Patent application no: A 00617 / 07.10.2022
(BOPI no. 4 / 2024)

Tittle: Topical product based on plant extract for skin condition and projected diseases combining inflammation and infectious processes

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NOVELTY:

- ✓ **The topical product is based on a standardized plant extract which cumulates active compounds from 51 vegetal species, HAY FLOWERS ' EXTRACT, respectively.**
- ✓ **HAY FLOWERS are a very complex vegetal raw material summing the pastoral flora of the country of origin.**
- ✓ **HAY FLOWERS consist of flowers, seeds, stems and leaves cumulating a plethora of active compounds.**

❑ TECHNICAL DESCRIPTION:

- ✓ **The topical product was designed for the purpose of medical device development.**
- ✓ **The topical product has been designed in two formulation variants, hydrogel and cream**, and they are addressed to skin conditions (e.g., acne and folliculitis) and other inflammatory diseases with treatment through the intervention at the skin level (e.g., joints' inflammations).
- ✓ **The two variants contain the following ingredients:** formulation ingredients (0.50% carbopol, 0.25...0.50% pemulen, 0.25... 0.50% plurol), natural conservatives (Vitamin E and 1.00...5.50% tamanu fruit oil), and 5.00% standardized extract from HAY FLOWERS' TEA (a commercial product based on 51 vegetal species).

❑ADVANTAGES:

- ✓ The complex chemical composition of the HAY FLOWERS' EXTRACT (HF) assures effective antiinflammatory and antimicrobial properties.
- ✓ The two formulas are homogeneous, stable and quickly penetrates the skin; they do not contain chemical preservatives; they have a pleasant herbal scent.
- ✓ The invention capitalizes the knowledge of the Romanian folk medicine, validated by hundreds of years of use.

❑ TECHNOLOGICAL, CHEMICAL ANALYTICAL AND PHARMACOLOGICAL ASPECTS:

- ✓HF is a standardized 40% ethanolic extract from HAY FLOWERS TEA with a precise content of **2 mg% gallic acid equivalents (GAE).** Figure 1 shows the chemical qualitative composition of the HF in phenolics (**HPTLC method**).
- ✓HF indicated antimicrobial efficacy against the *Staphylococcus aureus in vitro*.
- ✓HF indicated antiinflammatory efficacy by *in vivo* inflammatory rat model. Table 1 shows the pharmacological results on the hydrogel variant with 5.00% HF, tested on four groups of rats with paw edema induced with carrageenand antiinflammatory efficacy by *in vivo* inflammatory rat model.

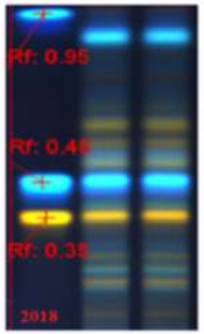

Figure 1 (left). HPTC analysis for chemical qualitative composition in polyphenols of HF in comparison with the reference compounds used: rutin/Rf-0.35, chlorogenic acid/Rf-0.45, caffeic acid/Rf-0.95.

Test groups	The evolution of volume edema (%) compared to negative control at 3 hours and 5 hours		The situation of volume edema at the end of the experiment (24 hours)
Positive control group	+ 17%	+27%	+ 37%
Group treated with the reference substance, a commercial product based on 5% diclofenac	+ 47%	+51%	+ 11%
Group treated with the test product, hydrogel formula based on 5% HAY FLOWERS' EXTRACT	+ 45%	+59%	-24%

Table 1. *In vivo* **pharmacological results in comparison with diclofenac 5%.**

❑ **CONCLUSION: The topical product proved an antiinflammatory activity superiour to that of the reference substance used (a commercial product based on 5% diclofenac), therefore the HAY FLOWERS' EXTRACT is effective in skin conditions and skin projected diseases combining inflammation and infectious processes.**

COMPOSITE MEMBRANES BASED ON BACTERIAL CELLULOSE AND PVA, USED AS A SUBSTRATE FOR OLEDS AND PROCESS FOR OBTAINING

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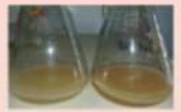
Patent application no. A/00729/2022, published in RO-BOPI 5/2024, RO138203 / 30.05.2024

NOVELTY

The invention relates to obtaining bacterial cellulose/PVA (polyvinyl alcohol) nanocomposite membranes, with improved transparency, as a substrate for flexible displays with organic light-emitting diodes (OLED), with use/applications in the electronic and optoelectronic fields.

