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(54) **Title:** METHOD FOR PRODUCTION OF LIPOSOMES

(57) **Abstract:** The present disclosure relates to a method for production of liposomes, in order to obtain high encapsulation efficiency of encapsulated agents with a reduced number of production steps, namely avoiding the extrusion step of the classical liposomal production process. The liposomes of the invention are intended to carry a therapeutic agent like an anticancer agent, antioxidant, anti-inflammatory, antipyretic, antibiotic, antiviral, antirheumatic, analgesic, growth-factor, or mixtures thereof.

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METHOD FOR PRODUCTION OF LIPOSOMES

Technical field

[0001] The present disclosure relates to a method for production of liposomes, in order to obtain high encapsulation efficiency of encapsulated agents with a reduced number of production steps.

Background Art

[0002] Liposomes are defined as artificial microscopic vesicles consisting of an aqueous core surrounded by one or more concentric phospholipid layers (lamellas) [1]. Liposomes have gained extensive attention as carriers for a wide range of therapeutic agents because of being both nontoxic and biodegradable, as they are composed of naturally occurring substances [2]. Liposomes show extensive potential applications as they are able to incorporate hydrophilic (in the aqueous compartment), hydrophobic (within lipidic membrane) and amphiphilic substances (lipid aqueous interface) [3]. Moreover, biologically active materials encapsulated into liposomes are protected from immediate dilution or degradation. For all these reasons liposomes are the most popular nanocarrier systems used since their discovery.

[0003] The widespread use of liposomes for several purposes has created the need to develop efficient and reproducible preparation methods with the greatest simplicity as possible. There are different methods for preparation of liposomes, with numerous variants. Because of its simplicity, most laboratory use the lipid thin-film hydration method, first described in 1965 [4]. However, the film method tend to be unsuitable for large scale production. Additionally, there are concerns about the use of chlorinated solvents.

[0004] The ethanol injection method is an interesting technique for GMP scaling-up liposomes production. It offers several advantages, *e.g.* simplicity, GMP friendly solvent,

fast implementation and reproducibility, as well as the fact that it does not cause lipid degradation or oxidative alterations. The ethanol injection method was first reported in 1973 by Batzri and Korn [5] as one of the first alternatives for the preparation of small unilamellar vesicles (SUVs) without sonication. By the immediate dilution of the ethanol in the aqueous phase, the lipid molecules precipitate and form bilayer planar fragments. Through energy dissipation in the system (by stirring and/or ultrasonication), the fragments of these lipid bilayers tend to decrease the exposure of the hydrophobic parts of their molecules to the aqueous environment, resulting in the curvature of these fragments which take a quasi-spherical structure. In the following years, several studies have investigated the preparation parameters of the ethanol injection technique (lipid concentration and composition, injection velocity, temperature of both phases, stirring rate, etc.) on the resulting liposome's characteristics (size distribution, zeta potential, drug encapsulation efficiency, etc.) [6].

[0005] In the classic ethanolic injection method, the ethanolic phase is in minor percentage comparatively to aqueous phase, usually 5-10%. After ethanol evaporation, the liposomal dispersion is extruded in order to reduce vesicles size. Briefly, classic ethanolic injection method comprises 3 key steps:

1. Injection of lipids (ethanol) in aqueous phase;
2. Extrusion to reduce liposomes size;
3. Remove non-encapsulated agents.

[0006] In general, liposomal therapeutic or imaging agents loading is achieved by either passive or active methods:

Passive loading involves dissolution of dried lipid films in aqueous solutions containing the agent of interest. This approach can only be used for water-soluble agents, and the efficiency of loading is often low (smaller than 5%). This method can be used for a wide range of compounds independently of their chemical structure.

Active loading involves the internalization of agents driven by a liposomal transmembrane pH gradient [7]. This process can be extremely efficient (higher

than 95%), resulting in high intraliposomal concentrations and minimal wastage of precious chemotherapeutic agents.

This method (active loading) however requires that molecule have a different protonation state at the extreme pHs of the buffers use inside and outside of liposomes. In such manner a given molecule will diffuse the lipid bilayer when two different pHs are set inside and outside the liposome. Thus, a pH gradient is the driving force to translocate and retain the amphiphilic weak bases and acids [8].

[0007] It also reported in the literature the active loading approach for a weakly basic amine therapeutic or imaging agents using a transmembrane ammonium sulfate gradient. In this case, the ammonia gradient drives a pH gradient, leading to active transport of the agent into the liposome. The sulfate then acts as a counterion for the ionized agent, causing it to precipitate within the liposome. This strategy has been applied to the production of liposomal doxorubicin in the case of Doxil. Myocet is another example of liposomal doxorubicin that is remotely loaded, although the pH gradient is established with citric acid [9].

[0008] In active loading process, after liposomes preparation with the classic ethanolic injection method, the extra-liposomal phase is removed, and then the agent is added to the extra-liposomal phase and the liposomes are incubated to allow the remote loading process to proceed. Briefly, active loading process comprises 5 key steps:

1. Injection of lipids (ethanol) in aqueous phase;
2. Extrusion to reduce liposomes size;
3. Remove of the extra-liposomal phase;
4. Incubation of liposomes with agents;
5. Remove non-encapsulated agents.

[0009] Document WO/2013/084208 (Paulo A. *et al*., 2013, Liposomes and its production method) describes a method of liposomal production which is the lipidic film hydration method.

[0010] Document US4752425A (Martin F. *et al*., 1988, High-encapsulation liposome processing method) describes a method for production of liposomes that use

chloroform. The liposomes produced present 1.5 microns or larger, needing extrusion to size reduction (where the originally encapsulated agent is lost).

[0011] Document US5549910A (Szoka F. *et al*., 1994, Preparation of liposome and lipid complex compositions) describes a method to obtain liposomes containing compounds which exhibit poor solubility in water, alcohols, and halogenated hydrocarbon solvents. In this method the lipids are dissolved in an aprotic solvent solution, which may additionally contain a lower alkanol if needed to solubilize them. This method requires extrusion to obtain liposomes with defined size.

[0012] Document US20120171280A1 (Zhang Y, 2011, Method of making liposomes, liposome compositions made by the methods, and methods of using the same) describes a method to obtain liposomes where the aqueous solution comprises ethylenediaminetetraacetic acid (EDTA) to encapsulation ascorbic acid or a salt thereof. The liposome composition have a selected mean particle size diameter of about 200-500 nm.

[0013] Document US 5316771A (Barenholz, Y. *et al*., 1994, Method of amphiphatic drug loading in liposomes by ammonium ion gradient) describes active loading of weak amphiphatic drugs into liposomes using transmembrane gradient.

[0014] Document US 5939096A (Clerc, S.Y. and Barenholz, 1999, Stably encapsulating a weak acid drug in liposomes, at a high concentration) describes liposomes encapsulated with a weak acid drug at a high concentration. The method employed a proton shuttle mechanism involved the salt of a weak acid to generate a higher inside/lower outside pH gradient.

[0015] Document WO201364911 relates to methods and compositions for producing lipid-encapsulated negatively-charged therapeutic polymers, such as nucleic acid, proteins and peptides, which are encapsulated within a lipid layer.

Document WO0105374 relates to methods and composition for producing lipid-encapsulated charged therapeutic agent particles, after mixture of preformed lipid vesicles, a charged therapeutic agent (with a charge opposite to the lipid) and a destabilizing agent.

General Disclosure of the Invention

[0016] The method of the description has the advantage of achieving a small molecule encapsulation efficiency in a targeted liposome equal to or better than previous methods without extra processing steps to produce nanoparticles. Polycharged molecules, namely with negative charges in their structure at neutral pHs (5-8) like methotextrate and doxorubicin encapsulate better with this method. Methotextrate is high encapsulation rates and doxorubicin with reduced number of steps. (table 2 and 3)

[0017] In the proposed alternative method, a higher encapsulation efficiency of the therapeutic or imaging agent is achieved using a pre-concentration method with an ethanol: aqueous phase at similar volume ratio, and the liposomes may be diluted at the end. The novel proposed method presents a reduced number of steps (only 2) which is desirable in an industrial process. These features are congregated for the first time on the same method, differentiating it from those reported in the literature.

[0018] The widespread use of liposomes for several purposes has created the need to develop preparation methods which should be efficient, reproducible and with the greatest simplicity possible. Existing methods remain laborious for industrial scale-up and/or achieving low encapsulation efficiency of the agent of interest. In this way, is imperative the development of a method with a reduced number of steps and that achieve high encapsulation efficiency of the encapsulated agent.

[0019] The lipids used to produce the liposomes may be changed or modified to customize the properties of the liposomal surface and membrane layer. There are different classes of lipids, based in their charge: neutral, cationic, and anionic. The addition of organic molecules to the phosphate head group creates a variety of phospholipid species such as phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylglycerol (PG) and phosphatidylcholine (PC). All these lipids could be used in liposomes production.

[0020] Unmodified liposomes do not survive long in circulation, as they are removed by macrophages. One of the first attempts to overcome these problems was focused on the manipulation of lipid membrane components in order to modify bilayer fluidity, as example by inclusion of a steroid. In this way, our liposomal formulations may

preferentially contain cholesterol (CH), which may vary from a molar ratio of 35-55%, preferably 35-40%. It was demonstrated that incorporation of cholesterol, into liposomes reduces interaction with blood proteins, by causing increased packing of phospholipids in the lipid bilayer.

[0021] Furthermore, in a preferential execution was include a synthetic polymer, polyethyleneglycol (PEG) to the liposomes. PEG-containing liposomes showed less binding to blood proteins, reduced RES uptake, and thus prolonged duration of liposomes in the circulatory system. This has extended the blood circulation of conventional liposomes to drug delivery, the conjugated phospholipid DSPE-MPEG was incorporated in lipidic film of these new formulations, in a molar ratio which may vary between 4-12%, preferably 5-10%.

[0022] It has also been demonstrated that surface-modified liposomes with gangliosides have a prolonged circulation time in the blood stream compared to non-modified ones. These characteristics are potentially useful for applications of gangliosides in immunotherapies. Several glycolipids have been tested in studies of RES uptake of liposomes after intravenous injection: the glycolipid GM1 (a brain-tissue-derived monosialoganglioside) significantly decreased RES uptake when incorporated on the liposome surface, and the formulation remained in blood circulation for several hours.

[0023] Active targeting exploits specific modification of liposomal surface with a targeting ligand, which can lead to their accumulation at the target site or intracellular delivery to target cells. The inclusion of certain ligands in liposomes allows the release of their contents intracellularly by receptor-mediated endocytosis. Targeting agent integration at membrane surface could be achieved by conjugation to phospholipid or fatty acyl chains or incorporated in the lipidic membrane.

[0024] There are different methods for preparation of liposomes, with numerous variants. In the ethanol injection method (5% ethanol), a fraction of the aqueous solution with water-soluble substances is passively encapsulated inside the vesicles. The advantage of this method is its simplicity, but only a very small percentage of water-soluble therapeutic or imaging agents can be encapsulated in this way.

[0025] In the remote loading, empty liposomes are generally prepared in an initial salt or low pH buffer. The extra-liposomal phase is then removed using dialysis or size exclusion chromatography, or by titrating the pH to slightly basic conditions. Finally, the agent is added to the extra-liposomal phase and the liposomes are incubated to allow the remote loading process to proceed [6]. The number of steps involved makes the production process difficult to scale up, constituting a barrier to further development of this standard approach.

[0026] Hence, we focus our efforts in the optimization of agent encapsulation inside liposomes, with a reduced production steps. Indeed, only a low amount of the agent used was encapsulated (*e.g.* 3-5% to methotrexate drug), being a high amount of agent wasted and this could be an issue in a scale-up process. In order to increase the encapsulated agent numerous conditions were tested in several steps of the production method. Namely: aqueous phase in organic phase containing the phospholipids (instead the opposite), do not remove ethanol, to perform the injection at room temperature instead of at 70ºC, to test different speeds of injection and several concentrations of organic phase (5% until 95%).

