Title: NEW CONJUGATES OF 2-FLUORO-2-DEOXY-GLUCOSE AND THEIR USES AS ANTI CANCER AGENTS

Abstract: The present invention concerns a compound of general formula (I) wherein: R₁, R₂ and R₃ mean, independently from the others, an hydrogen atom or an optionally substituted lower alkyl, a (C₁-C₇) acyl group or a benzyl, R₄ is an optionally substituted and/or interrupted hydrocarbon linker, X and Y are selected independently from each other from the group consisting of -NH₂, -NH-, -CO-, -O-, -NHR-, -NHC(O)H₂, -NHC(O)R-, -O(CO)R-, -S-S- and optionally substituted lower alkyl group. Z moiety represents an anti-neoplastic agent. n means 0, 1 or 2, and the pharmaceutically acceptable salts thereof. It relates also to the use of such compounds as anti cancer agents.
New conjugates of 2-fluoro-2-deoxy-glucose and their uses as anti cancer agents

The present invention relates to methods for treating cancer and precancerous cells and tissues, as well as compounds that are conjugates of glucose or analogs or derivatives thereof; and anti-cancer compositions for use in the methods of the invention.

The term "cancer" generally refers to any of a group of more than 100 diseases caused by the uncontrolled growth of abnormal cells. Unlike normal cells, which reproduce until maturation and then only as necessary to replace wounded cells, cancer cells can grow and divide endlessly, crowding out nearby cells and eventually spreading to other parts of the body.

Cancer can take the form of solid tumors and lymphomas, and non-solid cancers such as leukemia.

The principal problem of cancer therapy is achieving efficient and selective killing of tumor cells.

In effect, a great number of drugs used to kill cancer cells are also toxic to cells of normal tissue, and so side effects are often severe.

Furthermore, the majority of drug-mediated cancer therapies rely on drugs that selectively poison dividing cells. These drugs can be effective, because cancer cells generally divide more frequently than normal cells. Unfortunately, there are exceptions to this rule in most cancers, which means that such drugs almost inevitably are unable to kill all cells in a tumor.

Accordingly, there is still a need for cytotoxic compounds that preferentially target cancer cells and efficiently kill them.

To achieve in part this goal, scientists considered that inhibition of anaerobic glycolysis by metabolic poisons could be useful to preferentially target cancer cells. In effect, due to the markedly enhanced utilization of glucose in cancer cells mediated by increased activity of the proteins mediating these steps, the 2-deoxy-D-glucose and related conjugates are accumulated preferentially in cancer cells compared to normal cells.

Thus, the compound 2-deoxy-D-glucose (also known and referred to herein as 2-deoxyglucose and 2-DG) is such a metabolic poison. 2-DG inhibits glycolysis in cancer cells, as reported in the reference Woodward, 1954, Cancer Res. 14:599-605. However, 2-DG has not be approved for the treatment of cancer in the United States or in Europe.
Other known anti-cancer agents having a structure based on a glucose moiety attached to a cytotoxic agent have also been used to treat cancer. For example, Glufosfamide (beta-D-glucosyl-ifosfamide mustard) is an anti-cancer agent that can be described as a cytotoxic agent linked to a glucose moiety. This compound contains the cytotoxic agent ifosfamide coupled to glucose via an ester linkage at the oxygen atom at the 1-position of glucose (see U.S. Pat. No. 5,622,936). Prodrug forms of pharmacologically active substances, including anti-cancer agents, and that contain a glucose or other sugar moiety linked to a pharmacologically active agent either directly or through a spacer at the 1 position (see U.S. Pat. No. 5,621,002) or at the 2 position (see U.S. Pat. No. 7,001,888) have also been described.

However, while compounds have been made that contain a cytotoxic agent linked to glucose, most of those compounds have not been approved for the treatment of cancer, and none of those compounds appears to have significant specificity for cancer cells.

Accordingly, there remains a need for methods and compositions for treating cancer, including rumors, non-solid cancers, and cancer cells, that may be widely applicable in a variety of cancers.

The present invention provides such methods, as well as compounds and compositions useful in those methods.

In particular, the present invention derives in part from the unexpected discovery by the inventors that conjugates of 2-fluoro-2-deoxy-glucose or derivatives, and anti-neoplastic agents linked via non-releasable linkages experience enhanced activity in cancer cells.

Thus in a first aspect, the present invention provides compounds of general formula (I):

\[
\begin{align*}
\text{OR}_1 & \quad R_2 \quad \text{OR}_3 \\
\text{OR}_4 & \quad R_4 \quad \text{O} \\
\text{X} & \quad (R_5 \cdot Y)_n \quad \text{Z}
\end{align*}
\]  

(I)

\[
\text{OR}_1 \quad R_2 \quad \text{OR}_3 \\
\text{OR}_4 \quad R_4 \quad \text{O} \\
\text{X} \quad (R_5 \cdot Y)_n \quad \text{Z}
\]

wherein:

- \( R_1 \) and \( R_3 \) may be independently from the others, an hydrogen atom, or an optionally substituted lower alkyl, a \((C_1-C_7)\)acyl group or a benzyl, and preferably an hydrogen atom or a lower alkyl having 2 carbon atoms,
R is an optionally substituted and/or interrupted hydrocarbon linker,

X and Y are selected independently from each other, from the group consisting of -NH-, -NR'-, -CO-, -NH(CO)-, -NH(CO)NH-, -NR'(CO)-, -0(CO)NH-, -0(CO)NR'-, -(CO)NH-, -(CO)NR', -NH(CO)(R")NH(CO)-, -(CO)NH(R")-(CO)NH-, -O-, -(CO)O-, -NH(CO)O-, -SC(O)NH-, -NHSO\_2\_-, -NR'SO\_2\_-, -O(CO)-, -S-S-, -0C(0)NHR"C(0)NH-, -NHC(O)R"-, -OC(O)R"-, -OC(O)NH-R"- and -NHC(O)NH-R"-, and preferably are different one from the other, with R' being an optionally substituted lower alkyl group, and R" being a (C\_1-C\_j)alkylene,

Z moiety represents an anti-neoplastic agent,

n means 0, 1 or 2,

and the pharmaceutically acceptable salts thereof.

In particular, X and Y may be selected independently from each other, from the group consisting of -NH-, -NR'-, -CO-, -NH(CO)-, -NH(CO)NH-, -NR'(CO)-, -0(CO)NH-, -0(CO)NR'-, -(CO)NH-, -(CO)NR', -O-, -(CO)O-, -NH(CO)O-, -SC(O)NH-, -NHSO\_2\_-, -NR'SO\_2\_-, -O(CO)-, -S-S-, -0C(0)NHR"C(0)NH-, -NHC(O)R"-, -OC(O)R"-, -OC(O)NH-R"- and -NHC(O)NH-R"-.

In a further aspect, the present invention provides pharmaceutical composition including, in a physiological acceptable vehicle, at least one compound according to the invention.

In a further aspect, the present invention relates to the use of a compound according to the invention as an anti-cancer agent and in particular for preparing a pharmaceutical composition intended to the treatment of cancer and in particular solid cancer.

In a further aspect, the present invention provides a method for treatment of cancer, in particular solid cancer comprising the administration to a patient in need thereof, of at least a compound according to the instant invention.

The 2-fluoro-2-deoxy-glucose, 2-FDG, is a known reagent more particularly used for detecting cancer tissue in an animal based on the use of positron emission tomography (PET scan). These detecting methods takes advantage of the increased uptake and retention by malignant cells of 18F-labeled glucose derivative (FDG, 18F-2-fluoro-2-deoxyglucose). This glucose derivative, lacking a hydroxy group at the 2-position, cannot be further metabolized by the cells and is simply accumulated in the cells.
Unexpectedly, the inventors noticed that the conjugates based on the 2-fluoro-2-deoxy-glucose can be used to treat cancer tissue and cancer cells preferentially. The selectivity of the conjugates for preferentially killing cancer cells is provided by the increased transport, relative to non-cancer cells, of the conjugate due to the up-regulation of the glucose transporters (GLUTs) in cancer cells, as well as by, at least in some cancer cells, the up-regulated expression of hexokinase.

The term lower alkyl as used herein refers to a (Ci-C7)alkyl and in particular straight or branched-chain hydrocarbon radical of one to seven carbon atoms and cyclized manifestations thereof unless otherwise indicated. Included within the scope of this term are such moieties as methyl, ethyl, isopropyl, n-butyl, t-butyl, t-butylmethyl, cyclopropyl, N-propyl, pentyl, cyclopentyl, n-hexyl, cyclohexyl, cyclohexylmethyl, 2-ethylbutyl etc.

As used herein, the term "optionally substituted lower alkyl" means a lower alkyl as defined above optionally substituted by one or more group chosen from halogen atom, hydroxy group, (Ci-C?)alkoxy group and amino group.

More particularly, in the compounds, according to the invention, the linking group formed by R4 includes linear or acyclic portions, cyclic portions, aromatic rings or combinations thereof. It can be saturated or unsaturated.

Additionally, this linking group is sufficiently robust so that it is stable to reaction conditions used in conjugate assembly, e.g., the protection/deprotection chemistries used to prepare the conjugates of the invention:

More specifically, R4, when present, is of formula

- -(Arnylene)ru-(P)p-(Auylene)q-
- -(Alkylene)m-(P)p-(Arnylene)q-

or

- -(Alkylene)m-(P)p-(Alkylene)q-

wherein

- m, p and q mean, independently one from the others, 0 or 1 with the proviso that at least one of them is different from 0,
- Alkylene means an optionally substituted (C1-C7)alkylene group and preferably a (Ci-C3)alkylene and more preferably a methylene group,
- Arylene means an optionally substituted Cs to Cjo arylene or heteroarylene,
- P means a group as proposed for the definition of X and Y and preferably selected from -NH(CO)-, -NR(CO)-, -O(CO)NH-,-O(CO)NR’, -(C0)NH-,(C0)NR’-, O(CO)-,(C0)O-, -NH(CO)O-, -NR χc θO- and -S-S-, with R’ as previously defined, and more preferably -NH(CO)- or -(CO)NH-.

As used herein, the term "alkylene" refers to a saturated or unsaturated straight or branched chain or cyclic divergent hydrocarbon radical eventually substituted by one or more aryl groups. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, trimethylene, tetramethylene and the like. It is to be understood that where cyclic moieties are intended, at least three carbon atoms said alkylene must be present. Such cyclic moieties include cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene and cycloheptylene.

As used herein, the term "arylene" refers to divalent unsaturated aromatic radicals having a single ring such as phenylene, or multiple condensed rings, such as naphthylene or anthrylene.

Preferably, the arylene group is selected from the group consisting of benzylene, phenylene, biphenylene, anthrylene, phenylbenzylene, fluorenylene, naphthylene, dihydronaphthylene, tetrahydronaphthylene, indenylene and indanylene, and more preferably is the phenylene group.

As used herein, the term "heteroarylene" refers to a divalent radical which may be an aromatic monocycle, an aromatic bicycle, an aromatic tricycle, or a bicycle or a tricycle of which one or two of the cycles is aromatic and the other cycle(s) is or are partially hydrogenated, from C5 to C14 comprising within the cyclic system one, two or three heteroatoms, identical or different, selected among oxygen, nitrogen and sulphur.

Each one of these alkylene, arylene or heteroarylene groups may optionally comprise one or more substitutions, identical or different, for example one to three and more preferably one or two, selected from the group consisting of a halogen, the hydroxy group, a straight or linear (Ci-C7)alkyl group, (C5-C10)aryl group optionally substituted like a p-tolyl group, a straight or linear (Ci-C7)alkenyl group, a (Ci-C7)alkoxy group, a (C7-C13)arylalkoxy group, the cyano group, the nitro group, the amino group, a (Q-C7)alkylamino group, a HO-(Q-C7)alkyl- group, a H2N-(C1-C7)alkyl- group, a HO-(O=O)- group, a (C1-C7)alkyl-O-(C=O)- group, a (Q-C7)alkyl-(C=O)- group, a (C1-C7)alkyl-
(C=O)-(CrC₈)alkyl- group, a HSO₃(Ci-C₇)alkyl- group, a H₂N-(C=O)- group and a H₂N-(C=O)-(C,-C₇)alkyl- group.

The term halogen refers to fluorine, chlorine, bromine or iodine atom. Fluorine and chlorine are preferred halogen atoms in the framework of the present invention.

The term (Ci-C₇)alkoxy refers to alkoxy radical made up of an oxygen radical bearing a saturated straight or branched chain hydrocarbon radical of one to seven carbon atoms. Included within the scope of this tenia are methoxy, ethoxy, propoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, n-pentoxy, isopentoxy, sec-pentoxy, t-pentoxy, .. and the like.

A first class of such compounds of formula (Ⅰ), hereinafter referring to compounds of formula (Ia), is such that π is equal to zero.

Among this first class of compounds of formula (Ia), the compounds for which the therapeutical use is the most preferred are characterized in that X means;
- -O(CO)-,
- -NH(CO)-,
- -NH(CO)NH-or
- -NHC(O)-CH₂-.

A second class of such compounds of formula (Ⅱ), hereinafter referring to compounds of formula (Ib), is such that n is different from zero and R₄ comprises or is

Among this second class of compounds of formula (Ib), the compounds for which the therapeutical use is the most preferred are characterized in that X is selected from the group consisting of -NH-, -NH(CO)-, -O-, -O(CO)-, -O(CONH-), -NH(CO)O-, and -OC(O)NHCH₂C(O)NH and in particular -NH-, -NH(CO)-, -O-, -O(CO)-, -O(C)NH-, and especially -O-.

More particularly, Y is -NH(CO)-, -(CO)NH-, -O(CO)-, -OCONH-, -NH(CO)O-, and -NHC(O)CH₂-, in particular -NH(CO)-, -(CO)NH-, -O(CO)-, and -NHC(O)CH₂-, especially -NH(CO)- and -(CO)NH-, and preferably -NH(CO)-.
A third class of such compounds of formula (T), hereinafter referring to compounds of formula (Ic), is such that n is different from zero and $R_4$ includes or is a (Ci-C$_7$)alkylene group in particular a (C$_1$-C$_3$)alkylene group and more particularly a methylene group.

Among this third class of compounds of formula (Ic), the compounds for which the therapeutical use is the most preferred are characterized in that X and Y represent a group selected from the group consisting of -NH(CO)-, -(CO)NH-, -NH(CO)NH-, -O(CO)-, -O(CO)NH and -NH(CO)O-, and in particular -NH(CO)-, -(CO)NH-, -NH(CO)NH-, and especially -NH(CO)-.

The compounds of formula (Ic) characterized in that X and Y both represent -NH(CO)- or -(CO)NH-, and especially -NH(CO)-, and $R_4$ represents a methylene group are especially preferred.