EXPERIMENTAL

The composite membranes based on BC-PVA, according to the invention, consist in that they are made of bacterial cellulose matrix and 5-25% by weight polyvinyl alcohol (PVA), and the obtaining process, according to the invention, consists in that they are functionalized by in situ techniques, by direct addition of solutions of 5%, 7%, 10%, 12%, 15%, 20% and 25% polyvinyl alcohol PVA, in the bacterial cellulose incubation medium (biological synthesis). After completing the biotechnological process, bacterial cellulose-PVA composite membranes were obtained, which were processed according to the procedure.



Nanocellulose membrans obtained by biotechnological process via *Acetobacter xylinum fermentation*

purification

Purified bacterial cellulose-PVA membranes

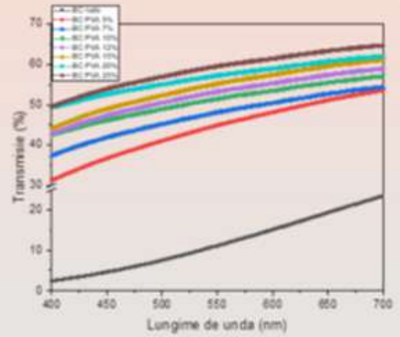


Figure 1. Optical transmission spectra of BC membranes and BC/PVA composite membranes

Technical problems – solutions:

- The technical solution consists in the possibility of obtaining new composite biomaterials, with improved properties (transparency), and will prove to be an interesting solution for the realization of green BC/PVA composites, which satisfy the need to explore minimal cost, biodegradable and renewable materials. Thus, the present invention achieves the obtaining of BC/PVA electroluminescent composite membranes/materials with applications in the electronic and optoelectronic fields, through a simple, fast and low cost method.

Application advantages:

The BC/PVA composite membranes, according to the invention, have the following advantages:

- flexible, transparent, chemically stable, biodegradable materials/films – environmentally friendly
- they are cheap, due to the renewable carbon source used to obtain bacterial cellulose
- biological synthesis is simply controlled and can be produced on a large scale

CONCLUSIONS

The nanocomposite membranes according to the invention, based on bacterial cellulose obtained by exploiting renewable resources (BC) and polyvinyl alcohol (PVA), following the research carried out, it was found that at a wavelength of 500 nm, an increase in optical transmission was observed by 33% for BC-PVA 5%, and up to 50% for BC-PVA 25%, by in situ functionalization of the bacterial cellulose membrane with polyvinyl alcohol having concentrations ranging between 5-25%, compared to native bacterial cellulose membranes.

Acknowledgement
This work was supported by PNCDI III - PN-III-P2-2.1-PED-2019-1459 Demonstration experimental project within the Financing Agreement no. 468PED/2020 Flexible organic electroluminescent diodes on bacterial cellulose substrate using electrospun transparent fibers as anode", Acronym: FOLEDBCfiberWEB

1-Benzyl-quinolone derivatives as dual inhibitors of DNA gyrase and Topoisomerase IV

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RO 138003A2

The present invention broadens the range of derivatives with the quinolone structure dual inhibitors of DNA gyrase and Topoisomerase IV with new compounds that correspond to the general formula I.

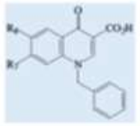
The structures of the compounds were designed using Spartan Wavefunction, Inc. Irvine CA USA. For each compound, the 3D structure of the CPK model was generated, the geometry was optimized by minimizing the energy, to obtain the most stable conformer, of minimum energy. The molecular descriptors and molecular properties were calculated (Table 1): mass, energy, solvation energy, frontier orbital energy, area, volume, total polar surface area (TPSA), ovality, water-octanol partition coefficient (logP), polarizability, dipole moment.

