NEW FAMILY OF MOLECULES AGAINST BACTERIA, VIRUSES AND CANCER

PATENTED TECHNOLOGY

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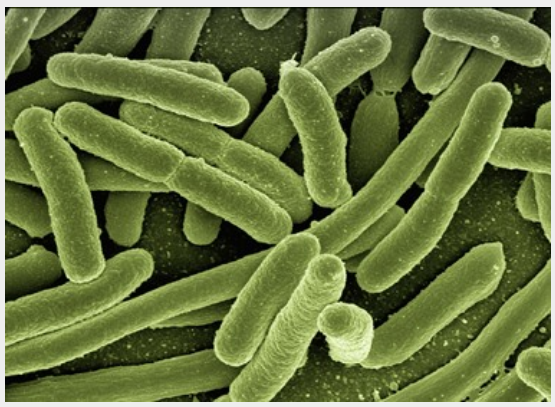
ABSTRACT

The research group "Catalytic Processes in Organic Synthesis" of the University of Alicante has developed a procedure to synthesize nucleosidic homologues (azanucleosides) in order to obtain molecules able to inhibit development of bacteria, viruses and cancer.

The main advantages of this technology are: easy process of synthesis and low cost drugs. It can be used in the following industrial sectors: pharmaceutical, food packaging films and containers, insecticides, etc.

These compounds have been synthesized in laboratory scale and preliminary biological in vitro test revealed inhibition of Herpes Simplex Virus (HSV-1), Escherichia coli and breast tumour cell line MCF-7. The research group is looking for companies acquiring this technology for licensing agreement, manufacturing agreement, technical cooperation or a combination of some of these services.



TECHNICAL DESCRIPTION

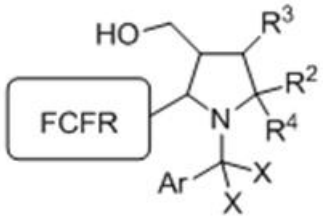
Microorganisms, especially bacteria, viruses and fungi, have developed resistance mechanisms against drugs. In most cases, infections have been acquired while surgery or blood transfusion took place. These long infections are very expensive for the public health, and for this reason, society needs new drugs able to inhibit microorganisms efficiently.

Recently, it has been proved that a wide family of nucleosidic antibiotics attack different stages of the cellular wall synthesis of

bacteria and fungi. These new molecules are ready to direct drugs to their biological targets, reducing undesirable secondary effects.

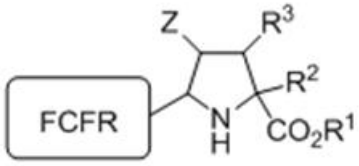
It was also demonstrated that viruses resistance to a nucleosidic drugs is more difficult to achieve. In this sense, demand of new drugs for the market with high antibacterial, antiviral and anticancer activity is permanently increasing.

This procedure concerns to a synthetic sequence to generate compounds with the following general structure:

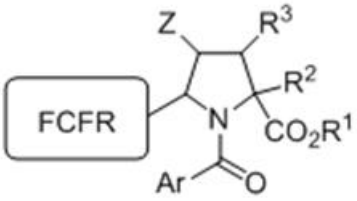


This procedure includes four steps:

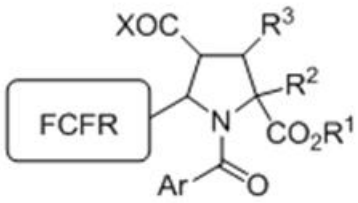
a) Elaboration of a first intermediate by a multicomponent reaction between an aldehyde, a nitrogenated base (purine or pyrimidine), an amino ester and a dipolarophile under mild reaction conditions.



b) Reaction of the previous molecule in a) with an acid chloride provides soluble molecules in order to facilitate penetration across the outer membrane of microorganisms.



c) Hydrolysis of the ester groups of the previously obtained compounds in b) affords the corresponding carboxylic acids as intermediate compounds.



d) Chemoselective reduction of COX or CO2H groups of molecules described in c) would finally lead to the compounds whose general structure was depicted at the beginning of this document.