A fourth class of such compounds of formula (I) hereinafter referring to compounds of formula (Id), is such that n is different from zero and $R_4$ means a radical of formula (Arylene)-P-(Alkylene), (Alkylene)-P-(Arylene) or (Alkylenc)-(P)-(Alkylene)- wherein:

- Arylene is

- Alkylene is a (Q-alkylene group and in particular a methylene group, and

- P is -NHCO-, CONH-, -NR'-, -S-S- or -NH-, and in particular -NHCO- or -CONH-, with $R'$ being as previously defined.

The compounds of formula (Id) characterized in that $R_4$ means a radical of formula (Arylene)-P-(Alkylene), (Alkylene)-P-(Arylene) wherein:

- Arylene is

- Alkylene is a methylene group, and

- P is -NHCO- or -CONH- are particularly preferred.
Among this last class of compounds, the compounds for which X represents \(-\text{O}\)- and Y represents \(-\text{NH(CO)}\)- or \(-\text{(CO)NH}\)-, and preferably \(-\text{NH(CO)}\)-, are especially preferred.

In one particular embodiment of the present invention, \(R_1, R_2\) and \(R_3\) are in formula I, Ia, Ib, Ic and Id different from hydrogen. More particularly, they mean an acyl group, and in particular an acetyl group.

In one other particular embodiment of the present invention, \(X\) and/or \(Y\) mean in formula I, Ia, Ib, Ic and Id \(-\text{NHC(O)}\)- or \(-\text{(O)CNH}\)-, and especially \(-\text{NHC(O)}\)-.

Regarding the anti-neoplastic agents, it is noticed that it can be chosen among a large number of anti-cancer agents including chemotherapeutic agents and radioisotopic agents.

To facilitate uptake of the conjugate through a glucose transporter, however, the anti-neoplastic agent is, in a preferred embodiment, a relatively small molecule, for example, a molecule having a molecular weight less than 1,000 daltons, preferably less than 800 daltons, and most preferably less than 500 daltons. In further preferred embodiments, the anti-neoplastic agent and the linking group together have a molecular weight of from about 100 to about 2000 daltons, or 250 to about 1500 daltons, or 300 to about 1250 daltons, or 400 to about 1000 daltons.

In particular, the attached anti-neoplastic agent is preferably an agent that kills dividing cells; arrests cell division, or prevents metastasis.

More particularly, the terms "anti-neoplastic agent" and "anti-cancer agent" refer to a compound that prevents, kills, or blocks the growth and spread of cancer cells. The term is inclusive of those agents that are considered alkylating agents, intercalating agents, antimetabolites, radionuclides, metal poisons, enzyme inhibitors, microtubule "inhibitors" and the like.

For obvious reasons, the choice of the anti-neoplastic agent may be operated with respect to the kind of cancer to be treated.

Thus, the methods and compounds of the present invention can be used to treat the most common cancers, including but not limited to bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head and neck cancer, leukemia, lung cancer, lymphoma, melanoma, non-small cell lung cancer, ovarian cancer, and prostate cancer.
In particular, the methods and compounds of the present invention can also be used to treat cancers that have originated in or metastasized to the bone, brain, breast, digestive and gastrointestinal systems, endocrine system, eye, genitourinary tract, germ cells, gynecological system, head and neck, hematologic system, blood, lung, respiratory system, thorax, musculoskeletal system, and skin.

The compounds of the present invention are generally applicable to all cancers but have particularly significant therapeutic benefit in the treatment of solid tumors, which are characterized by extensive regions of hypoxic tissue.

Thus, an agent like cyclophosphamide, doxorubicin and vincristine (CAV); etoposide and cisplatin (VP-16); and cyclophosphamide, doxorubicin and VP-16 (CAVP-16) has been reported for small cell lung cancer.

The most active drugs in the treatment of ovarian cancer have been alkylating agents or cross-linking agents, including cyclophosphamide, ifosfamide, melphalan, chlorambucil, thiopeta, cisplatin, and carboplatin.

The agents studied most extensively for treating prostate cancer are estramustine phosphate, predniniustine, and cisplatin.

Additionally, conjugates with 5-fluorouracil, camptothecin and camptothecin analogs are particularly useful for the treatment of colon cancer.

Microtubule "inhibitors," which may inhibit either microtubule assembly or disassembly, useful in the practice of the present invention include but are not limited to vincristine (Oncovin), vinblastine (Velban), pacUtaxel (Taxol, Paxene), vinorelbine (Navelbine), docetaxel (Taxotere), epothilone B or D or a derivative of either, and discodermolide or its derivatives.

Nitrosoureas useful in the practice of the present invention include but are not limited to 2-chloroethylNitrosourea, procarbazine (Matuala), lomustine, CCNU (CeeBU), carraustine (BCNU, BiCNU, Gliadel Wafer), and estramustine (Emcyt).

Nucleoside analogs useful in the practice of the present invention include but are not limited to mercaptopurine, 6-MP (Purinethol), fluorouracil, 5-FU, (fluorouracil) (Adrucil), thioguanine, 6-TO (Thioguanine), hydroxyurea (Rydrea), cytarabine (Cytosar-U, DepoCyt), floxuridine (FUDR), fludarabine (Fludara), pontostatin (Nipent), cladribine (Leustatin, 2-CdA), geracitabine (Gemzar), and capecitabine (Xeloda).
Therefore, the previous agents or derivatives thereof may be efficiently conjugated with 2-FDG according to the instant invention, for enhancing their uptake by cancer cells.

More particularly, the compounds according to the invention includes an anti-neoplastic agent selected among chlorambucil, nitrosoureas, and in particular 2-chloroethyl nitroso urea, cisplatin, carboplatin, fluorouracil, and their derivatives and is preferably chlorambucil or a derivative thereof.

The compounds of formula (I) can comprise one or more asymmetrical carbon atoms. They can thus exist in the form of enantiomers or of diastereoisomers. These enantiomers, diastereoisomers, as their mixtures, including the racemic mixtures form part of the invention.

The compounds of the invention may exist in the form of free bases or of addition salts with pharmaceutically acceptable acids.

Suitable pharmaceutically acceptable salts of compounds of formula (I) include base addition salts and where appropriate acid addition salts. Suitable physiologically acceptable base addition salts of compounds of formula (I) include alkali metal or alkaline metal salts such as sodium, potassium, calcium, and magnesium salts, and ammonium salts, formed with amino acids (e.g. lysine and arginine) and organic bases (e.g. procaine, phenylbenzylamine, ethanolamine diethanolamine and N-methyl glucosamine).

Suitable acid addition salts may be formed with organic acid and inorganic acids e.g. hydrochloric acid.

The compounds of formula (I) and or salts thereof may form solvates (e.g. hydrates) and the invention includes all such solvates.

More specifically, the instant invention is also directed to the following compounds:

3,4,6-tri-O-acetyl-4-{4-[bis(2-chloroethyl)amino]phenyl}butyrate]-2-deoxy-2-fluoro-αβ-D-glucopyranose (14a),

3,4,6-tri-O-i2yle-1-{4-[4-bis(2-chloroethyl)arnino3phenyl]butyrate]-2-deoxy-2-fluoro-αβ-D-glucopyranose (14b),

1-{4- [bis(2-chloroethyl)amino]phenyl}butyrate]-2-deoxy-2-fluoro- αβ-D-glucopyranose (14c).
N-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl)-4-{4-[bis(2-chloroethyl)amino]phenyl}butanamide (15a),
4-4-[bis(2-chloroethyl)amino]phenyl]-N-(2-deoxy-2-fluoro-β-D-glucopyranosyl)butanamide (15b),
N-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl)-4-{4-[bis(2-chloroethyl)amino]phenyl}butanamide (15a),
N-[3-(4-[bis(2-chloroethyl)amino]phenyl)propyl]urea (17a),
N-[3-(4-[bis(2-chloroethyl)amino]phenyl)propyl]-N'-2-deoxy-2-fluoro-β-D-glucopyranosyl)urea (17b),
N-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl)-4-{4-[bis(2-chloroethyl)amino]phenyl}butanamide (20a),
4-{4-[bis(2-chloroethyl)amino]phenyl]-N-[2-(2-deoxy-2-fluoro-β-D-glucopyranosylamino)-2-oxoethyl]butanamide (20b),
N-[2-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylamino)-2'-oxoethyl]-4-[bis(2-chloroethyl)amino]phenyl]butanamide (21a),
4-{bis(2-chloroethyl)amino]phenyl}]-N-[2-(2-deoxy-2-fluoro-β-D-glucopyranosylamino)-2-oxoethyl]butanamide (21b),
N-[4-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylamino)-4-oxobuty]]-4-[bis(2-chloroethyl)amino]phenyl]butanamide (22a),
4-{bis(2-oliloro6thyl)amino]phenyl}]-N-[4-(2-deoxy-2-fluoro-β-D-glucopyranosylamino)-4-oxobuty]butanamide (22b),
N-[3-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylamino)-3-oxopropyl]-4-[bis(2-chloroethyl)amino]phenyl]butanamide (31a),
4-[bis(2-chloroethyl)amino]phenyl]-N-[3-(2-deoxy-2-fluoro-β-D-glucopyranosylamino)-3-oxopropyl]butanamide (31b),
N-[4-(4-[bis(2-chloroethyl)amino]phenyl]butanoyloxy)phenyl]-3,4,6-t β-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranosylamine (34a),
N-[4-(4-[bis(2-chloroethyl)amino]phenyl]butanoyloxy)phenyl]-2-deoxy-2-fluoro-β-D-glucopyranosylamine (34b),
N-[4-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylamino)phenyl]-4-{4-[bis(2-chloroethyl)amino]phenyl]butanamide (37a),
N-[4-(2-deoxy-2-fluoro-β-D-glucopyranosylamide)phenyl]-4-[bis(2-chloroethyl)amino]phenyl]butanamide (37b),
The following compounds are particularly advantageous:

N-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-p-D-glucopyranosyl)-4-(4-{4-[bis(2-chloroethyl)amino]phenyl}butanamido)benzamide (20a),

4-(4-{4-[bis(2-chloroethyl)amiino]phenyl}butanamido-N-(2-deoxy-2-fluoro-β-D-glucopyranosyl)benzamide (20b),

N-[2-(3,4,6-tri-0-acetyl-2-deoxy-2-fluoro-p-D-glucopyranosylamino)-2-oxoethyl]-4-{4-[bis(2-chloroethyl)amino]phenyl}butanamide (21a),

4-{4-[bis(2-chloroethyl)amino]phenyl}-N-[2-(2-deoxy-2-fluoro-β-D-glucopyranosylamino)-2-oxoethyl]butanamide (21b),

N-{2-[4-(3,4,6-tri-0-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylamino)phenyl]amino-2-oxoethyl}-4-{4-[bis(2-chloroethyl)arnino]phenyl}butanamide (40a) and

4-{4-[bis(2-chloroethyl)arnino]phenyl} -N{2-[4-(2-deoxy-2-fluoro-β-D-glucopyranosylxy)phenyl]amino-2-oxoethyl}butanamide (40b).

The compounds of general formula (I) may be especially chosen from N-{2-(3,4,6-tri-0-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylamino)-2-oxoethyl}-4-{4-[bis(2-chloroethyl)arnino]phenyl}butanamide and N{2-[4-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylxy)phenyl]amino-2-oxoethyl} -4- {4-[bis(2-chloroethyl)arnino]phenyl}butanamide, and preferably N{2-[4-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylxy)phenyl]amino-2-oxoethyl} -4- {4-[bis(2-chloroethyl)arnino]phenyl}butanamide.

The compounds according to the invention may be obtained by a direct or indirect attachment of the anti-neoplastic agent to the 2-fluoro-2-deoxyglucose or derivatives. The linking chemistry has to be compatible with both the anti-neoplastic agent and the 2-FDG or derivatives and to provide a non releasable attachment between those two components. Indeed, the linkage must be effective for keeping the anti-neoplastic agent into the cancer cells a sufficient time.

Typically X and Y derive from functional groups that are used to interact with and form covaleiit bonds with functional groups in the components of the conjugates i.e. the 2-FDG and the anti-neoplastic agent.
Examples of functional groups prior to interaction include —NH₂, —NHNH₂, -ONH₂, -NH(C(O)NHNH₂), —OH, -CO₂H or -SH. Others suitable bond forming groups are well-known in the literature and can be used to prepare conjugates of the present invention.

One of skill in the art will understand that each of these functional groups can form a covalent linkage to a suitable functional group on the glucose portion or on the anti-neoplasic portion of the conjugate during synthesis of the conjugates.

For example, amino, hydroxy and hydrazino groups can each form a covalent bond with a reactive carboxyl group (e.g., a carboxylic acid chloride or activated ester such as an N-hydroxysuccinimide ester (NHS)).

Thus a possible deoxyglucose moiety for forming the conjugates of the present invention is an amino 2-FDG derivative. This compound has an amino group that provides a chemical handle for conjugations. Anti-neoplasic agent can be conjugated directly to this amino group via alkyl, amide, carbamate or sulfonamide linkages, for example.

In a first embodiment, the anti-neoplasic agent can be attached directly to 2-VDG or derivatives using, for example, an available functional group or the anti-neoplasic agent. Such a function may be also if necessary transformed in a more convenient function for obtaining the desired conjugate.

This embodiment is in particular considered for preparing compounds of formula (I) wherein n is zero and thus of formula (II):

\[
\begin{align*}
\text{with } R_i, R_2, R_3, X \text{ and } Z \text{ being as defined in formula (I).}
\end{align*}
\]

For example, X may be issued from the reaction of an hydroxyl function or an amino function located in position 1 of the 2-FDG with an acid function on the anti-neoplasic agent or from the reaction of an amino function located in position 1 of the 2-FDG with an isocyanate issued from the conversion of a carboxy group on the anti-neoplasic agent.

Such a synthesis is illustrated by the following Schemes 1a, b and c.

The following schemes involve the following compounds as starting materials.
It is noticed that a number of protected glucose compounds or derivatives are commercially available, or can be prepared according to well-established methods. In many instances, the glucose moiety having "n" hydroxy or amino groups, will have "n-1" protecting groups, thereby leaving one available reactive functional group located in position 1 for either the anti-neoplastic agent or a linking group. For the preparation of compounds possessing an ester linkage between the active drug and the anchor point of the carrier, the use of hydroxyl protecting groups others than acetate appeared preferable. Benzyl ethers were privileged.

**Scheme Ia**

**Scheme Ib**
In a second embodiment, a linking group may be used to attach the anti-neoplastic agent covalently to the 2-FDG derivative.

