A NEW CLASS OF FLUORESCENT STAINS WITH A STRUCTURE OF BETAINE AND TRIAZOLE SALTS

Product description

New betaines and triazole salts are innovative compounds of fluorescent properties, dedicated especially to the biomedical industry. Interest in the technology of generating of triazole betaines and adequate quaternary triazole salts condensed with heterocyclic combinations of pyridine and quinoline, results mainly from the fact that they can be applied to detection and marking of secondary amines and formaldehyde with the use of spectrophotometric method, as well as building of fluorescent markers of an ester's structure with *N-hydroxysuccinimide*, used for marking of medicaments, proteins, amino sugars, biogenic amines, or nucleic acids.

Effective method of stains generating has been developed and patented, based on the structure of 1,2-dihydro-[1,2,4]triazolo[4,3-*a*]pirydino-4-carboxylic acid derivatives, izoxazol[3,4-*b*]quinolin-3(*1H*)-on, 1,2-dihydro-[1,2,4]triazolo[4,3-*a*]quinolino-4-carboxylic acid derivatives.

Additionally, it has been indicated that both betaines and quaternary triazole salts, generated pursuant to reaction with mineral acid are, according to the invention, characterised by antibacterial and antifungal properties, which means that they potentially could be applied in treatment of bacterial and fungal infections. It has been proved that the proposed fluorescent markers (Safirinium P, Safirinium Q) can be used in visualisation of spores of e.g. *Bacillus subtilis* bacteria.

Key words

4,6-dimethylo-izoxazolo[3,4-b]piridin-3(1H)-e; izoxazolo[3,4-b]quinolin-3(1H)-on; (2,2-dialkilo-1,2-dihydro-[1,2,4]triazolo[4,3-a]quinolin-2-ium)-4-carboxylic acid derivatives, (2,2-dialkilo-1,2-dihydro-[1,2,4]triazolo[4,3-a]piridin-2-ium)-4-carboxylic acid derivatives, chemotherapeutic and fluorescent properties, Mannich tandem reaction - electrophilic amination

Legal status of the product

– Polish Patent Office:

PL 223740 "Izoxazolo[3,4-b]quinolin-3(1H)-on, 1,2-dihydro-[1,2,4]triazolo[4,3-a]piridino-4-carboxylic acid derivatives, and 1,2-dihydro-[1,2,4]triazolo[4,3-a]quinolino-4-carboxylic acid derivatives, their methods of generation and application" – submitted to the PPO on 20.09.2012, the decision on granting the patent of 16.02.2016 – entity solely entitled to the invention – Medical University of Gdańsk

The aim of the offer

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The subject of the offer is the elaborated technology developed by our native scientists, which is to generate stains from the group of betaines and triazole salts, i.e. 1,2-dihydro-[1,2,4]triazolo[4,3-*a*]piridino-4-carboxylic acid derivatives, izoksazolo[3,4-*b*]quinolin-3(*1H*)-on, 1,2-dihydro-[1,2,4]triazolo[4,3-*a*]quinolino-4-carboxylic acid derivatives, as strong fluorescent compounds for use in medical, bio-chemical, and environmental analysis, and as fluorescent markers (molecular probes) applicable in i.a. bio-imaging processes.

Foregoing funding of studies on the product

The work was financed from statutory research of Department of Chemical Technology of Drugs of Medical University of Gdańsk - work ST 38.

Analysis of competition on the market

Fluorescent stains are currently very popular and they are applicable in biochemistry, molecular biology, biochemical diagnostics, medical diagnostics, as well as in environmental analysis. Uniqueness of this group of compounds results from high fluorescent sensibility and resolving power of fluorescent techniques. Despite the fact that there are many fluorescent stains in use, their resource is relatively small and it mainly includes: fluorescein, rhodamine, cyanine stains, coumarin, quinolones, thiadiazoles, 1.8-naphthalene, pyrene, squaric acid derivatives, and metal complexes, which properties, both physical-chemical and photophysical, are modified during costly, multi-stage chemical transformations. A major challenge for scientists is extending the palette of widely used colours, which would enable their application in much greater spectral range involving UV-Vis-IR.
The market of fluorescent stains is increasing by a few percentage points every year, and between 2014-2016 it reached by over 30% higher value than in previous years. Interest in this group of compounds is increasing due to growing use of them in latest techniques of identification, imaging, and visualisation of cell structures, etc., which are reflected in diagnostics of many diseases.

Advantages of the product

The patented method of generating stains from the group of betaines and triazole salts, as well as characteristics of obtained stains feature many beneficial aspects. The method developed within the framework of the invention, describing generation of stains based on a structure of 1,2-dihydro-[1,2,4]triazolo[4,3-a]pirydino-4-carboxylic acid derivatives, izoxazol[3,4-b]quinolin-3(1H)-on, 1,2-dihydro-[1,2,4]triazolo[4,3-a]quinolino-4-carboxylic acid derivatives, enables obtaining of highly efficient stains, with efficiency >75%. Reactions occur fast, in easily accessible solvents, in a constant temperature.

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An interesting aspect is the way of generation of fluorescent stains, i.e. Safarinium P i Safarinium Q, which are formed due to an easy reaction of formaldehyde and secondary amines. Next, these stains are applicable in generating of fluorescent marks (fluorescent probes). What is more, an easy and effective fluorogenic reaction of a new type, known as Mannich tandem reaction, has been developed, which is conducted quantitatively in room temperature.

Pyridinic and quinolinic stains, which are generated according to the invention, feature high quantum efficiencies of fluorescence and large Stokes shifts, and solvent's polarity does not influence fluorescent properties - lack of solvatochromism. These compounds are characterised by differential solubility, very good in case of pyridinic and quinolinic betaines. The advantage of pyridinic stains, in comparison with quinolinic stains, is stability in physiological conditions, and at the same time preserving high reacticity towards amines and lower cost of generation.

Moreover, derivatives of [1,2,4]triazolo[4,3-a]quinoline of betainic structure feature interesting bacteriostatic activity, especially towards anaerobiotic bacteria, with lack of cytotoxic activity towards eukaryotic cells. MIC values of 6 g/ml foreordain new compounds to be qualified to a new class of potential antibacterial and antifungal drugs.

It has been proved that ester of acid 1,2-dihydro-[1,2,4]triazolo[4,3-a]piridino-4-carboxylic and ester of acid 1,2-dihydro-[1,2,4]triazolo[4,3-a]quinolino-4-carboxylic are suitable for fluorescent marking of peptides and bacterial spores. A great, indisputable advantage of the developed markers is high solubility in water, high quantum efficiency of fluorescence, large Stokes shifts, and photo-optical stability.

In addition, a great advantage of the proposed offer is the application of fluorogenic izoxazolo[3,4-b]quinolin-3(1H)-on to generate derivative of acid 1,2-dihydro-[1,2,4]triazolo[4,3-a]quinolino-carboxylic, used for detection and marking of quantitative formaldehyde and secondary aliphatic amines by the use of spectofluorimetric method.