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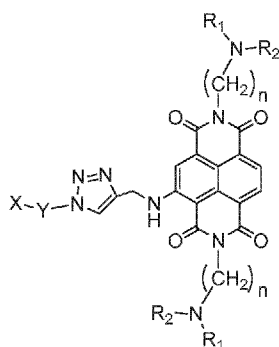
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(54) Title: NAPHTHALENE DIIMIDE COMPOUNDS FOR TREATMENT OF DISEASES



(I)

(57) Abstract: The invention relates to novel compounds which are naphthalene diimide sugar conjugates of general formula (I) and its procedure of obtainment. The compounds of the invention are used in therapy; particularly they have shown antiproliferative, antitrypanosomal and antimalarial activity.

## **NAPHTHALENE DIIMIDE COMPOUNDS FOR TREATMENT OF DISEASES**

The invention relates to novel compounds which are naphthalene diimides of general formula (I) and its procedure of obtainment. The compounds of the invention are used  
5 in therapy; particularly they have shown antiproliferative, antitrypanosomal and antimalarial activity.

### **BACKGROUND ART**

10 G-quadruplex (G4) are non-canonical higher-order nucleic acid structures that form on repeats of short guanine(G)-tracts, with the underlying structural motif being the planar arrangement of four strands of guanine bases stacked upon one another in DNA and RNA.

15 G4 structures at DNA level have been described and characterized in the telomeres of cells and in a number of oncogenic promoters such as the c-MYC, c-KIT, RET and KRAS genes. In addition, RNA G-quadruplexes are found in telomeric transcripts (TERRA) and in the untranslated mRNA regions (5'-UTRs) of several oncogenes.

20 The existence of G4 structures in vivo have been recently confirmed within living human cells reinforcing their biological relevance.

Currently, many studies have implicated G-quadruplexes in both positive and negative gene transcriptional regulation. In fact, G4's are viewed as emerging therapeutic  
25 targets in several pathologies such as cancer, neurodegenerative diseases and HIV. The validity of drug targeting G4 DNA/RNA due to their role modulating expression of associated genes has dramatically increased in the last few years.

The stabilization of a G4 structure in the telomere or a G4 structure found in a gene  
30 promoter by binding of small molecules directly leads to inhibition of the transcriptional machinery and down-regulation of expression of the targeted gene, with consequent therapeutically-useful inhibitory effects on aberrant cell growth of cancer cells. These binders are in general polyaromatic compounds with positively charged side chains that

interact through pi-pi stacking with the guanine tetrad of the G-quadruplex and through electrostatic interactions with the phosphates of the DNA or RNA skeleton in the G4.

5 The proof of principle linking G4 binding with biological responses is now available from genome mapping studies with a synthetic ligand known as Pyridostatin. Moreover, Quarfloxin, a fluoroquinolone derivative, is the first G4-binding small molecule that has progressed to clinical trials to date. Quarfloxin is believed to bind to multiple G4s in ribosomal DNA, affecting interaction with the protein nucleolin, leading to ribosome synthesis inhibition and apoptosis.

10

### Technical Problem

Another relevant G4 ligands are naphthalenedimide derivatives containing 3 to 4 charged side chains. These compounds have shown relevant cytotoxicity in cancer  
15 cells but they also show high cytotoxicity in non-cancerous cells.

In documents, WO2009068916A1 and US2010311739A1, naphthalenediimide derivatives with three to four side chains each containing an amino charged group are reported. Their pharmaceutical use is claimed for the treatment of cancer, preferentially  
20 cancer of the gastro-intestinal tract.

In document, US2014275062A1, naphthalenediimide compounds are described that possess four alkyl side chains functionalized with groups such as N-methylpiperazine, morpholine, furan, tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine, pyranose  
25 and OR1, where R1 is a C<sub>1</sub>-C<sub>4</sub> alkyl chain. Their pharmaceutical uses for cancer and more specifically for prostate cancer, lung cancer, renal cancer, pancreatic cancer or melanoma are claimed.

In document, Nadai et al 2011, Biochimie, vol. 93, pag. 1328-1340, naphthalene dimiides with two positively charges side chains and a third side chain containing  
30 groups capable of covalent interacting G-quadruplex DNA are reported. The authors propose their use for the treatment of lung cancer.

In document, Wang et al 2012, J. Med. Chem. vol. 55, pag. 3502–3512, naphthalenediimides with two side chains containing several amine groups on each chain are described. Their use for the treatment of lung cancer metastasis is proposed.

- 5 In document, Marchetti et al 2015, Bioorganic & Medicinal Chemistry, vol. 23, pag. 3819–3830, macrocyclic naphthalenediimides as G-quadruplex binders are reported. They possess two charged amino groups on the macrocycle. Their antiproliferative effect on several cancer cell lines is described.
- 10 In view of the prior art, there is a need to provide improved anti-cancer agents. In particular, there is a need to provide further naphthalene diimide derivatives which have improved G-quadruplex binding ability and anti-cancer effects.

#### **SUMMARY OF THE INVENTION**

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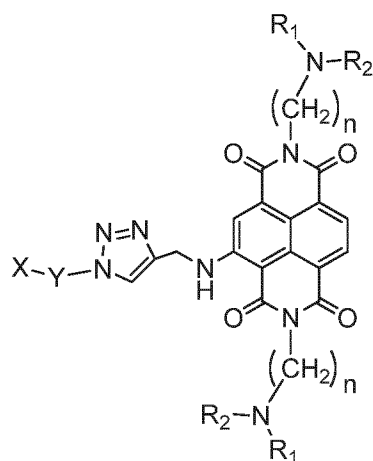
The present invention discloses novel compounds which are naphthalene diimides derivatives modified with just two charged side chains and that incorporate carbohydrates or small aliphatic chains on their structure directly linked to the central scaffold via a triazole ring. The invention also concerns pharmaceutical compositions

20 comprising the novel compounds and their use in therapy.

25

These modifications are incorporated to improve cell uptake through potential carbohydrate receptors and transporters or by their better capacity to be embedded in the cell membranes. Moreover, the new added chemical groups may improve G-quadruplex selectivity through extra interactions with the G-quadruplex target structure.

A first aspect of the present invention relates to a compound of general formula (I) or a pharmaceutically acceptable salt thereof



(I)

wherein

- 5  $R_1$  and  $R_2$  are each independently selected from substituted or unsubstituted  $C_{1-20}$  alkyl, substituted or unsubstituted  $C_{2-20}$  alkenyl, substituted or unsubstituted  $C_{2-10}$  alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted  $C_{3-20}$  cycloalkyl,  $C_{3-20}$  cycloalkylalkyl,  $C_{3-20}$  heterocyclyl, heterocyclylalkyl, or  $C_{1-10}$  alkoxy, or  $R_1$  and  $R_2$  together with the nitrogen atom to which they are attached form a substituted or unsubstituted, saturated or unsaturated, 5-8 member heterocyclic ring;
- $n$  is an integer from 2 to 12;
- Y is absent or selected from  $-O-(CH_2)_m-$ ,  $-N-(CH_2)_m-$ ,  $-S-(CH_2)_m-$ , or  $-(CH_2)_m-$ , being  $m$
- 15 an integer from 2 to 12;
- and X is selected from an H or an optionally substituted monosaccharide, an optionally substituted disaccharide, or an optionally substituted oligosaccharide in any of its isomeric forms which is attached to the rest of the molecule directly by one of the ring carbons or through a O-, N-, C- or S-glycosidic bond when Y is  $-O-(CH_2)_m-$ ,  $-N-(CH_2)_m-$ ,  $-(CH_2)_m-$ ,  $-S-(CH_2)_m-$ .
- 20

In one embodiment,  $R_1$  and  $R_2$  are each independently  $C_{1-20}$  alkyl, more preferably  $C_{1-10}$  alkyl, and even more preferably  $C_{1-5}$  alkyl. Further preferred is a compound wherein  $R_1$  and  $R_2$  are both identical and selected from methyl, ethyl, propyl, or butyl group.

- 25 Further preferred is a compound wherein  $R_1$  and/or  $R_2$  are methyl.

In another embodiment, n is an integer from 2 to 10, more preferably from 2 to 5, and even more preferably n is 3.

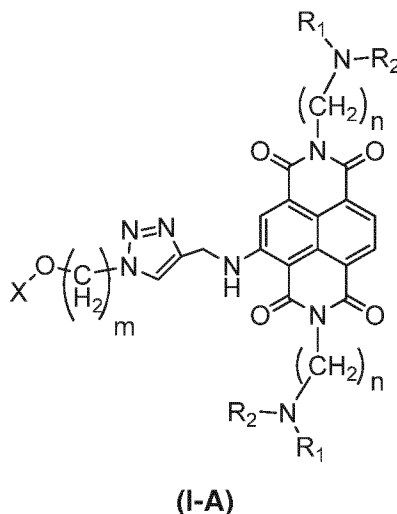
In another embodiment, the monosaccharide is selected from glucose, 6-deoxyglucose, mannose, galactose, glucosamine, galactosamine, N-acetylglucosamine, N-acetylgalactosamine, glucuronic acid, allose, altrose, gulose, idose, fucose, talose, ribose, deoxyribose, arabinose, xylose, lyxose, ribulose, xylulose, fructose, psicose, sorbose or tagatose. Further preferred, the monosaccharide is selected from glucose, 6-deoxyglucose, N-acetylglucosamine, mannose or galactose.  
Even further preferred, the selected monosaccharide is glucose or mannose.

In another preferred embodiment, the disaccharide is selected from sucrose, lactose, lactulose, allolactose, maltose, isomaltose, isomaltulose, trehalose, cellobiose, kojibiose, nigerose, sophorose, laminaribiose, gentiobiose, thiomaltose, mannobiose or their N-, C- or S-interglycosidic derivatives. Further preferred the disaccharide is selected from maltose, thiomaltose, lactose or gentiobiose or their N-, C- or S-interglycosidic derivatives. Even further preferred, the selected disaccharide is maltose or thiomaltose.

In another preferred embodiment, the term "oligosaccharide" refers to a polymer formed from monosaccharides joined by O-glycosidic bonds with a number of monomer units from 3 to 10, and it can occur associated with proteins or lipids. Among others, the oligosaccharides of the invention include oligosaccharides formed by the joining of three or more different monosaccharides by identical or O-glycosidic (with loss of a water molecule), mono or dicarbonyl link, which can also be  $\alpha$  or  $\beta$  depending hemiacetal or hemiketal -OH. In a preferred embodiment, the oligosaccharide is maltotriose, isomaltotriose, cellotriose, nigerotriose, melezitose or maltotriulose or its N-, C- or S-interglycosidic derivatives. In a more preferred embodiment, the oligosaccharide is maltotriose or its N-, C- or S-interglycosidic derivatives. In another preferred embodiment, the oligosaccharide is a fructooligosaccharide, galactooligosaccharide or mannanoligosaccharide.

In another embodiment, Y is absent or selected from  $-\text{O}-(\text{CH}_2)_m-$ , or  $-\text{S}-(\text{CH}_2)_m-$ , or  $(\text{CH}_2)_m-$ , being m an integer from 2 to 10, more preferably from 2 to 5, and even more preferably m is 2.

- 5 Yet in another embodiment, when Y is  $-\text{O}-(\text{CH}_2)_m-$ , the preferred compound is a compound of general formula (I-A)



- 10 wherein  $R_1$ ,  $R_2$ , n, m and X are as defined above for compounds of general formula (I).

