

Unit 1: Natural Products as Leads for New Pharmaceuticals

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Chemistry of Natural Products, subject code MPC104T, is a core Semester 1 subject of M.Pharm Pharmaceutical Chemistry. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject studies the molecules that living organisms make, and above all the ones that became medicines. Unit 1 makes the central argument with case histories: morphine, paclitaxel, lovastatin, the curare alkaloids and the great antibiotic families all began as natural products and were turned into drugs by chemical modification. Units 2 and 3 then study the great structural families one by one: alkaloids, flavonoids and steroids, then the terpenoids and the vitamins, each with its isolation methods and its classical structure proofs. Unit 4 changes scale, from molecules to the technology that now produces and discovers them: recombinant DNA, hybridomas, oligonucleotide and gene therapy, and the active constituents of the crude drugs of the indigenous system used for diabetes, liver dysfunction and tumors. Unit 5 closes the loop with the modern answer to the question the classical chemists answered by degradation: how IR, NMR and mass spectra together characterize a natural compound, worked through penicillin, morphine, camphor, vitamin D, quercetin and the digitalis glycosides. A student who completes this subject should be able to classify a natural product from its skeleton, outline how it would be isolated and proved, and explain how a natural lead was modified into the drug that patients actually receive.

1.1 Why natural products make leads

A **natural product** is a chemical compound produced by a living organism: a plant, a microbe, a fungus, a marine animal or a venomous creature. Most are **secondary metabolites**, molecules the organism makes not for its basic growth chemistry but for its life in the world: to poison a predator, kill a competing microbe, attract a pollinator or signal to its own kind. That ecological purpose is exactly why they interest pharmacologists. A molecule that evolved to bind a protein in another organism arrives pre-tested by evolution for biological activity, and its target is often a protein family that human physiology shares.

Four practical advantages follow:

- **Novel skeletons:** natural products occupy regions of chemical space that synthetic libraries rarely reach: bridged rings, dense stereochemistry, unusual heteroatom patterns. A new skeleton can mean a new mechanism.
- **Built in bioactivity:** the hit rate of natural extracts in bioassays is far higher than that of random synthetic compounds, because the molecules were selected to do something.
- **Lead, not drug:** the natural molecule itself is usually too toxic, too scarce, too unstable or too complex to be the medicine. Its role is to show where activity lives; chemistry then simplifies, strengthens or detoxifies it. This lead to analog sequence is the pattern of almost every section of this unit.
- **Supply can be engineered:** once a lead is valuable, supply is solved by cultivation, fermentation, semi-synthesis from an abundant relative, total synthesis, or biotechnology (Unit 4).

The development path is standard enough to draw:

FROM ORGANISM TO DRUG: THE NATURAL PRODUCT PATH

Source organism	(plant, microbe, fungus, venom)
Extraction and fractionation	(bioassay guided fractionation: activity tracked at every split)
Isolation and structure proof	(chromatography, crystallisation)
LEAD COMPOUND	(active, but flawed)
Molecular modification	(semi-synthesis, analog series, SAR)
Candidate drug	(preclinical, then clinical trials)

From Organism to Drug: the Lead Pathway



The lead shows where activity lives. Chemistry repairs the flaws.

WHAT MODIFICATION FIXES

Scarce supply: paclitaxel bark harvest gave way to semi-synthesis from yew needles

Unstable molecule: thienamycin became imipenem, then dehydropeptidase proof meropenem

Too toxic as found: podophyllotoxin became etoposide, acting on topoisomerase II

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Figure: The natural product path from source organism to candidate drug, with the lead compound as the central hand over from biology to chemistry.

The honest limitation is the mirror image of the advantage: complex natural molecules are hard to make, hard to modify at one position only, and often bind several targets. The history of this unit is the history of chemists paying that price only where the activity was worth it.

1.2 CNS drugs: the morphine alkaloids

Source and chemistry. Opium is the dried latex of the unripe seed capsule of the opium poppy, *Papaver somniferum*. It contains a family of benzyloquinoline derived alkaloids, of which morphine (about 10 percent of opium) is the principal analgesic, with codeine, thebaine, papaverine and noscapine alongside. Morphine, C₁₇H₁₉NO₃, is a phenanthrene alkaloid: three fused six membered rings and a dihydrofuran oxygen bridge, a phenolic hydroxyl, a secondary alcoholic hydroxyl, and a basic tertiary nitrogen held in a piperidine ring (the full structure proof is in Unit 2, section 2.6).

Action. Morphine is an agonist at opioid receptors, principally the mu receptor, in the brain, spinal cord and gut. Receptor activation reduces pain signalling and produces analgesia, sedation and euphoria, and also the adverse pattern that limits it: respiratory depression, constipation, nausea, tolerance and dependence.