In this general procedure, FCFR refers to a purine or pyrimidine base such as adenine, guanine, thymine, cytosine or uracyl, whilst R1, R2, Z, R3, R4, Ar, X y Z1-R are selected according to the previous studies performing using docking molecular simulation model.

TECHNOLOGY ADVANTAGES AND INNOVATIVE ASPECTS

MAIN ADVANTAGES OF THE TECHNOLOGY

This technology regards the synthesis of new compounds which are nucleoside homologues (azanucleosides) through a multicomponent 1,3-dipolar cycloaddition employing aldehydes bearing a purine or a pyrimidine base (or another heterocycle) similar to those employed in the genetic material by animals and plants.

Final compounds and their derivatives are **completely new**, and in most cases, starting aldehydes have not been described previously in scientific literature.

Presumably, these new drugs can be **more efficient, inexpensive and would avoid resistance mechanisms** of the pathogens against themselves.

Another advantage of these family of molecules is their capability of interact into DNA/RNA strands of the malicious

microorganisms or cells inhibiting their reproduction. Through this strategy, it will be able to increase the antimicrobial or anti-tumoural spectrum.

INNOVATIVE ASPECTS

This new technology allows to synthesize small molecules with a simple skeleton. **These molecules are not expensive** and the **procedure takes place in a mild reaction conditions with a total atom economy**. The multicomponent feature means that the domino sequence occurs previously to formation of the imino ester followed by the cycloaddition process.

The inhibitor potential character can be impressive. In addition, enantioselective synthesis of the most active molecules can be designed according previous experience of the research group in asymmetric catalysis involving 1,3-dipolar cycloadditions between azomethine ylides and electrophilic alkenes.

CURRENT STATE OF DEVELOPMENT

The research group "Catalytic Processes in Organic Synthesis" of the University of Alicante and several Spanish research groups constitute a multidisciplinary team with the aim to study deeply all the possibilities of these drugs. The experience of each group is internationally recognised, and all of them, support this project with a high level of implication.

These new molecules have been prepared in laboratory scale, and just a few preliminary standard tests have been performed in bacteria, virus and a cancer cell line. In particular, derivatives obtained from 5-formyluracyl, methyl glycinate and N-methylmaleimide have been selected for three in vitro tests, and the results were the following:

- 15% inhibition Herpes Simplex Virus (HSV-1), 50 µg/mL, CC50>200 µg/mL, EC50 36.
- 13% inhibition Escherichia coli (E. coli), 5.6 µM.
- 8% inhibition breast cancer cell line MCF-7, 1 mg/mL.

In addition, the research group is operating in a pilot plant of the University of Alicante. It works following ISO 9001:2000 and Good Manufacturing Practice (GMPs). GMP is really important because is a production and testing practice that helps to ensure a high quality product. Many countries have legislated that pharmaceutical and medical devices must follow GMPs procedures according to their legislation.

Pilot plant facilities of the University of Alicante

MARKET APPLICATIONS

This technology is framed within Pharmaceutical Chemistry, and relates to a method to synthesize nucleosidic homologues (azanucleosides) and their use in the manufacture of drugs for the treatment of:

- Bacteria diseases (Escherichia coli, etc.).
- Viral diseases (retroviruses such as hepatitis C, HIV, Herpes Simplex Virus, etc.).
- Cancer (breast tumour cell line MCF-7).

This family of molecules can also be applied in agriculture (phytosanitary treatments for fungal infections), and in the food industry (coating films to avoid microbial contamination).

COLLABORATION SOUGHT

The research group is looking for companies interested in acquiring this technology for commercial exploitation by:

- Licensing agreement.
- Financial support for all required tests.
- Agreements in technology transfer or knowledge transfer.

INTELLECTUAL PROPERTY RIGHTS

This technology has been protected by patent:

- Title of the patent: “Procedure to synthesize homologue azanucleosides derivatives.”
- Application number: P201300304.
- Application date: 27th March 2013.

MARKET APPLICATION (6)

Agri-food and Fisheries
Biology
Molecular Biology and Biotechnology
Pharmacology, Cosmetics and Ophthalmology
Medicine and Health
Chemical Technology