Yet a preferred embodiment is a compound having the formula (I-A) wherein:

- $R_1$  and  $R_2$  are each independently  $C_{1-20}$  alkyl, more preferably  $C_{1-10}$  alkyl, and even more preferably  $C_{1-5}$  alkyl. Further preferred is a compound wherein  $R_1$  and  $R_2$  are both  
 15 identical and selected from methyl, ethyl, propyl, or butyl group. Further preferred is a compound wherein  $R_1$  and/or  $R_2$  are methyl;

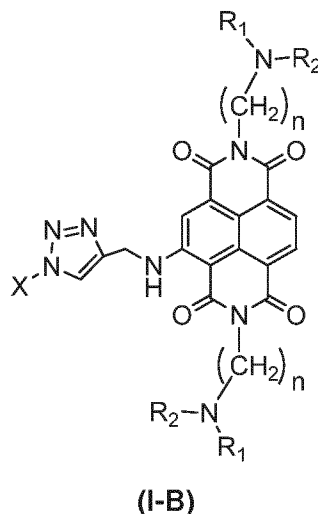
n is an integer from 2 to 10, more preferably from 2 to 5, and even more preferably n is 3;

- m is an integer from 2 to 10, more preferably from 2 to 5, and even more preferably m  
 20 is 2;

- and X is selected from glucose, 6-deoxyglucose, mannose, galactose, glucosamine, galactosamine, N-acetylglucosamine, N-acetylgalactosamine, glucuronic, allose, altrose, gulose, idose, fucose, talose, ribose acid, deoxyribose, arabinose, xylose, lyxose, ribulose, xylulose, fructose, psicose, sorbose, tagatose, sucrose, lactose,  
 25 lactulose, allolactose, maltose, isomaltose, isomaltulose, trehalose, cellobiose, gentiobiose, maltotriose, isomaltotriose, cellotriose, nigerotriosa, melezitose or

maltotriulosa. Further preferred the monosaccharide is selected from glucose, 6-deoxyglucose, N-acetylglucosamine, mannose or galactose. Even further preferred the selected monosaccharide is glucose or mannose.

- 5 Yet in another embodiment, when Y is absent, the preferred compound is a compound of general formula (I-B)



- 10 wherein  $R_1$ ,  $R_2$ ,  $n$  and  $X$  are as defined above for compounds of general formula (I).

Yet a preferred embodiment is a compound having the formula (I-B) wherein:

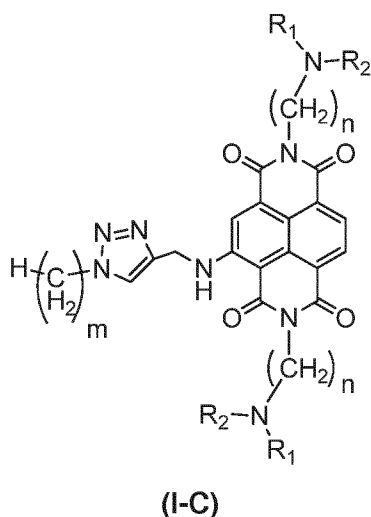
- $R_1$  and  $R_2$  are each independently  $C_{1-20}$  alkyl, more preferably  $C_{1-10}$  alkyl, and even more preferably  $C_{1-5}$  alkyl. Further preferred is a compound wherein  $R_1$  and  $R_2$  are both  
 15 identical and selected from methyl, ethyl, propyl, or butyl group. Further preferred is a compound wherein  $R_1$  and/or  $R_2$  are methyl;

$n$  is an integer from 2 to 10, more preferably from 2 to 5, and even more preferably  $n$  is 3;

- and  $X$  is selected from glucose, 6-deoxyglucose, mannose, galactose, glucosamine, galactosamine, N-acetylglucosamine, N-acetylgalactosamine, glucuronic, allose, altrose, gulose, idose, fucose, talose, ribose acid, deoxyribose, arabinose, xylose, lyxose, ribulose, xylulose, fructose, psicose, sorbose, tagatose, sucrose, lactose, lactulose, allolactose, maltose, isomaltose, isomaltulose, trehalose, cellobiose, gentiobiose, maltotriose, isomaltotriose, cellotriose, nigerotriose, melezitose or  
 20 maltotriulose. Further preferred the monosaccharide is selected from glucose, 6-  
 25

deoxyglucose, N-acetylglucosamine, mannose or galactose. Even further preferred the monosaccharide selected is glucose or mannose.

Yet in another embodiment, when Y is  $-(CH_2)_m-$ , the preferred compound is a  
 5 compound of general formula (I-C)



wherein  $R_1$ ,  $R_2$ ,  $n$ , and  $m$  are as defined above for compounds of general formula (I).

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Yet a preferred embodiment is a compound having the formula (I-C) wherein:

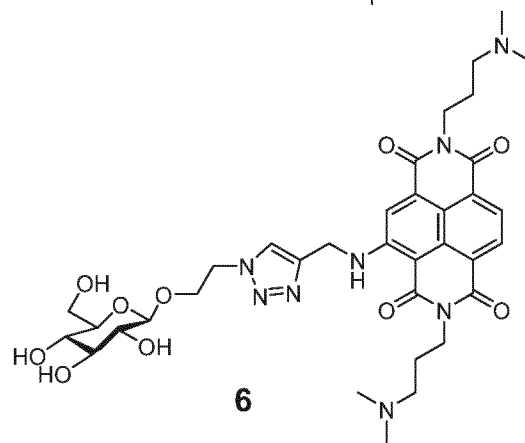
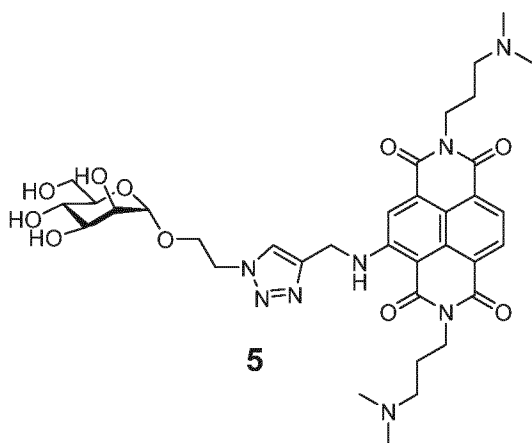
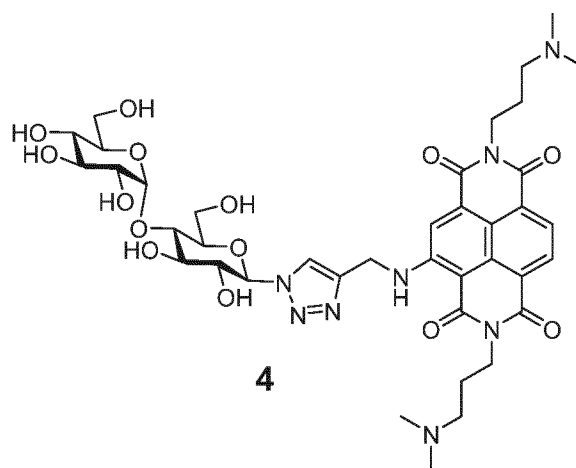
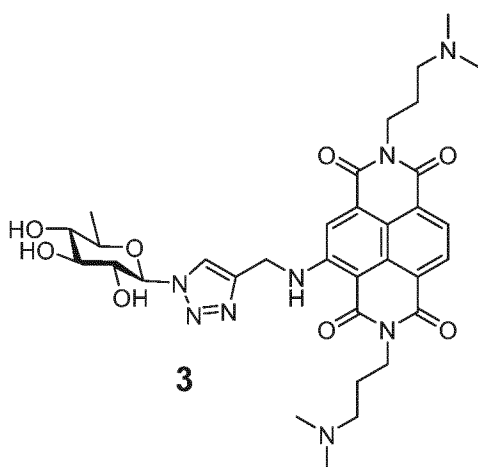
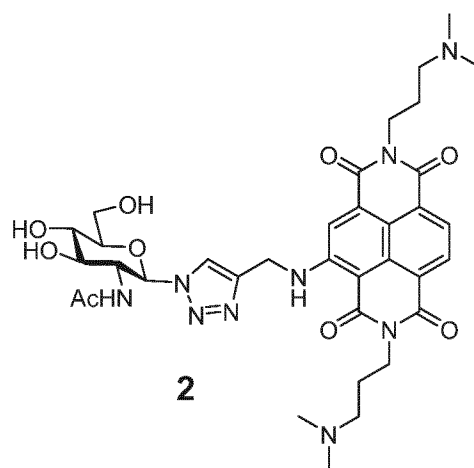
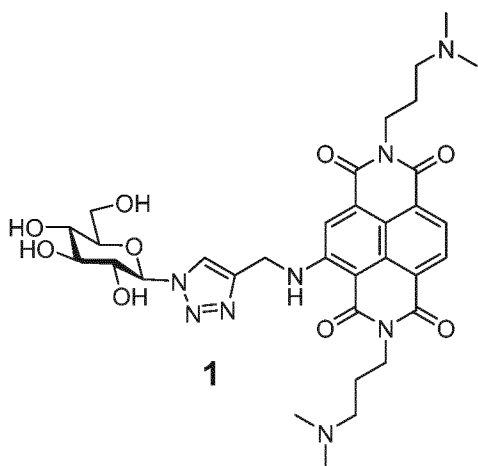
$R_1$  and  $R_2$  are each independently  $C_{1-20}$  alkyl, more preferably  $C_{1-10}$  alkyl, and even more preferably  $C_{1-5}$  alkyl. Further preferred is a compound wherein  $R_1$  and  $R_2$  are both identical and selected from methyl, ethyl, propyl, or butyl group. Further preferred is a  
 15 compound wherein  $R_1$  and/or  $R_2$  are methyl;

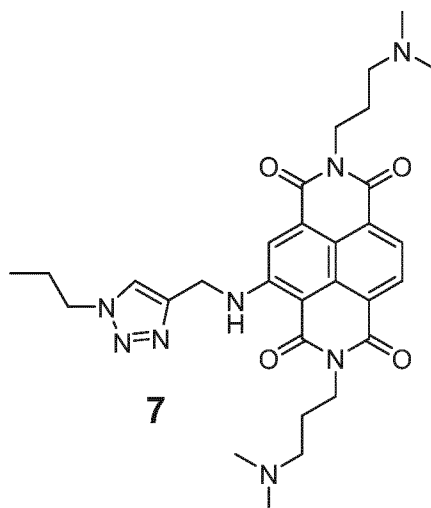
$n$  is an integer from 2 to 10, more preferably from 2 to 5, and even more preferably  $n$  is 3;

$m$  is an integer from 2 to 10, more preferably from 2 to 5, and even more preferably  $m$  is 3.

20

Particularly preferred compounds of formula (I) are selected from the group:





Also provided, a second aspect of the invention is a pharmaceutical composition comprising a compound of general formula (I) or a pharmaceutically acceptable salt thereof.

The third aspect of the invention provides a compound of general formula (I) or a salt thereof, for use in the manufacture of a medicament.

Another aspect of the invention provides use of a compound of general formula (I) or a salt thereof, or a pharmaceutical composition as defined above, in the manufacture of a medicament for prophylaxis or treatment of cancer, and for the treatment or prophylaxis of diseases derived from a parasitic infection.

The compounds of the present invention have been shown to be able to stabilize G-quadruplex regions in DNA to a greater extent than the anti-cancer agents of the prior art. Particularly, the compounds prepared have shown antiproliferative activity on three different cell lines (HT-29 human colon adenocarcinoma, MCF-7 human breast adenocarcinoma and HeLa human cervix adenocarcinoma) and low toxicity in non-carcinogenic cell line (MRC-5 human lung fibroblasts).

The more active compounds on HT-29 and MCF-7 are compounds 3, 5, 6 and 7. Moreover, compounds 3, 5, 6 and 7 show lower cytotoxicity in MRC-5 cell line.

The more active compounds on HeLa are compounds 3, 4, 5, 6 and 7, and they present low toxicity in MRC-5 cell line.

The compounds have also been shown to have antiparasitic activity for *Trypanosoma*  
5 *brucei* and for *Plasmodium falciparum*.

Compound 7 shows the best antitrypanosomal activity followed by compounds 1, 3, 5 and 6.

10 In the case of *Plasmodium falciparum*, the lowest IC<sub>50</sub> value was shown by compounds 3, 5, 6 and 7.

The compounds of the present invention may be present in the form of pharmaceutical acceptable salts. Pharmaceutically acceptable salts of the acidic or basic compounds  
15 of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

Pharmaceutically acceptable salts of the acidic compounds of the invention include  
20 salts with inorganic cations such as sodium, potassium, calcium, magnesium, zinc, and ammonium, and salts with organic bases. Suitable organic bases include N-methyl-D-glucamine, arginine, benzathine, diolamine, olamine, procaine and tromethamine.

Pharmaceutically acceptable salts of the basic compounds of the invention include  
25 salts derived from organic or inorganic acids. Suitable anions include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hyclate, hydrobromide, hydrochloride, iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate, napsylate, nitrate, oleate, pamoate, phosphate, polygalacturonate,  
30 stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate, triethiodide and triflate. Triflate salts of compound of general formula (I) are particularly preferred.

