Pharmaceutical compositions

VNIVERSITAT DE VALÈNCIA

R&D RESULT

Patent

Knowledge area

- Pharmacology
- Organic Chemistry

Collaboration

- Technology available for licensing
- Other collaborations

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Pharmaceutical agents for treating HIV-1 infections

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Background: Currently there is a critical need to develop new therapies to get rid of the infection caused by human immunodeficiency virus type-1 (HIV-1). The Rev Recognition Element (RRE) is a strongly conserved 350-nucleotide structure located in the *env* gene of HIV-1 RNA. Within subdomain IIB of the RRE, the unusually widened major groove of a large 5:6 internal loop forms a high-affinity complex with the arginine-rich α-helix of Rev, a virally-encoded 116-amino acid protein adopting a helix-turn-helix conformation. This initial interaction between internal loop IIB and the RNA-binding helix of Rev (Rev_{34-50}) is essential for virus viability, as it triggers a cascade of events allowing the transport of unspliced or incompletely spliced viral RNA molecules to the cytoplasm of the infected cell in the late phase of the virus cycle. These events include the incorporation of additional Rev molecules to the complex through helix-helix contacts and interactions with further sites on the RRE, and the tethering of this RRE-Rev ribonucleoprotein to the Crm1 host export factor.
Evidence accumulated in recent years indicates that Rev represents a pivotal target for HIV-1 therapy. However, up to now the rational design of Rev-based inhibitors has remained an elusive goal.

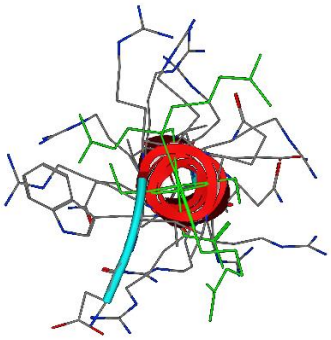
The invention: Researchers from UV, UCV, CIPF and ISCIII have design and synthesize new **compounds useful as pharmaceutical agents for treating HIV-1 infections** and related diseases. The compounds are based on a new, bilaterally-substituted terphenylene scaffold that mimics the RRE-binding α-helix of the HIV-1 protein Rev. Small organic compounds bearing this scaffold are able to bind to the RRE internal loop and inhibit the RRE-Rev_{34-50} interaction with IC_{50} values of 6.8 µM. These compounds bind to the RRE internal loop from the major groove, as intended in the original design, occupying the binding site of Rev_{34-50}. They block HIV-1 replication in cell cultures with EC_{50} values of 3.4 µM, and exhert this effect in transcriptional or post-transcriptional steps of the virus life cycle.

This is the first time that a new organic scaffold with demonstrated RNA-based activity has been designed *de novo*.

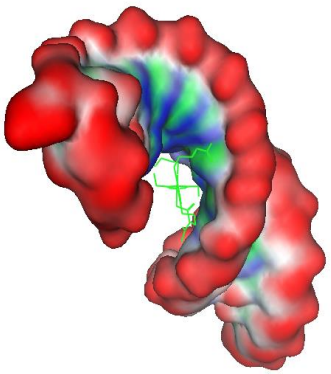
Applications: The new compounds and pharmaceutical compositions are useful as pharmaceutical agents for **treating HIV-1 infections and related diseases**.

Advantages: The main advantages provided by the new compounds are:

- RNA specificity in the same range as Rev_{34-50}.
- Capable of inhibiting the RRE-Rev interaction both *in vitro* and *ex vivo*.
- No cellular toxicity was detected in *ex vivo* assays.
- They have a novel, non-peptidic, synthetic scaffold able to recognize a strongly conserved viral RNA motif. This can result in a slower appearance of resistance relative to the compounds currently used in the clinic, which act on less conserved protein targets of the virus.



Superposition of the minimum-energy conformation of a bilaterally-substituted terphenyl (green lines) on the Rev_{34-50} α-helix.



Complex between the RRE (colored surface) and an hypothetical terphenyl molecule, (green lines) generated by docking.

OTRI oficina de transferència de resultats d'investigació

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