Molecular docking studies of the designed compounds were performed with CLC Drug Discovery Workbench to identify and visualize the ligand-receptor interaction mode.

The interactions of the designed compounds with a series of receptors extracted from the Protein Data Bank (https://www.rcsb.org) were studied (Figure 1, Figure 2-5):

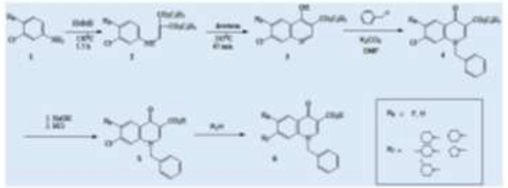
- *Staphylococcus aureus* DNA gyrase subunit A (PDB ID:5CDQ);
- *Multidrug efflux pump subunit AcrB -Escherichia coli* (PDB ID: 1T9U);
- *Streptococcus pneumoniae* DNA gyrase subunit B (PDB ID: 4Z2C);
- *Human estrogen receptor alpha* (PDB ID:3ERT).

1-Benzyl-quinolone derivatives are prepared by the Gould-Jacobs method – Reaction scheme No. 1 which consists of the condensation reaction of 3-substituted/unsubstituted-4-chloro-aniline (1) with ethyl ethoxymethylenemalonate at a temperature of 130^{0}C, for 1.5 hours and the cyclization of the anilinomethylenemalonate (2) obtained in the dowterm at 240-250^{0}C, for 45 minutes. Intermediate (3) (ethyl ester of 6substituted/unsubstituted-7-chloro-4-hydroxy-quinoline-3carboxylic acid) is further subjected to the alkylation reaction with benzyl chloride, in the presence of potassium carbonate and in N, N-dimethylformamide medium. The ethyl ester (4) is further subjected to a hydrolysis reaction, and the quinoline-3-carboxylic acid (5) following regiospecific substitution reactions of the chlorine in position 7 leads to compounds (6).



where:
R_6 = F,H.
R_7 = piperidinyl, 3-methyl-piperidinyl, pirolidinyl.

I: General Formula
New quinolones compounds



Scheme 1. Preparation of quionolone compounds

Table 1. Molecular properties of the designed compounds

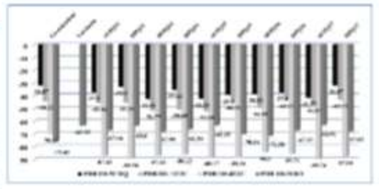


Figure 1. Docking score compared to the reference quinolone

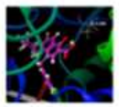


Figure 2 Compound 6FPQ14 docked in 5CDQ

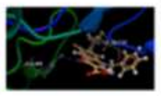


Figure3 Compound 6FPQ15 docked in 1T9U

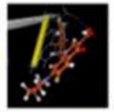


Figure 4 Compound 6FPQ17 docked in 4Z2C

Figure 5 Compound 6FPQ18 docked in 3ERT

Application: Laboratory

•for the synthesis of new derivatives starting from a number of the compounds disclosed in this invention;
• for the synthesis of the necessary quantity for the further preclinical studies. A series of compounds were sent to the European Academic Compound Library for studies to determine specific activity.

Advantages

•Quinolone derivatives shows a broad spectrum of activity against microorganisms encountered currently in the clinical practice;
•The preparation process proposed leads to the obtaining of quinolone derivatives with high yields and the corresponding purity.