[0027] The present invention consists in a new method of production of liposomes, wherein the hydrophobic components of liposomes are dissolved in ethanol, and injected in an aqueous phase at a rate of approximately 2 – 4 ml/min. under vigorous agitation. The initial volume ratio ethanol: aqueous phase is 1/1. After evaporation of ethanol or tangential flow filtration the liposomal dispersion should be diluted 1 to 10-fold, to the desirable final concentration.

[0028] In an embodiment,, pre-concentration method comprises 2 key steps:

- Injection of lipids (ethanol) in aqueous phase (1:1 v/v), followed of the dilution;
- Remove non-encapsulated agents.

[0029] In an embodiment, this method allows the achievement of high encapsulation efficiencies (*e.g.* ~40%) for polycharged agent like methotrexate, with a reduced number of steps (only 2). The initial pre-concentration (use of a lower aqueous volume) increase the phospholipid concentration and, consequently allow a higher encapsulation efficiency. Additionally, the use of initial 1:1 of ethanol:aqueous phase volume ratio

allows a balance between two phases with different polarities, increasing the encapsulation of the agents.

[0030] In an embodiment, the disclosure relates to a method for encapsulating an active ingredient in a liposome comprising the following sequencial steps:

- preparing an ethanolic phase by mixing hydrophobic molecules of phospholipids and an steroid with ethanol; preferably cholesterol;
- preparing an aqueous phase with an active ingredient and a targeting agent in a buffer solution;
- obtaining the liposomes by injecting the ethanolic phase in the aqueous phase, at a temperature from around 50 °C to around 80 °C, wherein the ethanolic/aqueous phase volume ratio is between 1:1 and 3:2;
- removing of the ethanol, by evaporation evaporation or tangential flow filtration;
- removing the remaining free active ingredient in a suitable way, namely by tangencial flow filtration;

wherein the targeting agent is a peptide that is conjugated with a liposomal component or incorporated in the lipidic membrane.

[0031] In another embodiment, the disclosure relates to a method, wherein it further comprises the step of diluting of the liposomal dispersion 1 to 10-fold in further diluted aqueous phase.

[0032] In a further embodiment, the disclosure relates to a method, wherein the ethanolic phase is injected at a rate of approximately 2-4 ml/minute.

[0033] In a further embodiment, the disclosure relates to a method, wherein the injecting step is performed under agitation.

[0034] In a further embodiment, the disclosure relates to a method, wherein the active ingredient is a drug, in particular an anticancer drug, antirheumatic drug, anti-neurodegenerative diseases drug, antioxidant drug, anti-inflammatory, drug antipyretic drug, antibiotic drug, antiviral drug, analgesic drug or combinations thereof.

[0035] In another embodiment, the disclosure relates to a method, wherein the targeting agent is a peptide selected from the following list with a degree of identity of

at least 90% of the following sequence: SEQ- ID. NO 1, SEQ- ID. NO 2 , SEQ- ID. NO 3, or mixtures thereof; comprising at least a sequence 95%, Preferably or at least 96% identical, or at least 97% identical, or at least 98% identical, or at least 99% identical, identical to SEQ- ID. NO 1, SEQ- ID. NO 2, SEQ- ID. NO 3, or mixtures thereof.

[0036] Methods for the alignment of sequences for comparison are well known in the art, such methods include GAP, BESTFIT, BLAST, FASTA and TFASTA. GAP uses the algorithm of Needleman and Wunsch ((1970) J Mol Biol 48: 443-453) to find the global (over the whole the sequence) alignment of two sequences that maximizes the number of matches and minimizes the number of gaps. The BLAST algorithm (Altschul et al. (1990) J Mol Biol 215: 403-10) calculates percent sequence identity and performs a statistical analysis of the similarity between the two sequences. The software for performing BLAST analysis is publicly available through the National Centre for Biotechnology Information (NCBI). Global percentages of similarity and identity may also be determined using one of the methods available in the MatGAT software package (Campanella et al., BMC Bioinformatics. 2003 Jul 10; 4:29. MatGAT: an application that generates similarity/identity matrices using protein or DNA sequences). Minor manual editing may be performed to optimise alignment between conserved motifs, as would be apparent to a person skilled in the art. The sequence identity values, which are indicated in the present subject matter as a percentage were determined over the entire amino acid sequence, using BLAST with the default parameters.

[0037] In another embodiment, the disclosure relates to a method, wherein the ethanol concentration, relative to the initial aqueous volume, is between 40% and 60%, preferably 50%.

[0038] In another embodiment, the disclosure relates to a method, wherein the temperature is 60 °C or 70 °C.

[0039] In another embodiment, the disclosure relates to a method, wherein the active ingredient is a polycharged molecule containing at least one negative charge at a pH of around 4 to around 7, particularly methotextrate or doxorubicin.

[0040] In a further embodiment, the disclosure relates to a method, wherein the aqueous phase is phosphate buffered saline, PBS.

[0041] In another embodiment, the disclosure relates to a method wherein the ethanolic phase comprises anionic, neutral or cationic phospholipids.

[0042] In a further embodiment, the disclosure relates to a method, wherein the ethanolic phase comprises phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines, phosphatidylglycerols and/or their derivates or mixtures thereof, in particular 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine.

[0043] In another embodiment, the disclosure relates to a method wherein the ethanolic phase comprises a steroid, a stealth agent, a targeting agent, or mixture of thereof.

[0044] In a further embodiment, the disclosure relates to a method wherein the steroid is cholesterol, and/or their derivate, in particular cholesteryl hemisuccinate.

[0045] In another embodiment, the disclosure relates to a method wherein the stealth agent is polyethylene glycol, PEG, or gangliosides

[0046] In a further embodiment, the disclosure relates to a method wherein the polyethylene glycol, PEG, is bound to a phospholipid, in particular distearoylphosphatidylethanolamine.

[0047] In another embodiment, the disclosure relates to a method wherein the targeting agent is incorporated in the lipidic membrane.

[0048] In another embodiment, the disclosure relates to a method wherein the active ingredient is an imaging or therapeutic agent.

[0049] In a further embodiment, the disclosure relates to a method wherein the imaging or therapeutic agent is hydrophobic or hydrophilic.

[0050] In another further embodiment, the disclosure relates to a method, wherein the imaging agent is a dye.

Detailed Description

[0051] The present disclosure relates to a method for production of liposomes, in order to obtain high encapsulation efficiency of encapsulated agents with a reduced number of production steps, namely avoiding the extrusion step of the classical liposomal production process. The liposomes of the invention are intended to carry a therapeutic

agent like an anticancer agent, antioxidant, anti-inflammatory, antipyretic, antibiotic, antiviral, antirheumatic, analgesic, growth-factor, or mixtures thereof.

[0052] The method of the description has the advantage of achieving a small molecule encapsulation efficiency in a targeted liposome equal to or better than previous methods without extra processing steps to produce nanoparticles.

[0053] In order to increase the encapsulated agent, with a reduced production steps, numerous conditions were tested in several steps of the production method. The results demonstrate that the initial percentage of ethanol significantly affected the encapsulation efficiency. A drastic increase in encapsulation efficiency has been noticed as the ethanol volume was higher than the classic 5% (50% relative to the initial aqueous phase), and also using a lower volume of aqueous solution of agent (the sample is afterwards diluted five times to get the usual agent concentration after ethanol evaporation or tangential flow filtration). Vesicles' size has been positively affected by the ethanol volume after this ratio be achieve. Indeed, batches having a higher ethanol volume (>50%) showed larger vesicles (< 150 nm) than liposome batches previously produced. These results may be attributed to the slower diffusion of ethanol related to its volume increase in aqueous phase, leading to the formation of higher sized liposomes due to the slow self-assembly of phospholipids. Accordingly, the smaller the vesicles' size, the smaller the aqueous core volume and the lower obtained encapsulation efficiencies, knowing that the hydrophilic agent is mainly encapsulated in the liposome aqueous core [10, 11]. However, a compromise between the encapsulation efficiency and size was obtained using 50% of initial ethanol volume. Liposomes obtained with this percentage of ethanol present small size (<150 nm) and PDI values (<0.1). Moreover, with these conditions, the extrusion process usually needed to decrease, and uniform vesicles' size is perfectly expendable.

Production of liposomes

[0054] In an embodiment, liposomes composed of DOPE/Cholesterol/DSPE-MPEG (54:36:10, molar ratio) were prepared using the ethanolic injection method. Briefly, lipids (DOPE, cholesterol and DSPE-MPEG) were dissolved in ethanol (5% in the classic

ethanol injection method; 50% in the new proposed pre-concentration method, relative to the initial 20% aqueous phase) at 60 °C.

[0055] The solution was injected under stirring to an aqueous solution (phosphate buffered saline, PBS). This process is done at 70 °C, remaining during the necessary time to evaporate all the ethanol volume.

[0056] In the classic ethanolic injection method liposomes are extruded to reduce their size. In the pre-concentration method, after ethanol evaporation or tangential flow filtration, liposomal dispersion is diluted five times in PBS (remaining 80% of volume is added). The free therapeutic or imaging agent that was not incorporated into liposomes was removed from the samples after passage through a gel filtration chromatography column (GE Healthcare) with 5 kDa cut-off (PD-10 Desalting Columns containing 8.3 mL of Sephadex G-25 Medium). Hydrophilic therapeutic or imaging agents (*e.g.* methotrexate and doxorubicin) are present in this aqueous phase in the classic ethanol injection method and in the new proposed pre-concentration method. In remote/active loading, after production in ammonium sulfate (120 mM, pH=8.5), the buffer is changed to Trizma®Base sucrose (10%, w/v, buffered at pH 9.0) and empty liposomes are incubated with the therapeutic or imaging agents.

[0057] Characterization of liposomes encapsulating methotrexate: comparative study between several production methods.

	Z. average (d.nm)	**PDI**	**Encapsulation efficiency (%)**	**Number of steps**
Pre-concentration method (50% ethanol relative to the initial aqueous buffer)	103.1 ± 2.333	0.117 ± 0.003	43.4	2 (no extrusion)
66% ethanol	343,3 ± 9,136	0.067 ± 0.029	41,6	2 (no extrusion)
66% ethanol	124,7 ± 0,635	0.061 ± 0.009	8,3	3 (extrusion)
33% ethanol	99.66 ± 0.095	0.240 ± 0.006	7.6	3 (extrusion)
Classic ethanolic injection method (5% ethanol)	117.7 ± 1.779	0.053 ± 0.018	5.7	3 (extrusion)

[0058] Table II - Characterization of liposomes encapsulating doxorubicin: comparative study between several production methods.