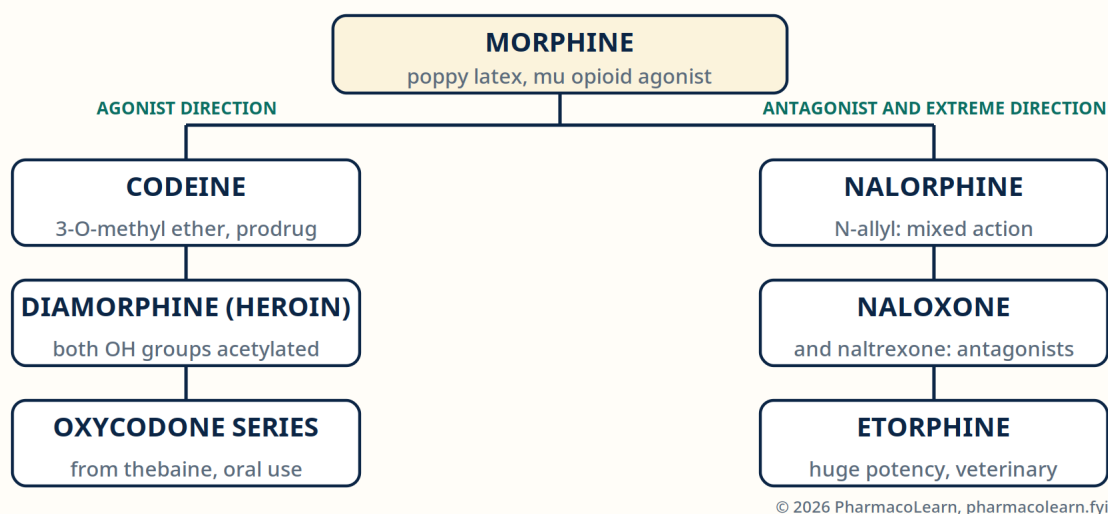
The lead at work. Morphine's modification history is the textbook of medicinal chemistry:

Compound	Change from morphine	Result
Codeine	Phenolic OH methylated (3-O-methyl)	Weaker oral analgesic and antitussive; a prodrug, converted by CYP2D6 to morphine
Diamorphine (heroin)	Both hydroxyls acetylated	Crosses into the brain faster, then hydrolyses to morphine; potency and abuse liability both rise

Compound	Change from morphine	Result
Oxycodone, hydrocodone	Ring changes from the thebaine series	Oral analgesics of the same family
Nalorphine	N-methyl replaced by N-allyl	Mixed agonist and antagonist; showed the path to pure antagonists
Naloxone, naltrexone	N-allyl or N-cyclopropylmethyl, 14-hydroxy series	Pure opioid antagonists: naloxone reverses overdose, naltrexone is used in dependence
Etorphine	Bulky lipophilic side chain (from thebaine)	Extraordinary potency, used only in veterinary large animal work

The SAR lesson is permanent: small changes at the nitrogen switch the same skeleton between agonist and antagonist, because the receptor reads the substituent as part of the activation signal.

One Skeleton, Many Drugs: Morphine Modifications



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Figure: Morphine as a lead: small edits at the oxygen and nitrogen positions produce agonists, antagonists and extremes of potency from one skeleton.

1.3 Anticancer drugs: taxanes and podophyllotoxin derivatives

Paclitaxel and docetaxel. Paclitaxel (Taxol) was isolated from the bark of the Pacific yew, *Taxus brevifolia*, in a US screening programme; stripping bark kills the tree, and the original supply crisis was solved chemically: the abundant needle constituent 10-deacetylbaaccatin III, from the renewable yew *Taxus baccata*, is converted by semi-synthesis into paclitaxel, and the same route with a different side chain gives **docetaxel**. Both are diterpenoids of the taxane family (Unit 3). Their mechanism is the opposite of the vinca alkaloids: where vincristine prevents microtubule assembly, paclitaxel **stabilises the microtubule polymer** and prevents the disassembly a dividing cell needs, so mitosis arrests and the cell dies. Clinically the taxanes are mainstays in ovarian, breast and lung cancers; the price of the mechanism is neutropenia and peripheral neurotoxicity, and paclitaxel's poor solubility historically required a castor oil derived vehicle.

Etoposide and teniposide. Podophyllotoxin is a lignan from the roots and rhizomes of *Podophyllum* species (the American mayapple, *Podophyllum peltatum*, and the Himalayan *Podophyllum hexandrum*). The natural compound itself binds tubulin and is too toxic to the gut for systemic use. Semi-synthetic glycosidic modification gave **etoposide** and **teniposide**, and the modification also changed the target: these derivatives act mainly by stabilising the complex between **topoisomerase II** and DNA, so the enzyme leaves double strand breaks behind. Etoposide is used in testicular, lung and blood cancers. Two exam points deserve emphasis: a natural lead's derivative can work by a different mechanism than the lead, and

glycosylation here was a property fix (solubility and handling) that turned into a pharmacology change.