In such embodiment, any of the commercially available bifunctional linking group can be used.

Alternatively, one of skill in the art can construct a linking group having at least two functional group to attach from one hand the 2-FDG and from the other hand the anti-neoplastic agent.

This embodiment, is more particularly concerned with the preparation of compounds of formula (III):

\[
\begin{align*}
\text{Scheme Ic} \\
\begin{array}{c}
\text{2} \\
\text{17a} \\
\text{17b}
\end{array}
\end{align*}
\]

with \( R_1, R_2, R_3, X, Y, \) and \( Z \) being as defined in formula (I).

Typically a linker or linking group has functional groups that are used to interact with and form covalent bonds with functional groups in the components (e.g., anti-neoplastic agents and glucose or glucose derivatives) of the conjugates described and used herein. Examples of functional groups on the linking groups (prior to interaction with other components) include \(-\text{NH}_2, -\text{NHNH}_2, -\text{ONH}_2, -\text{NHC(O)NHNH}_2, -\text{OH, -CO}_2\text{H, and— SH.}\)
Such synthesis is illustrated by the following Schemes 2a, b, c, c1, e and f in the case where Z is chlorambucil or a derivative thereof and by the following scheme 2g, in the case where Z is 2-chloroethylnitrosourea or a derivative thereof.
Scheme 2b

19a : $Q = \text{C}_6\text{H}_4$
19b : $Q = \text{CH}_2\text{NHCbz}$
19c : $Q = (\text{CH}_3)_3\text{N}$

19a : $Q = \text{C}_6\text{H}_4$
19b : $Q = \text{CH}_2$
19c : $Q = (\text{CH}_2)_3$

R = OAc

20a : $Q = \text{C}_6\text{H}_4$
21a : $Q = \text{CH}_2$
22a : $Q = (\text{CH}_2)_3$

R = OH

20b : $Q = \text{C}_6\text{H}_4$
21b : $Q = \text{CH}_2$
22b : $Q = (\text{CH}_2)_3$
Scheme 2c

EtO\text{-}C\text{-}Br \rightarrow EtO\text{-}C\text{-}N\text{₃} \rightarrow EtO\text{-}C\text{-}NH\text{₂}

\rightarrow EtO\text{-}C\text{-}N\text{₃} \rightarrow HO\text{-}C\text{-}H\text{-}C\text{-}H\text{-}C\text{-}Cl

\rightarrow \text{AcO}\text{-}N\text{₃} \rightarrow HO\text{-}O\text{-}N\text{₃} \rightarrow HO\text{-}O\text{-}N\text{₃}

Scheme 2d

HO\text{-}C\text{-}H\text{-}C\text{-}Cl \rightarrow O\text{₂N}\text{-}C\text{-}Cl

\rightarrow H\text{₂}N\text{-}O\text{-}C\text{-}Cl \rightarrow HO\text{-}O\text{-}N\text{₃}

\rightarrow HO\text{-}O\text{-}N\text{₃} \rightarrow HO\text{-}O\text{-}N\text{₃}
In Schemes 2a and 2b, the linking group firstly interacts with a free amino function of a 2-FDG derivative. The so-obtained coupling product, if necessary, is then activated to obtain a function able to interact with the carboxylic function of chlorambucil to lead to the expected conjugate of formula (III).

In Schemes 2c and 2d, the linking group firstly interacts with the anti-neoplastic agent, i.e. the chlorambucil and then its 2\textsuperscript{nd} function is activated for forming a covalently link with a free amino function or bromide of a 2-FDG derivative.

The following Examples illustrate in detail the preparation of some compounds according to the invention, and more particularly compounds chosen among compounds (14) to (76) and of formula (I).

The figures 1 present the CTW time course of B16 melanoma obtained for compounds 21a, 40a and chlorambucil administered at the MTD dosage (figure Ia) and 0.75 MTD dosage (figure Ib).

The figure 2 presents the CTW time course of CT 26 colon carcinoma cells obtained for compounds 21a, 40a and chlorambucil.

**EXPERIMENTAL PART**

All solvents and reagents obtained from commercial sources were used without further purification. Nuclear magnetic resonance spectra (IH NMR and 13C NMR) were performed on a Bruker AM 200, 400 or 500 spectrometer. Chemical shifts are reported in parts per million relative to the internal tetramethylsilane standard for IH NMR and the solvent for 13C NMR (acetone-d\textsubscript{6}, δ = 29.8 ppm; DMSO-d\textsubscript{6}, s = 39.5 ppm; CDC\textsubscript{13}, δ = 77.2 ppm) The abbreviations used for signal patterns are: br, broad; s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; td, doublet of triplets; q, quadruplet; qt, quintuplet; m, multiplet. Coupling constants (J values) are given in Hertz. Infrared (IR) spectra were recorded on a FTIR-Nicolet Impact 410 spectrophotometer, Melting points were determined on an Electrothermal digital apparatus (Reichert) and were uncorrected. Medium-pressure column chromatography was carried out on silica gel 60 (Chroinagel, 35-70 µm, SDS) using the indicated solvent mixture expressed as volume/volume ratios. Analytical thin-layer chromatography (TLC) was conducted on precoated silica gel plates (SDS, 60 F254, 0.2 mm thick) with both detection
by ultraviolet light and/or visualization with vanillin in sulfuric acid. Mass spectra were recorded on a Bruker Esquire-LC spectrometer, Electrospray ionization mass spectrometry (ESI-MS) was used in positive mode.

1,3,4,5-tetra-O-acetyl-2-deoxy-2-fluoro-\(\beta\)-D-glucopyranose 5 and its derivatives 6-13 (following Scheme 3) are the key intermediates for all the syntheses in which chlorambucil bonds directly or via a spacer to C-1 of the sugar moiety.

Scheme 3

\[ \text{3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-\(\beta\)-D-glucopyranosyl azide (7).} \]

A cold (0°C) solution of sodium azide (1.76 g, 27.1 inmol) in water (25 mL) is added dropwise, in 20 min, to 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-\(\alpha\)-D-glucopyranosyl
bromide 6 (2.51 g, 6.76 mmol), dissolved in acetone (30 mL). After stirring at room temperature, for 1 h, the white precipitate is filtered, thoroughly washed with water and dried under vacuum to offer azide 7 (1.88 g, 84%) as a white powder. The crystalline material was sufficiently pure (the, 1H NMR) and was used without recrystallization for the next step:

$$\text{C}_{12}\text{H}_4\text{dF}_3\text{NO}_7$$

$$M = 333.27 \text{ g mol}^{-1}$$

mp 135 °C

3.4.6-tri-0-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl amine (S).

10% Platinum on charcoal (400 mg) was added to a solution of azide 7 (1.99 g, 5.98 mmol) in THF/MeOH (55/55 mL), and the suspension was shaken with hydrogen gas for 1 h at atmospheric pressure and room temperature. After filtration of the suspension on celite, the filtrate was evaporated to dryness to provide amine 8 (1.80 g, 98%) as a white solid:

$$\text{C}_{12}\text{H}_8\text{FNO}_7$$

$$M = 307.28 \text{ g mol}^{-1}$$

mp 110 °C

3.4.6-tri-0-acetyl-1'-deoxy-2-fluoro-α,β-D-glucopyranose (9).

This compound (443 mg, 1.43 mmol) was prepared as a mixture of α- and β-anomers (57/43), according to the procedure described by Tai et al. (Bioorg. Med Chem. 2001, 9, 1133-1140), starting from tetraacetate 5 (500 mg, 1.43 mmol):

$$\text{C}_{12}\text{H}_{12}\text{FO}_8$$

$$M = 308.26 \text{ g mol}^{-1}$$

quantitative yield

Ethyl 3.4.6-tri-O-aceM^−deoxy^−fluoro-B-D-thioelucopyranoside (10).

This compound (2.95 g, 8.38 mmol) was prepared according to the procedure described by McCarter et al. (J. Am. Chem. Soc. 1997, 119, 5792-5797), starting from bromide 6 (3.59 g, 9.6 mmol):

$$\text{C}_{14}\text{H}_2\text{FO}_7\text{S}$$
yield 87%;
mp 125°C

5  Eth\(^3\)l 3,4,6-tri-0-benzyl-2-deoxy-2-fluoro-B-D-thioglucopyranoside (1D).

To a stirred solution of acetylated compound 10 (1.20 g, 3.41 mmol) in methanol (12 mL) was added sodium methoxide (54 mg, 1.02 mmol). After 1 h at room temperature, the mixture was evaporated to dryness. The remaining residue was dissolved in DMF (8 mL) and cooled in an ice cold bath, before the addition of NaH (60% dispersion in mineral oil, 613 mg, 15.3 mmol). The stirring was maintained until return to room temperature. Benzyl bromide (2.43 mL, 20.5 mmol) and potassium iodide (55 mg, 0.34 mmol) were added and the mixture was heated overnight at 60°C. After cooling, MeOH (0.5 mL) followed by water (50 mL) were added and the mixture was extracted twice with CH\(_2\)Cl\(_2\). The combined organic layers were washed with water (30 mL), dried over MgSO\(_4\) and evaporated in vacuo. The crude product was purified by silica gel chromatography (9:1 petroleum benzine: ethyl acetate), to give syrupy compound 11 (1.03 g, 61%):

\[
\text{C}_{29}\text{H}_{33}\text{FO}_{4}\text{S}
\]
\[M = 496.64 \text{ g.mol}^{-1}\]

10  3,4,6-tri-0-benzyl-2-deoxy-2-fluoro-\(\alpha\)-D-glucopyranosyl bromide (12).

This compound (1.08 g, 2.09 mmol) was prepared according to the procedure described by McCarter et al., starting from benzylated ethyl thioglycoside 11 (1.45 g, 2.92 mmol). Purification on a column of silica gel, eluting with CH\(_2\)Cl\(_2\), provided benzylated bromide 12 as an oil in 72% yield:

\[
\text{C}_{27}\text{H}_{38}\text{BrFO}_{4}
\]
\[M = 515.42 \text{ g.mol}^{-1}\]

15  3,4,6-tri-0-benzyl-2-deoxy-2-fluoro-\(\beta\)-D-glucopyranose (13).

To a solution of bromide 12 (1.08 g, 2.01 mmol) and water (0.1 mL, 0.56 mmol) in acetone (10 mL), was added, with stirring at 0°C, silver carbonate (635 mg, 2.3 mmol) in small portions. After stirring for 2 h at room temperature, the mixture was heated to 60°C for 1 h and filtered through celite. Removal of solvent and purification by silica
chromatography with cyclohexane:ethyl acetate (6:4) as mobile phase, afforded compound 13 (578 mg, 61%) as a solid corresponding to a mixture of α- and β-anomers (85/15):

\[ C_{27}H_{32}FO_{5} \]

\[ M = 452.52 \text{ g·mol}^{-1} \]

The reaction of 8, 9 and 13 with chlorambucil, activated by the N,N-dicyclohexylcarbodiimide (DCC) procedure, using either 4-(N,N-dimethylamino)pyridine (DMAP) or hydroxybenzotriazole (HOBt), gave the corresponding esters 14 and amides 15.

Example 1

CHCl3 (360 mg, 1.07 mmol) in CH2Cl2 (50 mL), chlorambucil (490 mg, 1.61 mmol), DCC (376 mg, 1.78 mmol) and DMAP (8.7 mg, 0.071 mmol) were added and stirred at room temperature for 22 h. The solid was removed by filtration, and the filtrate was washed consecutively with an aqueous solution of acetic acid and water, and dried over MgSO4, and concentrated under vacuum. The resulting residue was purified by silica gel chromatography, using cyclohexane: ethyl acetate (7:3) as eluent, to yield 14a (360 mg, 57%) as a syrup (α/β ratio = 25/75):

\[ C_{35}H_{34}Cl_{2}FNO_{9} \]

\[ M = 594.46 \text{ g·mol}^{-1} \]

Rf= 0.38 (cyclohexane:ethyl acetate 6:4)

IR (CCl4 solution) ν 1763 (vC=O), 1366 (δC=CH3), 1240, 1223, 1075, 1038 (vC=O) cm⁻¹;

1H NMR (200 MHz, CDCl₃) δ 7.12 (d, 2H, J₀ = 8.7 Hz, Hₐ₀), 7.10 (d, 2H, J₀ = 8.7 Hz, H₀), 6.69 (d, 2H, Hₐβ), 6.67 (d, 2H, H₀), 6.50 (d, 2H, Hₐβ), 5.85 (dd, 1H, J₁₂ = 8.1 Hz, J₁ = 3.1 Hz, H₁), 5.60 (td, 1H, J1β = J₃α = 9.6 Hz, J₃α = 12.1 Hz, H₃α), 5.43 (td, 1H, J₃α = J₃ = 9.2 Hz, J₃ = 14.2 Hz, H₃β), 5.14 (t, 1H, J₄δ = 9.8 Hz, H₄δ), 5.12 (t, 1H, J₄δ = 9.7 Hz, H₄β), 4.70 (ddd, 1H, J₂β = 48.6 Hz, H₂α), 4.49 (td, 1H, J₂β = 51.1 Hz, H₂β), 4.40-4.30 (m, 2H, H₆aa, H₆aβ), 4.16-4.04 (m, 3H, H₆bct,
H-6b β, H-5 α), 3.90 (ddd, IH, H-5 β), 3.75-3.64 (m, 16H, N(CH₂CH₂Cl)₂ α + β), 2.62 (m, 4H, CH₂Ph α + β), 2.48 (m, 4H COCH₂ α + β), 2.10-1.94 (m, 22H, OAc, CH₂CH₂CH₂ α + β);

13C NMR (50 MHz, CDCl₃) δ 171.55, 171.38, 170.59, 170.18, 169.94, 169.61, 169.54 (CO α + β); 144.63, 144.59 (C₆N α + β), 130.31, 130.16 (S₆CH₂ α + β), 129.91, 129.87, 112.35 (CH₆ α + β), 91.30 (C-1 β, J = 24.1 Hz), 88.39 (C-2 β, J₂F = 190.9 Hz), 88.31 (C-1a, J₁F = 22.2 Hz), 86.40 (C-2a, J₂P = 193.7 Hz), 72.90 (C-5 β), 72.87 (C-3 β, J₃F = 19.4 Hz), 70.73 (C-3a, J₃P = 19.4 Hz), 69.71 (C-5a), 67.76 (C-4a/ β, J₄F = 7.2 Hz), 65.47 (C-4a/ β, J₄P = 7.6 Hz), 61.46 (C-6 a + β), 53.75 (CH₂N a + β), 40.57 (CH₂Cl a + β), 33.82, 33.31 (CH₂Ph a + β, COCH₂ a + β), 26.54, 26.46 (CH₂CH₂CH₂ a + β), 20.78, 20.72, 20.64 (CH₃ a + β);

MS (ESI) m/z 594.24 [M+1]+.