	Z. average (d.nm)	PDI	Encapsulation efficiency (%)	Number of steps
Pre-concentration method (50% ethanol relative to the initial 20% aqueous buffer)	131.2 ± 1.124	0.109 ± 0.010	84.9	2 (no extrusion)
Classic ethanolic injection method (5% ethanol)	115.1 ± 0.551	0.048 ± 0.027	85.1	3 (extrusion)
Remote/active loading	124.8 ± 1.825	0.132 ± 0.020	76.1	5 (extrusion)

[0059] Table III - A to Z list of cancer drugs including combination treatments

A	L
Abemaciclib	Lanreotide Acetate
Abiraterone Acetate	Lapatinib Ditosylate
Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation)	Lartruvo (Olaratumab)
ABVD	Lenalidomide
ABVE	Lenvatinib Mesylate
ABVE-PC	Lenvima (Lenvatinib Mesylate)
AC	Letrozole
Acalabrutinib	Leucovorin Calcium
AC-T	Leukeran (Chlorambucil)
Actemra (Tocilizumab)	Leuprolide Acetate
Adcetris (Brentuximab Vedotin)	Levulan Kerastik (Aminolevulinic Acid)
ADE	Libtayo (Cemiplimab-rwlc)
Ado-Trastuzumab Emtansine	LipoDox (Doxorubicin Hydrochloride Liposome)
Adriamycin (Doxorubicin Hydrochloride)	Lomustine
Afatinib Dimaleate	Lonsurf (Trifluridine and Tipiracil Hydrochloride)
Afinitor (Everolimus)	Lupron (Leuprolide Acetate)
Akynzeo (Netupitant and Palonosetron Hydrochloride)	Lupron Depot (Leuprolide Acetate)
Aldara (Imiquimod)	Lutathera (Lutetium Lu 177-Dotatate)
Aldesleukin	Lutetium (Lu 177-Dotatate)
Alecensa (Alectinib)	Lynparza (Olaparib)
Alectinib	

Alemtuzumab	**M**
Alimta (Pemetrexed Disodium)	Marqibo (Vincristine Sulfate Liposome)
Aliqopa (Copanlisib Hydrochloride)	Matulane (Procarbazine Hydrochloride)
Alkeran for Injection (Melphalan Hydrochloride)	Mechlorethamine Hydrochloride
Alkeran Tablets (Melphalan)	Megestrol Acetate
Aloxi (Palonosetron Hydrochloride)	Mekinist (Trametinib)
Alunbrig (Brigatinib)	Mektovi (Binimetinib)
Ameluz (Aminolevulinic Acid)	Melphalan
Amifostine	Melphalan Hydrochloride
Aminolevulinic Acid	Mercaptopurine
Anastrozole	Mesna
Apalutamide	Mesnex (Mesna)
Aprepitant	Methotrexate
Aranesp (Darbepoetin Alfa)	Methylnaltrexone Bromide
Aredia (Pamidronate Disodium)	Midostaurin
Arimidex (Anastrozole)	Mitomycin C
Aromasin (Exemestane)	Mitoxantrone Hydrochloride
Arranon (Nelarabine)	Mogamulizumab-kpkc
Arsenic Trioxide	Mozobil (Plerixafor)
Arzerra (Ofatumumab)	Mustargen (Mechlorethamine Hydrochloride)
Asparaginase Erwinia chrysanthemi	MVAC
Atezolizumab	Myleran (Busulfan)
Avastin (Bevacizumab)	Mylotarg (Gemtuzumab Ozogamicin)
Avelumab	
Axicabtagene Ciloleucel	**N**
Axitinib	Nanoparticle Paclitaxel (Paclitaxel Albumin-stabilized Nanoparticle Formulation)
Azacitidine	Navelbine (Vinorelbine Tartrate)
Azedra (Iobenguane I 131)	Necitumumab
	Nelarabine
B	Neratinib Maleate
Bavencio (Avelumab)	Nerlynx (Neratinib Maleate)
BEACOPP	Netupitant and Palonosetron Hydrochloride
Beleodaq (Belinostat)	Neulasta (Pegfilgrastim)
Belinostat	Neupogen (Filgrastim)
Bendamustine Hydrochloride	Nexavar (Sorafenib Tosylate)
Bendeka (Bendamustine Hydrochloride)	Nilandron (Nilutamide)
BEP	Nilotinib
Besponsa (Inotuzumab Ozogamicin)	Nilutamide
Bevacizumab	Ninlaro (Ixazomib Citrate)
Bexarotene	Niraparib Tosylate Monohydrate
Bicalutamide	Nivolumab
BiCNU (Carmustine)	Nplate (Romiplostim)
Binimetinib	

Bleomycin	**O**
Blinatumomab	Obinutuzumab
Blincyto (Blinatumomab)	Odomzo (Sonidegib)
Bortezomib	OEPA
Bosulif (Bosutinib)	Ofatumumab
Bosutinib	OFF
Braftovi (Encorafenib)	Olaparib
Brentuximab Vedotin	Olaratumab
Brigatinib	Omacetaxine Mepesuccinate
BuMel	Oncaspar (Pegaspargase)
Busulfan	Ondansetron Hydrochloride
Busulfex (Busulfan)	Onivyde (Irinotecan Hydrochloride Liposome)
	Ontak (Denileukin Diftitox)
C	Opdivo (Nivolumab)
Cabazitaxel	OPPA
Cabometyx (Cabozantinib-S-Malate)	Osimertinib
Cabozantinib-S-Malate	Oxaliplatin
CAF	
Calquence (Acalabrutinib)	**P**
Campath (Alemtuzumab)	Paclitaxel
Camptosar (Irinotecan Hydrochloride)	Paclitaxel Albumin-stabilized Nanoparticle Formulation
Capecitabine	PAD
CAPOX	Palbociclib
Carac (Fluorouracil--Topical)	Palifermin
Carboplatin	Palonosetron Hydrochloride
CARBOPLATIN-TAXOL	Palonosetron Hydrochloride and Netupitant
Carfilzomib	Pamidronate Disodium
Carmustine	Panitumumab
Carmustine Implant	Panobinostat
Casodex (Bicalutamide)	Pazopanib Hydrochloride
CEM	PCV
Cemiplimab-rwlc	PEB
Ceritinib	Pegaspargase
Cerubidine (Daunorubicin Hydrochloride)	Pegfilgrastim
Cervarix (Recombinant HPV Bivalent Vaccine)	Peginterferon Alfa-2b
Cetuximab	PEG-Intron (Peginterferon Alfa-2b)
CEV	Pembrolizumab
Chlorambucil	Pemetrexed Disodium
CHLORAMBUCIL-PREDNISONE	Perjeta (Pertuzumab)
CHOP	Pertuzumab
Cisplatin	Plerixafor
Cladribine	Pomalidomide
Clofarabine	Pomalyst (Pomalidomide)

Clolar (Clofarabine)	Ponatinib Hydrochloride
CMF	Portrazza (Necitumumab)
Cobimetinib	Poteligeo (Mogamulizumab-kpkc)
Cometriq (Cabozantinib-S-Malate)	Pralatrexate
Copanlisib Hydrochloride	Prednisone
COPDAC	Procarbazine Hydrochloride
Copiktra (Duvelisib)	Procrit (Epoetin Alfa)
COPP	Proleukin (Aldesleukin)
COPP-ABV	Prolia (Denosumab)
Cosmegen (Dactinomycin)	Promacta (Eltrombopag Olamine)
Cotellic (Cobimetinib)	Propranolol Hydrochloride
Crizotinib	Provenge (Sipuleucel-T)
CVP	Purinethol (Mercaptopurine)
Cyclophosphamide	Purixan (Mercaptopurine)
Cyramza (Ramucirumab)	
Cytarabine	**Q**
Cytarabine Liposome	[No Entries]
Cytosar-U (Cytarabine)	
	R
D	Radium 223 Dichloride
Dabrafenib	Raloxifene Hydrochloride
Dacarbazine	Ramucirumab
Dacogen (Decitabine)	Rasburicase
Dacomitinib	R-CHOP
Dactinomycin	R-CVP
Daratumumab	Recombinant Human Papillomavirus (HPV) Bivalent Vaccine
Darbepoetin Alfa	Recombinant Human Papillomavirus (HPV) Nonavalent Vaccine
Darzalex (Daratumumab)	Recombinant Human Papillomavirus (HPV) Quadrivalent Vaccine
Dasatinib	Recombinant Interferon Alfa-2b
Daunorubicin Hydrochloride	Regorafenib
Daunorubicin Hydrochloride and Cytarabine Liposome	Relistor (Methylnaltrexone Bromide)
Decitabine	R-EPOCH
Defibrotide Sodium	Retacrit (Epoetin Alfa)
Defitelio (Defibrotide Sodium)	Revlimid (Lenalidomide)
Degarelix	Rheumatrex (Methotrexate)
Denileukin Diftitox	Ribociclib
Denosumab	R-ICE
DepoCyt (Cytarabine Liposome)	Rituxan (Rituximab)
Dexamethasone	Rituxan Hycela (Rituximab and Hyaluronidase Human)
Dexrazoxane Hydrochloride	Rituximab
Dinutuximab	Rituximab and Hyaluronidase Human
Docetaxel	Rolapitant Hydrochloride

Doxil (Doxorubicin Hydrochloride Liposome)	Romidepsin
Doxorubicin Hydrochloride	Romiplostim
Doxorubicin Hydrochloride Liposome	Rubidomycin (Daunorubicin Hydrochloride)
Dox-SL (Doxorubicin Hydrochloride Liposome)	Rubraca (Rucaparib Camsylate)
Durvalumab	Rucaparib Camsylate
Duvelisib	Ruxolitinib Phosphate
	Rydapt (Midostaurin)
E	
Efudex (Fluorouracil--Topical)	**S**
Eligard (Leuprolide Acetate)	Sancuso (Granisetron)
Elitek (Rasburicase)	Sclerosol Intrapleural Aerosol (Talc)
Ellence (Epirubicin Hydrochloride)	Siltuximab
Elotuzumab	Sipuleucel-T
Eloxatin (Oxaliplatin)	Somatuline Depot (Lanreotide Acetate)
Eltrombopag Olamine	Sonidegib
Emend (Aprepitant)	Sorafenib Tosylate
Empliciti (Elotuzumab)	Sprycel (Dasatinib)
Enasidenib Mesylate	STANFORD V
Encorafenib	Sterile Talc Powder (Talc)
Enzalutamide	Steritalc (Talc)
Epirubicin Hydrochloride	Stivarga (Regorafenib)
EPOCH	Sunitinib Malate
Epoetin Alfa	Sustol (Granisetron)
Epogen (Epoetin Alfa)	Sutent (Sunitinib Malate)
Erbitux (Cetuximab)	Sylatron (Peginterferon Alfa-2b)
Eribulin Mesylate	Sylvant (Siltuximab)
Erivedge (Vismodegib)	Synribo (Omacetaxine Mepesuccinate)
Erleada (Apalutamide)	
Erlotinib Hydrochloride	**T**
Erwinaze (Asparaginase Erwinia chrysanthemi)	Tabloid (Thioguanine)
Ethyol (Amifostine)	TAC
Etopophos (Etoposide Phosphate)	Tafinlar (Dabrafenib)
Etoposide	Tagrisso (Osimertinib)
Etoposide Phosphate	Talc
Evacet (Doxorubicin Hydrochloride Liposome)	Talimogene Laherparepvec
Everolimus	Tamoxifen Citrate
Evista (Raloxifene Hydrochloride)	Tarabine PFS (Cytarabine)
Evomela (Melphalan Hydrochloride)	Tarceva (Erlotinib Hydrochloride)
Exemestane	Targretin (Bexarotene)
	Tasigna (Nilotinib)
F	Tavalisse (Fostamatinib Disodium)
5-FU (Fluorouracil Injection)	Taxol (Paclitaxel)
5-FU (Fluorouracil--Topical)	Taxotere (Docetaxel)

Fareston (Toremifene)	Tecentriq (Atezolizumab)
Farydak (Panobinostat)	Temodar (Temozolomide)
Faslodex (Fulvestrant)	Temozolomide
FEC	Temsirolimus
Femara (Letrozole)	Thalidomide
Filgrastim	Thalomid (Thalidomide)
Firmagon (Degarelix)	Thioguanine
Fludarabine Phosphate	Thiotepa
Fluoroplex (Fluorouracil--Topical)	Tibsovo (Ivosidenib)
Fluorouracil Injection	Tisagenlecleucel
Fluorouracil--Topical	Tocilizumab
Flutamide	Tolak (Fluorouracil--Topical)
FOLFIRI	Topotecan Hydrochloride
FOLFIRI-BEVACIZUMAB	Toremifene
FOLFIRI-CETUXIMAB	Torisel (Temsirolimus)
FOLFIRINOX	Totect (Dexrazoxane Hydrochloride)
FOLFOX	TPF
Folotyn (Pralatrexate)	Trabectedin
Fostamatinib Disodium	Trametinib
FU-LV	Trastuzumab
Fulvestrant	Treanda (Bendamustine Hydrochloride)
Fusilev (Leucovorin Calcium)	Trexall (Methotrexate)
	Trifluridine and Tipiracil Hydrochloride
G	Trisenox (Arsenic Trioxide)
Gardasil (Recombinant HPV Quadrivalent Vaccine)	Tykerb (Lapatinib Ditosylate)
Gardasil 9 (Recombinant HPV Nonavalent Vaccine)	
Gazyva (Obinutuzumab)	**U**
Gefitinib	Unituxin (Dinutuximab)
Gemcitabine Hydrochloride	Uridine Triacetate
GEMCITABINE-CISPLATIN	
GEMCITABINE-OXALIPLATIN	**V**
Gemtuzumab Ozogamicin	VAC
Gemzar (Gemcitabine Hydrochloride)	Valrubicin
Gilotrif (Afatinib Dimaleate)	Valstar (Valrubicin)
Gleevec (Imatinib Mesylate)	Vandetanib
Gliadel Wafer (Carmustine Implant)	VAMP
Glucarpidase	Varubi (Rolapitant Hydrochloride)
Goserelin Acetate	Vectibix (Panitumumab)
Granisetron	VeIP
Granisetron Hydrochloride	Velcade (Bortezomib)
Granix (Filgrastim)	Vemurafenib
	Venclexta (Venetoclax)
H	Venetoclax

