INDOLE BASED NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR FOR THE TREATMENT OF HIV

Brief Description

A novel indole based non-nucleoside reverse transcriptase inhibitor for the treatment of HIV was discovered in our laboratories as part of a national drug design project. This compound was found to be very potent against HIV in a phenotypic assay, with an IC50 value of 1 nM. This is better than the most potent anti-HIV agent currently on the market. Furthermore, the compound exhibited low toxicity with a CC50 value of 30 μM, thereby providing a therapeutic index of over 30000.

Target Market

Pharmaceutical market

Value Proposition / Benefits

- Very potent novel NNRTI
- Low toxicity
- Short synthetic sequence potentially simple to scale up.

Unique Characteristics

- Highly potent indole based NNRTI, with very low toxicity
- Interactions optimised for π-π stacking interaction with Tys181, as well as a σ-π interaction with the conserved residue, Trp229.

Technical Description

The compound in question utilises an indole scaffold, substituted at the 2-, 3- and 5- positions to optimise interactions within the allosteric pocket of HIV RT. Key features of the compound include a double hydrogen bonding interaction to Lys101, facilitated by the indole NH and the substituent at the 2-position. The substituent at the 3-position fulfils two important roles: The first of these is a π-π stacking interaction with Tys181, as well as a σ-π interaction with the conserved residue, Trp229. The second interaction is occupation of a small hydrophobic pocket located in the vicinity of Val179. This particular substituent on the indole scaffold was designed to be somewhat flexible in comparison to our previous generation inhibitors. The result was a 100X improvement in potency. At the 5-position of the scaffold a halogen substituent effectively occupies another small hydrophobic pocket.

Innovation Status

A working prototype exists and a provisional South African patent application has been filed (2013/07447).

Principal Researchers

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