Example 2

3,4,6-tri-O-benzyl-1-f4-(4-[bis(2-chloroethyl)amino]dihexylbutyrate)-2-deoxy-2-fluoro-6-D-glucopyranose (14b) (see scheme 1a).

To a solution of 3,4,6-tri-O-benzyl-2-deoxy-2-fluoror-α,β-D-glucopyranose 13 (200 nig, 0.44 mmol) in CH₂Cl₂ (5 mL), chlorambucil (201 mg, 0.66 mmol), DCC (136 mg, 0.66 mmol) and DMAP (5 mg, 0.044 mmol) were added and stirred 17 h at room temperature. The solid was removed by filtration, and the filtrate was concentrated under vacuum. The resulting residue was purified by silica gel chromatography, using cyclohexane:ethyl acetate (85:15) as mobile phase, to yield 14b (319 mg, 98%) as a syrup (∆/β ratio = 70/30):

C₇H₁₂Cl₂FNO₆

M = 738.72 g.mor⁻¹

Rf = 0.33 (petroleum benzene:ethyl acetate 85:15)

IR (NaCl) ν 3064, 3031 (νC=O), 1754 (νC=O), 1117, 1052, 1027 (νC=O) cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 7.38-7.15 (m, 30H, HAT), 7.10 (d, 4H, Jα = 8.5 Hz), 7.26 (d, 2H, Jα = 8.0 Hz, Hα α), 6.74 (d, 2H, Jα = 3.9 Hz, H-1 α), 5.73 (dd, IH, J₁F = 3.1 Hz, J₁F = 8.1 Hz, H-1 β), 4.91 (d, IH, Jα = 11.1 Hz, OCH₂Ph α + β), 4.86 (d, IH, Jα = 10.5 Hz, OCH₂Ph α), 4.84 (d, IH, OCH₂Ph β), 4.78 (d, IH, Jα = 11.1 Hz,
Hz, OCH₂Ph ω), 4.77 (d, IH, J = 11.2 Hz, OCH₂Ph β), 4.67 (ddd, IH, J₂,3 = 9.3 Hz, J₂,F = 48.8 Hz, H-20), 4.62 (d, IH, J = 11.3 Hz, OClbPh β), 4.61 (d, IH, J = 12.3 Hz, OCH₂Ph ω), 4.52 (d, 2H, J = 10.7 Hz, OCH₂Ph α+β), 4.50 (d, 1H, J = 12.1 Hz, OCH₂Ph ω), 4.48 (d, IH, J = 11.9 Hz, OCH₂Ph β), 4.48 (td, IH, J₂,3 = 8.2 Hz, J₂,F = 51.1 Hz, H-2 β), 4.06 (td, IH₃J₃,F = 9.0 Hz, J,F = 12.3 Hz, H-3 ω), 3.86-3.61 (m, 25H, H-3 β, H-4 α+β, H-5 α+β, H-6 α+β, N(CH₂CH₂Cl)₂ α+β), 2.62-2.58 (m, 4H, CH₂CH₂Ph α+β), 2.45-2.38 (m, 4H, COCH₂ α+β), 1.94 (qt. 4H, J = 7.5 Hz, CH₂CH₂CH₂ α+β);

¹³C NMR (50 MHz, CDCl₃) δ 171.97, 171.70 (CO α+β), 144.42 (CA N α+β), 138.23, 137.92 (C₆H₄ α+β), 130.58 (CA₂CH₂ α+β), 129.84, 128.55, 128.14, 128.03, 112.45 (CH₄ α+β), 92.21 (C-2 β, J₂,F = 187.4 Hz), 91.59 (C-1 β, J₁,F = 24.6 Hz), 90.27 (C-2 α, J₂,F = 190.6 Hz), 89.23 (C-1 α, J₁,F = 22.7 Hz), 83.21 (C-3 β, J₃,F = 16.0 Hz), 80.66 (C-3 α, J₃,F = 16.0 Hz), 76.25 (C-4 α+β, J₄,F = 8.8 Hz), 75.79 (C-5 β), 75.55, 75.27, 75.20, 75.17, 73.69 (OCH₂Ph α+β), 72.79 (C-5 α), 67.98 (C-6 α+β), 53.77 (CH₂N α+β), 40.57 (CH₂Cl α+β), 33.88, 33.59, 33.47 (CH₂CH₂Ph α+β), COCHl₂ α+β), 26.60 (CH₂CH₂CH₂ α+β).

Example 3

1|4-(4-tbis(2-chloroethyl)amiP 04phen'g)butyratet-2-deoxy-2-fluoro-α,β-D-fslucopyranose (14c) see scheme 1a).

To a suspension of 10% palladium on charcoal (1.5 g) in THF/EtOH (12/24 mL) was added the benzylated glycoside 14b (1.78 g, 2.41 mmol), followed by ammonium formate (850 mg, 13.5 mmol). The mixture was refluxed for 3.5 h and then allowed to cool to room temperature, filtered on celite, and concentrated under vacuum. The crude product was purified by silica gel chromatography, eluting with cyclohexane: ethyl acetate (1:9), to yield the dcbenzylated product 14c (400 mg, 35%) as a brown oil (α/β ratio = 55/45):

C₂₀H₂₈Cl₂FNO₆

M = 468.35 g·mol⁻¹

RF= 0.49 (cyclohexane:ethyl acetate 1:9)

IR(NaCl) ν 3418 (ν'O), 1738 (ν'c=αι), 1078 (ν'c-αι) cm⁻¹;

¹H NMR (200 MHz, acetone-d₆) δ 7.18 (d, 4H, J₀ = 8.7 Hz, H₆, α+β), 6.81 (d, 4H, H₆, α+β), 6.41 (d, IH, J₁,ω = 3.9 Hz, H-1 ω), 5.85 (dd, IH, J₁,ω = 8.1 Hz, J₁,F = 3.1 Hz, H-1 β), 5.02 (br s, IH, OH), 4.90 (br s, IH, OH), 4.71 (br s, IH, OH), 4.53 (ddd, IH, J₂,=
9.4 Hz, $J_{2F} = 48.7$ Hz, H-2α), 4.25 (td, IH, $J_{2,3} = 8.5$ Hz, $J_{2,7} = 52.0$ Hz, H-2β), 4.19-3.49 (m, 26H, N(CH$_2$CH$_2$)$_2$ α+β, H-3 α+β, H-4 α+β, H-5 α+β, 2H-6 α+β), 2.65 (t, 4H, $J = 7.6$ Hz, CH$_2$Ph α+β), 2.55-2.41 (m, 4H, COCH$_2$ α+β), 2.00-1.93 (m, 4H, CH$_2$CH$_2$CH$_2$ α+β);

$^{13}$C NMR (50 MHz, acetone-<sup>-</sup>D<sub>6</sub>) δ 171.86, 171.81 (CO α+β), 145.25 (CA$_4$N α+β), 130.57 (CA$_4$CH$_2$ α+β), 129.96, 112.70 (CH$_{Ar}$ α+β), 92.02 (C-2β, $J_{2F} \approx 184.2$ Hz), 92.00 (C-1β, $J_{1F} = 21.7$ Hz), 89.88 (C-2α, $J_{2F} = 184.5$ Hz), 89.47 (C-1α, $J_{1F} = 22.6$ Hz), 78.00 (C-5β), 75.43 (C-3β, $J_{3F} = 16.6$ Hz), 75.18 (C-5α), 72.51 (C-3α, $J_{3F} = 16.8$ Hz), 70.44 (C-4α/β, $J_{4F} = 8.0$ Hz), 70.16 (C-4α/β, $J_{4F} = 8.1$ Hz), 61.62, 61.57 (C-6 α+β), 53.47 (CH$_2$N α+β), 41.20 (CH$_2$Cl α+β), 33.99, 33.92, 33.58, 33.37 (CH$_2$Ph α+β, COCH$_2$ α+β), 27.20, 27.05 (CH$_2$CH$_2$CH$_2$ α+β).

MS (ESI) nVz 468.54 [M+I<sup>+</sup>].

**Example 4**

N-(3,4,7-tiy-0-4,1-ddeoxy-2-fluoro-β-D-glucopyraQβ-syl)-4-14-fbis(2-cjlk>roethyl)$\text{a}$ πiinol phenyl) butanamide (I 5α; see scheme Iib).

Amino-sugar 8 (189 mg, 0.61 mmol) was dissolved in anhydrous DMF (10 mL) and chlorambucil (187 mg, 0.61 inmol), DCC (127 mg, 0.61 mmol), and HOBT (92 mg, 0.67 mmol) were added. The solution was stirred for 20 h at room temperature, filtered, concentrated in vacuo, and purified by silica gel chromatography (cyclohexane:ethyl acetate 6:4) to give 15a (184 mg, 51%) as a white solid:

C$_{26}$H$_{35}$Cl$_2$F$_2$N$_2$O$_8$

M = 593.48 g mol$^{-1}$

Rf= 0.25 (cyclohexane:ethyl acetate 6:4)

IR (KBr) v 3327 (v$_{NH}$), 1750 (v$_{C=O}$carboxyl), 1676 (v$_{O}$amide), 1520 (v$_{NH}$), 1244, 1069, 1032 (v$_{C-O}$) Cm$^{-1}$;

$^1$H NMR (200 MHz, CDCl$_3$) δ 7.08 (d, 2H, $J_{o} = 8.6$ Hz, H$_{\beta}$); 6.69 (d, 2H, H$_{\beta}$), 6.04 (d, 1H, $J = 9.3$ Hz, NH), 5.44-5.28 (m, 2H, H-3, H-1), 5.03 (t, 1H, $J_{3,4} = J_{4,5} = 9.7$ Hz, H-4), 4.31 (dd, 1H, $J_{5}=4.4$ Hz, $J_{6b,6a} = 12.5$ Hz, H-6a), 4.26 (td, 1H, $J_{2,3} = 50.8$ Hz, J$_{i_{2}}$ = J$_{2,3} = 9.2$ Hz, H-2), 4.06 (dd, 1H, $J_{i_{5,6}} = 2.0$ Hz, H-6b), 3.86 (ddd, 1H, H-3), 3.76-3.58 (m,
8H, N(CH$_2$CH$_2$Cl)$_2$, 2.58 (t, 2H, J = 7.3 Hz, CH$_2$Ph), 2.25 (t, 2H, J = 7.3 Hz, COCH$_2$), 2.08, 2.07, 2.04 (each s, 3*3H, OAc), 1.94 (m, 2H, CH$_2$CH$_2$CH$_2$);

$^{13}$C NMR (50 MHz, CDCl$_3$); $\delta$ 173.24, 170.68, 169.92, 169.85 (CO), 144.14 (C$_2$N), 131.00 (C$_6$CH$_2$), 129.88, 112.70 (CH$_2$), 88.50 (C-2, J$_{F}$ = 191.2 Hz), 77.62 (C-I), 73.78 (C-5), 73.50 (C-3, J$_{3F}$ = 19.3 Hz), 67.93 (C-4, J$_{4F}$ = 7.0 Hz), 61.65 (C-6), 53.89 (CH$_2$N), 40.45 (CH$_2$Cl), 35.68 (COCH$_2$), 33.89 (CH$_2$Ph), 26.77 (CH$_2$CH$_2$CH$_2$), 20.82, 20.76, 20.70 (CH$_3$);

MS (ESI) m/z 593.30 [MH-I]$^+$.

Example 5

4-{(bis(2-chloroethyl)amino)1,4-benzodioxin-2-yl}-(2-deoxy-2-fluoro-D-glucopyranosyl)B-1-Pbutapamide (15b) (see scheme Ib).

To a stirred solution of acetylated compound 15a (140 mg, 0.24 mmol) in methanol (7 mL) was added sodiura methoxide (1 mg). After 4 h at room temperature, the mixture was evaporated to dryness and purified on silica gel (10:90 iodo, 0:100 cyclohexane;ethyl acetate gradient) to afford 15b (63 mg, 57%) as a solid:

C$_{20}$H$_{29}$Cl$_2$FN$_2$O$_5$

M = 467.37 g.mol$^{-1}$

mp 168$^\circ$C

Rf = 0.11 (cyclohexane;ethyl acetate 1:9)

IR(KBr) $\nu$ 3310 (v$_{NH}$, VOH), 1655 (v$_{CO}$), 1519 (v$_{NH}$), 1092, 1057 (v$_{C-O}$) cm$^{-1}$;

$^1$H NMR (200 MHz, acetone-d$_6$); $\delta$ 7.81 (d, IH, J = 9.1 Hz, NH), 7.06 (d, 2H, J$_0$ = 8.8 Hz, H$_2$A), 6.70 (d, 2H, H$_2$A), 5.19 (td, IH, J$_{IH}$ = J$_{N_H}$ = 9.2 Hz, J$_{IH}$ = 2.3 Hz, H-I), 4.77 (d, IH, J = 4.4 Hz, OH), 4.39 (br s, IH, OH), 4.06 (td, IH, J$_{23}$ = 9.0 Hz, J$_{24}$ = 50.9 Hz, H-2), 3.80-3.58 (m, 12H, N(CH$_2$CH$_2$Cl)$_2$, 2H-6, H-3, H-4), 3.63-3.32 (m, 2H, OH, H-5), 2.51 (t, 2H, J = 7.6 Hz, CH$_2$Ph), 2.21 (t, 2H, J = 7.9 Hz, COCH$_2$), 1.84 (qt, 2H$_5$ CH$_2$CH$_2$CH$_2$);

$^{13}$C NMR (50 MHz, acetone-d$_6$); $\delta$ 173.47 (NHCO), 145.55 (C$_5$N), 131.43 (C$_6$CH$_2$), 130.36, 113.07 (CH$_{Ar}$), 92.42 (C-2, J$_{2F}$ = 183.6 Hz), 79.10 (C-5), 78.06 (C-I, J$_{1F}$ = 23.2 Hz), 76.76 (C-3, J$_{3F}$ = 16.8 Hz), 71.51 (C-4, J$_{4F}$ = 7.7 Hz), 62.47 (C-6), 53.89 (CH$_2$N)$_2$ 41.62 (CH$_2$Cl), 36.02 (COOH$_2$), 34.70 (CH$_2$Ph), 28.07 (CH$_2$CH$_2$CH$_2$);

MS (ESI) m/z 467.15 [MH-I]$^+$. 
The acetylated compound 17a was obtained from chlorambucil in two steps comprising the formation of the isocyanate 16 and its reaction with 3-amino-sugar 8.

