COMPOUNDS WITH A BENZO[A]CARBAZOLE STRUCTURE AND THEIR USES

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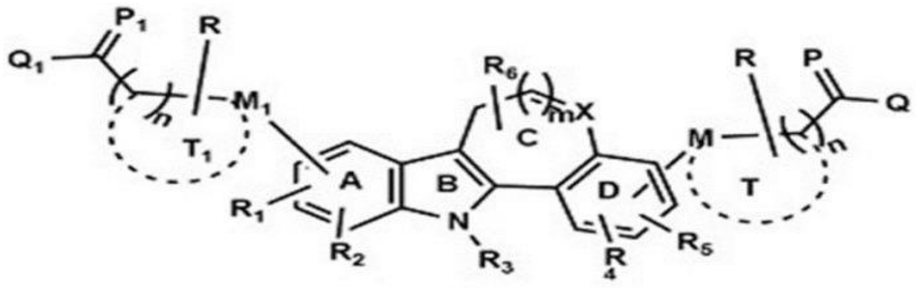
Invention

The present invention concerns the **development of new derivatives with apoptosis-modulating action by inhibition of the MDM2/p53 complex**.

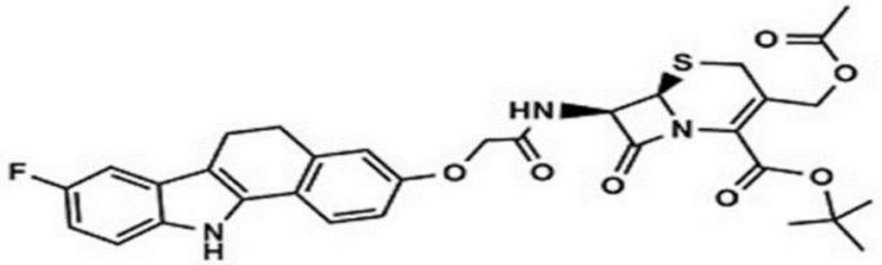
Inhibition of MDM2/p53 is one of the therapeutic targets in cancer, immunology and infectious diseases in which, by activation of p53, oncogenic effects can be induced in host cells.

The patented compounds possess **apoptosis-modulating properties** by **inhibition of MDM2 (or MDMX) binding to the transcription factor p53**. Inhibition of the formation of this complex induces an accumulation of intracellular levels of p53 , exerting positive effects in tumors, inflammatory processes, immune diseases and in some infectious diseases (bacteria, viruses or protozoa). The molecules, appropriately substituted, are suitable for both therapeutic purposes (e.g., chemotherapy) and diagnostic use, only if properly functionalized. A representative example of compound I (shown in figure) is the RM37 derivative that effectively reaches the intracellular MDM2 target with high affinity, presenting low toxicity to normal host cells.

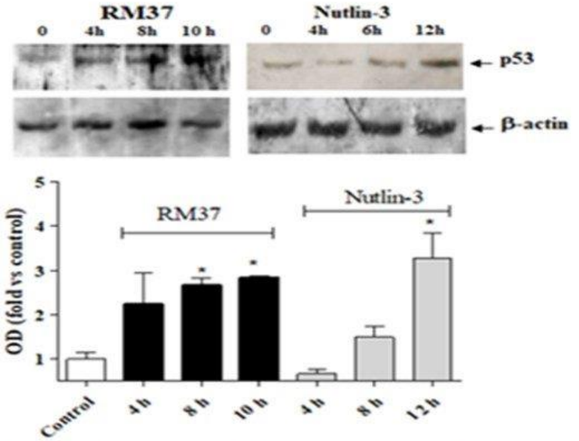
Drawings
& pictures



I



I, RM37



RM37 induce la stabilizzazione di p53. L'incubazione di una linea cellulare di glioblastoma multiforme umano con RM37 ha portato ad un aumento dipendente dal tempo dei livelli proteici di p53 (8 e 10 ore), suggerendo che la stabilizzazione di p53 possa essere dovuta a una riduzione della degradazione mediata da MDM2. Nutlin-3 ha indotto un significativo accumulo di proteina p53 dopo 12 ore di trattamento.

Industrial applications

Pharmaceutical compositions containing patented molecules as the active ingredient may be effective candidates for use in chemotherapy or as labeled derivatives for the diagnosis of diseases with abnormalities of p53 function and MDM2/X overexpression. Such compounds may thus find application in.

- Oncology;
- Immunology;
- Hematology;
- Gastroenterology;
- Neurology;
- Cardiopulmonary diseases;
- treatment of infections by bacteria, viruses, protozoa (activity claimed in a newly filed patent application).

ADVANTAGES

- Potency and selectivity of action toward RM37 target (IC_{50} = 220 nM, Nutlin-3 IC_{50} = 290 nM):
- Low toxicity to normal host cells;
- Lack of antibiotic activity;
- Good bioavailability;
- Easily accessible synthetic processes.

Possible developments

The totally novel chemical entities showed **good inhibitory properties of MDM2/p53 binding** on cancer cell lines (e.g., U343MG and T98G of glioblastoma). Compound RM37 demonstrates a clear intracellular effect: a) it inhibits MDM2/p53 binding, b) its binding to MDM2 activates the gene trans-activation function of p53, c) it stabilizes intracellular p53 levels better than Nutlin-3 (reference drug). The **antitumor effect** of RM58 and RM37 is similar to that of Nutlin-3 by inducing apoptosis of U343MG and T98G cells.

The studies proceed toward optimizing the molecular structure of the best candidates and to evaluate their efficacy, potency, and toxicity by *in vitro* test.

The inventors are interested in future collaborations to increase the technological readiness of the invention and expand innovative drugs opportunities, considering licensing or transferring the patented invention to interested companies.

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