1.4 Cardiovascular drugs: lovastatin, teprotide and dicoumarol

Lovastatin. Lovastatin is a fungal polyketide metabolite, isolated from *Aspergillus terreus* (a close relative, mevastatin, came first from *Penicillium* species). It is given as a lactone, which hydrolyses in the body to the open beta-hydroxy acid; that acid is a competitive inhibitor of **HMG-CoA reductase**, the rate limiting enzyme of cholesterol synthesis, because it mimics the enzyme's natural intermediate. The result is reduced hepatic cholesterol, increased LDL receptor expression, and lower blood LDL. The whole statin class descends from this fungal lead: the later members (simvastatin by simple modification, then fully synthetic atorvastatin and rosuvastatin) kept the enzyme binding pharmacophore the natural product revealed.

Teprotide and the ACE inhibitors. Teprotide is a nonapeptide from the venom of the Brazilian pit viper *Bothrops jararaca*. Venom peptides that potentiated bradykinin were found to inhibit the angiotensin converting enzyme (ACE), and the peptide itself lowered blood pressure but could not be given orally. Studying how its C-terminal proline and carboxylate bound the enzyme's zinc guided the design of **captopril**, the first oral ACE inhibitor: a small sulfhydryl compound built to present the same binding features. Teprotide never became a drug; it is one of the purest examples in this course of a natural product whose value was the information it carried.

Dicoumarol and the coumarin anticoagulants. Cattle fed spoiled sweet clover (*Melilotus* species) developed a haemorrhagic disease; the cause was traced to **dicoumarol**, a bis(4-hydroxycoumarin) formed when fungi act on the plant's coumarin. Dicoumarol antagonises vitamin K, blocking the gamma-carboxylation that activates clotting factors II, VII, IX and X. It was used clinically, and its structure led to the simpler synthetic **warfarin**, for decades the standard oral anticoagulant, whose action is now known to centre on inhibition of the vitamin K epoxide reductase complex (VKORC1).

1.5 Neuromuscular blocking drugs: the curare alkaloids

Curare is the arrow poison of South American hunting peoples, prepared from plants such as *Chondrodendron tomentosum* and *Strychnos toxifera*. Its principal alkaloid, **tubocurarine**, is a bulky benzyliisoquinoline alkaloid carrying two nitrogen atoms, one quaternary. Tubocurarine is a competitive antagonist at the nicotinic acetylcholine receptor of the neuromuscular junction: it occupies the receptor without activating it, so the muscle cannot be signalled to contract. Surgeons turned the poison into a tool: controlled, reversible paralysis for anaesthesia.

Tubocurarine's faults (ganglion blockade, histamine release, long and variable action) drove the analog programme: **atracurium** was designed to self-destruct by Hofmann elimination at body pH and temperature, giving predictable offset in organ failure; **vecuronium** and **rocuronium** are steroidal neuromuscular blockers built on an androstane skeleton carrying the same two nitrogen pharmacophore, a bridge to Unit 2's steroid chemistry. The lesson: the pharmacophore of a natural poison can be transplanted onto a wholly different, better behaved skeleton.

1.6 Antimalarial drugs and analogues

Quinine and the synthetic quinolines. Quinine, from the bark of the *Cinchona* tree, was the first effective antimalarial and is a quinoline methanol alkaloid whose structure (Unit 2 territory) set the template for the synthetic 4-aminoquinolines, above all **chloroquine**: the quinoline nucleus concentrates in the parasite's food vacuole and blocks the detoxification of haem into haemozoin, so free haem kills the parasite. Widespread chloroquine resistance ended its reign in most regions, but the natural product had defined

both target space and scaffold.

Artemisinin and its derivatives. Artemisinin (qinghaosu) was isolated from *Artemisia annua*, a herb of the Chinese materia medica, by the group of Tu Youyou, who found that a low temperature ether extraction preserved the activity that hot preparations destroyed. Chemically it is a sesquiterpene lactone containing an **endoperoxide bridge**, the essential feature: inside the parasite, iron from digested haemoglobin cleaves the peroxide and generates carbon centred radicals that damage parasite proteins and membranes. Artemisinin itself is poorly soluble in both water and oil and has a short half life, so the drugs used are its derivatives: **dihydroartemisinin** (reduction of its lactone carbonyl), **artemether** (its methyl ether) and **artesunate** (a water soluble hemisuccinate ester for injection). Artemisinin based combination therapies (ACTs), pairing a fast artemisinin derivative with a longer acting partner drug, are the World Health Organization recommended first line treatment for *Plasmodium falciparum* malaria; emerging partial resistance in several regions is the standing warning of this section.