The compounds of the invention can be administered to a patient in need thereof by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical administration, and inhalation.

- 5 For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents,  
10 lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate and lactase.

Corn starch and alginic acid are suitable disintegrating agents. Binding agents may  
15 include starch and gelatine. The lubricating agent, if present, will generally be magnesium stearate, stearic acid or tale. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

20 Capsules for oral use include hard gelatine capsules in which the active ingredient is mixed with a solid diluent and soft gelatine capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds  
25 of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride.

Aqueous suspensions according to the invention may include suspending agents such  
30 as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

The compounds of the present invention may be used in the treatment of other diseases. The disease may be selected from the group consisting of cardiovascular diseases, disorders of the peripheral and central nervous system, inflammation, urological diseases, developmental disorders, cancer, metabolic diseases, viral, 5 bacterial and endocrinological diseases and disorders of the gastroenterology system in a mammal.

In a preferred embodiment, the cancer may be parathyroid gland adenoma, parathyroid gland hyperplasia, parathyroid gland carcinoma, squamous carcinoma, renal 10 carcinoma, breast carcinoma, prostate carcinoma, lung carcinomas, osteosarcomas, clear cell renal carcinoma, prostate cancer, lung cancer, breast cancer, gastric cancer, ovarian cancer, bladder cancer, anal cancer, bone cancer, brain tumors, gastrointestinal tumors, cervical cancer, colorectal cancer, eye cancer, head cancer, neck cancer, kidney cancer, laryngeal cancer, liver cancer, mouth cancer, 15 nasopharyngeal cancer, oral cancer, pancreatic cancer, nasal cavity cancer, pituitary tumor, rectal cancer, skin cancer, small intestine cancer, stomach cancer, testicular cancer, thyroid cancer, urethral cancer, uterine cancer, vaginal cancer, vulvar cancer, leukemia, melanomas, lymphomas, sarcomas or gliomas. Typically the compounds of the invention are used to treat gastric cancer.

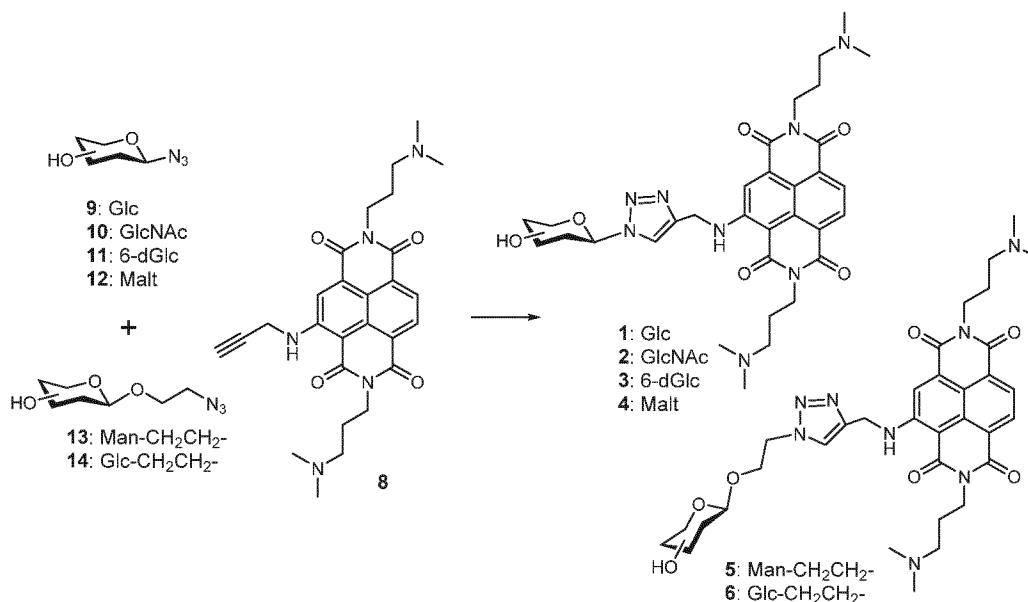
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In another preferred embodiment the disease may be african trypanosomiasis, chagas, leishmaniosis, blastocystosis, cryptosporidiosis, amoebiasis, giardiasis, sarcosystosis, toxoplasmosis, trichomoniasis or malaria. Typically the compounds of the invention are used to treat african trypanosomiasis, chagas or malaria.

25

In the treatment, a therapeutically effective amount of a compound of general formula (I), or a salt thereof, is administered to a patient in need thereof.

The last aspect of the invention provides the synthetic route to the novel compounds of 30 this invention is based on a synthesis wherein compounds **1-6** were prepared by reaction of derivative **8** with azido glycosides **9-12** and 2-azidoethyl glycosides **13-14** following the general procedure:



In the present invention, the term “alkyl” refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl). The term “C<sub>1-20</sub> alkyl” refers to an alkyl group as defined above having up to 20 carbon atoms, optionally substituted by at least one of the substituents as defined above.

The term “alkenyl” refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or branched chain having about 2 to about 20 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl. The term “C<sub>2-20</sub> alkenyl” refers to an alkenyl group as defined above having up to 20 carbon atoms, optionally substituted by at least one of the substituents as defined above.

The term “alkynyl” refers to a straight or branched chain hydrocarbonyl radical having at least one carbon-carbon triple bond, and having in the range of 2 to up to 20 carbon atoms (with radicals having in the range of 2 to up to 10 carbon atoms presently being preferred) e.g., ethynyl, propynyl, and butynyl. The term “C<sub>2-10</sub> alkynyl” refers to an alkynyl group as defined above having up to 20 carbon atoms, optionally substituted by at least one of the substituents as defined above.

The term “aryl” refers to aromatic radicals having in the range of 5 up to 20 carbon atoms such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, and biphenyl.

- 5 The term “heteroaryl” refers to an optionally substituted 5 to 20 member aromatic ring having one or more heteroatoms selected from N, O, and S as ring atoms. The heteroaryl may be a mono-, bi- or tricyclic ring system. Examples of such “heterocyclic ring” or “heteroaryl” radicals include, but are not limited to, oxazolyl, thiazolyl, imidazolyl, pyrrolyl, furanyl, pyridinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, carbazolyl, quinolyl, isoquinolyl, azetidyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnolyl, dioxolanyl, indolizyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, tetrazolyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyrrolidinyl, pyridazinyl, oxazolyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, isoindolyl, indolyl, isoindolyl, octahydroindolyl, octahydroisoindolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, and isochromanyl. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure. The term “substituted heteroaryl” also includes ring systems substituted with one or more oxide (-O-) substituents, such as pyridinyl N-oxides.

The term “arylalkyl” refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g.,  $-\text{CH}_2\text{C}_6\text{H}_5$  and  $-\text{C}_2\text{H}_5\text{C}_6\text{H}_5$ .

- 30 The term “heteroarylalkyl” refers to a heteroaryl ring radical as defined above directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group that results in the creation of a stable structure.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of about 3 to 20 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include perhydronaphthyl, adamantyl and norbornyl groups, bridged cyclic groups, and spirobicyclic groups, e.g., spiro (4,4) non-  
5 2-yl. The term "C<sub>3-20</sub> cycloalkyl" refers to a cycloalkyl group as defined above having up to 20 carbon atoms.

The term "cycloalkylalkyl" refers to a cyclic ring-containing radical containing in the range of about 3 up to 20 carbon atoms directly attached to an alkyl group which are  
10 then attached to the main structure at any carbon from the alkyl group that results in the creation of a stable structure such as cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl.

The term "heterocyclyl" refers to a heterocyclic ring radical. The heterocyclic ring  
15 radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclylalkyl" refers to a heterocyclic ring radical as defined above directly bonded to an alkyl group. The heterocyclylalkyl radical may be attached to the main  
20 structure at carbon atom in the alkyl group that results in the creation of a stable structure. Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, oxazolidiny, piperidiny, piperaziny,  
25 4-piperidonyl, pyrrolidiny, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny, and 1,1-dioxo-thiomorpholiny.

The term "alkoxy" denotes an alkyl, cycloalkyl, or cycloalkylalkyl group as defined  
30 above attached via an oxygen linkage to the rest of the molecule. The term "substituted alkoxy" refers to an alkoxy group where the alkyl constituent is substituted (i.e., -O-(substituted alkyl) wherein the term "substituted alkyl" is the same as defined above for "alkyl". For example "alkoxy" refers to the group -O-alkyl, including from 1 to 10 carbon atoms of a straight, branched, cyclic configuration and combinations thereof

attached to the parent structure through oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, and cyclohexyloxy.

The term "heterocyclic ring" refers to a non-aromatic 3 to 8 member ring radical which consists of carbon atoms and at least one heteroatom selected from nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a mono-, bi-, tri- or tetracyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "substituted" unless otherwise specified, refers to substitution with any one or any combination of the following substituents which may be the same or different and are independently selected from hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio (=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted heterocyclalkyl ring, substituted or unsubstituted guanidine, -COORx, -C(O)Rx, -C(S)Rx, -C(O)NRxRy, -C(O)ONRxRy, -NRyRz, -NRxCONRyRz, -N(Rx)SORy, -N(Rx)SO2Ry, -(=N-N(Rx)Ry), -NRxC(O)ORy, -NRxRy, -NRxC(O)Ry-, -NRxC(S)Ry -NRxC(S)NRyRz, -SONRxRy-, -SO2NRxRy-, -ORx, -ORxC(O)NRyRz, -ORxC(O)ORy-, -OC(O)Rx, -OC(O)NRxRy, -R<sub>x</sub>NRyC(O)Rz, -R<sub>x</sub>ORy, -R<sub>x</sub>C(O)ORy, -R<sub>x</sub>C(O)NRyRz, -R<sub>x</sub>C(O)Rx, -R<sub>x</sub>OC(O)Ry, -SRx, -SORx, -SO2Rx, and -ONO2, wherein Rx, Ry and Rz in each of the above groups can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted

heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, or substituted heterocyclalkyl ring, or any two of Rx, Ry and Rz may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 membered ring, which may optionally include heteroatoms which may be the same or different and are selected from O, NRx (e.g., Rx can be hydrogen or C<sub>1-6</sub> alkyl) or S. Substitution or the combinations of substituents envisioned by this invention are preferably those that result in the formation of a stable or chemically feasible compound. The term stable as used herein refers to the compounds or the structure that are not substantially altered when subjected to conditions to allow for their production, detection and preferably their recovery, purification and incorporation into a pharmaceutical composition. The substituents in the aforementioned "substituted" groups cannot be further substituted. For example, when the substituent on "substituted alkyl" is "substituted aryl", the substituent on "substituted aryl" cannot be "substituted alkenyl".

The term "halo", "halide", or, alternatively, "halogen" means fluoro, chloro, bromo or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

The term "monosaccharide" primarily means a monosaccharide, which consists of one saccharide unit. Illustrative monosaccharides include trioses, tetroses, pentoses, hexoses, heptoses, octoses, and nonoses, such as, glucose, 6-deoxyglucose, mannose, galactose, glucosamine, galactosamine, N-acetylglucosamine, N-acetylgalactosamine, glucuronic, allose, altrose, gulose, idose, fucose, talose, ribose acid, deoxyribose, arabinose, xylose, lyxose, ribulose, xylulose, fructose, psicose, sorbose or tagatose.

The term "disaccharide" refers to any sugar having two monosaccharide units. The monosaccharide units may exist as either ketones or aldehydes, and may have either a cyclic or acyclic structure. When a monosaccharide exists as a cyclic structure, the monosaccharide may exist as a hemiacetal or hemiketal, among other forms. Moreover, when a monosaccharide exists as a cyclic structure, either anomer is

included within this definition. In forming a disaccharide, the monosaccharide units may bond to form either reducing disaccharides or non-reducing disaccharides. In some embodiments, the disaccharide includes, but is not limited to, disaccharides containing glucose, fructose, and galactose. In some embodiments, the disaccharide includes, but is not limited to, sucrose, lactose, maltose, trehalose, and isomaltulose. In some embodiments, the disaccharide carbohydrate is maltose.