**Example 6**

**N-f3,4,6-tri-O-acetyl-2-deoxy-1-fluoro-B-D-glucopyranosyl N'-[3-(4-**

N-hydroxyethyl)amino-phenyl]propylurca (17a) (see scheme 1c).

a) **N-thiophenylhydroxyethyl]-4-(3-isocyanatopropyl)phenylamitite (16)**

This compound was prepared according to the procedure described by Valu et al. (*J. Med. Chem.*, 1990, 33, 3014-3019) to a solution of chlorambucil 2 (500 mg, 1.65 mmol) in acetone (6 mL) cooled to -5°C, was added dropwise NEt$_3$ (0.25 mL, 1.81 mmol). Then the solution was treated with ethylchloroformate (0.17 mL diluted in 2 mL acetone, 1.81 mmol) and ten minutes later, sodium azide (0.21 g, 3.23 mmol) in 1 ml water was added. Stirring is maintained in an ice cold bath for 30 min, then the mixture was poured into ice water (300 mL) and extracted with toluene (2 x 120 mL). The combined, dried, organic layers were heated under reflux for 1.5 h. After evaporation of the solvent under reduced pressure, compound 36 (400 mg, 81%) was obtained as an orange-coloured oily liquid, directly used for the next step.

C$_{16}$H$_{18}$Cl$_2$N$_2$O

M = 301.21 g mol$^{-1}$

Rf$= 0.30$ (petroleum benzine:ethyl acetate 4:6)

IR (NaCl) $v$ 2276 ($v$N=N=O) cm$^{-1}$;

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.07 (d, 2H$_3$J$_D$ = 8.7 Hz, H$_A$), 6.64 (d, 2H, H$_B$), 3.76-3.58 (m, SH, N(CH$_2$CH$_2$Cl)$_2$), 3.30 (t, 2H, $J = 6.6$ Hz, CH$_2$NCO), 2.63 (t, 2H, $J = 7.4$ Hz, CH$_2$Ph), 1.88 (q, 2H, CH$_2$CH$_2$CH$_2$);

$^1$C NMR (50 MHz, CDCl$_3$) $\delta$ 144.58 (CO), 129.76, 112.37 (CHA), 53.67 (QH$_2$N), 42.22, 40.59 (CH$_2$Cl, C$_{3}$H$_2$NCO), 32.92, 31.49 (CH$_2$Ph, CH$_2$C$_{3}$H$_2$CH$_2$).

b) **N-(3,4,6-trrt-0-acetyl-2-deoxy-1-fluoro- 3-(4-[bis(2-chloroethyl)aminophenyl] propyl)urca (17a)**

To amino-sugar 8 (200 mg, 0.65 mmol) dissolved in CH$_2$Cl$_2$/THF (1.5/2 mL) was added isocyanate 16 (215 mg, 0.72 mmol) in CH$_2$Cl$_2$ (0.5 mL), and the mixture was
stirred overnight at room temperature. After evaporation of the solvent, the concentrate
was purified by column chromatography on silica gel with ethyl acetate:methanol (6:4 to 7:3 gradient) as developing solvent to give compound 17a (200 mg, 50%) as a red powder:

\[ \text{C}_{20}\text{H}_{30}\text{OCl}_2\text{F}_7\text{N}_3\text{O}_8 \]

\[ M = 608.49 \text{ g/mol} \]

\[ \text{Rdt} = 50 \% \]

\[ \text{mp} 91^\circ\text{C} \]

\[ \text{Rf= 0.40 (petroleum benzine:ethyl acetate 4:6)} \]

**1H NMR** (200 MHz, CDCl₃) \( \delta \) 7.06 (d, 2H, \( J_\beta = 8.6 \text{ Hz, } \text{H}_\delta \)), 6.63 (d, 2H, \( \text{H}_\alpha \)), 5.46-5.23 (m, 2H, \( \text{H}-1, \text{H}-3 \)), 5.01 (t, IH, \( J_{3-4a} = J_{4-3} = 9.7 \text{ Hz, } \text{H}-4 \)), 4.84 (br t, IH, \( J = 5.1 \text{ Hz, } \text{NTiC}_2 \)), 4.33 (dd, IH, \( J_{\text{6,6b}} = 12.5 \text{ Hz, } J_{\text{5,6h}} = 4.3 \text{ Hz, } \text{H}-6a \)), 4.20 (td, IH, \( J_{2-F} = 50.5 \text{ Hz, } J_{\text{1,2} = 9.2 \text{ Hz, } \text{H}-2} \)), 4.06 (dd, IH, \( J_{\text{5,6b}} = 2.1 \text{ Hz, } \text{H}-6b \)), 3.82 (ddd, IH, \( \text{H}-S \)), 3.65 (m, 8H, \( \text{NICH}_2\text{CH}_2\text{Cl}_2 \)), 3.23 (m, 2H, \( \text{NHCH}_2 \)), 2.55 (t, 2H, \( J = 7.4 \text{ Hz, } \text{CH}_3\text{Ph} \)), 2.09, 2.07, 2.05 (each s, 3*3H, OAc), 1.78 (qt, 2H, \( \text{CH}_2\text{CH}_2\text{CH}_2 \));

**13C NMR** (50 MHz, CDCl₃) \( \delta \) 170.76, 170.03, 169.91 (COCH₂), 156.84 (NHEO), 144.43 (C₂N), 130.53 (C₆H₅CH₂), 129.63, 112.29 (CH₃), 88.54 (C-2, \( J_{2-F} = 190.6 \text{ Hz, } \text{H} \)), 79.59 (C-I, \( J_{\text{1,1} = 22.2 \text{ Hz, } \text{H} \)), 73.67 (C-3, \( J_{3,4} = 19.5 \text{ Hz, } \text{H} \)), 73.20 (C-5), 68.15 (C-4, \( J_{\text{4,4'} = 7.1 \text{ Hz, } \text{H} \)), 61.72 (C-6), 53.63 (CH₂N), 40.61 (CH₂Cl), 40.03 (NHCH₂), 31.99, 31.87 (CH₂Ph, CH₃CH₂CH₂), 20.73 (CH₃);

MS (ESI) m/z 608.19 [M+1]⁺.

**Example 8**

N-f3*(4-tbis^2-chloroethyl)aminophenyl>propyl-N²-C2-deoxy-2-fluoro-B-

P-eHCOPyraBPsylDrea (17b) (see scheme lc>.

To a stirred solution of acetylated compound 17a (200 mg, 0.33 mmol) in methanol (12 mL) was added sodium methoxide (2 mg) and the mixture was stirred at room temperature for 3 h. After neutralization with IRC 50 Amberlite ion-exchange resin (H⁺), filtration and evaporation to dryness, the residue was purified on silica gel (10% methanol in ethyl acetate) to yield compound 17b (75 mg, 45%) as an oil:

\[ \text{C}_{20}\text{H}_{30}\text{OCl}_2\text{F}_7\text{N}_3\text{O}_8 \]
M = 482.38 g mol⁻¹

Rf = 0.15 (ethyl acetate:methanol 9:1)

IR (KBr) ν 3348 (νO-H), 1750 (vC=O), 1078, 1028 (vC-O) cm⁻¹;

¹H NMR (200 MHz, acetone-δ) δ 7.09 (d, 2H, J₆ = 8.8 Hz, O₆), 6.72 (d, 2H, J₆, 6.4 Hz), 6.23 (t, 1H, J₃, 2H = 5.8 Hz, H₂), 5.09 (td, IH, 4.80 Hz), 4.80 (d, IH, J = 4.4 Hz, OH), 4.43 (d, IH, J = 4.4 Hz, OH), 4.02 (td, IH, J₂,F = 50.9 Hz, J₂,₂ = 8.9 Hz, H₂), 3.84-3.67 (m, 12H, N(CH₂CH₂Cl)₂, H-3H-4H-2H-6), 3.40-3.36 (m, 2H, H-5, OH), 3.16 (t, 2H, J = 6.4 Hz, NHCH₂), 2.53 (t, 2H, J = 7.7 Hz, CH₂Ph), 1.74 (qt, 2H₃CH₂CH₂CH₂)

¹³C NMR (50 MHz, acetone-δ) δ 158.49 (NHCO), 145.38 (C²N), 131.37 (CA₃CH₂), 130.23, 113.01 (CHA₃), 92.30 (C-2, J₁,F = 195.0 Hz), 79.97 (C-I, J₃,F = 25.0 Hz), 78.50 (C-5), 76.73 (C-3, J₃,F = 16.9 Hz), 71.39 (C-4, J₄,F = 7.2 Hz), 62.36 (C-6), 53.84 (CH₂N), 41.62 (CH₂Cl), 40.27 (NHCH₂), 32.84, 32.55 (CH₂Ph, CH₃CH₂CH₂CH₂)

MS (ESI) m/z 482.16 [M+H].

For the preparation of compounds 20b, 21b and 22b for which 4-aminobenzamide (20b), 2-aminoethanamide (21b) or 4-aminobutanamide (22b) was used as a spacer arm between the sugar residue and chlorambucil, the synthetic methods depicted in Scheme 2b have been adopted.

Example 9

N-(3,4,6-tri-0-acetyl-2-deoxy-2-f uoro-β-D-glucopyranosyl) -4-(4-4-bis(2-chloroethyl)Wmin ølphenUbutaDamido'leibizftmtdec (20a) (see scheme 1a).

a) N-f3,4,6-tri-0-acetyl-2-deoxy-2-f uoro-B-D-elucopyranosyl) -4-

To a stirred solution of the amino-sugar 8 (200 mg, 0.65 mmol) and triethylamine (274 µL, 1.95 mmol) in anhydrous THF (2 mL) stirred over 4Å molecular sieves, was added dropwise a solution of 4-nitrobenzoyl chloride (181 mg, 0.977 mmol) in anhydrous THF (1 mL). The mixture was stirred at 0°C for 30 min and at room temperature for 4 h. After evaporation, the residue was diluted with ethyl acetate and washed consecutively with IN aqueous HCl, saturated aqueous NaHCO₃ and water. Then the solution was dried over MgSO₄ and concentrated under reduced pressure. The resulting
residue was purified by silica gel chromatography, using petroleum benzine:ethyl acetate (6:4) as eluent, to yield 18a (200 mg, 67%) as a colourless oil;

\[ \text{C}_{19}\text{H}_{21}\text{FN}_{2}\text{O}_6 \]
\[ \text{M} = 456.38 \text{ g mol}^{-1} \]

\[ \text{Rf} = 0.46 \text{ (petroleum benzerethyl acetate 6:4)} \]

IR (NaCl) \( \nu 3368 (\nu_{\text{NH}}), 1747 (\text{C} = \text{O}), 1687 (\nu_{\text{C} = \text{O}}) \text{ m}, 1531 (\nu_{\text{C} = \text{N}}); \]
\[ \delta_{\text{H}}(\text{CH}_3) 1350 (\nu_{\text{CH}}), 1231, 1069, 1038 (\nu_{\text{C} = \text{O}}) \text{ cm}^{-1}; \]

\[ ^1\text{H} \text{ NMR} (200 \text{ MHz}, \text{CDCl}_3) \delta 8.30 (d, 2H, J = 8.8 \text{ Hz, H}_A), 8.06 (d, 2H, H_A), 7.68 (d, IH, J = 9.0 \text{ Hz, NH}), 5.65 (td, IH, J_{3,2} = 9.0 \text{ Hz, J}_4, 1.8 \text{ Hz, H-1}), 5.47 (td, IH, J_{2,3} = J_{3,4} = 9.8 \text{ Hz}, J_{3,F} = 13.7 \text{ Hz, H-3}), 5.05 (t, 1K, J_{4,s} = 9.8 \text{ Hz, H-4}), 4.65 (td, IH, J_{2,F} = 50.2 \text{ Hz, H-2}), 4.44 (dd, IH, J_{6,a,b} = 12.6 \text{ Hz, J}_{5,s,a} = 4.1 \text{ Hz, H-6a}), 4.07 (dd, IH, J_{5,s,a} = 1.6 \text{ Hz, H-6b}), 3.97 (ddd, IH, H-5), 2.30 (4, 2H, J_5 = 2.09, 2.05 (each s, 3*3H, OAc)); \]

\[ ^1\text{C} \text{ NMR} (50 \text{ MHz}, \text{CDCl}_3) \delta 170.80, 170.47, 169.87 (\text{COCH}_3), 165.84 (\text{NHCO}), 150.22 (\text{CA}_2\text{NO}_2), 138.58 (\text{CA}_2\text{CO}), 128.85, 123.97 (\text{CH}_3\text{CO}), 88.37 (\text{C}-2, J_2 = 191.2 \text{ Hz}), 78.18 (\text{C}-1, J_1 = 22.8 \text{ Hz}), 73.99 (\text{C}-5), 73.42 (\text{C}-3, J_{3,F} = 19.2 \text{ Hz}), 68.01 (\text{C}-4, J_{4,F} = 7.0 \text{ Hz}), 61.51 (\text{C}-6), 20.81, 20.68 (\text{CH}_3). \]

b) N-f3.4.6-tri-O-acet>1-2-deoxy^2-fluoro-B-P-glacopyra \( \cosv\pi-2-fN-\)
b<hzvloxycarboxylatnt \( \pi_o)->cceta\pi\text{tide} (18b). \]

Amitio-sugar 8 (2.06 g, 6.72 mmol) was dissolved in anhydrous DMF (100 \( \nu nL) \) and N-Cbz-glycine (1.69 g, 8.06 mmol), DCC (1.66 g, 8.06 mmol), and HOBt (1.09 g, 8.06 mmol) were added. The solution was stirred overnight at room temperature, filtered and concentrated in vacuo. The addition of CH$_2$Cl$_2$ and a new filtration allowed the elimination of additional DCU, Evaporation of the filtrate followed by purification on silica gel (6:4 to 4:6 petroleum benzine:ethyl acetate gradient) gave compound 18b (2.29 g, 69%) as a yellowish oil:

\[ \text{C}_{22}\text{H}_{27}\text{FN}_{2}\text{O}_{10} \]
\[ \text{M} = 498.46 \text{ g mol}^{-1} \]

\[ \text{Rf} = 0.41 \text{ (petroleum benzerethyl acetate 5:5)} \]

IR (KBr) \( \nu 3400 (\nu_{\text{OH}}), 1749 (\nu_{\text{C} = \text{O}}), 1384 (\nu_\text{C} = \text{O}); \]
\[ \delta_{\text{H}}(\text{CH}_3) 1350 (\nu_{\text{CH}}), 1231, 1036 (\nu_{\text{C} = \text{O}}) \text{ cm}^{-1}; \]

\[ ^1\text{H} \text{ NMR} (200 \text{ MHz}, \text{CDCl}_3) \delta 7.36 (m, 5H, H_{A^1}), 7.19 (d, IH, J = 9.2 \text{ Hz, CNH}), 5.48 (m, IH, CH$_2$NHO), 5.44-5.23 (m, 2H, H-1, H-3), 5.14 (s, 2H, OCH$_2$Ph), \]
5.03 (t, IH, J3,4 = J4,5 = 9.8 Hz, H-4), 4.31 (td, IH, J1,2 = J2,3 = 9.0 Hz, J2,F = 50.4 Hz, H-2),
4.29 (dd, IH, J5,6 = J6,5 = 12.5 Hz, H-6a), 4.06 (dd, IH, J5,6b = 2.1 Hz, H-6b),
3.95 (d, 2H, J = 5.1 Hz, COCH2NH), 3.83 (ddd, IH, H-5), 2.08, 2.06, 2.04 (each s, 3x3H, OAc).

