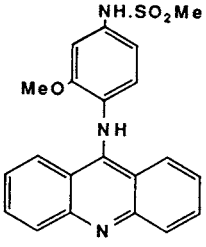


AIBN Azo *bis*-isobutylnitrile

ALOPAECIA Loss of hair

AMPHIPATHIC molecules that contain both a hydrophilic and a hydrophobic moiety.

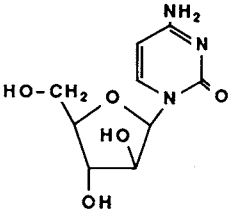
AMSACRINE (m-AMSA; structure as given)



meta- isomer

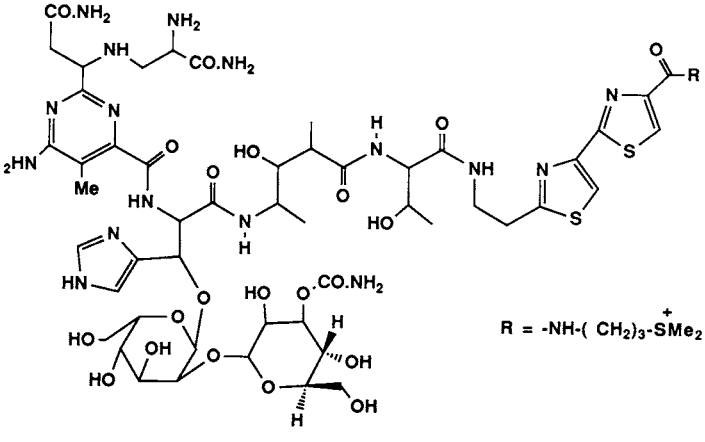
ANTIPYRETIC An agent used to control body temperature.
ARA-C CYTOSINE ARABINOSIDE (structure as given)

Ara - C or cytosine arabinoside



BIOGENETIC EQUIVALENT A substance available to the plant which may be converted by enzymic action to a metabolite needed for biogenesis.
BLEOMYCIN (structure as given)

Bleomycin A_2



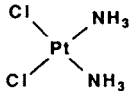
CEREBELLAR ATAXIA Motor abnormality associated with lesions in the cerebellum

CHLOROTIC Pertaining to a kind of anaemia sometimes affecting girls at puberty, characterised by a pale or greenish hue of the skin.

CHROMATIN Chromosal material composed of DNA and proteins.

CISPLATIN (structure as given)

Cisplatin or *cis*- diamminedichloroplatinum



COLLIN'S REAGENT for the selective oxidation of alcohols using chromium trioxide/pyridine.

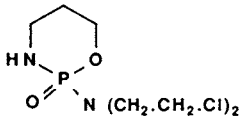
CONCANAVALLIN A Globular protein of molecular weight 26,000 with two identical subunits, each containing 237 aminoacids.

COREY'S METHOD for the stepwise oxidation of allylic alcohols and aldehydes to carboxylic acids using manganese dioxide/hexane followed by manganese dioxide/CN^-/methanol/acetic acid.

COSY A two dimensional NMR technique used to identify coupled protons

CYCLOPHOSPHAMIDE (structure as given)

Cyclophosphamide



R- form

CYTOTOXIC NUCLEOSIDES Nucleosides which can damage cells.

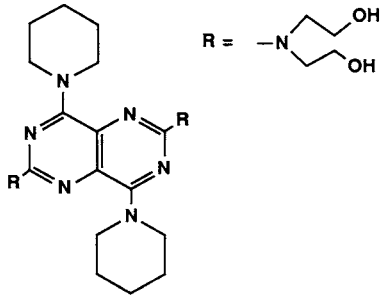
DABCO 1,4-Diazabicyclo-[2,2,2]-octane.

DDQ 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL Di-isobutylaluminium hydride

DIPYRIDAMOLE (structure as given)

Dipyridamole



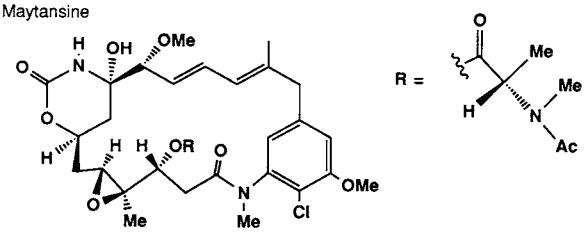
DIURETIC Treatment to excite discharge of urine.

DMAD Dimethyl acetylenedicarboxylate.