The compounds of the present invention represented by the formula (I) and, more specifically, the specific compounds pertaining to this previously described general formula may include isomers, depending on the presence of multiple bonds (for example, Z, E), including optical isomers or enantiomers, depending on the presence of chiral centres, and tautomers. The individual isomers, enantiomers or diastereoisomers, and the mixtures thereof, fall within the scope of the present invention. The individual enantiomers or diastereoisomers, and the mixtures thereof, may be separated by means of conventional techniques. "Tautomers" are understood to be the two isomers that differ only in the position of a functional group because between the two forms there is a chemical balance in which a migration of a group or atom occurs.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skilled in the art to which this invention belongs. Methods and materials similar or equivalent to those described herein can be used in the practice of the present invention. Throughout the description and claims the word "comprise" and its variations are not intended to exclude other technical features, additives, components, or steps. Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The following examples are provided by way of illustration and are not intended to be limiting of the present invention.

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## BRIEF DESCRIPTION OF THE DRAWINGS

**FIG. 1.** Efficacy of  $\beta$ -glcC2-NDI (6) and NDI-prop (7) in subcutaneous tumour xenografts, evaluated in terms of tumour growth over time.

FIG. 2. Average mouse weight over time for the four experimental groups of mice.

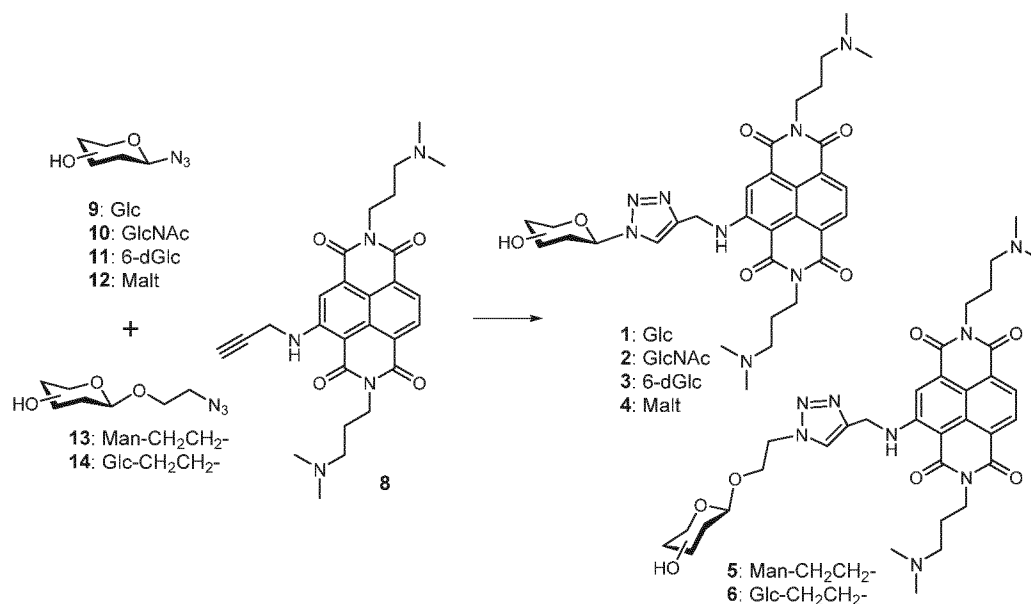
## EXAMPLES

5

### Example 1. Synthesis of naphthalene diimide carbohydrate conjugates

Compounds **1-6** were prepared by reaction of derivative **8** with azido glycosides **9-12** and 2-azidoethyl glycosides **13-14** following the general procedure. To a suspension of azido glycosides **9-12** and 2-azidoethyl glycosides **13-14** in alcohols, a solution of (+)-sodium L-ascorbate, copper(II) salt and **8** in water was added. The resulting mixture was stirred at r. t. for 2 hrs. The resulting red solution was concentrated and the final product was purified by reverse phase chromatography (CH<sub>3</sub>CN:H<sub>2</sub>O as eluent).

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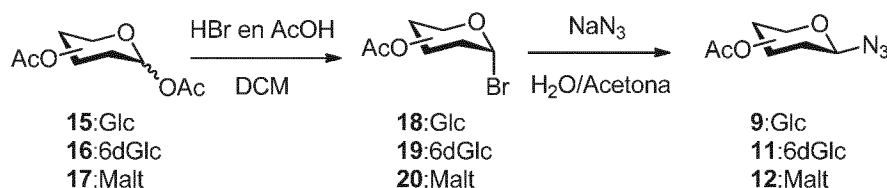


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Azido glycosides **9-12** and 2-azidoethyl glycosides **13-14** were synthesized as described previously. Briefly, reaction of acetobromo sugars with sodium azide followed by deprotection under basic conditions yielded the corresponding azido glycosides. In the case of the 2-azidoethyl glycosides, glycosylation with 2-bromoethanol followed by reaction with sodium azide and treatment with sodium methoxide resulted in the desired compounds.

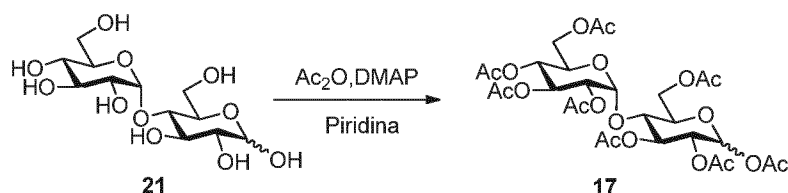
Azido glycosides **9** and **11-12** were obtained following the reported procedure (Miyake H, Otsuka C. Nishimura S, Nitta Y, J. Biochemistry **2002**, Vol.131, 587-591) from the corresponding peracetylated derivatives.

5



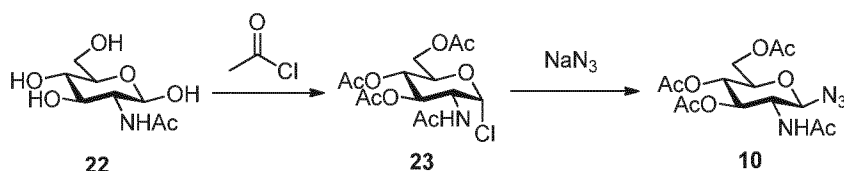
Compound **17** is obtained by acetylation of maltose with acetic anhydride, pyridine and 4-dimethylaminopyridine.

10



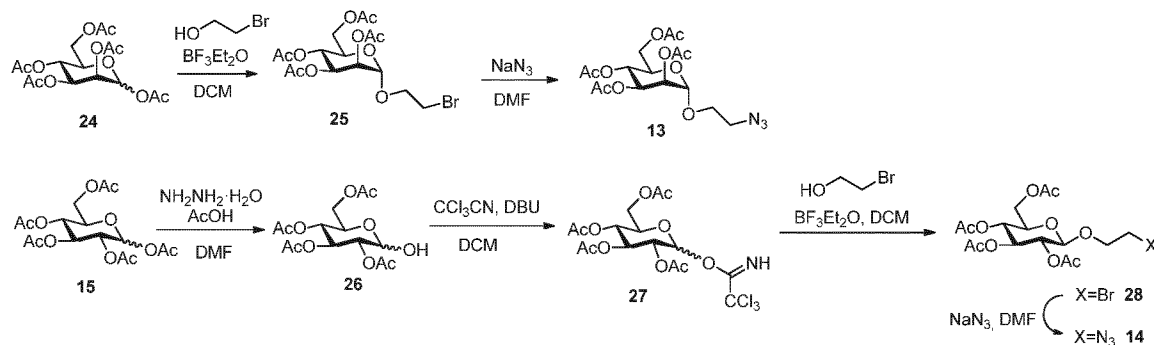
Azido glycoside **10** is obtained by the method reported previously (Soli, E.D.; Manoso, A. S.; Patterson, M.C., and DeShong, P., J.Org.Chem., **1999**, Vol.64 (9), 3171-3177) from N-acetylglucosamine.

15



20

2-azidoethyl glycosides **13-14** were prepared following established procedures (Quagliotto, P.; Viscardi, G.; Barolo, C.; D'Angelo, D.; Barni, E.; Compari, C.; Duce, E. and Fisicaro, E.; J.Org.Chem, 2005, Vol.70, 9857-9866) from the corresponding peracetylated derivatives.

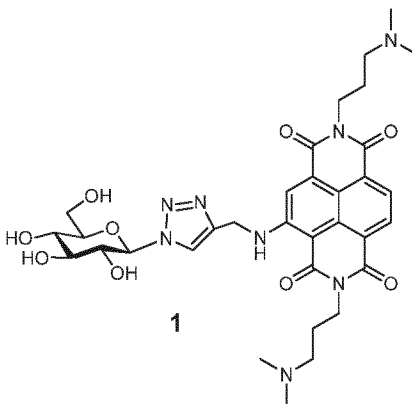


Propargyl naphthalene diimide compound **8** was prepared according to the following procedure:

- 5 4,9-dibromo-2,7-bis[3-(dimethylamino)propyl]-Benzo[Imn][3,8]phenanthroline-1,3,6,8(2H,7H)-tetrone (dibromo-substituted-NDI) and propargylamine were mixed in a polar organic solvent and heated for 2 hrs. The resulting red solution was concentrated and the product was purified by reverse phase chromatography.

## 10 Example 2. Compound characterization of final compounds 1-6

### Compound 1

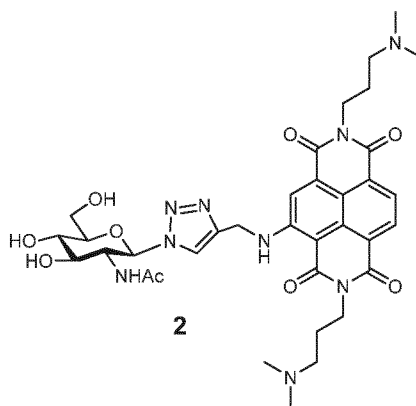


- 15 <sup>1</sup>H-NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.42 (d, J = 7.8 Hz, 1H, H<sub>AR</sub>), 8.37 (s, 1H, H<sub>AR</sub>), 8.22 (s, 1H, H<sub>AR</sub>), 8.16 (d, J = 7.8 Hz, 1H, H<sub>AR</sub>), 5.68 (d, J = 9.2 Hz, 1H, H<sub>1</sub>), 4.94 (s, 2H, NHCH<sub>2</sub>), 4.21 (t, J = 6.7 Hz, 4H, 2xCH<sub>2</sub>N), 3.97 – 3.87 (m, 2H, H<sub>2</sub>, H<sub>6</sub>), 3.76 – 3.71 (m, 1H, H<sub>6</sub>), 3.62 – 3.59 (m, 2H, H<sub>5</sub>, H<sub>3</sub>), 3.53 – 3.47 (m, 1H, H<sub>4</sub>), 3.30 – 3.24 (m, 4H, 2xNCH<sub>2</sub>), 2.95 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>), 2.94 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>), 2.24 – 3.17 (m, 4H, 2xCH<sub>2</sub>).
- 20 <sup>13</sup>C-NMR (101 MHz, Methanol-d<sub>4</sub>) δ 167.10(CO), 164.66(CO), 164.39(CO), 164.20(CO), 153.09(C<sub>AR</sub>), 149.71(C<sub>AR</sub>), 132.08(C<sub>AR</sub>), 130.29(C<sub>AR</sub>), 128.98(CH<sub>AR</sub>),

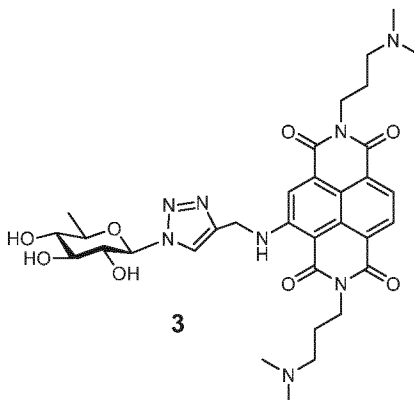
127.30(C<sub>AR</sub>), 125.53(C<sub>AR</sub>), 124.36(CH<sub>AR</sub>), 120.92(CH<sub>AR</sub>), 120.57(CH<sub>AR</sub>), 116.94(C<sub>AR</sub>), 101.02(C<sub>AR</sub>), 89.70(C<sub>1</sub>), 81.24(C<sub>3</sub>), 78.50(C<sub>5</sub>), 74.14(C<sub>2</sub>), 70.98(C<sub>4</sub>), 62.38(C<sub>6</sub>), 56.83((a)CH<sub>2</sub>), 56.76((a)CH<sub>2</sub>), 43.61(NHCH<sub>3</sub>), 39.56(NHCH<sub>2</sub>), 38.12((c)CH<sub>2</sub>), 24.63((b)CH<sub>2</sub>).