5c) N-(3,4,6-tri-Q-acetyl^-deoxy-l-fl αoro-B-D-g-ucoPyranosylVS-
azidopropanamide fl8c).

A stirred solution of 4-azidobutyric acid (354 mg, 2.74 mmol) in CH2Cl2 (15 mL) was treated with triethylamine (460 μL, 3.29 mmol). The mixture was cooled to 0°C, treated with ethyl chloroformate (275 μL, 2.88 mmol), and stirred at ambient temperature for 30 min. Then, amino-sugar 8 (561 mg, 1.83 mmol) was added, and the mixture was stirred one day at ambient temperature. The mixture was suspended in saturated aqueous Na2CO3 and extracted three times with CH2Cl2. The organic extracts were combined, dried over MgSO4, and concentrated under reduced pressure. The crude product was purified by column chromatography using petroleum benzine:ethyl acetate (4:6) as the eluent, to give compound 18c (660 mg, 86%) as a solid:

C16H22FN4O8
M = 418.38 g.mol
mp 880°C

Rf= 0.33 (petroleum benzine:ethyl acetate 5:5)
IR (NaCl) υ 3688 (vN=O), 2102 (vαN=O), 1750 (vC=Oester), 1678 (vOamide), 1544
(δ=NH), 1369 (δαOra), 1232, 1068, 1035 (vC=O) cm
1H NMR (200 MHz, CDCl3) δ 7.05 (d, IH, J = 9.3 Hz, NH), 5.42 (m, 2H, H-I, H-3), 5.02 (t, IH, J3,4 = J4,5 = 9.8 Hz, H-4), 4.40 (td, IH, J1,2 = J2,3 = 9.1 Hz, J2,F = 50.3 Hz, H-2), 4.35 (dd, IH, J6a,6b = 12.6 Hz, J5,6a = 4.2 Hz, H-6a), 4.06 (dd, IH, J5,6b = 1.9 Hz, H-6b), 3.88 (ddd, IH, H-5), 3.38 (t, 2H, J = 6.5 Hz, CH2N3), 2.38 (t, 2H, J = 7.1 Hz, COCH2), 2.08, 2.07, 2.06 (each s, 3x3H, OAc), 1.91 (qt, 2H, J = 7.0 Hz, CH2CH2CH2);

13C NMR (50 MHz, acetone-*) δ 172.45, 170.27, 169.75, 169.71 (CO), 89.14 (C-2, J2.C = 187.5 Hz), 77.53 (C-1, J1,F = 22.7 Hz), 73.87-73.50 (C-3, C-5), 68.60 (C-4, J4,F = 7.5 Hz), 62.23 (C-6), 50.94 (CH2N3), 32.79 (COCjHa), 24.67 (CH2CH2CH2), 20.19 (CH3).
d) **4-amino-N-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-6-D-glucopyranosyl-D-phenylamide (198).**

To a suspension of 10% palladium on charcoal (25 mg) in THF/MeOH (7.5/7.5 mL) was added the nitro compound 18a (100 mg, 0.22 mmol). The mixture was hydrogenated at atmospheric pressure for 3 h, filtered on celite, and concentrated to yield the reduced product 19a (86 mg, 91%) as a light yellow solid which was used in the next step without further purification:

\[
\text{C}_{18}H_{23}F_{2}N_{2}O_{12}
\]

\[ M = 426.40 \text{ g.mol}^{-1} \]

\[ \text{mp} \ 133^\circ \text{C} \]

IR (NaCl) \( v \) 3469, 3378 (\( \nu \mathrm{NH} \)), 1744 \( \nu \mathrm{C} = \mathrm{O} \) (cm\(^{-1} \)), 1630 \( \delta \mathrm{C} = \mathrm{O} \) (cm\(^{-1} \)), 1604 \( \delta \mathrm{N} \) (cm\(^{-1} \)), 1511 \( \delta \mathrm{NH} \) (cm\(^{-1} \)), 1368 (\( \delta \mathrm{CH}_3 \)).

\[ 1^H \text{NMR (200 MHz, CDCl}_3 \} \delta 7.69 (d, 2H, \_J = 8.6 \text{ Hz, H-1}), 7.26 (d, \text{ IH, J} = 8.1 \text{ Hz, H-2}), 6.65 (d, 2H, H-1'), 5.60 (td, \text{ IH, J} = 9.3 \text{ Hz, J}_4 = 1.8 \text{ Hz, H-1}), 5.40 (td, \text{ IH, J} = 9.3 \text{ Hz, H-2}, 4.34 \text{ (dd, IH, J}_6 = 12.5 \text{ Hz, J}_5 = 4.2 \text{ Hz, H-6a}), 4.03 (dd, \text{ IH, J}_5 = 4.2 \text{ Hz, H-6b}), 3.84 (ddd, \text{ IH, H-5}), 2.07, 2.06, 2.04 \text{ (each s, 3x3H, OAc);} \]

\[ 13^C \text{NMR (50 MHz, CDCl}_3 \} \delta 170.86, 170.17, 170.05 \text{ (COCH}_3 \}, 167.55 \text{ (NHCO)}, 150.76 \text{ (CA}_4 \text{NH}_2 \}, 129.58 \text{ (CH}_3 \text{C-)}, 122.23 \text{ (CA}_4 \text{CO), 114.12 \text{ (CHA}_3 \}, 88.42 \text{ (C-2, J}_2 = 190.1 \text{ Hz), 78.15 \text{ (C-I, J}_1 = 22.4 \text{ Hz), 73.90-73.57 \text{ (C-3, C-5}), 68.08 \text{ (C-4, J}_4 = 6.9 \text{ Hz), 61.66 \text{ (C-6), 20.76, 20.72 \text{ (CH}_3 \).} \]

e) **N-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-6-D-glucopyranosyl-D-phenylamide (19b).**

A solution of the N-protected derivative 18b (690 mg, 1.38 mmol) in THF/MeOH (5/5 mL) was stirred under hydrogen atmosphere in the presence of 10% palladium on charcoal (190 mg) for 20 h at room temperature. Filtration of the catalyst on celite and evaporation of the solvent yield the deprotected product 19b (465 mg, 92%) as a solid:

\[
\text{C}_{14}H_{21}F_{2}N_{2}O_{8}
\]

\[ M = 364.33 \text{ g.mol}^{-1} \]
mp 96°C

IR(KBr) ν 3435 (vNH), 1750 (vC=O), 1370 (C-H), 1239, 1069 (vC-O) cm⁻¹;

1H NMR (200 MHz, CDCl₃) ν 8.24 (d, IH, J = 9.4 Hz, QNH), 5.47-5.34 (ra, 2H, H-I, H-3), 5.06 (t, IH, J₃=J₄= 9.8 Hz, H-4), 4.39 (td, IH, J₁₂=J₂₂ = 9.1 Hz, J₂F = 50.5 Hz, H-2), 4.30 (dd, IH, J₅J₆ = 4.3 Hz, J₆J₆b = 12.6 Hz, H-6a), 4.08 (dd, IH, J₅J₆b = 2.1 Hz, H-6b), 3.87 (ddd, IH, H-5), 3.44 (s, 2H, CH₂NH₂), 2.08, 2.05 (each s, 3x3H, OAc);

13C NMR (50 MHz, CDCl₃) δ 172.84, 170.73, 170.09 (CO), 88.52 (C-2, J₂F = 190.7 Hz), 77.30 (C-I, J₁F = 23.8 Hz), 73.79-73.38 (C-3, C-5), 68.05 (C-4, J₄F = 6.8 Hz), 61.78 (C-6), 44.16 (CH₂NH₂), 20.76, 20.67 (CH₃).

f) 3-amino-N-f3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-B-D-glucopyranosylpropaam.de (19cV)

To a suspension of 10% palladium on charcoal (75 mg) in CH₂CVMEOH (20/10 mL) was added the azido compound 18c (200 mg, 0.478 mmol). The mixture was hydrogenated at atmospheric pressure for 7 h, filtered on celite, and concentrated to yield the compound 19c (180 mg, 96%) as a white solid;

C₁₆H₂₅FN₂O₈

M = 392.38 g mol⁻¹

IR (NaCl) ν 3406 (vNH), 1748 (vC=O), 1666 (vC=O), 1370 (δβγδ), 1236, 1035 (νC=O) cm⁻¹;

1H NMR (200 MHz, acetone-) δ 8.86 (d, IH, J = 8.8 Hz, NH), 8.27 (br s, 2H, NH₂), 5.46-5.29 (m, 2H, H-I, H-3), 4.83 (t, IH, J₅J₆ = 9.6 Hz, H-4), 4.44 (td, IH, J₂F = 50.2 Hz, J₂J₁ = 9.0 Hz, H-2), 4.09 (dd, IH, J₆J₆b = 13.4 Hz, J₅J₆b = 5.1 Hz, H-6a), 3.92-3.87 (m, 2H, H-6b, H-5), 3.00 (m, 2H, CH₂NH₂), 2.42-2.39 (m, 2H, COCH₂), 2.01-1.83 (m, 11H, 3CH₃, CH₂CH₃CH₂);

13C NMR (50 MHz, acetone-) δ 173.28, 170.81, 170.26, 170.09 (CO), 89.30 (C-2, J₂F = 188.2 Hz), 78.15 (C-I, J₁F = 23.0 Hz), 74.38-73.92 (C-3, C-5), 69.15 (C-4, J₄F = 7.6 Hz), 62.68 (C-6), 46.86 (CH₂NH₂), 33.40 (COCH₂), 24.70 (CH₂CH₂CH₂), 20.63 (CH₃).
g) \( \text{N-f}3,4,6\text{-tri-0-acetyl-2-deo } \chi\text{-2Fu or o-\beta-D-2lucopyranosyl } \text{f}4-(4-(4-}
\text{fists2-eh.oroethy}.\text{amino})\text{phenyllbutanamido}\text{benzamide} \) (20a).

A solution of chlorambucil (217 mg, 0.72 mmol) in \( \text{CH}_2\text{Cl}_2 \) (5 mL) was treated with triethylamine (120 \( \mu \text{L}, 0.86 \text{ mmol})}. The mixture was cooled to \( 0^\circ \text{C} \), treated with ethyl chloroformate (72 \( \mu \text{L}, 0.75 \text{ mmol})}, and stirred at ambient temperature for 30 min. A solution of amine 19a (277 mg, 0.65 mmol) in \( \text{CH}_2\text{Cl}_2 \) (5 mL) was added, and the mixture was stirred for one day at ambient temperature. The mixture was suspended in saturated aqueous \( \text{Na}_2\text{CO}_3 \) and extracted three times with \( \text{CH}_2\text{Cl}_2 \). The organic extracts were combined, dried over \( \text{MgSO}_4 \), and concentrated under reduced pressure. The crude product was purified by column chromatography using petroleum benzene:ethyl acetate (5:5 to 3:7) as the eluent, to give compound 20a (370 mg, 80\%) as a beige powder:

\[
\text{C}_{13}\text{H}_{40}\text{Cl}_5\text{FN}_3\text{O}_9
\]

\[
\text{M} = 712.60 \text{ g} \cdot \text{mol}^{-1}
\]

\[
\text{mp} 165^\circ \text{C}
\]

\[
\text{Rf} = 0.37 \text{ (petroleum benzene:ethyl acetate 4:6)}
\]

IR (KBr) \( \nu = 3235 \) (\( \nu_{\text{NH}} \)), 1749 (\( \nu_{\text{C}=\text{O}} \)), 1670 (\( \nu_{\text{C}=\text{O} \text{amido}} \)), 1520 (8NH). \( ^{13}\text{C} \) NMR (50 MHz, MeOD) \( \delta = 174.73, 172.27, 171.47, 171.34, 169.88 \) (\( \text{CO} \)), 145.99 (\( \text{C}_{\text{A}}\text{N} \)), 143.91 (\( \text{C}_{\text{NH}} \)), 131.60 (\( \text{C}_{\text{A}}\text{CH} \)), 130.66, 129.66 (\( \text{CH}_{\text{A}} \)), 129.30 (\( \text{C}_{\text{A}}\text{CO} \)), 120.23, 113.54 (\( \text{CHA}^* \)), 89.46 (\( \text{C}_{-2}, J_{2\text{F}} = 187.7 \text{ Hz} \)), 79.24 (\( \text{C}_{-1}, J_{1\text{F}} = 23.2 \text{ Hz} \)), 74.95 (\( \text{C}_{-3}, J_{3\text{F}} = 19.4 \text{ Hz} \)), 74.60 (\( \text{C}_{-3} \)), 69.55 (\( \text{O}\)), 65.55 (\( \text{CH}_2\text{Ph} \)), 28.50 (\( \text{CH}_2\text{CH}_2\text{CH}_2 \)), 20.58 (\( \text{CH}_3 \));

MS (ESI) m/z 712.33 [M+H] \(^+\).
Example 10

4-(4-{4-bis(2-chloroethyl)aminolphenylbutanamido}-N-(2-deoxy-2-fluoro-C-D-glucopyranosyl)obetuzamide (20b).

