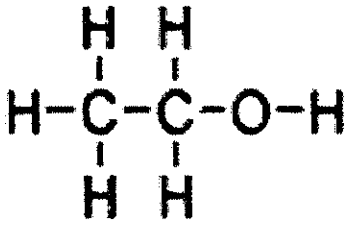
Zeist Mock Trial
Generipharm BV v Ethix Plc

An Introduction to the Technical Background

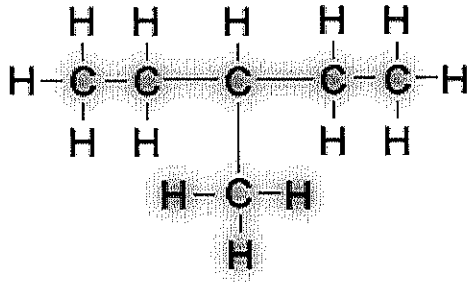
Structural Formulae

- Most drugs are organic chemical compounds
- Chemical compounds are made up of atoms joined together by bonds
- The structural formula of a compound is a two dimensional representation of how the atoms in that compound are connected (using the chemical symbol for the elements to represent the atoms e.g. C = carbon, O = oxygen, H = hydrogen and N = nitrogen)
- For example, ethanol (C_2H_6O) has the structural formula:



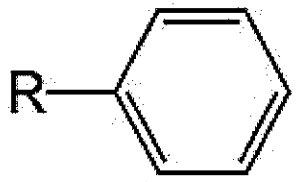
Nomenclature

- The following terminology is used in the 'factual background' to the present case:
- *Alkyl radical (or alkyl group)* = a hydrocarbon chain. The naming convention is based upon the number of carbon atoms e.g. methyl (named after methane) = CH_3, ethyl = C_2H_5, propyl = C_3H_7 etc.
- An alkyl group may be *branched* or *unbranched*, depending on whether the alkyl chain is a straight chain or has branches. For example 3-methylpentane has a straight chain of 5 carbon atoms, with a methyl group branching off at the third carbon:



Nomenclature

- An alkyl group may be *substituted* or *unsubstituted* depending on whether or not the hydrocarbon chain has other substituent groups
- *Halogen atom* = one of a series of non-metal elements comprising fluorine, chlorine, bromine and iodine
- *Hydroxyl radical (or hydroxyl group)* = the O-H functional group
- *Phenyl group (or benzene ring)* = C_6H_5, 6 carbon atoms arranged in a hexagonal ring of alternating single and double bonds:

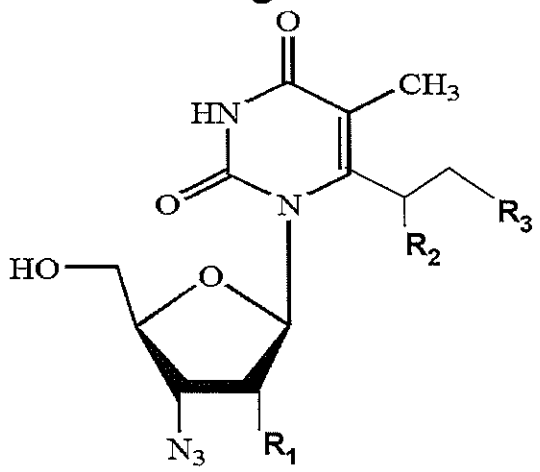


Markush Formulae

- A 'Markush' formula is a structural formula in which multiple chemical groups are allowed at one or more positions in the compound
- A 'Markush' formula is a shorthand way to describe a chemical structure that avoids the need to list all possible permutations (which may be vast) in a patent claim. In other words it is a generic representation of a class of compounds
- Those parts of the compound where substitution with a functional group selected from a defined list is permitted are typically denoted with an 'R'.
- Where there is more than one site at which a selection needs to be made, these sites are indicated R_1, R_2, R_3 etc.
- The identity of each such 'R' group will then be defined in the claim (as a list of all permitted substituent groups)

The Prior Art Formula

- In the present case, the following Markush formula, Formula A is in the prior art:



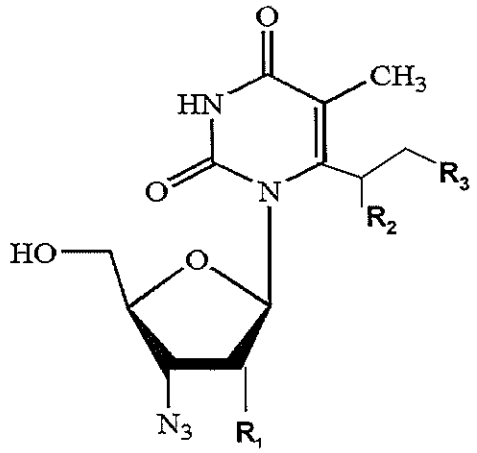
- In which:
  - R_1 is defined as one of the following: a hydrogen atom or a branched or unbranched, unsubstituted alkyl radical containing 1 to 6 carbon atoms
  - R_2 is a halogen atom; and
  - R_3 is a hydrogen atom, a hydroxyl radical or a branched or unbranched alkyl radical containing 1 to 5 carbon atoms optionally substituted with one or more substituents chosen from halogen atoms, hydroxyl radicals and phenyl groups

The Prior Art Formula

- It will be appreciated that at each of 3 positions (R_1, R_2 and R_3) a selection needs to be made from a large number of possible substituent groups. Accordingly, Formula A covers thousands of different compounds
- The prior art in the present case teaches that compounds described by Formula A inhibit cell division in vitro and are toxic to mouse tumours.
- Compounds within the scope of Formula A were under investigation as anti-cancer drugs before the priority date of the patent-in-suit

The Formula of the Patent

- In the present case, the following Markush formula, Formula B is claimed in the patent-in-suit:



- In which:
  - R_1 is limited to a hydrogen atom
  - R_2 is a halogen atom; and
  - R_3 is a hydroxyl radical or an unbranched alkyl radical containing 1 to 3 carbon atoms optionally substituted with a single hydroxyl radical or a phenyl group

The Formula of the Patent

- In this case a selection needs to be made at R_2 and R_3 (albeit from a shorter list of possible substituents than is the case for Formula A), but not at R_1
- Formula B is a much more narrowly defined subgroup of about 100 chemical compounds; all of which also fall within the broader scope of the prior art formula, Formula A
- The patent-in-suit is concerned with the discovery that compounds defined by Formula B block the activity of the HIV enzyme, reverse transcriptase, in an in vitro assay
- The in vitro assay used in the examples of the patent-in-suit is highly predictive of efficacy as an anti-retroviral agent in man and on this basis the patent promises that compounds described by Formula B will be therapeutically active against AIDS