- 5 HRMS(ES<sup>+</sup>): Calcd. for C<sub>33</sub>H<sub>42</sub>N<sub>8</sub>NaO<sub>9</sub>(M+Na): 717.2972; found: 717.2963.

### Compound 2



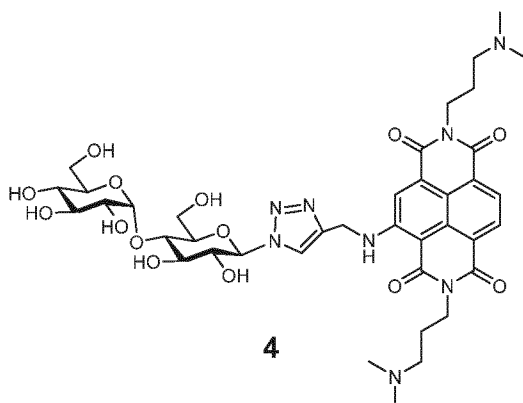
- 10 <sup>1</sup>H-NMR (400 MHz, Methanol-d<sub>4</sub>) δ 10.43 (s, 1H, NH), 8.89 (s, 1H, NH), 8.70 (d, J = 7.8 Hz, 1H, H<sub>AR</sub>), 8.45 (s, 1H, H<sub>AR</sub>), 8.43 (d, J = 7.8 Hz, 1H, H<sub>AR</sub>), 8.36 (s, 1H, H<sub>AR</sub>), 5.88 (d, J = 9.7 Hz, 1H, H<sub>1</sub>), 5.08 (s, 2H, 2xNHCH<sub>2</sub>), 4.41 – 4.34 (m, 5H, 2xCH<sub>2</sub>N, H<sub>2</sub>), 4.0 (d, J = 11.9 Hz, 1H, H<sub>5</sub>), 3.89 – 3.65 (m, 4H, H<sub>3</sub>, H<sub>4</sub>, H<sub>6</sub>), 3.42 (bs, 4H, 2xNCH<sub>2</sub>), 3.05 (s, 12H, 2xN(CH<sub>3</sub>)<sub>2</sub>), 2.34 – 2.29 (m, 4H, 2xCH<sub>2</sub>), 1.78 (s, 3H, NHCOCH<sub>3</sub>).
- 15 <sup>13</sup>C-NMR (101 MHz, Methanol-d<sub>4</sub>) δ 165.14(COCH<sub>3</sub>), 164.94(CO<sub>1</sub>), 164.76(CO<sub>6</sub>), 164.70(CO<sub>7</sub>), 164.42(CO<sub>12</sub>), 153.35(C<sub>AR9</sub>), 132.14(C<sub>AR2,11</sub>), 131.82(CH<sub>AR3</sub>), 129.36(C<sub>AR(triazol)</sub>), 88.37(C<sub>1</sub>), 81.29(C<sub>5</sub>), 75.80(C<sub>3</sub>), 71.33(C<sub>4</sub>), 62.26(C<sub>6</sub>), 56.87((a)CH<sub>2</sub>), 56.82((a)CH<sub>2</sub>), 56.55(C<sub>2</sub>), 43.65(NCH<sub>3</sub>), 43.63(NCH<sub>3</sub>), 43.60(NCH<sub>3</sub>), 39.28((c)CH<sub>2</sub>), 38.01(NHCH<sub>2(13)</sub>), 24.70((b)CH<sub>2</sub>), 22.53(NHCOCH<sub>3</sub>).
- 20 HRMS(ES<sup>+</sup>): Calcd. for C<sub>35</sub>H<sub>45</sub>N<sub>9</sub>NaO<sub>9</sub>(M+Na): 758.3238; found: 758.3218.

Compound 3

<sup>1</sup>H-NMR (400 MHz, Methanol-d<sub>4</sub>) δ 10.34 – 10.22 (m, 1H, NH), 8.36 (s, 1H, H<sub>AR</sub>), 8.33 (d, J = 26.6 Hz, 2H, H<sub>AR3</sub>), 8.09 (s, 1H, H<sub>AR</sub>), 8.07 (d, J = 16.1 Hz, 2H, H<sub>AR4</sub>), 5.66 (d, J = 9.0 Hz, 1H, H<sub>1</sub>), 4.89(s, 2H, NH-CH<sub>2(13)</sub>) 4.17 (s, 4H, (c)CH<sub>2</sub>), 3.98 (t, J = 9.1 Hz, 1H, H<sub>2</sub>), 3.65 (dd, J = 9.5, 5.8 Hz, 1H, H<sub>5</sub>), 3.56 (t, J = 9.0 Hz, 1H, H<sub>3</sub>), 3.21 (dd, J = 15.8, 7.4 Hz, 3H, (a)CH<sub>2</sub>, H<sub>4</sub>), 2.96 (d, J = 7.1 Hz, 12H, NCH<sub>3</sub>), 2.25 – 2.10 (m, 4H, (b)CH<sub>2</sub>), 1.32 (d, J = 5.9 Hz, 3H, H<sub>6</sub>).

<sup>13</sup>C-NMR (101 MHz, MeOD) δ 166.85(CO<sub>1</sub>), 164.43(CO<sub>6</sub>), 164.12(CO<sub>7</sub>), 163.96(CO<sub>12</sub>), 152.83(C<sub>AR9</sub>), 144.87(C<sub>AR</sub>), 131.99(C<sub>AR2,11</sub>), 129.98(CH<sub>AR3</sub>), 128.67(C<sub>AR(triazol)</sub>), 127.00(C<sub>AR5</sub>), 125.44(C<sub>AR8</sub>), 124.07(CH<sub>AR4</sub>), 123.84(C<sub>AR</sub>), 120.77(CH<sub>AR(triazol)</sub>), 120.22(C<sub>AR10</sub>), 100.73(C<sub>AR14,15</sub>), 89.63(C<sub>1</sub>), 78.28(C<sub>3</sub>), 76.69(C<sub>5</sub>), 76.51(C<sub>4</sub>), 74.34(C<sub>2</sub>), 56.80((a)CH<sub>2</sub>), 56.73((a)CH<sub>2</sub>), 43.63(NCH<sub>3</sub>), 40.04, 39.44(CH<sub>2(13)</sub>), 38.79((c)CH<sub>2</sub>), 38.22((c)CH<sub>2</sub>), 25.58((b)CH<sub>2</sub>), 24.63((b)CH<sub>2</sub>), 18.15(C<sub>6</sub>).

HRMS(ES<sup>+</sup>): Calcd. for C<sub>33</sub>H<sub>42</sub>N<sub>8</sub>NaO<sub>8</sub>(M+Na): 701.3023; found 701.3007.

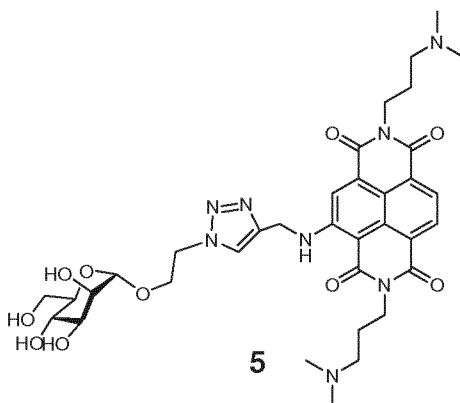
Compound 4

<sup>1</sup>H-NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.40 (s, 1H, H<sub>AR</sub>), 8.27 (d, J = 7.8 Hz, 1H, H<sub>AR</sub>), 8.08 (s, 1H, H<sub>TRIAZOL</sub>), 8.02 (d, J = 7.8 Hz, 1H, H<sub>AR</sub>), 5.74 (d, J = 9.1 Hz, 1H, H<sub>1A</sub>), 5.24

(d,  $J = 3.8$  Hz, 1H,  $H_{1B}$ ), 4.87(s, 2H,  $NHCH_2$ ) 4.20 – 4.10 (m, 4H, (c) $CH_2$ ), 4.03 (t,  $J = 9.2$  Hz, 1H,  $H_{2A}$ ), 3.94 – 3.80 (m, 5H,  $H_{61A}, H_{61B}, H_{6'1A}, H_{6'1B}, H_{3A}$ ), 3.80 – 3.60 (m, 6H,  $H_{3B}, H_{5B}, H_{4A}, H_{5A}$ ), 3.49 (dd,  $J = 9.7, 3.7$  Hz, 1H,  $H_{2B}$ ), 3.29 – 3.23 (m, 5H,  $H_{4B}, (a)CH_2$ ), 3.17 (d,  $J = 6.2$  Hz, 2H), 2.94 (d,  $J = 6.1$  Hz, 12H,  $NCH_3$ ), 2.25 – 2.08 (m, 4H, (b) $CH_2$ ).

- 5  $^{13}C$ -NMR (101 MHz, Methanol- $d_4$ )  $\delta$  166.84(CO), 164.42(CO), 164.11(CO), 163.98(CO), 152.84( $C_{AR}$ ), 132.11( $C_{AR}$ ), 132.03( $C_{AR}$ ), 129.99( $C_{AR}$ ), 128.67( $CH_{AR}$ ), 127.00( $C_{AR}$ ), 125.48( $C_{AR}$ ), 124.08( $CH_{AR}$ ), 124.02( $C_{AR}$ ), 120.83( $CH_{AR}$ ), 120.23( $CH_{AR}$ ), 102.98( $C_{AR}$ ), 100.73( $C_{1B}$ ), 89.52( $C_{1A}$ ), 80.49( $C_{3B}$ ), 79.69( $C_{4A}$ ), 78.24( $C_{5A}$ ), 75.06( $C_{5B}$ ), 74.95( $C_{3A}$ ), 74.12( $C_{2B}$ ), 73.79( $C_{2A}$ ), 71.55( $C_{4B}$ ), 62.79( $C_{6A}$ ), 61.85( $C_{6B}$ ) 56.80((a) $CH_2$ ), 43.62( $NHCH_3$ ), 39.40( $NHCH_2$ ), 38.75((c) $CH_2$ ), 38.18((c) $CH_2$ ), 24.59((b) $CH_2$ ).
- 10 HRMS( $ES^+$ ): Calcd. for  $C_{39}H_{52}N_8NaO_{14}(M+Na)$ : 879,3501; found: 879.3478.