To a solution of acetylated compound 20a (172 mg, 0.241 mmol) in methanol (15 mL) was added sodium methoxide (2 mg) and the mixture was stirred at room temperature for 4 h. After neutralization with IRC 50 Amberlite ion-exchange resin (H+), filtration and evaporation to dryness, the residue was purified on silica gel (5% methanol in ethyl acetate) to yield compound 20b (105 mg, 74%) as a white powder:

\[ C_{27}H_{31}Cl_{2}F_{4}N_{3}O_{6} \]

M = 586.49 g.mol⁻¹

Decomposition at 230°C

RF = 0.64 (ethyl acetate-methano) 9:1

IR (KBr) νv3011 (VNH, VgH), 1658 (vou), 1519 (δNH), 1089, 1045 (νC–O) cm⁻¹;

\(^1\)H NMR (200 MHz, DMSO) δ 10.12 (s, IH, PhNHCO), 9.04 (d, IH, J = 8.9 Hz, C=NH), 7.83 (d, 2H, J = 8.8 Hz, H Ar), 7.67 (d, 2H, J = 6.4 Hz, H Ar), 6.64 (d, 2H, J = 8.6 Hz, H Ar), 5.54 (d, IH, J = 5.4 Hz, OH), 5.19 (m, 2H, OH, H-I), 4.59 (t, IH, J = 5.6 Hz, OH), 4.29 (td, IH, J = 8.9 Hz, J = 50.6 Hz, H-2), 3.70-3.05 (m, 13H, N(CH₂CH₂Cl)₂, H-3, H-4, H-5, 2H-6), 2.48 (m, 2H, CH₂Ph), 2.31 (t, 2H, J = 7.3 Hz, COCH₂), 1.81 (qt, 2H, CH₂CH₂CH₂);

\(^{13}\)C NMR (50 MHz, DMSO) δ 171.54, 166.02 (CO), 144.44 (CAHN), 142.47 (CAHN), 129.72 (CAH₂), 128.32, 128.40 (CH Ar), 127.56 (C CO), 118.15, 111.91 (CH Ar), 91.10 (C-2), 172.82 (H Ar), 78.73 (C-SI 77.42 (C-I, J = 22.9 Hz), 19.8 (C-3, J = 16.2 Hz), 69.85 (C-4, J = 7.6 Hz), 60.55 (C-6), 52.22 (CH₂N), 41.14 (CH₂Cl), 35.85 (COGH₂), 33.54 (CH₂Ph), 26.85 (CH₂CH₂CH₂);

MS (ESI) m/z 586.14 [M+H].

Example 11

N-2-f3,43,·-tri-O-acetyl^deoxy^-fluoro-B-D-glucopyranosylamlno)-2-

oxoethyl-4-t4-tbischloroethylaminoethylUbutanainide(21a).

Amino derivative 19b (1.02 g, 2.80 mmol) was dissolved in anhydrous DMF (70 mL) and chlorambucil (939 mg, 3.09 mmol), DCC (636 mg, 3.09 mmol), and HOBt (417 mg, 3.09 mmol) were added. The solution was stirred 19 h at room temperature,
filtered and concentrated in vacuo. The addition of ethyl acetate and a new filtration allowed the elimination of additional DCU. Evaporation of the filtrate followed by purification on silica gel (4:6 to 2:8 petroleum benzeneethyl acetate gradient) gave compound 21a (945 mg, 64%) as a white solid:

\[
C_{28}H_{38}Cl_2F_3N_9O_9
\]

\[ M = 650.53 \text{ g mol}^{-1} \]

mp 106 °C

Rf= 0.20 (petroleum benzine:ethyl acetate 4:6)

IR (KBr) ν 3368 (vNH), 1750 (vC=O), 1653 (vC=O), 1519 (vNH), 1230,

1069, 1034 (vCO)

\[ ^{1}H \text{NMR} (200 \text{ MHz, CDCl}_3) \delta 8.08 (d, IH, J = 9.1 \text{ Hz, Cachsen}) \]

7.06 (d, 2H, J = 8.5 Hz, H-4), 6.63 (d, 2H, H-3), 7.46 (br t, IH, J = 4.6 Hz, CH\(_2\)NH), 5.41-5.29 (m, 2H, H-1, H-3), 5.03 (t, 1H, J\(_{3,4} = 9.7 \)Hz, H-4), 4.40 (td, IH, J\(_{2,3} = 9.0 \)Hz, J\(_{2,3} = 50.3 \)Hz, H-2). 4.26 (dd, IH, J\(_{5,6a} = 4.2 \)Hz, J\(_{6a,6b} = 12.7 \)Hz, H-6a), 4.09-4.01 (m, 3H, H-6b, H-7).

\[ ^{13}C \text{NMR} (50 \text{ MHz, CDCl}_3) \delta 173.98, 170.71, 170.01, 169.84, 169.74 (C0), 145.58 (C\(_{A}N\)), 130.36 (CA\(_2\)C), 129.78, 112.36 (CH\(_{A}C\)), 88.37 (C-2, J\(_{2,3} = 191.0 \)Hz), 77.38 (C-1) 73.76-73.29 (C-3, C-S), 68.02 (C4/ 4\(_{A}F\) = 6.7 Hz), 61.77 (C-6), 53.70 (CH\(_2\)N), 43.68 (COCH\(_2\)NH), 40.67 (CH\(_2\)Cl), 35.00 (COCH\(_2\)CH\(_2\)), 34.02 (CH\(_{iPh}\)) 27.19 (CH\(_2\)CH\(_2\)CH\(_2\));

MS (ESI) m/z 650.26 [M+H]+.

25

**Example 12**

4\(^{4}\)-fluoro-2-chloroethyl>amino1phenvU-N-t2-f2-deuxy-2-fluoro- β-D-

glucoDyranosvlaniipo)-2-oxoethyl|butaaamide (21b).

To a solution of acetylactd compound 21a (126 mg, 0.194 mmol) in methanol (5 mL) was added sodium methoxide (2 mg) and the mixture was stirred at room temperature for 3.5 h. After neutralization with IRC 50 Amberlite ion-exchange resin (H+), filtration and evaporation to dryness, the residue was purified on silica gel (10% methanol in ethyl acetate) to yield compound 21b (100 mg, 98%) as a white powder:
C₂₂H₂₃Cl₂FN₃O₆
M = 524.42 g.mol⁻¹
mp llO °C
Rf= 0.50 (10% methanol in ethyl acetate)

IR (KBr) ν 3315 (VOH, VNH), 1647 (vC=O), 1519 (vC), 1249, 1081, 1039 (vC=O) cm⁻¹;

¹H NMR (200 MHz, acetone-δ) δ 8.19 (d, IH, J = 9.3 Hz, CI NH), 7.51 (t, IH, J = 5.5 Hz, CH₂NH), 7.08 (d, 2H, J₀ = 8.6 Hz, Hₐ₀), 6.70 (d, 2H, B₀), 5.21 (td, IH, Jₐ₂ = 9.1 Hz, J₉₋₀ = 1.8 Hz, H-I), 4.99 (br d, IH, J = 3.4 Hz, OH), 4.62 (br s, IH, OH), 4.15 (td, IH, J₂₃ = 8.8 Hz, J₂,F = 50.8 Hz, H-2), 4.09 (br s, 1H, OH), 3.95 (d, 2H, COCH₂NH), 3.79-3.66 (in, 11H, N(CH₂CH₂Cl)₂, H-3, 2H-6), 3.42 (m, 2H, H-4, H-5), 2.53 (t, 2H, J = 7.5 Hz, CH₂Ph), 2.27 (t, 2H, J = 7.3 Hz, COCH₂CH₂), 1.86 (qt, 2H, CH₂CH₂CH₂);

¹³C NMR (50 MHz, acetone-δ) δ 174.39, 171.08 (CO), 145.45 (C₂, N), 131.49 (C₂CH₂), 130.36, 113.04 (CHA), 92.13 (C-2, J₂,F = 183.9 Hz), 79.08 (C-5), 78.13 (C-I, J₁,F = 23.3 Hz), 76.55 (C-3, J₃,F = 16.7 Hz), 70.94 (C-4, J₄,F = 4.0 Hz), 62.02 (C-6), 53.89 (CH₂N), 43.31 (COCH₂NH), 41.65 (CH₂Cl), 35.87 (COCH₂CH₂), 34.76 (CH₂Ph), 28.27 (CH₂CH₂CH₂);

MS (ESI) m/z 524.12 [M+1]⁺.

Example 13
N-f4-(3,4,6-tri-Q-acetV--2-deoxy-2-fluoro- β-D-clucopyranosylamiM Θ-4- oxobutvII-4-(4Mbis(2-chloroethvOam-nolphenyl)butananiide(22a).

A solution of chlorambucil (130 mg, 0.43 mmol) in CH₂Cl₂ (4 mL) was treated with triethylamine (72 µL, 0.52 mmol). The mixture was cooled to 0°C, treated with ethyl chloroformate (43 µL, 0.45 mmol), and stirred at ambient temperature for 30 min. Amine 19c (168 mg, 0.43 mmol) was then added, and the mixture was stirred 2 days at ambient temperature. The mixture was suspended in saturated aqueous Na₂CO₃ and extracted three times with CH₂Cl₂. The organic extracts were combined, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate as developing solvent, to give compound 22a (70 mg, 24%) as a beige powder:

C₃₀H₄₂Cl₂FN₅O₉
M = 678.58 g.mol⁻¹
mp 95 °C
Rf= 0.26 (ethyl acetate)
IR (NaCl) ν 3295 (vNH), 1749 (vc-cW, 1647 1542 (δ N H ), 73% as a solid:
C₂₄H₃₆Cl₂F₃N₃O₆
M = 552.47 g.mol⁻¹
mp 161 °C
Rf= 0.24 (10% methanol in ethyl acetate)

**Example 14**

4-(4-I)-llysr2-chIqoeth1ljamigol ppenvK-N-f4-(2-deoxy-2-f ur0-o-6-l)
glucoPyranosylaniinoV4-oxob utyllbuta əamide (22b).

To a solution of acetylated compound 22a (100 nag, 0.18 mmol) in methanol (5
niL) was added sodium methoxide (2 mg) and the mixture was stirred at room temperature
for 6.5 h. After neutralization with IRC 50 Amberlite ion-exchange resin (H+), filtration
and evaporation to dryness, the residue was purified on silica gel (10% methanol in ethyl
acetate) to yield compound 22b (69 mg, 72%) as a solid:
C₂₉H₃₆Cl₂FN₅O₆
M = 552.47 g.mol⁻¹
mp 161 0°C
Rf= 0.24 (10% methanol in ethyl acetate)
IR (KBr) ν 3525, 3309 (ν_{OH}), 1641 (ν_{C=O}), 1550, 1519 (ν_{C=N}), 1355 (ν_{CH}), 1093, 1045 (ν_{CO}) cm⁻¹;

1H NMR (200 MHz, acetone-d₆) δ 8.13 (d, IH, J = 9.2 Hz, C=NH), 7.18-7.05 (m, 3H, H₆), 6.72 (d, 2H, J₇ = 8.7 Hz, H₁₀), 5.19 (td, 1H, J₆,₇ = 9.0 Hz, J₆,F = 2.2 Hz), 4.78 (br s, IH, OH), 4.45 (br s, IH, OH), 4.12 (td, 1H, J₁₂ = 9.0 Hz, J₁₂,F = 50.9 Hz, H₂), 3.90-3.51 (m, 12H, N(CH₂CH₂Cl)₂), H₂-3, H₄-5, 3.40 (m, 2H, OH, H₅), 3.23 (q, 2H, J = 6.4 Hz, CH₃N), 2.52 (t, 2H, J = 7.4 Hz, CH₃Ph), 2.28-2.13 (in, 4H, 2CH₂CO), 1.96-1.73 (m, 4H, 2CH₂CH₂CH₂);

13C NMR (50 MHz, MeOD) δ 176.30, 176.18 (νCO), 145.98 (C=N), 131.73 (CA₁CH₂), 130.60, 113.54 (CH₂A₀), 92.27 (C-2), J₂,F = 184.4 Hz), 79.75 (C=5), 78.59 (CA₁, J₁,F = 23.3 Hz), 76.93 (C-3, J₃,F = 16.9 Hz), 71.11 (C-4, J₄,F = 7.6 Hz), 62.35 (C-6), 54.55 (CH₂N), 41.71 (CH₂Cl), 39.75 (CH₂CH₂CH₂NH), 36.55 (CH₂CH₂CH₂Ph), 35.23 (CH₂CH₂CH₂Ph), 34.34 (CH₂CH₂CH₂NH), 28.94 (CH₂CH₂CH₂Ph), 26.34 (CH₂CH₂CH₂NH);

MS (ESI) m/z 552.14 [M+1].

Following compounds 31 have been obtained by the reaction pathway depicted on Scheme 2c, proceeding by the preliminary coupling of chlorambucil with the spacer before the N-glycosylation, contrary to the formers 20, 21 and 22.

Example 15

N-\[3-(3,4,6-tri-O-acetyl\)deoxy\]^\^-fluoro-B^D-glucopyranosylaminoVS-oxopropylM-ta-Fbisd-chloroethyUaminolphenylbutanamide (31a) (see Scheme 2c).

a) 4-azidobutyric acid ethyl ester (24).

A stirred solution of 4-bromobutyric acid ethyl ester 23 (2.21 mL, 15.4 mmol) and sodium azide (2 g, 30.8 mmol) in acetone/water (22.5/7.5 mL) was heated under reflux for 7 h. The MeOH was removed in vacuo and residue was partitioned between CH₂Cl₂ and water. The product was extracted three times with CH₂Cl₂, the combined organic extracts were dried over MgSO₄ and evaporated to dryness, to give the azido ester 24 (2.19 g, 90%) as a colorless oil:

C₈H₁₁N₃O₂
\[ M = 157.17 \text{ g mol}^{-1} \]

IR (NaCl) \(\nu = 2100 (\nu_{\text{MN3}}), 1735 (\nu_{\text{C=O}}), 1256, 1175 (\nu_{\text{C-O}}) \text{ cm}^{-1}\)

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta 8.4.15 (q, 2H, J = 7.1 \text{ Hz}, \text{CH}_2\text{CH}_2\text{O}), 3.36 (t, 2H, J = 6.7 \text{ Hz}, \text{CH}_2\text{N}_3), 2.41 (t, 2H, J = 7.3 \text{ Hz}, \text{COCH}_2), 1.91 (q, 2H, J = 7.1 \text{ Hz}, \text{CH}_2\text{CH}_2\text{CH}_2), 1.27 (t, 3H, CH\_3);\)

\(^3\)C NMR (50 MHz, CDCl\(_3\)) \(\delta 172.54 (\text{CO})_5 60.53 (\text{CH}_2\text{CH}_3), 50.66 (\text{CH}_2\text{N}_3), 31.38 (\text{COCH}_2), 24.28 (\text{CH}_2\text{CH}_2\text{CH}_2), 14.18 (\text{CH}_3).\)

4-azidobutyric acid (25V)

Potassium hydroxide (3.9 g, 69.6 mmol) was added to a solution at 0°C of 4-azidobutyric acid ethyl ester 24 (2.19 g, 13.9 ramol) in a mixture of 32 mL MeOH and 26 mL water. The solution was stirred at room temperature for 6 h and then evaporated. The residue was partitioned between CH\(_2\)Cl\(_2\) and water. The aqueous layer was extracted twice with CH\(_2\)Cl\(_2\), acidified to pH 1 with IN aqueous HCl and extracted five times with Et\(_2\)O. The organic extracts were combined, dried over MgSO\(_4\) and evaporated to dryness, to afford the azido acid 25 (1.77 g, 99%) as a colorless oil. The \(^1\)H NMR analysis confirmed the product to be pure and it was used directly in the next step:

\[ \text{C}_4\text{H}_7\text{N}_2\text{O}_2 \]

\[ M = 129.12 \text{ g mol}^{-1} \]

IR (NaCl) \(\nu = 3650-2500 (\nu_{\text{OH}}), 2103 (\nu_{\text{MN}}), 1712 (\nu_{\text{C=O}}), 1259, 1169 (\nu_{\text{C-O}}) \text{ cm}^{-1}\)

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta 11.07 (\text{br s, IH, COOH}), 3.38 (t, 2H, J = 6.7 \text{ Hz}, \text{CH}_2\text{N}_3), 2.48 (t, 2H, J = 7.2 \text{ Hz}, \text{COCH}_2), 1.92 (q, 2H, J = 7.0 \text{ Hz}, \text{CH}_2\text{CH}_2\text{CH}_2);\)

\(^3\)C NMR (50 MHz, CDCl\(_3\)) \(\delta 179.33 (\text{CO}), 50.49 (\text{CH}_2\text{N}_3), 30.99 (\text{COCH}_2), 23.96 (\text{CH}_2\text{CH}_2\text{CH}_2).\)

3-azidopropionie acid ethyl ester (27).