DMSA Dimethylsilylamide.
DOXORUBICIN See adriamycin.
ENTEROHEPATIC CIRCULATION The cycling of compounds through the liver and intestine.
ERYTHROPHAGOCYTIC LYMPHOSTIOCYTOSIS A malignancy of white cells that are highly phagocytic.
EUKARYOTIC (eucaryotic) pertaining to an organism whose cells contain a limiting membrane around the nuclear material.
FETIZON'S METHOD Oxidation with silver carbonate freshly precipitated onto Celite.
FIBROBLAST CELL LINE derived from elongated cells present in connective tissue and capable of forming collagen fibre.
FREMY'S SALT Potassium nitrosodisulphonate $K_4[(SO_3)_2NO]_2$.
HARDWOOD includes *both* coniferyl and sinapyl residues in its lignin in contrast to softwood lignin, which is largely derived from coniferyl alcohol.
HELA CELLS from a patient, Helen Lane, with carcinoma of the uterine cervix.
HEPATOTOXIC relates to an agent capable of damaging the liver.
HMPA Hexamethylphosphoramide.
HMDS Hexamethyldisilylamide $HN(SiMe_3)_2$ commonly used as the lithio derivative.
IFOSFAMIDE An isomer of cyclophosphamide where both amide groups carry one chloroethyl substituent.
IMMUNOBLOTTING Transferring proteins to special nitrocellulose filters where they can be tested for their capacity to react with specific antibodies.
IMMUNOMODULATOR A bioreactive substance that effects the physiological response of cells derived from the immune system.
INDOR Internuclear double resonance used mainly in proton spectra to detect coupling by monitoring the amplitude of one transition, while sweeping a low power excitation through the frequency range of the other.
KARPLUS RELATION relates the magnitude of the coupling between vicinal protons to the dihedral angle between the linking C—H bonds.
L 1210 CELL LINE A lymphocytic mouse leukemic cell line which has been used extensively for routine screening programs of chemical agents and natural products for cytotoxic activity.
LAMELLAE (middle) The inner of two membranes which enclose the chloroplasts, which are the sites of photosynthesis.
LANTHANIDE SHIFT REAGENTS Paramagnetic lanthanide β-diketoenolate complexes which associate with basic organic functional groups.
LDA Lithium di-isopropylamide.
LEUKEMIA Malignant neoplasms of white cell precursors.
LEUKOPAENIA An abnormally low white cell count.
LHDS Lithium hexamethyldisilylamide.
LTBA Lithium tri-*t*-butoxyaluminium hydride.
LTBH Lithium triethyl borohydride.
LYMPHOCYTIC Associated with or related to lymphocytes.
LYMPHOMA Malignancies that are characterised by the proliferation of cells native to the lymphoid tissues.

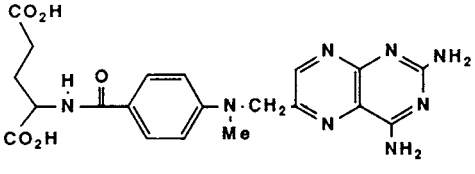
LYMPHOCYTIC S49 CELL LINE A transformed cell line established from a lymphoma induced in a BALB/c mouse. These cells retain many of the properties of thymocytes.
LYMPHOCYTIC LEUKAEMIA Leukaemic cells that arise from white blood cell precursors of the lymphocyte.
MACROPHAGE any large mononuclear phagocyte.
MAYTANSINE (structure as given).

Maytansine



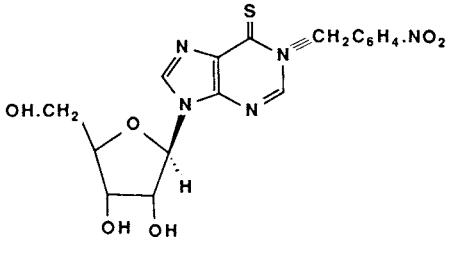
METHOTREXATE (structure as given).

Methotrexate



MITOGEN a substance which stimulates mitosis and the transformation of lymphocytes including those associated with lectin.
MURINE relating to mice.
NADH The reduced form of nicotinamide-adenine dinucleotide.
NASAL EMPYEMA A collection of pus within the nasal passage.
NASOPHARYNX Part of the pharynx lying directly behind the nasal passages and above the soft palate.
NBMPR 4-nitrobenzylthioinosine (structure as given).

NBMPR or 4-nitrobenzylthioinosine

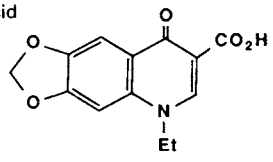


NBS N-bromosuccinimide.
NEUTROPHILS White blood cells that contain horseshoe-shaped nuclei and neutrophilic granules.

OCULOCUTANEOUS TELANGIECTASIA A group of abnormal prominent capillaries, venules and arterioles that create small focal red lesions in the eye.

OXOLINIC ACID (structure as given).

Oxolinic acid



PERIPHERAL NEUROPATHY A nervous disease or disorder involving the peripheral nervous system.

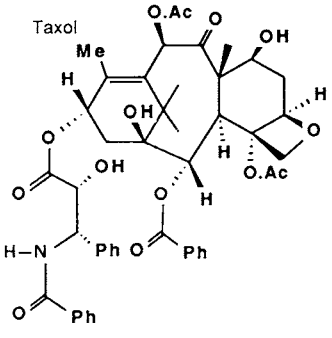
PHAGOCYTE A scavenger cell which ingests bacteria, foreign particles etc.

SPLENOCYTE A phagocytic mononuclear leukocyte of the spleen.

TAL Tyrosine ammonia lyase

TAXOL (structure as given).

Taxol

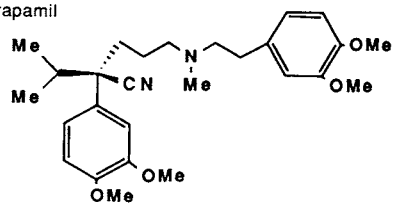


TFA Trifluoroacetic acid

THROMBOCYTOPENIA A reduction in platelet count.

VERAPAMIL (structure as given)

Verapamil



VESICANT Any agent used in chemical warfare to blister and burn body tissues by contact with the skin or by inhalation.

VINCRISTINE (structure as given).

Vincristine