## 15 Compound 5



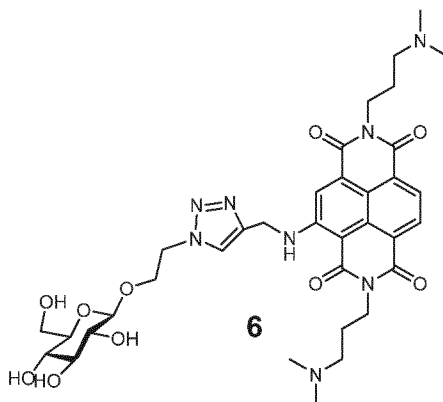
- $^1H$ -NMR (400 MHz, Methanol- $d_4$ )  $\delta$  10.38 (s, NH), 8.76 (s, NH), 8.48 (d,  $J = 7.6$  Hz, 1H,  $H_{AR3}$ ), 8.22 (s, 2H,  $H_{AR10}, H_{triazol}$ ), 8.15 (s, 1H,  $H_{AR4}$ ), 4.95 (s, 2H, (13) $CH_2$ ), 4.83( $H_1$ ) 4.70 (s, 2H,  $CH_2(16)$ ), 4.32 – 4.18 (m, 4H, (c) $CH_2$ ), 4.18 – 4.09 (m, 1H,  $CH_2$ ), 3.88 (dd,  $J = 10.9, 5.9$  Hz, 1H,  $H_4$ ), 3.74 – 3.45 (m, 5H,  $H_5, H_6, (17)CH_2$ ), 3.32 (dd,  $J = 3.2, 1.7$  Hz, 22H, (a) $CH_2, H_2$ ) 3.18 (d,  $J = 4.3$  Hz, 3H,  $CH_2(16)$ ), 2.95 (s, 12H,  $NCH_3$ ), 2.29 – 2.13 (m, 4H, (b) $CH_2$ ).
- 20

- $^{13}C$ -NMR (101 MHz, Methanol- $d_4$ )  $\delta$  167.21(CO<sub>1</sub>), 164.78(CO<sub>6</sub>), 164.48(CO<sub>7</sub>), 164.30(CO<sub>12</sub>), 153.15( $C_{AR9}$ ), 132.08( $C_{AR2,11}$ ), 130.43( $CH_{AR3}$ ), 129.12( $C_{AR(triazol)}$ ), 127.44( $C_{AR5}$ ), 125.55( $C_{AR8}$ ), 124.48( $CH_{AR4}$ ), 120.78( $CH_{triazol}$ ), 120.75 ( $C_{AR10}$ ), 120.70, 101.61( $C_1$ ), 101.20( $C_{AR14,15}$ ), 74.82( $C_2$ ), 72.48( $C_3$ ), 71.85( $C_5$ ), 68.30( $C_4$ ),
- 25

66.84((17)CH<sub>2</sub>), 62.59(C<sub>6</sub>), 56.81((a)CH<sub>2</sub>), 51.44((16)CH<sub>2</sub>), 43.63(NCH<sub>3</sub>), 39.41((c)CH<sub>2</sub>), 38.67((c)CH<sub>2</sub>), 38.15 (NHCH<sub>2</sub>(13)), 24.70((b)CH<sub>2</sub>).

HRMS(ES<sup>+</sup>): Calcd. for C<sub>35</sub>H<sub>46</sub>N<sub>8</sub>NaO<sub>10</sub>(M+Na): 761.3235; found: 761.3259.

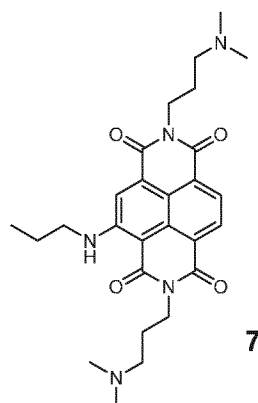
## 5 Compound 6



<sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O) δ 8.22 (d, J = 7.6 Hz, 1H, H<sub>AR</sub>), 8.13 (s, 1H, H<sub>AR</sub>), 7.97 (d, J = 7.6 Hz, 1H, H<sub>AR</sub>), 7.87 (s, 1H, H<sub>AR</sub>), 4.81 (s, 2H, NHCH<sub>2</sub>), 4.64 (s, 2H), 4.28 (d, J = 7.7 Hz, 1H, H<sub>1</sub>), 4.23-4.19 (m, 1H), 4.06 (bs, 4H, 2xCH<sub>2</sub>N), 3.68 (d, J = 12.3 Hz, 1H), 3.47-3.40 (m, 1H), 3.29-3.19 (m, 6H, 2xNCH<sub>2</sub>, OCH<sub>2</sub>), 3.09 – 2.93 (m, 3H), 2.86 (s, 6H, 6xNCH<sub>3</sub>), 2.85 (s, 6H, 6xNCH<sub>3</sub>), 2.07 (bs, 4H, 2xCH<sub>2</sub>).

<sup>13</sup>C-NMR (75 MHz, D<sub>2</sub>O) δ 165.3(CO), 163.8(CO), 163.6(CO), 163.2(CO), 151.4(C<sub>AR</sub>), 130.9(C<sub>AR</sub>), 128.2(C<sub>AR</sub>), 126.7(CH<sub>AR</sub>), 125.2(C<sub>AR</sub>), 124.9(C<sub>AR</sub>), 124.8(C<sub>AR</sub>), 124.5(CH<sub>AR</sub>), 122.3(CH<sub>AR</sub>), 119.7(CH<sub>AR</sub>), 118.5(C<sub>AR</sub>), 102.2(C<sub>1</sub>), 99.3(C<sub>AR</sub>), 75.7, 75.3, 72.9, 69.4, 67.8, 60.5, 55.2(NCH<sub>2</sub>), 55.1(NCH<sub>2</sub>), 50.4, 42.7(NCH<sub>3</sub>), 37.9(NHCH<sub>2</sub>), 37.6 (CH<sub>2</sub>N), 37.0(CH<sub>2</sub>N), 22.8(CH<sub>2</sub>).

HRMS(ES<sup>+</sup>): Calcd. for C<sub>35</sub>H<sub>47</sub>N<sub>8</sub>O<sub>10</sub> (M<sup>+</sup>): 739.3415; found: 739.3465.

Compound 7

<sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O) δ δ 8.09 (d, J = 7.9 Hz, 1H, H<sub>AR</sub>), 7.85 (d, J = 7.9 Hz, 1H, H<sub>AR</sub>), 7.65 (s, 1H, H<sub>AR</sub>), 4.07-3.98 (m, 4H), 3.37 (t, J = 2.2 Hz, 2H), 3.25-3.05 (m, 4H), 2.86 (s, 6H), 2.84 (s, 6H), 2.10-2.05 (m, 4H), 1.78-1.68 (m, 4H), 1.04 (t, J = 7.3 Hz, 3H).

<sup>13</sup>C-NMR (75 MHz, D<sub>2</sub>O) δ δ 165.1(CO), 163.6(CO), 163.3(CO), 163.0(CO), 151.8, 130.6, 128.3, 126.5, 124.9, 123.8, 121.6, 120.0, 118.1, 97.8, 55.1, 44.6, 44.4, 42.6, 37.6, 37.0, 22.6, 21.9, 10.6

HRMS(ES<sup>+</sup>): Calcd. for C<sub>27</sub>H<sub>35</sub>N<sub>5</sub>O<sub>4</sub>Na (M+Na): 516.2587; found: 516.2577.

Example 3. Biological activity

Cell culture: Cell culture media were purchased from Gibco (Grand Island, NY, USA). Fetal bovine serum (FBS) was a product of Harlan-Seralab (Belton, U.K.). Supplements and other chemicals not listed in this section were obtained from Sigma Chemicals Co. (St. Louis, Mo., USA). Plastics for cell culture were supplied by Thermo Scientific<sup>TM</sup> BioLite. All tested compounds were dissolved in DMSO at a concentration of 10 mg/mL and stored at -20°C until use. Cell lines were maintained in Dulbecco's modified Eagle's medium (DMEM) containing glucose (1 g/L), glutamine (2 mM), penicillin (50 IU/mL), streptomycin (50 µg/mL) and amphoterycin (1.25 µg/mL), supplemented with 10% FBS.

Cytotoxicity assays: The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma Chemical Co., St. Louis, MO) dye reduction assay in 96-well microplates was used, as previously described.<sup>[35]</sup> Some 5 x 10<sup>3</sup> cells of HT-29, MCF-7, HeLa or

MRC-5 cells in a total volume of 100  $\mu$ L of their respective growth media were incubated with serial dilutions of the tested compounds. After 2 days of incubation (37 °C, 5% CO<sub>2</sub> in a humid atmosphere), 10  $\mu$ L of MTT (5 mg/ml in PBS) were added to each well and the plate was incubated for further 4 h (37 °C). The resulting formazan was dissolved in 150  $\mu$ L of 0.04 N HCl/2-propanol and read at 550 nm. Each determination was carried out in triplicate and all experiments were repeated at least three times.

In vitro antitrypanosomal activity against Trypanosoma brucei

Bloodstream forms (BSF) of *T. brucei brucei* 'single marker' S427 (S16) were grown at 37 °C, 5% CO<sub>2</sub> in HMI-9 medium supplemented with 10% (heat-inactivated fetal bovine serum, hiFBS). Drug susceptibility assay was performed as described in Carvalho L et al., 2015 (Antimicrob Agents Chemother. 2015 Oct;59(10):6151-60). Briefly, parasites (1  $\times$  10<sup>4</sup> BSF per mL) were incubated in 96-well plates with increasing concentration of drugs/compounds for 72 h at 37 °C, 5% CO<sub>2</sub> in culture medium. Cell proliferation was determined using the alamarBlue® assay (B. Raz, et al., Acta Trop 68 (1997) 139-147). The Alamar Blue assay is used to determine drug sensitivity of African trypanosomes (*T.b. rhodesiense* and *T.b. gambiense*) in vitro. Fluorescence was recorded with an Infinite® F200 microplate reader (Tecan Austria GmbH, Austria) equipped with 550 and 590 nm filters for excitation and emission wavelengths, respectively.

In vitro antimalarial activity against Plasmodium falciparum

Drug effects on in vitro *P. falciparum* growth were measured in microtiter plates according to Desjardins et al. [Antimicrob Agents Chemother. 1979 Dec;16(6):710-8]. The final volume in each well was 200  $\mu$ L, consisting of 50  $\mu$ L of complete medium (RPMI 1640 + 10% AB human serum) without (controls) or with drug and 150  $\mu$ L of *P. falciparum*-infected erythrocyte (3D7 strain) suspension (1.5% final hematocrit and 0.6% parasitemia). The drugs dissolved in DMSO, were diluted in complete medium so that the final DMSO concentration never exceeded 0, 25%. After 48 h incubation at 37°C, 30  $\mu$ L of complete medium containing 0.6 $\mu$ Ci [3H]-hypoxanthine were added to each well. After 18 h at 37°C, cells were lysed using an automatic cell harvester and the parasite macromolecules, including radioactive nucleic acids, were retained onto glass fiber filters. The filters were counted for radioactivity, after adding scintillation

cocktail, in a liquid scintillation spectrometer. Radioactivity background was obtained from incubation of non-infected erythrocytes under the same condition, and deduced. Parasitic viability was expressed as IC<sub>50</sub> which is the drug concentration leading to 50% parasite growth inhibition.

5

Antiproliferative activity of prepared compounds

| <u>COMPOUND</u>  | <u>IC<sub>50</sub> (uM)</u> |              |             |              |
|------------------|-----------------------------|--------------|-------------|--------------|
|                  | <u>HT-29</u>                | <u>MCF-7</u> | <u>HeLa</u> | <u>MRC-5</u> |
| β-glc-NDI (1)    | 2.92 ± 0.48                 | 1.37 ± 0.81  | 1.56 ± 0.70 | 0.89 ± 0.33  |
| β-glcNAc-NDI (2) | 2.26 ± 1.03                 | 1.06 ± 0.01  | 0.95 ± 0.76 | 0.51 ± 0.01  |
| β-6dglc-NDI (3)  | 0.40 ± 0.08                 | 0.69 ± 0.71  | 0.35 ± 0.05 | 0.91 ± 0.32  |
| β -malt-NDI (4)  | 1.85 ± 0.19                 | 1.42 ± 0.38  | 0.54 ± 0.34 | 2.04 ± 0.05  |
| α-manC2-NDI (5)  | 0.42 ± 0.05                 | 0.15 ± 0.04  | 0.29 ± 0.14 | 0.84 ± 0.28  |
| β -glcC2-NDI (6) | 0.36 ± 0.13                 | 0.24 ± 0.16  | 0.24 ± 0.03 | 0.73 ± 0.17  |
| NDI-prop (7)     | 0.12 ± 0.02                 | 0.07 ± 0.01  | 0.29 ± 0.18 | 0.42 ± 0.13  |

10

Antitrypanosomal and antimalarial activity of prepared compounds

| <u>COMPOUND</u>  | <u>IC<sub>50</sub> (uM)</u> |                     |
|------------------|-----------------------------|---------------------|
|                  | <i>T.brucei</i>             | <i>P.falciparum</i> |
| β-glc-NDI (1)    | 0.024 ± 0.001               | 0.35 ± 0.63         |
| β-glcNAc-NDI (2) | 0.089 ± 0.007               | 0.36 ± 0.07         |
| β-6dglc-NDI (3)  | 0.017 ± 0.007               | 0.22 ± 0.12         |
| β-malt-NDI (4)   | 0.098 ± 0.001               | 0.37 ± 0.08         |
| α-manC2-NDI (5)  | 0.021 ± 0.003               | 0.18 ± 0.10         |
| β-glcC2-NDI (6)  | 0.017 ± 0.009               | 0.27 ± 0.19         |
| NDI-prop (7)     | 0.009 ± 0.001               | 0.09 ± 0.01         |
| Chloroquine      | - -                         | 0.001 ± 0.003       |