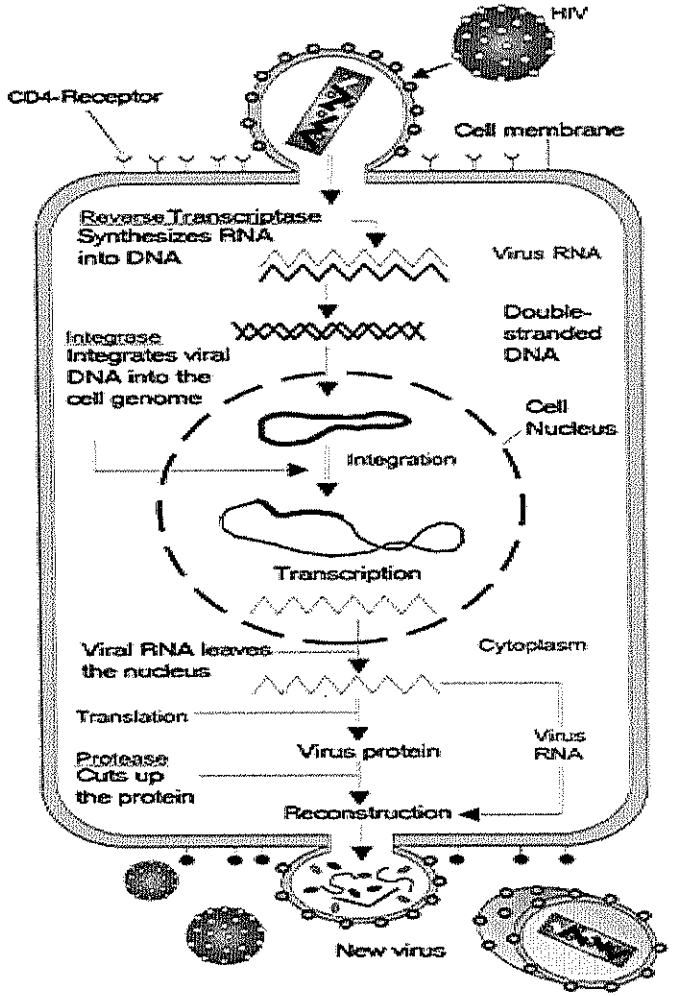
The Human Immunodeficiency Virus

- HIV primarily recognises and infects vital cells in the human immune system (such as 'helper T cells'). As infection takes control, the body's immune system becomes compromised and the body becomes progressively more susceptible to other 'opportunistic' infections
- HIV is a 'retrovirus'. That is to say its genetic material is in the form of single stranded RNA (not the 'classic' DNA double helix).
- Once inside a target cell HIV converts its RNA into double-stranded DNA. The DNA copy of the viral genome is then integrated into the host cell's own DNA.
- The virus then uses the human cell's own machinery to reproduce within the body and, after a time, to multiply and attack the body's immune system

HIV Lifecycle

- Upon entry to the target cell the RNA genome is converted into double stranded DNA by the HIV enzyme reverse transcriptase
- The viral DNA so formed enters the nucleus of the cell and is then integrated into the host cell's own DNA
- The viral DNA may then lie latent within the host's own DNA for many years
- After a period of time (typically between a few months and 20 years) the virus is triggered to become active and start to replicate
- A large number of virus particles will then be liberated and will infect other cells of the immune system, greatly impairing the body's ability to protect against infection (AIDS)

HIV Lifecycle



Reverse Transcription

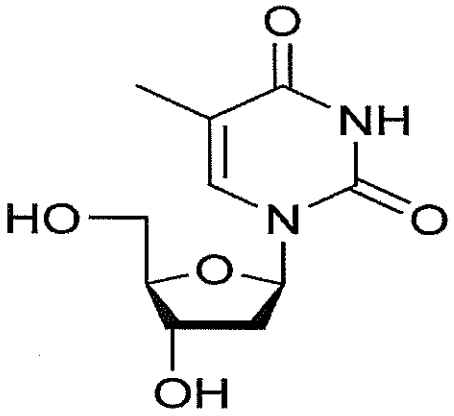
- The central thesis of molecular genetics is that genetic information flows from DNA to RNA and then to protein. In this way the genetic code within the sequence of the DNA double helix determines which proteins are produced
- Transcription is the synthesis of RNA from DNA. Hence reverse transcription is the reverse of this; the process by which RNA is converted into DNA.
- Reverse transcription is necessary for the HIV genome to become incorporated into the host cell's own genetic material. This allows the virus to evade detection by the body's defences and to reproduce
- Thus reverse transcription is a key step in the HIV lifecycle and an attractive target for drug therapies

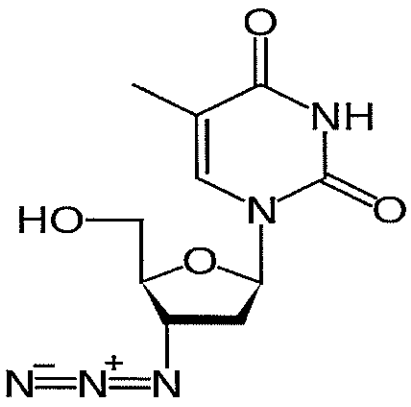
Reverse Transcriptase Inhibitors

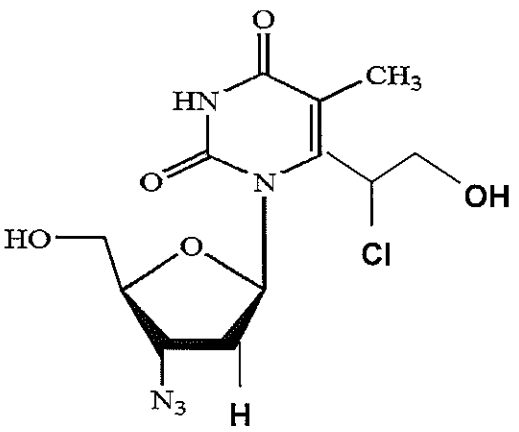
- The first major class of drugs found useful in slowing HIV infections are 'reverse transcriptase inhibitors'. These include AZT and 3TC and act by blocking the reverse transcription of viral RNA into DNA
- Reverse transcriptase inhibitors are analogues of one of the four nucleotides that are the building blocks of DNA (e.g. AZT is an analogue of thymidine). As a result of this structural similarity the reverse transcriptase enzyme mistakenly incorporates the drug into the growing DNA strand (e.g. AZT instead of thymidine)
- However, a structural difference between the reverse transcriptase inhibitor and the naturally occurring nucleotide prevents further chain growth once the drug molecule has been incorporated into the growing chain.
- Thus the formation of viral DNA, and hence new viruses, is halted