Halaven (Eribulin Mesylate)	Verzenio (Abemaciclib)
Hemangeol (Propranolol Hydrochloride)	Vidaza (Azacitidine)
Herceptin (Trastuzumab)	Vinblastine Sulfate
HPV Bivalent Vaccine, Recombinant	Vincristine Sulfate
HPV Nonavalent Vaccine, Recombinant	Vincristine Sulfate Liposome
HPV Quadrivalent Vaccine, Recombinant	Vinorelbine Tartrate
Hycamtin (Topotecan Hydrochloride)	VIP
Hydrea (Hydroxyurea)	Vismodegib
Hydroxyurea	Vistogard (Uridine Triacetate)
Hyper-CVAD	Vizimpro (Dacomitinib)
	Voraxaze (Glucarpidase)
I	Vorinostat
Ibrance (Palbociclib)	Votrient (Pazopanib Hydrochloride)
Ibritumomab Tiuxetan	Vyxeos (Daunorubicin Hydrochloride and Cytarabine Liposome)
Ibrutinib	
ICE	**W**
Iclusig (Ponatinib Hydrochloride)	[No Entries]
Idarubicin Hydrochloride	
Idelalisib	**X**
Idhifa (Enasidenib Mesylate)	Xalkori (Crizotinib)
Ifex (Ifosfamide)	Xeloda (Capecitabine)
Ifosfamide	XELIRI
IL-2 (Aldesleukin)	XELOX
Imatinib Mesylate	Xgeva (Denosumab)
Imbruvica (Ibrutinib)	Xofigo (Radium 223 Dichloride)
Imfinzi (Durvalumab)	Xtandi (Enzalutamide)
Imiquimod	
Imlygic (Talimogene Laherparepvec)	**Y**
Inlyta (Axitinib)	Yervoy (Ipilimumab)
Inotuzumab Ozogamicin	Yescarta (Axicabtagene Ciloleucel)
Interferon Alfa-2b, Recombinant	Yondelis (Trabectedin)
Interleukin-2 (Aldesleukin)	
Intron A (Recombinant Interferon Alfa-2b)	**Z**
Iobenguane I 131	Zaltrap (Ziv-Aflibercept)
Ipilimumab	Zarxio (Filgrastim)
Iressa (Gefitinib)	Zejula (Niraparib Tosylate Monohydrate)
Irinotecan Hydrochloride	Zelboraf (Vemurafenib)
Irinotecan Hydrochloride Liposome	Zevalin (Ibritumomab Tiuxetan)
Istodax (Romidepsin)	Zinecard (Dexrazoxane Hydrochloride)
Ivosidenib	Ziv-Aflibercept
Ixabepilone	Zofran (Ondansetron Hydrochloride)
Ixazomib Citrate	Zoladex (Goserelin Acetate)
Ixempra (Ixabepilone)	Zoledronic Acid

	Zolinza (Vorinostat)
J	Zometa (Zoledronic Acid)
Jakafi (Ruxolitinib Phosphate)	Zydelig (Idelalisib)
JEB	Zykadia (Ceritinib)
Jevtana (Cabazitaxel)	Zytiga (Abiraterone Acetate)
K	
Kadcyla (Ado-Trastuzumab Emtansine)	
Kepivance (Palifermin)	
Keytruda (Pembrolizumab)	
Kisqali (Ribociclib)	
Kymriah (Tisagenlecleucel)	
Kyprolis (Carfilzomib)	

[0060] Table IV- A to Z list of drugs used in rheumatoid arthritis therapy

A	M
Abaloparatide (parathyroid hormone)	Magnacet
Abatacept	Maxidone
Acetaminophen (children and infants)	Meclofenamate sodium
Acetaminophen 325mg	Mediproxen
Acetaminophen 500 mg	Medrol
Acetaminophen 650 mg	Mefenamic acid
Acetaminophen with codeine	Meloxicam
Acetylsalicylic acid (aspirin)	Menest
Actemra	Menostar
Activella	Methadone hydrochloride
Actonel	Methadose
Adalimumab	Methotrexate
Addaprin	Methylprednisolone
Advil	Miacalcin
Alendronate	Millipred
Alendronate with vitamin D	Milnacipran
Aleve	Mitigare
Allopurinol	Mobic
Ambien	Morphine sulfate
Ambien CR	Morphine sulfate oral solution
Amitriptyline hydrochloride	Morphine sulfate with naltrexone
Amrix	Motrin
Anacin	Motrin IB
Anacin (aspirin free)	MS Contin
Anakinra	Mycophenolate mofetil
Anaprox	
Anaprox DS	N
Apremilast	Nabumetone
Arava	Nalfon
Arthrotec	Naprelan
Atelvia	Naprosyn
Avinza	Naproxen and esomeprazole magnesium
Azasan	Naproxen sodium (over-the-counter)
Azathioprine	Naproxen sodium (prescription)
Azulfidine	Neoral
Azulfidine EN-Tabs	Neurontin
	Norco
B	
Baricitinib	O
Baycadron	Olumiant

Bayer	Opana
Belimumab	Oramorph SR
Benlysta	Orapred
Betamethasone	Orencia
Binosto	Otezla
Boniva	Otrexup
Brisdelle	Oxaprozin
Bufferin	Oxycodone
	Oxycodone hydrochloride with acetaminophen
C	Oxycodone with aspirin
Calcitonin (nasal spray)	Oxycodone with ibuprofen
Cambia	OxyContin
Canakinumab	Oxymorphone hydrochloride
Cataflam	
Celebrex	**P**
Celecoxib	Paroxetine
Celestone	Paxil
CellCept	PediaCare Fever Reducer/Pain Reliever
Cequa (solution)	Pediapred
Certolizumab pegol	Pegloticase
Cevimeline	Pennsaid
Children's Tylenol	Percocet
Cimzia	Percodan
Climara Pro	Pexeva
Clinoril	Pilocarpine
Cocet	Piroxicam
Cocet Plus	Plaquenil
Colchicine	Ponstel
Colcrys	Prednisolone
Combunox	Prednisone
Conjugated estrogens/bazedoxifene	Prednisone Intensol
ConZip	Pregabalin
Cortef	Prelone
Cortisone acetate	Premphase
Cosentyx	Prempro
Cyclobenzaprine	Primlev
Cyclophosphamide	Probenecid
Cyclosporine	Probenecid and colchicine
Cyclosporine ophthalmic emulsion/solution	Prolia
Cymbalta	Prozac
D	**R**
Daypro	Raloxifene hydrochloride

Denosumab	Rasuvo
Dexamethasone	Rayos
DexPak	Reclast
Diclofenac	Remicade
Diclofenac potassium	Renflexis (infliximab-abda, biosimilar to Remicade)
Diclofenac sodium	Reprexain
Diclofenac Sodium liquid/gel	Restasis (emulsion)
Diclofenac sodium with misoprostol	Rheumatrex
Diflunisal	Risedronate sodium
Dolophine	Rituxan
Duavee	Rituximab
Duexis	Roxicet
Duloxetine	Roxicodone
Dyspel	Rybix ODT
	Ryzolt
E	
EC-Naprosyn	**S**
Ecotrin	Salagen
Effexor XR	Sandimmune
Embeda	Sarafem
Enbrel	Sarilumab
Endocet	Savella
Endodan	secukinumab
Estrace	Sertraline
Estratab	Simponi, Simponi Aria
Estrogens	Stelara
Estrogens with progesterone	Sulfasalazine
Etanercept	Sulfazine
Etodolac	Sulfazine EC
Evista	Sulindac
Evoxac	
Excedrin	**T**
	Taltz
F	Teriparatide (parathyroid hormone)
Febuxostat	TH Ibuprofen
Feldene	Therafeldamine
Fenoprofen calcium	Tivorbex
FeverAll	Tocilizumab
Fexmid	Tofacitinib (extended release)
Flexeril	Tofacitinib (immediate release)
Fluoxetine	Tolmetin sodium
Flurbiprofen	Tramadol
Forteo	Tramadol (extended release)

Fortical	Tramadol with acetaminophen
Fosamax	Trexall
Fosamax Plus D	Tylenol Arthritis Pain
	Tylenol Extra Strength
G	Tylenol Regular Strength
Gabapentin	Tylenol with Codeine No.2
Gengraf	Tylenol with Codeine No.3
Genpril	Tylenol with Codeine No.4
Golimumab	Tymlos
Gralise	
	U
H	Uloric
Horizant	Ultracet
Humira	Ultram
Hycet	Ultram-ER
Hydrocet	Ustekinumab
Hydrocodone bitartrate	
Hydrocodone bitartrate with acetaminophen	**V**
Hydrocodone bitartrate with ibuprofen	Venlafaxine
Hydrocortisone	Veripred 20
Hydrogesic	Vicodin
Hydroxychloroquine sulfate	Vicoprofen
Hydroxypropyl cellulose pellets	Vimovo
Hysingla ER	Vivlodex
	Voltaren
I	Voltaren XR
Ibandronate	
Ibuprofen (over-the-counter)	**X**
Ibuprofen (prescription)	Xatmep
Ibuprofen with famotidine	Xeljanz
Ilaris	Xeljanz XR
Imuran	Xodol
Indocin	Xolox
Indomethacin	
Infant's Tylenol	**Z**
Inflectra (infliximab-dyyb, biosimilar to Remicade)	Zamicet
Infliximab	Zipsor
Intermezzo	Zohydro ER
I-Prin	Zoledronic acid
ixekizumab	Zoloft
	Zolpidem
K	Zolvit
Kadian	Zometa

Ketoprofen	Zorvolex
Kevzara	Zurampic
Kineret	Zydone
Krystexxa	Zyloprim
KS Ibuprofen	
L	
Lacrisert	
Leflunomide	
lesinurad	
Lorcet	
Lortab	
Lyrica	