In vivo HT-29 xenograft mice study

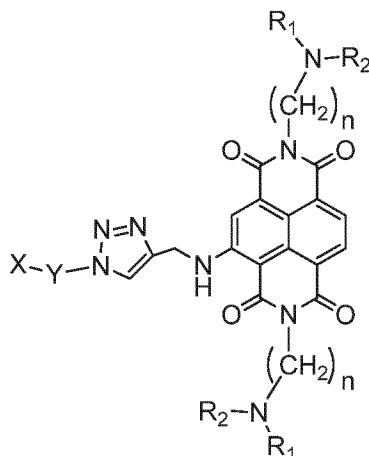
Two carb-NDI G-quadruplex ligands,  $\beta$ -glcC2-NDI (6) and NDI-prop (7) were examined. A therapeutic schedule of two different concentrations was explored for  $\beta$ -glcC2-NDI (6) and only one concentration for NDI-prop (7) due to toxicity reasons. Compound concentration used were 0.02 mmol/Kg (19.32 mg/Kg) and 0.04 mmol/Kg (38.65 mg/Kg) for  $\beta$ -glcC2-NDI (6), and 0.02 mmol/Kg (11.33 mg/Kg) for NDI-prop (7). A HT-29 colon cancer tumour xenograft mice model, with three doses per week during two weeks (6 doses total) with i.p. compound administration were investigated. Treatment started on Day 13 when tumour size was 200 mm<sup>3</sup> and mice were sacrificed on Day 27 due to endpoint reasons (mice weight loss or tumour size over 2000 mm<sup>3</sup>). According to Figure 1, NDI-prop (7) showed no clear differences with the control group, and  $\beta$ -glcC2-NDI (6) shows a dose-dependent anti-tumour response, with the higher 0.04 mmol/Kg dose producing a significantly greater effect than the 0.02 mmol/Kg regimen. At Day 24, an average of ca 35% decrease in tumour size was observed over the group of six animals used in comparison to the control group.

Figure 2 shows that no significant weight reduction or adverse effects such as tumour ulceration were observed in either group at any time during the course of the experiments. Eye examination of intestines and kidney from control and treated animals showed no signs of tissue damage. Liver showed signs of inflammation for NDI-prop (7) and  $\beta$ -glcC2-NDI (6) groups in comparison with no inflammation in the control group.

Whole-animal imaging using IVIS (PerkinElmer) technology showed slight accumulation of NDI-prop (7) near the tumor area but not inside the tumour. No other areas showed accumulation, in accordance to a whole body general distribution of the compound. Similar results were observed for  $\beta$ -glcC2-NDI (6) with some small accumulation in the brain, kidneys and in the urinary system.

## CLAIMS

1. Compound of general formula (I) or a pharmaceutically acceptable salt thereof



(I)

wherein

$R_1$  and  $R_2$  are each independently selected from substituted or unsubstituted  $C_{1-20}$  alkyl, substituted or unsubstituted  $C_{2-20}$  alkenyl, substituted or unsubstituted  $C_{2-10}$  alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted  $C_{3-20}$  cycloalkyl,  $C_{3-20}$  cycloalkylalkyl,  $C_{3-20}$  heterocyclyl, heterocyclylalkyl, or  $C_{1-10}$  alkoxy, or  $R_1$  and  $R_2$  together with the nitrogen atom to which they are attached form a substituted or unsubstituted, saturated or unsaturated, 5-8 member heterocyclic ring;

$n$  is an integer from 2 to 12;

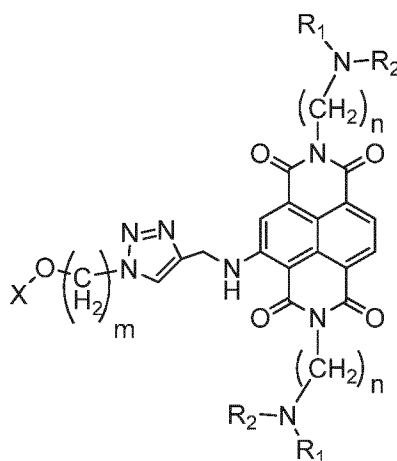
$Y$  is absent or selected from  $-O-(CH_2)_m-$ ,  $-N-(CH_2)_m-$ ,  $-S-(CH_2)_m-$ , or  $-(CH_2)_m-$ , being  $m$  an integer from 2 to 12;

and  $X$  is selected from an H or an optionally substituted monosaccharide, an optionally substituted disaccharide, or an optionally substituted oligosaccharide in any of its isomeric forms which is attached to the rest of the molecule directly by one of the ring carbons or through a O-, N-, C- or S-glycosidic bond when  $Y$  is  $-O-(CH_2)_m-$ ,  $-N-(CH_2)_m-$ ,  $-(CH_2)_m-$ ,  $-S-(CH_2)_m-$ .

2. Compound according to claim 1, wherein  $R_1$  and  $R_2$  are each independently  $C_{1-10}$  alkyl.

3. Compound according to claim 2, wherein  $R_1$  and  $R_2$  are each independently  $C_{1-5}$  alkyl.
4. Compound according to claim 3, wherein  $R_1$  and/or  $R_2$  are methyl.
5. Compound according to any of claims 1 to 4, wherein  $n$  is an integer from 2 to 5.
6. Compound according to any of claims 5, wherein  $n$  is 3.
- 10 7. Compound according to any of claims 1 to 6, wherein  $X$  is a monosaccharide selected from glucose, 6-deoxyglucose, mannose, galactose, glucosamine, galactosamine, N-acetylglucosamine, N-acetylgalactosamine, glucuronic acid, allose, altrose, gulose, idose, fucose, talose, ribose, deoxyribose, arabinose, xylose, lyxose, ribulose, xylulose, fructose, psicose, sorbose or tagatose.
- 15 8. Compound according to any of claims 1 to 6, wherein  $X$  is a disaccharide selected from sucrose, lactose, lactulose, allolactose, maltose, isomaltose, isomaltulose, trehalose, cellobiose, kojibiose, nigerose, sophorose, laminaribiose, gentiobiose or mannanose or their O-, N-, C- or S-interglycosidic derivatives.
- 20 9. Compound according to any of claims 1 to 8, wherein  $Y$  is selected from  $-O-(CH_2)_m-$ ,  $-S-(CH_2)_m-$ , or  $-(CH_2)_m-$ .
10. Compound according to any of claims 1 to 9, wherein  $m$  is an integer from 2 to 5.
- 25 11. Compound according to claim 10, wherein  $m$  is 2.
12. Compound according to any of claims 1 to 8, wherein  $Y$  is absent.
- 30 13. Compound according to claim 1, wherein the compound is a compound of general formula (I-A)

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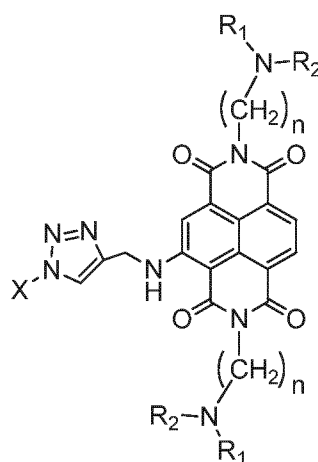


(I-A)

wherein  $R_1$ ,  $R_2$ ,  $n$ ,  $m$  and  $X$  is as defined in any of claims 1-8.

5

14. Compound according to claim 13, wherein  $m$  is 2.
15. Compound according to claim 1, wherein the compound is a compound of general formula (I-B)



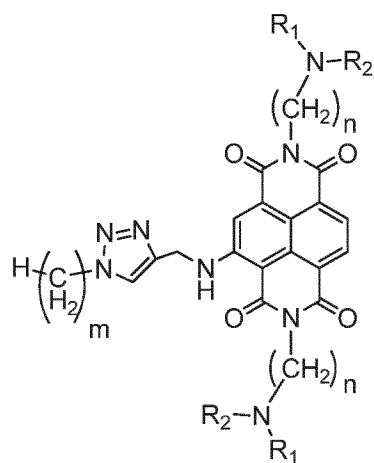
(I-B)

wherein  $R_1$ ,  $R_2$ ,  $n$  and  $X$  is as defined in any of claims 1-8.

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- 15 16. Compound according to claim 1, wherein the compound is a compound of general formula (I-C)

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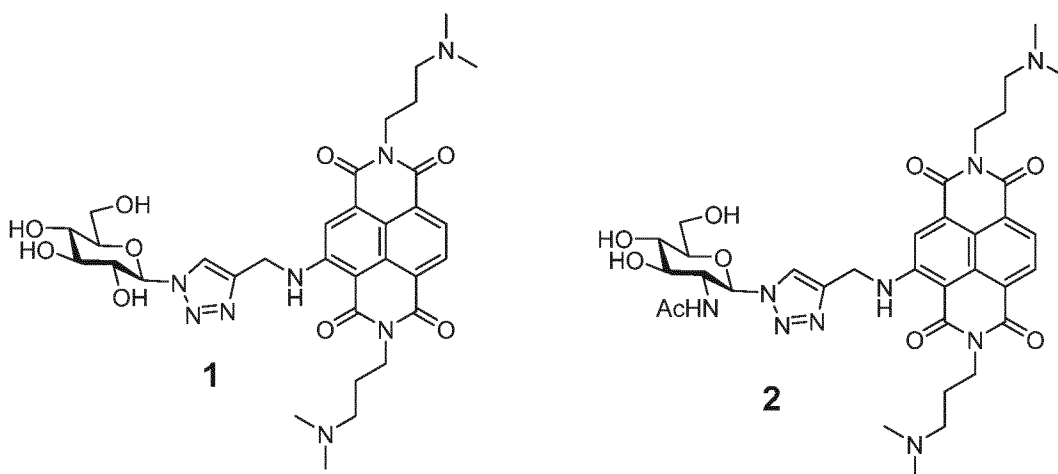
(I-C)

wherein  $\text{R}_1$ ,  $\text{R}_2$ ,  $n$ , and  $m$  is as defined in any of claims 1-8

5

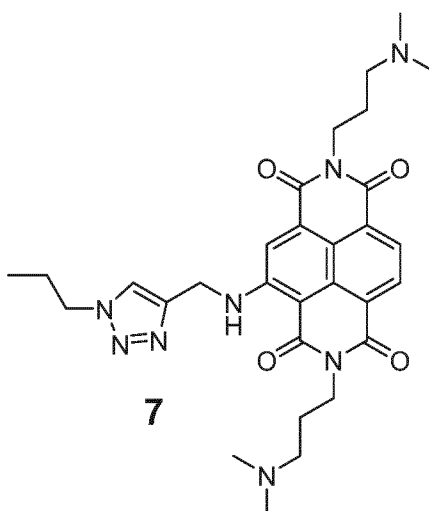
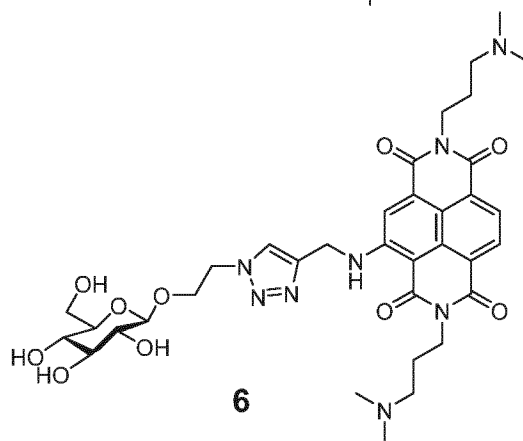
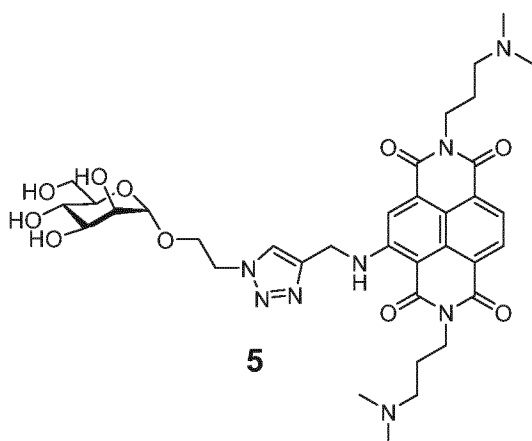
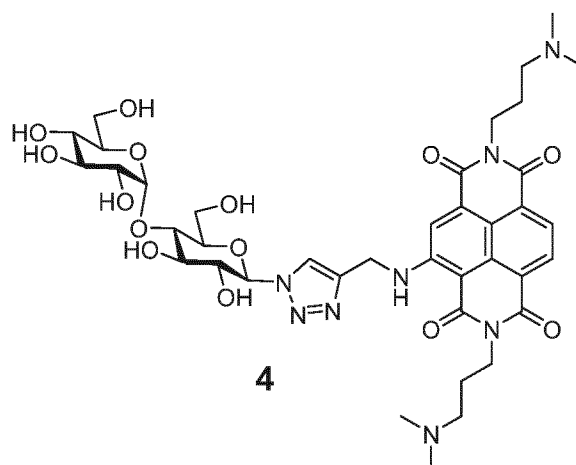
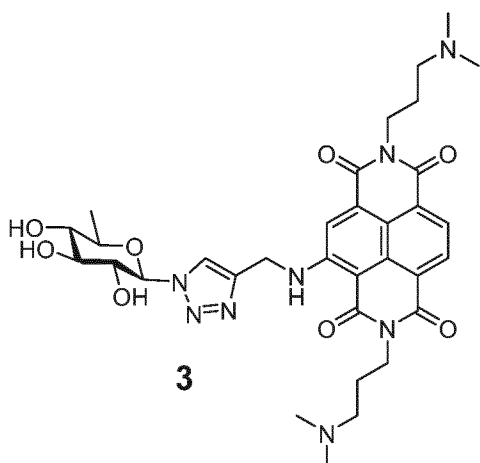
17. Compound according to claim 16, wherein  $m$  is 3.