Reverse Transcriptase Inhibitors

- Etirovir, a compound within the scope of Formula B of the patent-in-suit, has been commercialised by Ethix plc and shown to be highly effective for the treatment of AIDS
- Etirovir, like AZT, is a thymidine analogue that acts by inhibiting HIV reverse transcriptase





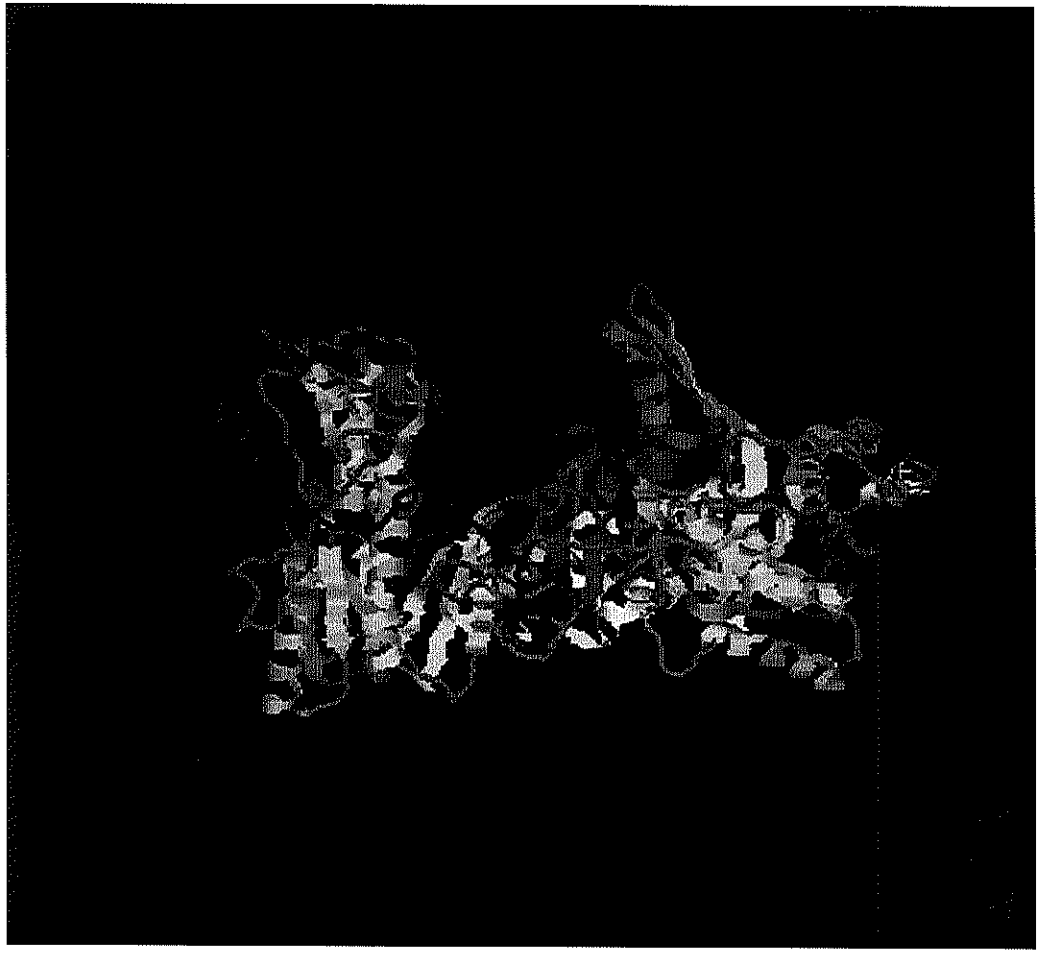


- Thymidine

AZT

Etirovir

3D Structure of Reverse Transcriptase



3D Structure of Reverse Transcriptase

- The 3D structure of HIV reverse transcriptase was well known at the priority date of the patent-in-suit (as was the mechanism of action of reverse transcriptase and of earlier reverse transcriptase inhibitors such as AZT)
- In particular the size and shape of the active site of reverse transcriptase was known at the priority date
- The active site of an enzyme is the 'pocket' in which the substrates enter (in this case the viral RNA template, the growing DNA strand and the nucleotide building blocks) and catalysis happens
- The skilled person at the priority date would have understood that if the side chains of the drug are too bulky it will not fit the active site of reverse transcriptase and so there will be no inhibitory effect