[0061] Table IVA to Z list of dyes

A	**G**
Acetaldehyde-2,4-dinitrophenylhydrazone analytical standard, for environmental analysis	2-(β-D-Galactosidoxy)naphthol AS-LC
5-Acetamido-3-[4-[3-[4-(2,4-di-tert-pentylphenoxy)butylcarbamoyl]-4-hydroxy-1-naphthoxy]phenylazo]-4-hydroxy-2,7-naphthalenedisulfonic acid disodium salt Dye content 90 %	Gallocyanine Dye content 90 %
Acetone-2,4-dinitrophenylhydrazone environmental standard, 99%	Gentian violet for microscopy (Bact., Hist.)
3-Acetylnoradamantane technical grade, 85%	Gentian Violet meets USP testing specifications
Acid Blue 25 Dye content 45 %	Giemsa stain technical grade, used as a blood stain
Acid Blue 29 Dye content 40 %	Giemsa stain certified by the Biological Stain Commission
Acid Blue 80 Dye content 40 %	Giemsa Stain, Modified Solution (for the staining (of cellular blood components and blood parasites))
Acid Blue 113 Dye content 50 %	Glutaraldehyde bis(2,4-dinitrophenylhydrazone) analytical standard, for environmental analysis
Acid Blue 129 Dye content 25 %	Guinea Green B Dye content 50 %
Acid Fuchsin used in tissue staining	**H**
Acid Fuchsin calcium salt certified by the Biological Stain Commission, Dye content ≥60 %	H+LC:L[49]Cematein for microscopy (Hist.)
Acid Green 25 Dye content ≥60 %	Hematoxylin
Acid Orange 8 Dye content 65 %	Hematoxylin certified by the Biological Stain Commission
Acid Red 1 Dye content 60 %	1-Heptyl-4-(4-pyridyl)pyridinium bromide 95%
Acid Red 183 Dye content 30 %	6-Hexadecanoyl-2-(((2-(trimethylammonium)ethyl)methyl) amino)naphthalene chloride solid
Acid Violet 7 Dye content 40 %	4'-Hydroxy-4-biphenylcarboxylic acid 99%
Acid Yellow 17 Dye content 60 %	1-(2-Hydroxyethyl)-1,2,3,4-tetrahydro-2,2,4,7-tetramethylquinoline 97%
Acid Yellow 25 Dye content 40 %	8-Hydroxyjulolidine 97%
Acridine 97%	Hydroxy naphthol blue disodium salt ACS reagent
Acridine Orange hemi(zinc chloride) salt Dye content 90 %	2-Hydroxy-1,4-naphthoquinone 97%
Acridine Orange hydrochloride hydrate ≥98% (HPLC)	2-(4-Hydroxyphenyl)-5-pyrimidinol 90%
Acridine Orange hydrochloride solution 10 mg/mL in H2O	1-(4-Hydroxyphenyl)-2,4,6-triphenylpyridinium hydroxide inner salt hydrate 97%
Acridine Orange 10-nonyl bromide	**I**
Acriflavine	Immersion oil viscosity 150 cSt (lit.)
Acriflavine hydrochloride	Immersion oil viscosity 1,250 cSt (lit.)
Adrenochrome	Indigo synthetic, Dye content 95 %
ADVASEP™-7 solid	Indigo carmine for microscopy (Bact., Hist.), indicator (pH 11.5-14.0)
Alcian Blue solution 1% in 3% acetic acid, pH 2.5	Indigo carmine certified by the Biological Stain Commission, Dye content 85 %
Alcian Blue 8GX powder	Indophenol
Alcian Blue 8GX certified by the Biological Stain Commission	Indophenol Blue Dye content 60 %
Alcian Blue 8GX for microscopy (Bact., Bot., Hist.)	Indoxyl β-D-galactopyranoside
Alcianblue 8GX solution for microscopy, 1% in solution (in 3% acetic acid)	Indulin B practical grade
Alcian Blue, pyridine variant Dye content ≥85 %	1-Iodo-3,5-dinitrobenzene 98%
Alexa Fluor 350	Iodonitrotetrazolium chloride Used in colorimetric assays.
Alexa Fluor 405	5-Iodosalicylaldehyde 97%

Alexa Fluor 488	IR-797 chloride Dye content 70 %
Alexa Fluor 532	Isopentyl nitrite 96%
Alexa Fluor 546	4-(4-Isothiocyanatophenylazo)-N,N-dimethylaniline 97%
Alexa Fluor 555	**J**
Alexa Fluor 568	Janus Green B certified by the Biological Stain Commission, Dye content 65 %
Alexa Fluor 594	JC-1 solid
Alexa Fluor 647	Jenner's stain suitable for blood stain
Alexa Fluor 680	Jenner's stain certified by the Biological Stain Commission
Alexa Fluor 750	**K**
Alizarin Dye content 97 %	Keratin azure
Alizarin Blue Black B	**L**
Alizarin Red S certified by the Biological Stain Commission	Lacmoid
Alizarin Yellow GG Dye content 50 %	Leishman's stain used as histology stain
Allophycocyanin	Leit-Silver for electron microscopy
Allura Red AC Dye content 80 %	Leucoberbelin Blue I Dye content 65 %
Amaranth Dye content 85-95 %	Leucocrystal Violet
p-Amidinophenyl p-(6-amidino-2-indolyl)phenyl ether dihydrochloride	Leucomalachite Green
1-Aminoanthraquinone 97%	Light Green SF Yellowish crystalline
4-Amino-1,1'-azobenzene-3,4'-disulfonic acid monosodium salt Dye content 95 %	Light Green SF Yellowish certified by the Biological Stain Commission
3-Amino-3-deoxydigoxigenin hemisuccinamide, succinimidyl ester	Lissamine™ Green B Dye content 60 %
N-(4-Amino-2,5-diethoxyphenyl)benzamide	Lithium carbonate puriss. p.a., ACS reagent, reagent (for microscopy), ≥99.0% (T)
2-Amino-5,6-dimethylbenzimidazole 97%	LR white acrylic resins Medium
4-Amino-3,6-disulfo-1,8-naphthalic anhydride dipotassium salt	Lucifer Yellow CH dilithium salt fluorescent stain
N-(5-Aminopentyl)biotinamide trifluoroacetate salt solid	Lucifer Yellow VS dilithium salt ~85%
2-(3-Aminophenylsulfonyl)ethanol hydrochloride 97%	Lugol solution for microscopy (Bact., Bot.)
4-Aminophthalonitrile 98%	Lumichrome
8-Aminopyrene-1,3,6-trisulfonic acid trisodium salt ≥96.0% (HPCE), solid	**M**
Aniline Blue diammonium salt certified by the Biological Stain Commission	Malachite Green oxalate salt Technical grade
Aniline Blue solution 2.5% in 2% acetic acid	Malachite Green oxalate salt certified by the Biological Stain Commission
N-[(3-(Anilinomethylene)-2-chloro-1-cyclohexen-1-yl)methylene]aniline monohydrochloride 94%	Malachite Green Carbinol hydrochloride Dye content 85 %
8-Anilino-1-naphthalenesulfonic acid	Malonaldehyde bis(phenylimine) monohydrochloride 97%
8-Anilino-1-naphthalenesulfonic acid hemimagnesium salt hydrate for fluorescence, ≥95% (perchloric acid titration)	Martius Yellow Dye content 85 %
Anisaldehyde solution	Martius Yellow sodium salt monohydrate 98%
Anthrone ACS reagent, 97%	May-Grünwald Stain
Arsenazo III calcium-sensitive dye	Melanin from Sepia officinalis
Astrazon Orange G	Metanil Yellow for microscopy (Hist.), indicator (pH 1.2-2.3)
Auramine O Dye content ≥80 %, certified by the Biological Stain Commission	Metanil Yellow Dye content 70 %
1-Azidoadamantane 97%	4-(4-Methoxybenzylamino)-7-nitrobenzofurazan
Azobenzene 98%	4-Methoxybiphenyl 97%

Azocarmine G	3-Methoxydiphenylamine 98%
Azomethine-H monosodium salt hydrate ~95%	1-Methoxy-5-methylphenazinium methyl sulfate ≥95%
Azophloxine for microscopy (Hist.)	2-Methoxy-N4-phenyl-1,4-phenylenediamine 95%
Azure B certified by the Biological Stain Commission	6-Methoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole 97%
Azure B prepared by direct synthesis	6-Methoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole hydrochloride 97%
Azure A chloride Dye content ≥70 %	6-Methoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-1-carboxylic acid 97%
Azure A chloride certified by the Biological Stain Commission	2-Methyl-2-adamantanol 97%
Azure A eosinate	1-(Methylamino)anthraquinone 98%
Azure B eosinate	Methyl 3-amino-5,6-dichloro-2-pyrazinecarboxylate 97%
Azure II powder	Methyl Blue
Azure II eosinate	Methyl Blue certified by the Biological Stain Commission
Azure B tetrafluoroborate Dye content 95 %	4,4′-Methylenebis(N,N-dimethylaniline) 98%
B	Methylene blue certified by the Biological Stain Commission
Bacteriochlorophyll from Rhodopseudomonas sphaeroides	Methylene Blue hydrate suitable for nucleic acid staining, BioReagent
Basacryl Red GL Dye content 19 %	Methylene Blue solution for microscopy, concentrate according to Ehrlich, concentrated, aqueous solution
Basic Blue 3 Dye content 25 %	Methylene Blue solution 1.4 % (w/v) in 95% ethanol
Basic Blue 41 Dye content 40 %	Methylene Blue solution for microbiology
Basic Fuchsin for microscopy (Bact., Bot., Hist.), indicator (pH 1.0-3.1)	4,5-Methylenedioxy-1,2-phenylenediamine dihydrochloride Fluorogenic reagent
Basic Fuchsin special for flagella, certified	Methylene Violet (Bernthsen) certified by the Biological Stain Commission, Dye content ≥65 %
Basic Fuchsin certified by the Biological Stain Commission, Dye content ≥88 %	Methylene Violet 3RAX Dye content 90 %
Basic Fuchsin Dye content >85 %	Methyl Green zinc chloride salt, ~85%
Bathocuproinedisulfonic acid disodium salt for spectrophotometric det. of Cu, Fe	Methyl Green zinc chloride salt, for microscopy (Bact., Bot., Hist.)
Bathophenanthrolinedisulfonic acid disodium salt hydrate ≥95%	Methyl Green zinc chloride salt, certified by the Biological Stain Commission, Dye content 85 %
Benzaldehyde-2,4-dinitrophenylhydrazone environmental standard, 99%	Methyl Green zinc chloride salt, <0.5% crystal violet, Dye content 80 %
Benzaldehyde tosylhydrazone 98%	4-Methyl-3-nitrobenzyl chloride 97%
Benzidine ≥98.0% (N)	Methyl Orange ACS reagent, Dye content 85 %
Benzidine ISOPAC®, ≥98.0% (N)	4-Methylphthalonitrile 99%
Benzidine dihydrochloride ≥99% (titration)	Methyl Purple in H2O
Benzophenone imine 95%	Methyl Red ACS reagent, crystalline
N-Benzylideneaniline 99%	Methyl Red hydrochloride ACS reagent
N-Benzylidenebenzenesulfonamide 97%	Methyl Red sodium salt Crystalline
N-Benzylidenebenzylamine contains 100 ppm MEHQ as stabilizer, 99%	Methyl Red sodium salt ACS reagent, Dye content 95 %
Biotin-4-Fluorescein	Methyl violet 2B certified by the Biological Stain Commission
bisBenzimide H 33258 ≥98% (HPLC and TLC)	Methyl Violet B base Dye content 85 %
bisBenzimide H 33342 trihydrochloride ≥98% (HPLC and TLC)	Mordant Blue 9 Dye content 50 %
Bis(cyclohexanone)oxaldihydrazone	Mordant Orange 1 Dye content 70 %
Bis(1,3-dibutylbarbituric acid) trimethine oxonol ≥95% (HPLC)	Morin hydrate for microscopy (Fl.), for the determination of Al, Be, Zn, Ga, In, Sc, 1-2 mol/mol water
N,N′-Bis(2,5-di-tert-butylphenyl)-3,4,9,10-perylenedicarboximide Dye content 97 %	MTT Formazan powder