18. A compound according to claim 1 selected from:



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19. A pharmaceutical composition comprising a compound of general formula (I) according to any of claims 1 to 18.

20. Use of a compound of general formula (I), or a salt thereof according to any of claims 1 to 18, for the manufacture of a medicament.
21. Use of a compound of general formula (I), or a salt thereof, according to any of  
5 claims 1 to 18, for the manufacture of a medicament for the prophylaxis and/or treatment of cancer.
22. Use of a compound of general formula (I) according to claim 21 wherein the cancer  
10 is selected from parathyroid gland adenoma, parathyroid gland hyperplasia, parathyroid gland carcinoma, squamous carcinoma, renal carcinoma, breast carcinoma, prostate carcinoma, lung carcinomas, osteosarcomas, clear cell renal carcinoma, prostate cancer, lung cancer, breast cancer, gastric cancer, ovarian cancer, bladder cancer, anal cancer, bone cancer, brain tumors, gastrointestinal tumors, cervical cancer, colorectal cancer, eye cancer, head cancer, neck cancer,  
15 kidney cancer, laryngeal cancer, liver cancer, mouth cancer, nasopharyngeal cancer, oral cancer, pancreatic cancer, nasal cavity cancer, pituitary tumor, rectal cancer, skin cancer, small intestine cancer, stomach cancer, testicular cancer, thyroid cancer, urethral cancer, uterine cancer, vaginal cancer, vulvar cancer, leukemia, melanomas, lymphomas, sarcomas or gliomas.
- 20 23. Use of a compound of general formula (I), or a salt thereof, according to any of claims 1 to 18, for the manufacture of a medicament for the prophylaxis and/or treatment of diseases derived from a parasitic infection.
- 25 24. Use of a compound of general formula (I) according to claim 23 wherein the disease is selected from african trypanosomiasis, chagas, leishmaniosis, blastocystosis, cryptosporidiosis, amoebiasis, giardiasis, sarcosystosis, toxoplasmosis, trichomoniasis or malaria.

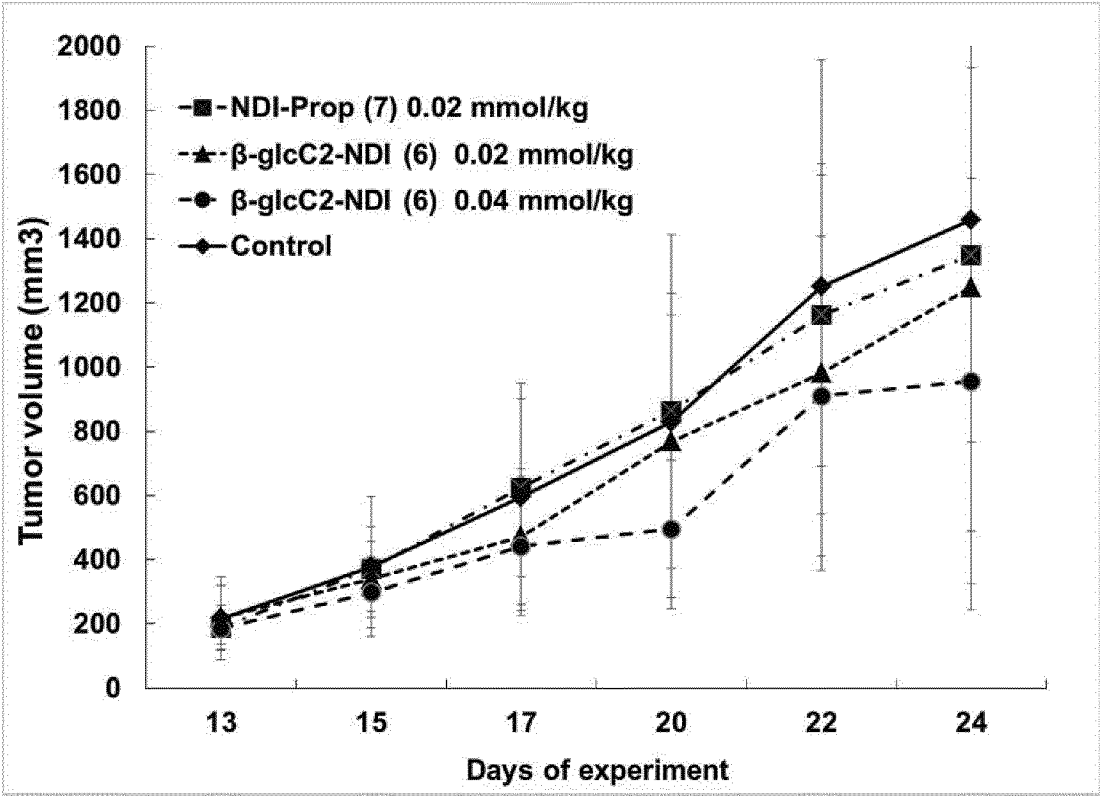


FIG. 1

2/2

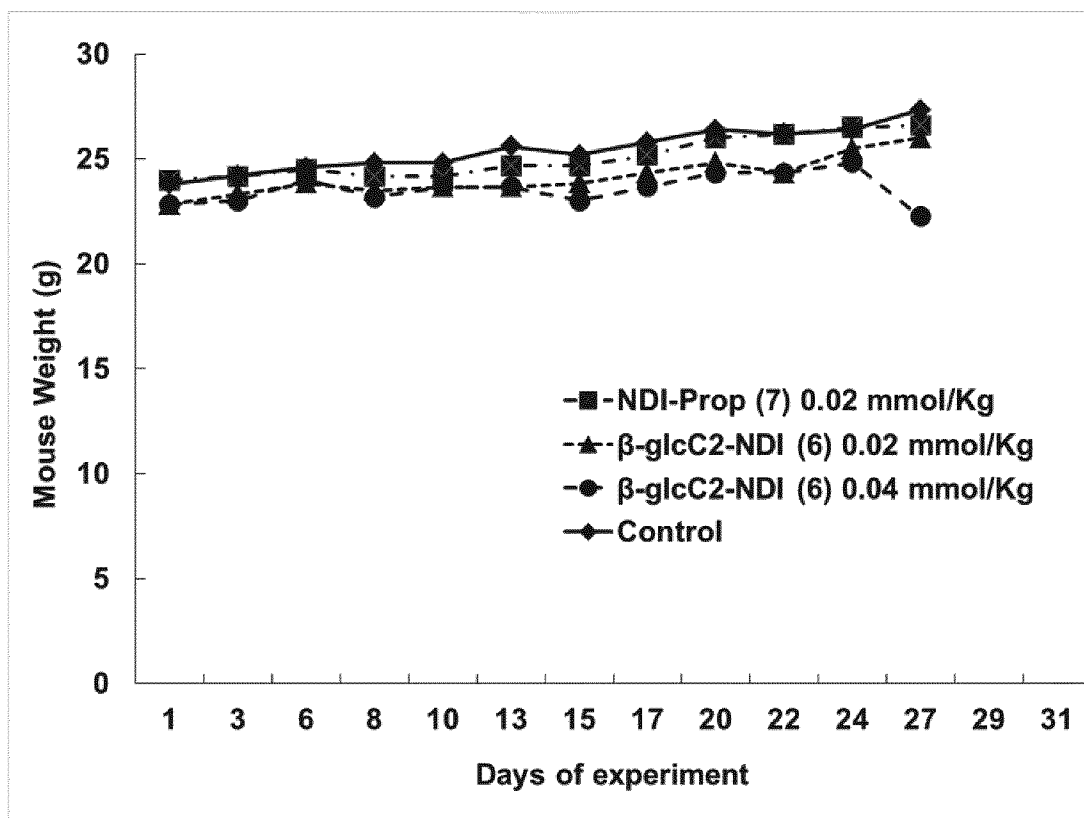


FIG. 2

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2017/074773

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07D471/04 A61K31/4375 A61P35/00 A61P33/00  
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)  
C07D A61K A61P

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, CHEM ABS 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 2009/068916 A1 (UNIV LONDON PHARMACY [GB]; GUNARATNAM MEKALA [GB]; CUENCA FRANCISCO [E] 4 June 2009 (2009-06-04) cited in the application claims 1, 17; compound 15<br>----- | 1-24                  |
| Y         | US 2014/275062 A1 (NEIDLE STEPHEN [GB] ET AL) 18 September 2014 (2014-09-18) cited in the application claims 1, 8; compound MM43<br>-----<br>-/-                                | 1-24                  |



Further documents are listed in the continuation of Box C.



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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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

30 November 2017

Date of mailing of the international search report

08/12/2017

Name and mailing address of the ISA/

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Authorized officer

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/074773

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                              | Relevant to claim No. |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | <p>GUOCAN YU ET AL: "Carbon Nanotube/Biocompatible Bola-Amphiphile Supramolecular Biohybrid Materials: Preparation and Their Application in Bacterial Cell Agglutination", ADVANCED MATERIALS, vol. 25, no. 44, 1 November 2013 (2013-11-01), pages 6373-6379, XP055425418, DE<br/> ISSN: 0935-9648, DOI: 10.1002/adma.201302942<br/> figures 1-5; compound ND</p> <p>-----</p> | 1-24                  |
| A         | <p>EMILIA C. CALVARESI ET AL: "Glucose conjugation for the specific targeting and treatment of cancer", CHEMICAL SCIENCE, vol. 4, no. 6, 1 January 2013 (2013-01-01), pages 2319-2333, XP055395433, United Kingdom<br/> ISSN: 2041-6520, DOI: 10.1039/c3sc22205e<br/> figures 2-10</p> <p>-----</p>                                                                             | 1-24                  |
| Y         | <p>HE XIAO-PENG ET AL: "Carbohydrate CuAAC click chemistry for therapy and diagnosis", CARBOHYDRATE RESEARCH, PERGAMON, GB, vol. 429, 29 March 2016 (2016-03-29), pages 1-22, XP029561762, ISSN: 0008-6215, DOI: 10.1016/J.CARRES.2016.03.022<br/> page 2 - page 3; figure 1</p> <p>-----</p>                                                                                   | 1-24                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/074773

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date         |
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| WO 2009068916                             | A1                  | 04-06-2009                 | EP 2227470 A1 15-09-2010    |
|                                           |                     |                            | JP 5366968 B2 11-12-2013    |
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| US 2014275062                             | A1                  | 18-09-2014                 | NONE                        |
| -----                                     |                     |                            |                             |