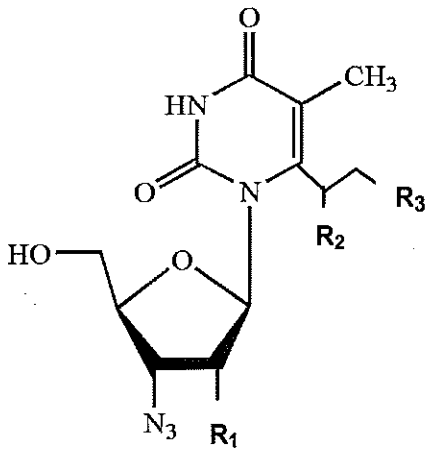
Symposium Zeist 2010

Debat 1 Mini trial

Prior art:

- The prior art, an earlier granted patent, discloses and claims a broad class of chemical compounds represented by the following 'Markush' formula (covering thousands of compounds) – **Formula A**:



Wherein R1 = a hydrogen atom or a branched or unbranched, unsubstituted alkyl radical containing 1 to 6 carbon atoms

And R2 = a halogen atom

And R3 = 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.

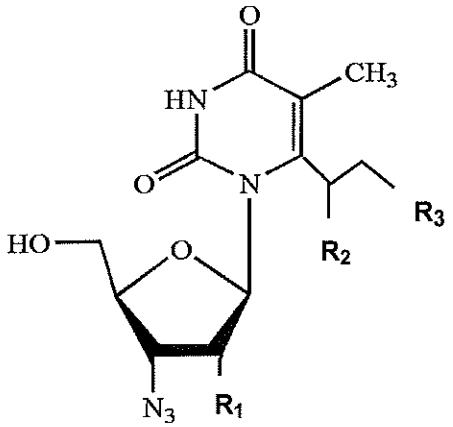
- The prior art teaches that compounds represented by Formula A inhibit cell division in vitro and are toxic to malignant tumours in mice. Before the priority date of the patent-in-suit, compounds within the scope of the formula were under investigation for their therapeutic efficacy in the treatment of different cancers.

Patent-in-suit:

- The patent-in-suit concerns the discovery that a particular, more narrowly defined sub-group of about 100 chemical compounds falling within the scope of the prior art formula, Formula A, also show activity in blocking the activity of the HIV enzyme, reverse transcriptase, in an in vitro assay. This assay, which is well known in the art and can be performed without undue effort, is highly predictive of efficacy as an anti-retroviral agent in man and on the basis of this assay it is promised that such compounds will be therapeutically useful in treatment of AIDS.

- The patent-in-suit is drafted as a selection i.e. that a novel sub-group of compounds falling within the scope of Formula A have been shown to possess a newly identified activity. However, there is no data to indicate whether or not other compounds outside the claimed sub-group, but within the scope of the prior art formula, also show activity in the reverse transcriptase inhibition assay.

- The claimed sub-group is defined as follows – **Formula B**:



Wherein R1 = a hydrogen atom

And R2 = a halogen atom

And R3 = 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.

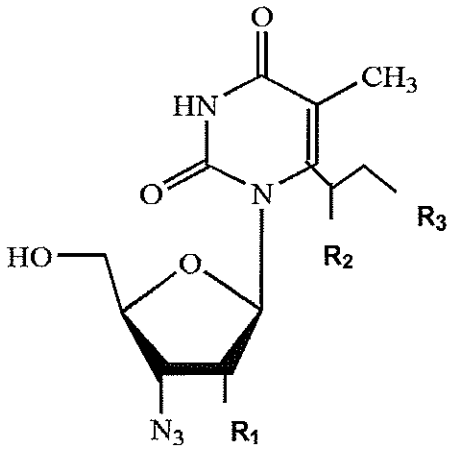
Although this sub-group falls within the scope of Formula A it is not disclosed in the prior art as a preferred sub-group and no compound within the scope of Formula B is specifically referred to in the prior art (for example as a preferred embodiment or in an example).

- The data in the patent-in-suit is very limited: only six compounds have been tested in the in vitro reverse transcriptase assay and shown to have activity (Examples 1-6) . However, the claims are not restricted to those compounds that have actually been tested, but extend to cover a group of about 100 structurally related compounds (represented by Formula B). There is no explanation in the patent (for example structure-activity analysis) to explain the extrapolation from the limited data in the specification to Formula B.

- The patent-in-suit describes a process for making the claimed compounds and provides detailed examples of the synthetic process. Following the teaching of the patent and using the 'common general knowledge' of organic synthesis, the skilled person would (without undue effort) be able to make all of the compounds within the scope of Formula B.

- The granted claims are as follows:

1. Compounds of general formula:



in which R1 represents a hydrogen atom, R2 represents a halogen atom and R3 represents 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.

2. A pharmaceutical composition which contains a product according to claim 1 optionally combined with one or more pharmaceutically acceptable products, whether inert or physiologically active.

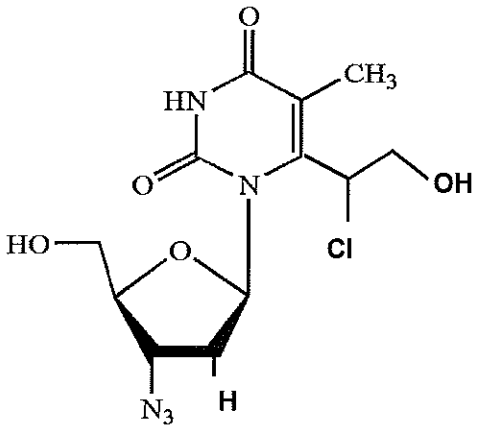
3. Use of compounds according to claim 1 optionally combined with one or more other physiologically active ingredients, for the preparation of a medicament for the treatment or prophylaxis of human retroviral infections including human immunodeficiency virus.

Subsequent work:

By patentee, Ethix Plc -

- A compound within the scope of Formula B (R2 = chlorine and R3 = hydroxyl) has been developed and commercialised by the patentee, Ethix plc, and (when used in combination with other antiretrovirals) it is a highly effective and successful product for the treatment of AIDS. This product, Etirovir, is not specifically referred to in the patent; although it is covered by claim 1 (a product claim for compounds of Formula B). Etirovir is not the subject of any of the examples of the patent and nor is it the subject of a separate claim or of a claim for a subset of compounds within the scope of Formula B.

- Etirovir has the following structure:



By party seeking revocation, Generipharm BV -

- A party seeking to revoke the patent-in-suit (Generipharm BV) performs experiments on compounds within the scope of Formula B. These experiments show that whilst the majority of compounds tested possess the claimed activity at varying levels (in the same in vitro reverse transcriptase assay as described in the patent) a number of compounds (3 out of 20 tested) do not show any activity at all (notwithstanding that they all possess the activity promised in the prior art patent – e.g. in vitro inhibition of cell division and toxicity to mice tumours). The assay was performed in the same way as described in the examples of the patent-in-suit and with a high degree of scientific rigour.

- However, the 3 compounds that have been shown in these experiments to be inactive in the in vitro reverse transcriptase assay of the patent all contain, as the R3 group, a branched or unbranched alkyl radical substituted with a phenyl group. Before the priority date of the patent-in-suit the 3D structure of the active site of the HIV reverse transcriptase enzyme had been published (with much fanfare). The skilled person would have been aware of these studies at the priority date and would have understood from them that bulky side chains (such as an alkyl group substituted with a phenyl radical) would not fit in the active site of the enzyme and so would not be expected to have an inhibitory effect on reverse transcriptase activity.