1,3-Bis[4-(dimethylamino)phenyl]-2,4-dihydroxycyclobutenediylium dihydroxide, bis(inner salt) Dye content 90 %	Murexide ACS reagent
[4-[Bis(2-hydroxyethyl)amino]phenyl]-1,1,2-ethylenetricarbonitrile 98%	**N**
Bismarck Brown R for microscopy (Bact., Hist.)	2,3-Naphthalenedicarbonitrile 97%
Bismarck Brown Y certified by the Biological Stain Commission, Dye content 50 %	2,3-Naphthalenedicarboximide 97%
N,N′-Bis(salicylidene)-1,2-phenylenediamine 97%	α-Naphtholbenzein indicator (pH 8.2-10.0)
Brilliant Black BN Dye content 60 %	α-Naphtholbenzein indicator grade
Brilliant Blue G solution Concentrate	Naphthol Blue Black Dye content ~50 %
Brilliant Blue R Dye content ~50 %, Technical grade	Naphthol Blue Black Dye content 80 %
Brilliant Blue R pure	Naphthol Green B Technical grade
Brilliant Blue G pure	Naphthol Green B for microscopy (Hist.), for complexometry
Brilliant Blue R Concentrate suitable for SDS-PAGE, methanol solution	Naphthol AS-GR phosphate disodium salt
Brilliant Blue R Staining Solution ethanol solution	Naphthol AS-MX phosphate disodium salt phosphatase substrate
'Brilliant Cresyl blue' for microscopy (Vit.), mixture of toluidine blue and waterblue	Naphthol AS phosphate
Brilliant Cresyl Blue ALD Certified by the Biological Stain Commission	Naphthol AS phosphate disodium salt
Brilliant Cresyl Blue ALD certified by the Biological Stain Commission	α-Naphtholphthalein practical grade
Brilliant Green Dye content ~90 %	Naphthol Yellow S for microscopy (Hist.), for the precipitation (of amino acids and peptides)
Brilliant Green certified by the Biological Stain Commission	1-Naphthyl red hydrochloride Dye content 85 %
Brilliant Yellow Dye content ≥50 %	Neutral Red powder, BioReagent, suitable for cell culture
Bromaminic acid sodium salt	Neutral Red Dye content ≥90 %
Bromobimane ≥97%	Neutral Red certified by the Biological Stain Commission
4′-Bromo-(1,1′-biphenyl)-4-ol 97%	New Coccine Dye content 75 %
Bromochlorophenol Blue Dye content 95 %	Nigrosin certified by the Biological Stain Commission
Bromocresol Green ACS reagent, Dye content 95 %	Nigrosin water soluble For use as a biological stain
Bromocresol Green sodium salt crystalline	Nile Blue A Dye content ≥75 %
Bromocresol Green sodium salt ACS reagent, Dye content 90 %	Nile Blue A certified by the Biological Stain Commission
Bromocresol Green sodium salt solution 0.04 wt. % in H2O	Nile Red Technical grade
Bromocresol Green/Methyl Red, mixed indicator solution in methanol	Nitrazine Yellow indicator grade, Dye content 85 %
Bromocresol Green Sultone Form for microscopy (Bot., Hist., Vit.), indicator (pH 3.8-5.4)	4-Nitroazobenzene technical grade, 90%
Bromocresol Purple BioReagent, suitable for indicator, Dye content 90 %	3-Nitrobenzaldoxime 99%
Bromocresol Purple Technical grade	4-Nitrobenzenediazonium tetrafluoroborate 97%
Bromocresol Purple for microscopy (Hist., Vit.), indicator (pH 5.2-6.8)	4-Nitroguaiacol 97%
Bromocresol Purple sodium salt indicator grade, Dye content 90 %	4-Nitroguaiacol potassium salt hydrate 98%
Bromocresol Purple solution 0.04 wt. % in H2O	4-(4-Nitrophenylazo)resorcinol Dye content 90 %
Bromophenol Blue	2-(3-Nitrophenylsulfonyl)ethanol 97%
Bromophenol Blue ACS reagent	4-Nitrophthalamide 99%
Bromophenol Blue sodium salt for molecular biology, for electrophoresis	3-Nitrophthalimide 97%
Bromophenol Blue sodium salt	4-Nitrophthalimide 98%
Bromophenol Blue sodium salt Dye content 90 %, ACS reagent	3-Nitrophthalonitrile 99%

Bromophenol Blue solution 0.04 wt. % in H2O	4-Nitrophthalonitrile 99%
2-(5-Bromo-2-pyridylazo)-5-(diethylamino)phenol 97%	Nitrotetrazolium Blue chloride ~98% (TLC)
Bromothymol Blue ACS reagent, Dye content 95 %	Nitrotetrazolium Blue chloride powder, electrophoresis grade
Bromothymol Blue sodium salt powder	Nitrotetrazolium Blue chloride monohydrate
Bromothymol Blue sodium salt ACS reagent	3-Noradamantanamine hydrochloride 95%
Bromothymol Blue sodium salt solution 0.04 wt. % in H2O	3-Noradamantanecarboxylic acid 97%
2-Bromo-1,1,3-trimethoxypropane 95%	Nuclear Fast Red
Bromoxylenol Blue indicator grade, Dye content 95 %	Nuclear Fast Red for microscopy (Bot., Hist.)
6-tert-Butyl-2,3-naphthalenedicarbonitrile 94%	Nuclear Fast Red
4-tert-Butylphthalic anhydride 95%	**O**
4-tert-Butylphthalonitrile 98%	Octyl acetate ≥99%
N-tert-Butyl-α-(2-sulfophenyl)nitrone sodium salt 95%	Oil Blue N Dye content 96 %
Sulfobromophthalein disodium salt hydrate used to study hepatocyte transport functions	Oil Red O certified by the Biological Stain Commission
C	Oil Red O solution 0.5% in isopropanol
Calcein Used for the fluorometric determination of calcium and EDTA titration of calcium in the presence of magnesium.	Oil Red O solution 0.5% in propylene glycol
Calcein AM solution 4 mM in DMSO, ≥90% (HPLC), solution	Oil Red EGN
Calcium Ionophore A23187 mixed calcium magnesium salt Approximate 1:1 molar ratio Ca:Mg. Actual content given on label.	Orange G for NA electrophoresis
Calconcarboxylic acid	Orange G certified by the Biological Stain Commission
Calmagite indicator grade	Orange G certified by the Biological Stain Commission, Dye content 80 %
Calmagite triethanolammonium salt	Orange II sodium salt (Certified by the Biological Stain Commission), Dye content ≥85 %
Canada balsam Mounting medium for microscopy	Orange OT Dye content 75 %
Carbazole ≥95% (GC)	Orcein synthetic
Carbol Fuchsin	Orcein synthetic, certified by the Biological Stain Commission
Carbostyril 124 99%	Orcinol monohydrate colorimetric detection reagent
6-Carboxy-4′,5′-dichloro-2′,7′-dimethoxyfluorescein N-hydroxysuccinimide ester	Osmium tetroxide Sealed ampule.
5-Carboxyfluorescein 99% (HPLC)	Oxacillin sodium salt monohydrate
6-Carboxyfluorescein ~97% (HPLC)	**P**
5-Carboxyfluorescein diacetate ~95% (HPLC)	Para Red Dye content 95 %
5(6)-Carboxyfluorescein diacetate Mixed isomers ≥90% (HPLC)	Pararosaniline hydrochloride
N-Carboxymethyl-6-(2,2-dicyanovinyl)-1,2,3,4-tetrahydroquinoline ≥98% (HPLC)	Pararosaniline acetate Dye content 90 %
5-Carboxytetramethylrhodamine	Pararosaniline Base Dye content 95 %
Cardiogreen polymethine dye	Pararosaniline Base crystalline
Carmine powder	Patent Blue VF Dye content 50 %
Carmine certified by the Biological Stain Commission	PDAM for HPLC derivatization
Carminic acid	4-Pentylbicyclo[2.2.2]octane-1-carboxylic acid 99%
Celestine blue Dye content 80 %	Perylene sublimed grade, ≥99.5%
Chicago Sky Blue 6B powder	Perylene ≥99%
Chlorazol Black	Phenazine ethosulfate ≥95%
1-Chloro-9,10-bis(phenylethynyl)anthracene 99%	Phenolphthalein puriss., meets analytical specification of Ph Eur., BP, 98-101% (calc. to the dried substance)

2-Chloro-5-methylaniline 99%	Phenolphthalein ACS reagent
2′-Chloro-5′-methylbenzanilide 97%	Phenolphthalein solution 0.5 wt. % in ethanol: water (1:1)
5-Chloro-2-methylindole 97%	Phenolphthalein bisphosphate tetrasodium salt ~95%
2-Chloro-6-nitrobenzaldehyde 97%	Phenol Red powder, BioReagent, suitable for cell culture
Chlorophenol Red indicator grade	Phenol Red ACS reagent
Chlorophyll a from Anacystis nidulans algae	Phenol Red sodium salt powder, BioReagent, suitable for cell culture, suitable for insect cell culture
Chlorophyll b from spinach ≥90% (HPLC), ≤0.5% Chlorophyll a	Phenol Red sodium salt
4-Chloro-7-sulfobenzofurazan ammonium salt	Phenol Red sodium salt ACS reagent, Dye content 90 %
Chromeazurol B	Phenol red solution 0.5%, liquid, sterile-filtered, BioReagent, suitable for cell culture
Chromeazurol S Dye content 50 %	Phenosafranin Dye content 80 %
Chromotrope 2R suitable for modified Gomori Trichrome stain	3-Phenoxyphthalonitrile 98%
Chromotrope FB Dye content 50 %	4-Phenoxyphthalonitrile 98%
Chrysin 97%	N-[5-(Phenylamino)-2,4-pentadienylidene]aniline monohydrochloride 98%
Chrysoidine G for microscopy (Bact., Bot., Vit.)	4-(Phenylazo)diphenylamine 97%
Chrysophenine Dye content 65 %	4-Phenylazophenol 98%
Cibacron Brilliant Yellow 3G-P	1-Phenyl-2,3-naphthalenedicarboxylic anhydride 98%
Clobetasone butyrate ≥98%	5-Phenyl-2-[2-[[5-phenyl-3-(3-sulfopropyl)-2(3H)-benzoxazolylidene]methyl]-1-butenyl]-3-(3-sulfopropyl)benzoxazolium hydroxide inner salt, sodium salt Dye content 90 %
Collodion solution for microscopy, 2% in amyl acetate	2-(Phenylsulfonyl)ethanol 97%
Congo Red certified by the Biological Stain Commission, BioXtra	Phloroglucinol Used to detect the presence of wood fiber.
Congo Red Dye content ≥35 %	Phloxine B antibacterial fluorescent dye
Coomassie Violet R200 Dye content 50 %	Phloxine B Dye content ≥80 %, certified by the Biological Stain Commission
Coproporphyrin I tetramethyl ester ≥90% (HPLC)	Pinacyanol bromide Dye content 95 %
Coumarin 6 98%	Pinacyanol chloride
Coumarin 7 98%	Poly(1-methoxy-4-(O-disperse Red 1))-2,5-phenylenevinylene
Coumarin 314 Dye content 97 %	Ponceau S BioReagent, suitable for electrophoresis
Coumarin 334 Dye content 99 %	Ponceau S for microscopy (Hist.)
Coumarin 343 Dye content 97 %	Ponceau S Dye content 75 %
o-Cresolphthalein indicator grade	Ponceau S solution BioReagent, suitable for electrophoresis, 0.1 % (w/v) in 5% acetic acid
o-Cresolphthalein Complexone powder	Ponceau BS Dye content ~60 %
m-Cresol Purple indicator grade, Dye content 90 %	Ponceau SS Dye content 80 %
m-Cresol Purple sodium salt Dye content 90 %	Ponceau Xylidine Dye content ≥60 %
Cresol red indicator grade, Dye content 95 %	Potassium indigotetrasulfonate Dye content 85 %
Cresol Red sodium salt indicator grade	Potassium indigotrisulfonate ozone-scavenging reagent
Cresyl Violet acetate certified by the Biological Stain Commission	Procion® Red MX-5B Dye content 40 %
Crocein Scarlet 7B	Proflavine hemisulfate salt hydrate powder
Croconic acid 98%	Propidium iodide ≥94.0% (HPLC)
Crotonaldehyde-2,4-dinitrophenylhydrazone analytical standard, for environmental analysis	Propidium iodide solution solution (1.0 mg/ml in water)
Crystal Ponceau 6R	Propionaldehyde-2,4-dinitrophenylhydrazone analytical standard, for environmental analysis
Crystal Violet Dye content ≥90 %	Prussian blue soluble for microscopy