1.7 Antibiotics I: the macrolides

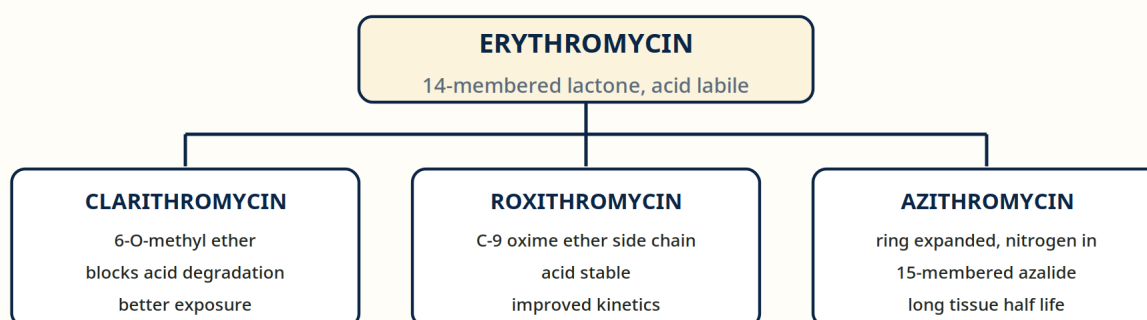
Erythromycin, from the soil actinomycete *Saccharopolyspora erythraea*, is built on a 14 membered macrocyclic lactone ring (erythronolide) carrying two sugars, one of them an amino sugar. It binds the 50S bacterial ribosomal subunit at the 23S rRNA of the peptide exit tunnel and blocks translocation of the growing peptide chain. Erythromycin is acid labile: stomach acid degrades it to inactive products, and its bitterness and gut motility effects limit it.

The semi-synthetic answers are a model exam answer:

Drug	Modification	What it fixed
Clarithromycin	6-O-methylation of erythromycin	Blocks the acid degradation pathway; better stability, exposure and tissue levels
Roxithromycin	Oxime ether extension at C-9	Improved acid stability and pharmacokinetics
Azithromycin	Ring expanded to 15 members, nitrogen inserted (an azalide)	Long tissue half life, once daily short courses, strong intracellular and tissue penetration

The ribosome reads all four almost identically; the patient experiences four quite different drugs. That is molecular modification doing pharmacokinetic, not pharmacodynamic, work.

Erythromycin and its Semi-Synthetic Family



Same ribosome target, four different drugs: the changes work on pharmacokinetics.

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Figure: The macrolide family: three semi-synthetic repairs of erythromycin, all aimed at stability and exposure rather than a new target.

1.8 Antibiotics II: beta-lactams, cephalosporins and carbapenems

All beta-lactam antibiotics share the strained four membered beta-lactam ring, whose carbonyl acylates the active site serine of bacterial penicillin binding proteins (PBPs), the enzymes that cross link peptidoglycan; the wall weakens and the bacterium lyses. The penicillins themselves are the subject of the spectral study in Unit 5; this section covers the two families the syllabus names beside them.

Cephalosporins descend from cephalosporin C, from the fungus *Acremonium chrysogenum* (formerly *Cephalosporium acremonium*). Its nucleus, 7-aminocephalosporanic acid (7-ACA), differs from the penicillin nucleus by a six membered dihydrothiazine ring fused to the beta-lactam, and it offers **two** positions for modification: the 7-acyl side chain (spectrum and beta-lactamase stability) and the 3-substituent (pharmacokinetics and some spectrum). Successive clinical generations traded on these positions: early members stronger against Gram positive cocci, later generations reaching Gram negative bacilli including, for ceftazidime and cefepime, *Pseudomonas*, and ceftaroline regaining activity against MRSA. The natural nucleus was a platform, not a finished drug.

Carbapenems descend from **thienamycin**, from *Streptomyces cattleya*: the same beta-lactam warhead on a five membered ring in which carbon replaces the sulfur of penicillin, with a trans hydroxyethyl side chain that confers remarkable stability to most beta-lactamases. Thienamycin itself was too unstable in concentrated solution and is degraded in the kidney by dehydropeptidase I. The fixes define the family: **imipenem** (a stabilised N-formimidoyl derivative) is given with **cilastatin**, an inhibitor of that renal enzyme; **meropenem** carries a 1-beta-methyl group that makes it intrinsically stable to dehydropeptidase, needing no partner. Carbapenems hold the broadest spectrum of the beta-lactams and are reserved accordingly, which is why carbapenem resistant organisms are a first order clinical threat.

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