Acknowledgement
This patent has been financed through the NUCLEU Program, which is implemented with the support of MCDI, project no. PN 19-41 01 02

6-Chloroquinolone derivatives with antimicrobial activity

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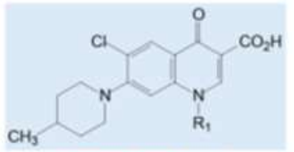
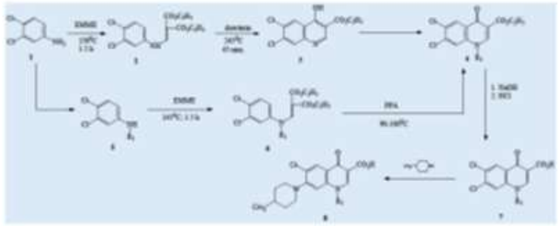
RO 134117A2

The invention relates to derivatives with a quinolone structure: 1-(substituted)-6-chloro-7-(4-methyl-piperidiny()-1,4-dihydro-quinoline-3-carboxylic acid (I), with antimicrobial activity against gram-positive and gram-negative microorganisms, in which R_1 is allyl, isopropyl or benzyl. Derivatives with a quinolone structure are used in the treatment of infections caused by gram-positive and gram-negative microorganisms. The synthesis of the new quinolones followed a Gould-Jacobs cyclization process (Scheme 1). This method consists of the condensation reaction of 3,4-dichloroaniline (1) with ethyl ethoxymethylenemalonate at a temperature of 130^0 C, for 1.5 hours and the cyclization of the anilinomethylenemalonate (2) obtained in the dowterm at 240-250^{0}C, for 45 minutes. The intermediate (3) (ethyl ester of 6,7-dichloro-4-hydroxy-quinoline-3-carboxylic acid) is further subjected to the alkylation reaction with alkyl halide: allyl chloride or benzyl chloride, in the presence of potassium carbonate and in N, N-dimethyl formamide medium. The ethyl ester (4) (where R_1 is allyl or benzyl) is further subjected to a hydrolysis reaction, and the quinoline-3-carboxylic acid (7) following regiospecific substitution reactions of chlorine in position 7 leads to compounds (8). To obtain quinolin-3-carboxylic acid derivatives, where R_1 is *isopropyl*, the modified Gould-Jacobs method was used, in which the reaction of ethyl ethoxymethylenemalonate takes place with an N-monosubstituted aniline (5). Aniline (5) is obtained by reductive amination reactions of some ketones with sodium triacetoxyborohydride. Aniline (5) is further subjected to a condensation reaction with ethyl ethoxymethylenemalonate at a temperature of 150-160^0 C, for 1-2 hours. To induce cyclization with the direct formation of ethyl N-alkyl-4-oxo-quinolin-3-carboxylate (4) (where R1 is isopropyl), the presence of a strong acid (e.g. polyphosphoric acid) is required. (The cyclization reaction of compound (6) takes place at a temperature of 80-100^0 C, for 1-2.5 hours). The ethyl ester (4) (where R1 is *isopropyl*) undergoes a hydrolysis reaction, and the quinoline-3-carboxylic acid (7) following regiospecific substitution reactions of the chlorine in position 7 leads to the final compounds (8). Among all the synthesized compounds, it was observed that compound 6ClPQ 4 (1-allyl-6-chloro-7-(4-methyl-piperidiny()-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid) has an activity comparable to compound FPQ 4 (1-allyl-7-fluoro-7-(4-methyl-piperidinyl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid) on all 3 strains tested: *E. Coli*, S.*Aureus* and *P.Aeruginosa*.



I: General Formula
New quinolones compounds

where:
R_1 = allyl, *isoflpropy*, benzyl.



Scheme 1. Preparation of quionolone compounds

Table 1. *In vitro* Antibactrial activity

Compound	Organism (MIC μg/ml)		
	E. coli	*St.aureus*	*Ps. aeruginosa*
FPQ 4*	12,5	1,56	>25
6ClPQ 4	12.5	1.56	>25
6ClPQ 11	>25	>25	>25
6ClPQ 12	>25	2	>25

*L. Pintilie si alții, Biotehnol.Lett.,2003,8(2), 1200

Application: Laboratory

•for the synthesis of new derivatives starting from a number of the compounds disclosed in this invention;
• for the synthesis of the necessary quantity for the further preclinical studies.

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•Quinolone derivatives shows a broad spectrum of activity against microorganisms encountered currently in the clinical practice;
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