Crystal Violet ACS reagent, ≥90.0% anhydrous basis	Purpurin Dye content 90 %
Crystal Violet certified by the Biological Stain Commission	1-Pyrenebutyric acid N-hydroxysuccinimide ester 95%
Crystal violet solution 1%, aqueous solution	3,4-Pyridinedicarbonitrile 96%
Crystal Violet lactone Dye content 97 %	3,4-Pyridinedicarboxamide 98%
Curcumin from Curcuma longa (Turmeric), powder	1-(2-Pyridylazo)-2-naphthol indicator grade
N-[3-Cyano-3-[4-(dicyanomethyl)phenyl]-2-propenylidene]-N-ethyl-ethaniminium inner salt	4-(2-Pyridylazo)resorcinol 96%
9-Cyano-N,N,N'-triethylpyronine-N'-caproic acid N-hydroxysuccinimide ester chloride ≥85% (HPLC)	4-(2-Pyridylazo)resorcinol monosodium salt hydrate
9-Cyano-N,N,N'-triethylpyronine-N'-caproic acid N4-(maleimidoethyl)piperazide chloride ≥80% (HPLC)	3-(2-Pyridyl)-5,6-di(2-furyl)-1,2,4-triazine-5',5''-disulfonic acid disodium salt
Cyclohexanone 2,4-dinitrophenylhydrazone ≥99%	3-(2-Pyridyl)-5,6-diphenyl-1,2,4-triazine-4',4''-disulfonic acid sodium salt BioXtra
D	Pyrocatechol Violet suitable for indicator
DAPI, dilactate ≥98% (HPLC)	Pyrogallol Red
Darrow Red certified by the Biological Stain Commission, Dye content ≥65 %	Pyronin Y for NA electrophoresis
o-Dianisidine dihydrochloride ≥95%	Pyronin B Dye content ≥30 %
o-Dianisidine dihydrochloride Suitable for use in glucose determination	Pyronin B certified by the Biological Stain Commission, Dye content 40 %
o-Dianisidine dihydrochloride for enzymic, spectrophotometric determination, vial of 5 mg	Pyronin Y for microscopy (Bot., Fl., Hist.)
4,5-Dibromobenzene-1,2-diol 90%, technical grade	Pyronin Y certified by the Biological Stain Commission, Dye content 50 %
4',5'-Dibromofluorescein Dye content 95 %	**Q**
2,5-Dibromo-6-isopropyl-3-methyl-1,4-benzoquinone	Qdot 525
3,6-Dibutoxy-1,2-benzenedicarbonitrile 97%	Qdot 565
2,5-Dibutoxy-4-(4-morpholinyl)benzenediazonium tetrafluoroborate Dye content 95 %	Qdot 605
1,4-Dibutoxy-2,3-naphthalenedicarbonitrile 99%	Qdot 655
4-(Dibutylamino)benzaldehyde 98%	Qdot 705
4-(2-(6-(Dibutylamino)-2-naphthalenyl)ethenyl)-1-(3-sulfopropyl)pyridinium hydroxide inner salt ≥95% (HPLC), solid	Qdot 800
N,N-Dibutylaniline 97%	Quinaldine Red Dye content 95 %
2,4-Dichlorobenzenediazonium 1,5-naphthalenedisulfonate hydrate	Quinoline Yellow for microscopy (Hist.), mixture of mono- and disulfonic acid sodium salt
3,6-Dichloro-1,2-benzenedithiol 95%	Quinoline Yellow Dye content 95 %
1,2-Dichloro-4,5-dinitrobenzene 98%	Quinoline Yellow Mixture of the mono- and disulfonic acids of Quinoline Yellow
2',7'-Dichlorofluorescein ~90% (TLC), crystalline	**R**
2',7'-Dichlorofluorescein ACS reagent	Reactive Black 5 Dye content ≥50 %
2,6-Dichloroindophenol sodium salt hydrate suitable for vitamin C determination, BioReagent	Reactive Blue 4 Dye content 35 %
2,6-Dichloroquinone-4-chloroimide	Reactive Green 19 practical grade
6-(2,2-Dicyanovinyl)-N-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline	Reactive Orange 16 Dye content ≥70 %
trans-4-(Diethylamino)cinnamaldehyde 98%	Reactive Red 120
7-Diethylamino-3-(4-maleimidophenyl)-4-methylcoumarin ≥95% (HPLC), solid	Reichardt's dye Dye content 90 %
1,1'-Diethyl-2,2'-carbocyanine iodide 97%	Remazol Brilliant Blue R anthraquinone dye
1,1'-Diethyl-2,2'-cyanine iodide 97%	Renin Substrate 1
1,1'-Diethyl-4,4'-cyanine iodide	Resazurin sodium salt certified by the Biological Stain Commission
N,N-Diethyl-p-phenylenediamine oxalate salt	Resorcinol BioXtra, ≥99%

Diethyl 3,4-pyridinedicarboxylate 97%	Resorufin Dye content 95 %
3,3′-Diethylthiacyanine iodide Dye content ~97 %	Rhodamine 6G Dye content 99 %
Dihydroethidium ≥95%	Rhodamine 6G Dye content ~95 %
Dihydrorhodamine 123 ≥95%	Rhodamine 6G perchlorate Dye content 99 %
2′,4′-Dihydroxy-3′-methylacetophenone technical grade, 90%	Rhodamine B ≥95% (HPLC)
1,3-Dihydroxynaphthalene ≥99%, crystalline	Rhodamine 110 chloride Dye content ≥88 %
1,4-Dihydroxy-2,3-naphthalenedicarbonitrile 97%	Rhodamine 123 mitochondrial specific fluorescent dye
4,7-Dihydroxy-1,10-phenanthroline Dye content ≥30 %	Rhodamine B base Dye content 97 %
1,3-Diiminobenz[f]isoindoline 95%	Rhodamine B isothiocyanate–Dextran average mol wt ~10,000
1,3-Diiminoisoindoline 97%	Rhodamine B isothiocyanate mixed isomers
3,3′-Dimethoxybenzidine dihydrochloride technical grade	Rhodanile Blue A complex of Nile Blue and Rhodamine B., Dye content 75 %
(2,5-Dimethoxyphenyl)acetyl chloride 99%	RIM-1 ≥90% (HPLC)
2,4-Dimethoxytoluene 99%	Rose bengal Dye content 95 %
4-(Dimethylamino)benzaldehyde suitable for histochemical demonstration of nitro blue tetrazolium reduction in neutrophils	Rose Bengal sodium salt Dye content ≥85 %
4-(Dimethylamino)cinnamaldehyde chromogenic reagent for indoles and flavanols	Rose Bengal diacetate
4-Dimethylamino-2-methylazobenzene	Rose Bengal lactone 95%
2-[4-(Dimethylamino)styryl]-1-ethylpyridinium iodide ≥99% (HPLC), solid	p-Rosolic acid Dye content 85 %
2-[4-(Dimethylamino)styryl]-N-methylbenzoxazolium perchlorate	Rubrene powder
N,N-Dimethyl-4,4′-azodianiline 97%	Ruthenium Red Technical grade
N,N′-Dimethyl-9,9′-biacridinium dinitrate used as chemiluminescent reagent	Ruthenium Red for microscopy, ≥85% (calc. on dry substance, AT)
N,N-Dimethylindoaniline Dye content 97 %	**S**
3,3-Dimethyl-2-methylene-1-phenylindoline	Saffron crude source of crocetin and crocein
N,N-Dimethyl-1-naphthylamine ≥98.0% (GC)	Safranin O Dye content ≥85 %
N,N-Dimethyl-4-nitrosoaniline 97%	Safranin O certified by the Biological Stain Commission
N,N-Dimethyl-p-phenylenediamine dihydrochloride suitable for peroxidase test, ≥99.0% (titration)	Safranin O for microscopy (Bact., Bot., Hist.), indicator (pH 0.3-1.0)
1,4-Dimethylpyridinium iodide 99%	Schiff's fuchsin-sulfite reagent suitable for detection of glycoproteins
1,4-Dimethylpyridinium p-toluenesulfonate 98%	Scopoletin ≥99%
3,5-Dinitroaniline 97%	Silver diethyldithiocarbamate
4,4′-Dinitro-2-biphenylamine 98%	Silver Enhancer Kit
10-(2′,4′-Dinitrophenylazo)-9-phenanthrol	Silver enhancer solution A
3,5-Dinitrosalicylic acid used in colorimetric determination of reducing sugars	Silver enhancer solution B
1,1′-Dioctadecyl-4,4′-bipyridinium dibromide 97%	Silver nitrate BioXtra, >99% (titration)
3,3′-Dioctadecyloxacarbocyanine perchlorate	Silver nitrate ReagentPlus®, ≥99.0% (titration)
4-(2-[6-(Dioctylamino)-2-naphthalenyl]ethenyl)-1-(3-sulfopropyl)pyridinium inner salt ≥95% (HPLC), solid	Silver proteinate ~8% Ag basis
1,3-Diphenylacetone p-tosylhydrazone 98%	Solvent Blue 38 practical grade
2-Diphenylacetyl-1,3-indandione-1-hydrazone 98%	Solvent Blue 59 Dye content 98 %
1,2-Diphenylindole 94%	Solvent Green 3 Dye content 95 %
N-(Diphenylmethylene)glycine tert-butyl ester 98%	Stains-All ~95%
2,6-Diphenyl-4H-thiopyran-4-one 96%	trans-4-Stilbenemethanol
Direct Blue 71 Dye content 50 %	Sudan I Dye content ≥95 %

Direct Blue 15 suitable for Histopaque® system, suitable for viability studies of collagenase-treated rat liver cells	Sudan II Dye content 90 %
Direct Red 23 Dye content 30 %	Sudan III Technical grade
Direct Red 80 Dye content 25 %	Sudan III certified by the Biological Stain Commission, BioXtra
Direct Red 81 Dye content 50 %	Sudan IV certified by the Biological Stain Commission, BioXtra
Direct yellow 27	Sudan IV Dye content ≥80 %
Disperse Black 9 Dye content 97 %	Sudan Black B certified by the Biological Stain Commission
Disperse Blue 1 Dye content 30 %	Sudan Blue II Dye content 98 %
Disperse Blue 3 Dye content 20 %	Sudan Orange G Dye content 85 %
Disperse Blue 14 Dye content 97 %	Sudan Red 7B for microscopy (Bot., Hist.)
Disperse Orange 1 Dye content ~15 %	Sudan Red 7B Dye content 95 %
Disperse Orange 13 Dye content 90 %	Sulfanilic acid azochromotrop ≥80%
Disperse Orange 13 Dye content 15 %	2-Sulfobenzoic acid cyclic anhydride technical grade, 90%
Disperse Yellow 3 Dye content 30 %	Sulfochlorophenol S sodium calcium salt
Dithizone Practical Grade	Sulforhodamine 101
Dithizone ACS reagent, ≥85.0%	Sulforhodamine B sodium salt Technical grade
E	Sunset Yellow FCF Dye content 90 %
Eosin B certified by the Biological Stain Commission, Dye content 90 %	SYBR® Green II RNA gel stain 10,000 × in DMSO Green Alternative
Eosin B for microscopy (Fl., Hist.), adsorption and fluorescent indicator	SYBR® Green I nucleic acid gel stain 10,000 × in DMSO Green Alternative
Eosin B Dye content 95 %	SynaptoGreen™ C4 ≥95% (HPLC), solid
Eosin Y Dye content ~99 %	SynaptoRed™ C2 ≥95% (HPLC), solid
Eosin Y	Syringaldazine 99%
Eosin Y disodium salt Dye content ≥85 %	**T**
Eosin Y disodium salt certified by the Biological Stain Commission	Tannic acid Source: Chinese natural gall nuts
Eosin Y solution 5 wt. % in H2O	Tetrabromophenol Blue Dye content 85 %
Eriochrome® Black T ACS reagent (indicator grade)	Tetrabromophenol Blue sodium salt Dye content 85 %
Erioglaucine disodium salt	3',3'',5',5''-Tetrabromophenolphthalein ethyl ester potassium salt indicator grade
Erythrosin B Dye content ≥95 %	3,4,5,6-Tetrabromophenolsulfonephthalein Dye content 95 %
Erythrosin B certified by the Biological Stain Commission, Dye content 90 %	Tetrabromo-2-sulfobenzoic acid cyclic anhydride
Erythrosin extra bluish for microscopy (Bact., Hist.), adsorption and fluorescent indicator	Tetrabutylammonium bis(3,6-dichloro-1,2-benzenedithiolato)nickelate 98%
Erythrosin extra bluish certified by the Biological Stain Commission	Tetrabutylammonium bis(4-methyl-1,2-benzenedithiolato)nickelate 98%
Erythrosin yellowish blend	Tetrachlorophthalonitrile 98%
Ethidium bromide ~95% (HPLC)	Tetrachrome Stain (MacNeal)
Ethidium bromide monoazide ≥95% (HPLC), solid	2,3,6,7-Tetrahydro-8-hydroxy-1H,5H-benzo[ij]quinolizine-9-carboxaldehyde 98%
Ethidium homodimer I solution ≥95%, 2 mM in DMSO	1,2,3,4-Tetrahydro-2,2,4,7-tetramethylquinoline 97%
5-[3-Ethoxy-4-(3-ethyl-5-methyl-2(3H)-benzothiazolylidene)-2-butenylidene]-3-ethyl-2-[(3-ethyl-4,5-diphenyl-2(3H)-thiazolylidene)methyl]-4,5-dihydro-4-oxothiazolium iodide Dye content 95 %	3',3'',5',5''-Tetraiodophenolsulfonephthalein Dye content 90 %
3-Ethoxy-4-methoxybenzaldehyde 99%	1,2,3,3-Tetramethyl-3H-indolium iodide 98%
2-[3-(3-Ethyl-2(3H)-benzothiazolylidene)-2-methyl-1-propenyl]-3-[3-(sulfooxy)butyl]benzothiazolium hydroxide inner salt Dye content 90 %	2,2,4,4-Tetramethyl-3-pentanone imine 95%

