Chemistry and Pharmacology of Natural Products

Lignans

Chemical, biological and clinical properties
CHEMISTRY AND PHARMACOLOGY OF NATURAL PRODUCTS

Series Editors: Professor J.D. Phillipson, The School of Pharmacy, University of London; Dr D.C. Ayres, Department of Chemistry, Queen Mary College, University of London; H. Baxter, formerly at the Laboratory of the Government Chemist, London.

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Lignans

Chemical, biological and clinical properties

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To students and colleagues in Westfield College,
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
Preface

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 litera-
ture. Dr Paul Dewick offered valuable criticism of the section on biosyn-
thesis 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.
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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
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Mr Herbert Baxter.

London  D.C. Ayres  January 1990
New York  J.D. Loike
Glossary for lignans

ACTINOMYCIN D (structure as given)

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

ADRIAMYCIN (structure as given)

A1BN Azo bis-isobutyl nitrile

ALOPECIA Loss of hair

AMPHIPATHIC molecules that contain both a hydrophilic and a hydrophobic moiety.
**Glossary for lignans**

AMSACRINE (m-AMSA; structure as given)

ANTIPYRETIC An agent used to control body temperature.

ARA-C CYTOSINE ARABINOSIDE (structure as given)

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)

Beomycin A₂
Glossary for lignans

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 Chromosomal material composed of DNA and proteins.

CISPLATIN (structure as given)

Cisplatin or cis-diaminedichloroplatinum

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 amino acids.

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

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.
Glossary for lignans

DMSA  Dimethylisoualamide.
DOXORUBICIN  See adriamycin.
ENTEROHEPATIC CIRCULATION  The cycling of compounds through the liver and intestine.
ERYTHROPHAGOCYTIC LYMPHOMATOYOSIS  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.
FETON’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 fibres.
FREMY’S SALT  Potassium nitrooxodisulphonate K4[(SO4)2NO2].
HARDWOOD includes both conifer and sinapyl residues in its lignin in contrast to softwood lignin, which is largely derived from conifer 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 Hexamethyldisiloxane HN(SiMe3)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 leukaemic cell line which has been used extensively for routine screening programs of chemical agents and natural products for cytotoxic activity.
LAMELLA (middle) The inner of two membranes which enclose the chloroplasts, which are the sites of photosynthesis.
LANTHANIDE SHIFT REAGENTS  Paramagnetic lanthanide β-diketoneolate complexes which associate with basic organic functional groups.
LDA Lithium di-isopropylamide.
LEUKEMIA  Malignant neoplasms of white cell precursors.
LEUKOAENIA  An abnormally low white cell count.
LHDS Lithium hexamethyldisiloxane.
LTFB Lithium tri-n-butylaluminum hydride.
LYMPHOCTYC  Associated with or related to lymphocytes.
LYMPHOMA  Malignancies that are characterised by the proliferation of cells native to the lymphoid tissues.
Glossary for lignans

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).

\[
\text{Maytansine}
\]

METHOTREXATE (structure as given).

\[
\text{Methotrexate}
\]

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 EMPIRYMA 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).

\[
\text{NBMPr or 4-nitrobenzylthioinosine}
\]

NBS N-bromosuccinimide.

NEUTROPHILS White blood cells that contain horseshoe-shaped nuclei and neutrophilic granules.
**Glossary for lignans**

**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](image)

**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](image)

**TFA** Trifluoroacetic acid

**THROMBOCYTOPENIA** A reduction in platelet count.

**VERAPAMIL** (structure as given)

![Verapamil](image)

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

VINCRISTINE  (structure as given).

Vincristine