5-Ethyl-5,6-dihydro-3,8-dinitro-6-phenyl-6-phenanthridinol 97%	N,N,N',N'-Tetramethyl-p-phenylenediamine dihydrochloride ≥95%, powder
Ethyl 3,5-dimethyl-2-pyrrolecarboxylate 98%	Tetramethylrhodamine-5-isothiocyanate
Ethyl eosin certified by the Biological Stain Commission	Tetramethylrhodamine methyl ester perchlorate ≥95%
Ethyl 4'-hydroxy-4-biphenylcarboxylate 98%	Tetranitroblue tetrazolium chloride
3-Ethyl-2-methylbenzothiazolium iodide	Tetrazolium Blue Chloride used in colorimetric determination of reducing compounds
Ethyl Orange sodium salt indicator grade, Dye content 90 %	Tetrazolium Violet
2-(Ethylthio)benzothiazole 97%	TFLZn potassium salt ≥90% (TLC)
2-Ethyl-2-thiopseudourea hydrobromide 98%	TFLZn-AM ≥90% (TLC)
N-Ethyl-o-toluidine 97%	Thiazole Orange Dye content ~90 %
Ethyl Violet cationic triarylmethane dye	Thiazolyl Blue Tetrazolium Bromide 98%
Ethyl viologen diperchlorate 98%	Thioflavine S practical grade
Evans Blue Dye content ≥75 %	Thioflavin T used as stain for amyloid
F	Thionin acetate salt certified by the Biological Stain Commission, Dye content ≥85 %
Fast Black K Salt hemi(zinc chloride) salt practical grade	Thymol Blue ACS reagent
Fast Blue BB Salt hemi(zinc chloride) salt Dye content ≥80 %	Thymol Blue sodium salt ACS reagent, Dye content 95 %
Fast Blue BB Salt hemi(zinc chloride) salt for microscopy (Hist.)	Thymolphthalein ACS reagent, Dye content 95 %
Fast Blue RR	Thymoquinone ≥98%
Fast Blue RR Salt crystalline	o-Tolidine ≥97%, powder
Fast Blue B Salt Dye content ~95 %	Toluidine Blue O Technical grade
Fast Corinth V zinc chloride double salt Dye content 90 %	Toluidine Blue O certified by the Biological Stain Commission
Fast Dark Blue R Salt	Toluidine Red Dye content 70 %
Fast Garnet GBC sulfate salt diazonium dye	3,4,5-Trihydroxybenzamide 98%
Fast Garnet GBC base 97%	Tris(4-nitrophenyl)amine technical grade
Fast Green FCF Dye content ≥85 %	Trypan Blue Dye content 60 %
Fast Green FCF certified by the Biological Stain Commission	Trypan Blue powder, BioReagent, suitable for cell culture
Fast Red B tetrafluoroborate salt Dye content 95 %	Trypan Blue solution 0.4%, liquid, sterile-filtered, suitable for cell culture
Fast Red ITR	**U**
Fast Red RC Salt	Uniblue A sodium salt
Fast Red Violet LB base	**V**
Fast Red Violet LB Salt Dye content ≥90 %	Valeraldehyde-2,4-dinitrophenylhydrazone environmental standard, 99%
Fat Brown B	Vanillin azine 99%
Ferroin indicator solution 0.1 wt. % in H2O	Variamine Blue RT Salt
FIM-1	Victoria Blue R Dye content 80 %
FIM-1 diacetate	Victoria Pure Blue BO Dye content 90 %
Fluorescein sodium salt used as fluorescent tracer	Violamine R Dye content 60 %
Fluorescein-5-EX N-hydroxysuccinimide ester	**W**
Fluoresceinamine, isomer I	Wright stain suitable for blood stain
Fluorescein diacetate used as cell viability stain	Wright stain certified by the Biological Stain Commission
Fluorescein (free acid) Dye content 95 %	Wright Stain solution for microscopy
Fluorescein 5(6)-isothiocyanate ≥90% (HPLC)	**X**
Fluorescein isothiocyanate isomer I suitable for protein labeling, ≥90% (HPLC), powder	p-Xylene-bis(N-pyridinium bromide) ≥95% (TLC)

Fluorescein isothiocyanate isomer I ≥97.5% (HPLC)	Xylene Cyanol FF Dye content ≥75 %
Fluorescein isothiocyanate isomer I–Celite® suitable for fluorescent labeling techniques	Xylene Cyanol FF for molecular biology, BioReagent
Fluorescein Sodium salt - CAPS solution for fluorescence, ≥95.0% (HPLC)	Xylenol Blue indicator grade, Dye content 90 %
Fluorescent Brightener 28 used as a stain and brightening agent	Xylenol Orange tetrasodium salt ACS reagent
Fluorinert™ FC-40	Xylidyl blue I
4-Formylbenzene-1,3-disulfonic acid disodium salt hydrate 97%	Z
Fura 2-AM ≥95% (HPLC)	Zincon sodium salt Dye content ≥75 %
Fura-2 LeakRes (AM) ≥85%	Zinquin ≥95% (HPLC), solid
Fusidic acid	Zinquin ethyl ester ≥95% (HPLC), solid
Plasmocorinth B Dye content 60 %	

[0062] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and/or the understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise. It is also to be understood that unless otherwise indicated or otherwise evident from the context and/or the understanding of one of ordinary skill in the art, values expressed as ranges can assume any subrange within the given range, wherein the endpoints of the subrange are expressed to the same degree of accuracy as the tenth of the unit of the lower limit of the range.

[0063] The term "comprising" whenever used in this document is intended to indicate the presence of stated features, integers, steps, components, but not to preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

[0064] The disclosure is of course not in any way restricted to the embodiments described and a person with ordinary skill in the art will foresee many possibilities to modifications thereof without departing from the basic idea of the disclosure as defined in the appended claims.

[0065] The above described embodiments are obviously combinable.

[0066] The following dependent claims set out particular embodiments of the disclosure.

SEQUENCE LISTING

SEQ- ID. NO.1: Folic acid-DRDDQAAWFSQY

SEQ- ID. NO 2: KDEPQRRSARLSAKPAPPKPEPKPKKAPAKK-DRDDQAAWFSQY

SEQ- ID. NO 3: YQSFWAAQDDRD-KDEPQRRSARLSAKPAPPKPEPKPKKAPAKK

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C L A I M S

1. Method for encapsulating an active ingredient in a liposome comprising the following sequencial steps:

   preparing an ethanolic phase by mixing hydrophobic molecules of phospholipids and ansteroid with ethanol,

   preparing an aqueous phase with an active ingredient and a targeting agent in a buffer solution;

   obtaining the liposomes by injecting the ethanolic phase in the aqueous phase, at a temperature from around 50 °C to around 80 °C, wherein the ethanolic/aqueous phase volume ratio is between 1:1 and 3:2;

   removing of the ethanol;

   removing the remaining free active ingredient in a suitable way, namely by tangencial flow filtration;

   wherein the targeting agent is a peptide that is conjugated with a liposomal component or incorporated in the lipidic membrane.

2. Method according to the previous claim wherein the ethanol removal is by evaporation or tangential flow filtration.
3. Method according to any of the previous claims, wherein the steroid is cholesterol.
4. Method according to the previous claims wherein the cholesterol is cholesteryl hemisuccinate.
5. Method according to any of the previous claims, wherein it further comprises the step of diluting of the liposomal dispersion 1 to 10-fold in further diluted aqueous phase.
6. Method according to any of the previous claims, wherein the ethanolic phase is injected at a rate of approximately 2-4 ml/minute.
7. Method according to the previous claims, wherein the ethanol concentration, relative to the initial aqueous volume, is between 40% and 60%, preferably 50%.

8. Method according to any of the previous claims, wherein the temperature is 60 °C or 70 °C.
9. Method according to any of the previous claims, wherein the active ingredient is a polycharged molecule containing at least one negative charge at a pH of around 4 to around 7.
10. Method according to any of the previous claims, wherein the active ingredient is a drug, in particular an anticancer drug, antirheumatic drug, anti-neurodegenerative diseases drug, antioxidant drug, anti-inflammatory, drug antipyretic drug, antibiotic drug, antiviral drug, analgesic drug or combinations thereof.
11. Method according to any of the previous claims, wherein the injecting step is performed under agitation.
12. Method according to any of the previous claims, wherein the targeting agent is at least a peptide selected from the following list with a degree of identity of at least 90% of the following sequence: SEQ- ID. NO 1, SEQ- ID. NO 2 , SEQ- ID. NO 3, or mixtures thereof.
13. Method according to any of the previous claims, wherein the aqueous phase is phosphate buffered saline, PBS.
14. Method according to any of the previous claims wherein the ethanolic phase comprises anionic, neutral, or cationic phospholipids.
15. Method according to any of the previous claims wherein the ethanolic phase phospholipids are selected from a list consisting of: phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines, phosphatidylglycerols and/or their derivates or mixtures thereof, in particular 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine.
16. Method according to any of the previous claims wherein the ethanolic phase further comprises a stealth agent, a targeting agent, or mixture of thereof.
17. Method according to any of the previous claims wherein the stealth agent is polyethylene glycol, PEG, or gangliosides

18. Method according to any of the previous claims wherein the polyethylene glycol, PEG, is bound to a phospholipid, in particular distearoylphosphatidylethanolamine.
19. Method according to any of the previous claims wherein the targeting agent is incorporated in the lipidic membrane.
20. Method according to any of the previous claims wherein the active ingredient is an imaging or therapeutic agent.
21. Method according to any of the previous claims wherein the imaging or therapeutic agent is hydrophobic or hydrophilic.
22. Method according to any of the previous claims, wherein the imaging agent is a dye.
23. Method according to the previous claim wherein the active ingredient is methotextrate, doxorubicin or mixtures thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/054346

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/127 A61K31/00 A61K47/50
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2017/223135 A1 (MODERNATX INC [US]) 28 December 2017 (2017-12-28)	1-22
A	page 1, lines 1-24, 33-41 page 2, lines 1, 11, 23-26 page 5, lines 34-35 page 6, lines 31-34 page 8, lines 33-38 page 13, lines 28-38 page 14, lines 20-31 page 20, lines 24-27 page 23, lines 36-40 page 24, lines 30-40 page 30, line 35 claims 1-22 page 7, lines 6-7 ----- -/--	23

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2020	09/09/2020

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 2016/228573 A1 (NIYIKIZA CLET [US] ET AL) 11 August 2016 (2016-08-11) paragraph [0014] paragraph [0093] paragraph [0152] paragraph [0185] -----	1-5,7-22
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2020/054346

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