A stirred solution of 3-bromopropionic acid ethyl ester 26 (2.11 mL, 16.6 mmol) and sodium azide (2.15 g, 32.2 mmol) in MeOH/water (22.5/7.5 mL) was heated under reflux for 6.5 h. The MeOH was removed in vacuo and residue was partitioned between CH\(_2\)Cl\(_2\) and water. The product was extracted four times with CH\(_2\)Cl\(_2\) and the combined organic extracts were dried over MgSO\(_4\). After removal of the solvent followed
by flash chromatography, eluting with petroleum benzine:ethyl acetate (9:1), provided the azido ester 27 (1.01 g, 43%) as yellowish liquid:

\[
\text{CsH}_2\text{N}_3\text{O}_2
\]

\[
M = 143.15 \text{ g mol}^{-1}
\]

RF = 0.53 (petroleum benzine:ethyl acetate 9:1)

IR (NaCl) \nu 2103 (\nu\text{N}_3), 1732 (\nu\text{C=O}), 1190, 1026 (\nu\text{C-O}) \text{ cm}^{-1};

\[^1\text{H} \text{NMR (200 MHz, CDCl}_3\text{)} \delta 4.18 \text{ (q, 2H, } J = 7.1 \text{ Hz, CH}_2\text{CH}_2\text{O)}_1 3.58 \text{ (t, 2H, } J = 6.5 \text{ Hz, CH}_2\text{N}_3)_3, 2.58 \text{ (t, 2H, COCH}_2)_1, 1.28 \text{ (t, 3H, CH}_3);

\[^{13}\text{C} \text{NMR (50 MHz, CDCl}_3\text{)} \delta 170.82 \text{ (CO), 60.91 (CH}_2\text{CH}_3)_1, 46.78 \text{ (CH}_2\text{N}_3)_3, 33.98 \text{ (COCH}_2)_1, 14.11 \text{ (CH}_3)_3.

3-aminoproDionic acid ethyl ester (28).

10% palladium on charcoal (92 mg) was added to a solution of the azido derivative 27 (460 mg, 3.21 mmol) in THF/MeOH (7.5/7.5 mL). The reaction mixture was then submitted to a hydrogen atmosphere at room temperature for 6 h. After filtration on celite and evaporation of solvent, compound 28 (306 mg, 81%) was obtained as a colourless oil:

\[
\text{C}_3\text{H}_7\text{NO}_2
\]

\[
M = 117.15 \text{ g mol}^{-1}
\]

\[^1\text{H} \text{NMR (200 MHz, CDCl}_3\text{)} \delta 4.16 \text{ (q, 2H, } J = 7.1 \text{ Hz, CH}_2\text{CH}_2\text{O)}_2 2.99 \text{ (t, 2H, } J = 6.3 \text{ Hz, CH}_2\text{NH}_2)_3, 2.46 \text{ (t, 2H, COCH}_2)_1, 1.54 \text{ (s, 2H, CH}_3\text{NH}_2)_2, 1.27 \text{ (t, 3H, CH}_3).

b) 3-(4-{(4-fbis(2-choroethyl)anunolphe ylibnt\text{ ramido})proDioiiic add ethyl ester (29).

A solution of chlorambucil (874 mg, 2.79 mmol) in CH\text{}_2\text{Cl}_2 (16 mL) was treated with triethylamine (480 \mu\text{L}, 3.45 mmol). The mixture was cooled to 0°C, treated with ethyl chloroformate (290 \mu\text{L}, 3.02 mmol), and stirred at ambient temperature for 30 min. A solution of the amino ester 28 (306 mg, 2.61 mmol) in CH\text{}_2\text{Cl}_2 (3 mL) was added, and the mixture was stirred one day at ambient temperature. The mixture was suspended in saturated aqueous Na\text{aC}_3\text{ and extracted three times with CH}_2\text{Cl}_2. The organic extracts were combined, dried over MgSO\text{4}, and concentrated under reduced pressure. The crude
product was purified by silica gel chromatography (8:2 to 3:7 petroleum benzene:ethyl acetate gradient), to give compound 29 (491 mg, 47%) as a brown oil:

\[
\text{C}_{19}\text{H}_{28}\text{Cl}_2\text{N}_2\text{O}_3
\]

\[M = 403.35 \text{ g.mol}^{-1}\]

\[\text{IR (NaCl)} \nu 3410 (\nu\text{NH}), 1727 (\nu\text{CO}), 1653 (\nu\text{C=O}), 1518 (\delta\text{CH}), 1265 (\delta\text{C-O})\]

\[\text{\textsuperscript{1}H NMR (200 MHz, CDCl}_3\delta 7.06 (d, 2H, J_0 = 8.5 \text{ Hz, H_A}), 6.61 (d, 2H, H_B), 5.92 (s, 2H, J = 5.9 \text{ Hz, CH}_2\text{N}, 3.50 (q, 2H, J = 7.1 \text{ Hz, CH}_3\text{CH}_2O), 3.75-3.57 (m, 8H, N(CH}_2\text{Cl})_2, 1.89 (q, 2H, CH}_2\text{CH}_2\text{CH}_2, 1.26 (t, 3H, CH}_3)\]

\[\text{\textsuperscript{13}C NMR (50 MHz, CDCl}_3\delta 172.86 (CO), 144.38 (C_\text{Ar}N), 130.74 (Q_\text{ArCH}_2), 129.76, 112.26 (CHA), 60.81 (CH}_3\text{CH}_2O), 53.68 (CH}_2N), 40.60 (CH}_2\text{Cl}, 35.98, 34.85, 34.14, 34.10 (CH}_2\text{COOEt, CH}_2\text{N}, CH}_2\text{Ph, CH}_2\text{CONH}, 27.40 (CH}_2\text{CH}_2\text{CH}_2, 14.26 (CH}_3)\]

c) 3-(4-{4-tbis(2-chloroethyl)amino}butyraii-tido)propionic acid

(30).

Lithium hydroxide (65 mg, 2.7 mmol) was added to a solution of 29 (435 mg, 1.08 mmol) in a mixture of 15 mL EtOH and 7.5 mL water. The solution was stirred at room temperature for 4.5 h and then evaporated. The residue was partitioned between CH2Cl2 and water. The aqueous layer was acidified to pH 1 with IN aqueous HCl (2.7 mL) and extracted twice with CH2Cl2. The organic extracts were combined, dried over MgSO4 and evaporated to dryness, to afford acid 30 (400 mg, 98%) as a solid:

\[
\text{C}_{17}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_3
\]

\[M = 375.30 \text{ g.mol}^{-1}\]

\[\text{mp 102}^\circ\text{C}\]

\[\text{RF} = 0.63 \text{ (ethyl acetate:methanol 9:1)}\]

\[\text{IR (NaCl)} \nu 3326 (\nu\text{OH}), 3200-2300 (\nu\text{CO}), 1720 (\nu\text{COO} \text{solid}), 1615 (\nu\text{O-O} \text{solid})\]

\[\text{H NMR (200 MHz, CDCl}_3\delta 9.53 (br s, \text{IH, OH}), 7.05 (d, 2H, J_0 = 8.6 \text{ Hz, H_A}), 6.61 (d, 2H, H_A), 6.25 (br t, \text{IH, J = 5.8 Hz, NH}, 3.74-3.56 (m, 8H, N(CH}_2\text{CH}_2\text{Cl})_2)\]
3.50 (q, 2H, J = 5.8 Hz, CH$_2$NH), 2.55 (m, 4H, CH$_2$Ph, CH$_3$COOH), 2.1S (t, 2H, J = 7.2 Hz, CH$_2$CONH), 1.88 (qt, 2H, CH$_2$CH$_2$CH$_2$)

$^1$C NMR (50 MHz, CDCl$_3$) δ 176.63, 173.79 (CO), 144.49 (CArN)$_3$ 130.56 (Car$^2$H$_2$), 129.79, 112.30 (CH$_{Ar}$), 53.69 (CH$_2$N), 40.67 (CH$_2$Cl), 35.96, 34.99, 34.10 (CH$_2$COOH, CH$_2$NH, CH$_2$Ph$_1$NHCOCH$_2$), 27.39 (CH$_2$CH$_2$CH$_2$).

d) N-f3-(3.4,6-tri-0-acetyl-2-deoxy-2-fluoro-B-D-glucopyranosyl) 3-oxoDrot+yl-4-(4-rbis(2-chloroethyl)amino-sugar \[\text{31a}^{\theta}\]- 3-oxoDrot+yl-4-(4-rbis(2-chloroethyl)amino-sugar \[\text{31a}^{\theta}\].

A solution of acid 30 (33 mg, 0.09 mmol) in CH$_2$Cl$_2$ (2 mL) was treated with triethylamine (26 µL, 0.18 mmol). The mixture was cooled to 0°C, treated with ethyl chloroformate (9 µL, 0.09 mmol), and stirred at ambient temperature for 30 min. Then, amino-sugar 8 (24.5 mg, 0.08 mmol) was added, and the mixture was stirred 4 days at ambient temperature. The mixture was suspended in saturated aqueous Na$_2$CO$_3$ and extracted three times with CH$_2$Cl$_2$. The organic extracts were combined, dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (2:8 to 1:9 petroleum benzine:ethyl acetate gradient), to give expected compound 31a (47 mg, 88%) as a beige solid:

\[\text{C}_{29}\text{H}_{40}\text{Cl}_2\text{FN}_3\text{O}_9\]
\[\text{M} = 664.56 \text{g/mol}^{-1}\]

mp 103 °C

Rf= 0.19 (petroleum benzene:ethyl acetate 2:8),

IR (KBr) ν 3309 (ν$_{NH}$), 1751 (ν$_{C=O}$amide), 1676, 1647 (ν$_{COOH}$amide), 1519 (5NH), 1367 (δ$_{C\text{H}_3}$), 1228, 1066, 1034 (ν$_{C\text{O}}$) cm$^{-1}$.

$^1$H NMR (200 MHz, CDCl$_3$) δ 7.90 (d, IH, J = 8.9 Hz, C$_1$NH), 7.04 (d, 2H, J$_{2}$ = 8.5 Hz, H$_{6a}$), 7.70, 6.61 (d, 2H, H$_{6a}$), 6.37 (br t IH, J = 5.5 Hz, CH$_2$NHCOH), 5.46-5.30 (m, 2H, H-1, H-3), 5.03 (t, IH, J$_{3,4}$ = J$_{4,5}$ = 9.8 Hz, H-4), 4.40 (td, IH, J$_{1,2}$ = J$_{2,3}$ = 9.1 Hz, J$_{2,4}$ = 50.4 Hz, H-2), 4.28 (dd, IH, J$_{5,6}$ = 12.5 Hz, J$_{5,8}$ = 4.3 Hz, H-6a), 4.04 (dd, 1H, J$_{5,6}$ = 1.4 Hz, H-6b), 3.84 (m, IH, H-5), 3.73-3.47 (m, 1OH, N(CH$_2$COCl)$_2$, C&NH), 2.52 (m, 4H, CH$_2$Ph, COCH$_2$CH$_2$NH), 2.19-2.04 (m, HH, COCH$_2$CH$_2$CH$_2$, 3OAc), 1.87 (m, 2H, CH$_2$CH$_2$CH$_2$).

$^1$C NMR (50 MHz, MeOD) δ 176.25, 174.45 (CONH), 172.19, 171.43, 171.27 (COCH$_3$), 145.99 (CArN)$_3$, 131.81 (CA$_2$CH$_2$), 130.63, 113.57 (CHAT), 89.57 (C-2, J$_{2,1}$ = 8.5 Hz, H$_{6a}$), 78.89 (COCH$_3$), 48.36 (CArH$_2$), 44.50 (COCH$_3$), 35.53 (COCH$_3$), 30.51 (COCH$_3$), 25.49 (COCH$_3$).
188.6 Hz), 78.51 (C-I, \( J_{\alpha} = 22.9 \text{ Hz} \)), 74.81 (C-3, \( J_{3\beta} = 19.5 \text{ Hz} \)), 74.53 (C-5), 69.50 (C-4, \( J_{4\beta} = 7.3 \text{ Hz} \)), 62.98 (C-6), 54.58 (CH\(_2\)), 41.72 (OFCI), 36.44, 35.15 (CO\(\text{OE}_2\)Cl\(_2\)NH, CO\(\text{CH}_2\)\(\text{CH}_2\)Ph), 28.89 (CH\(_2\)\(\text{CH}_2\)\(\text{CH}_2\)), 20.58 (CH\(_3\))

MS (ESI) m/z 538.06 [M+H].

**Example 16**

4-f4-bis(2-chloroethynamtaio]phe \(\alpha\)-N-r3-(2-deoxy-2-fluoro-\(\beta\)-D-

[\(\text{D-glucopyr}\) \(\alpha\)-posylamino]-3-oxoptery) \(\beta\)-butanamid \(\beta\) (31b).

To a stirred solution of acetylated compound 31a (120 mg, 0.18 mmol) in methanol (10 mL) was added sodium methoxide (2 mg) and the mixture was stirred at room temperature for 6.5 h. After neutralization with IRC 50 Amberlite ion-exchange resin (H\(^+\)), filtration and evaporation to dryness, the residue was purified on silica gel (10% methanol in ethyl acetate) to yield compound 31b (80 mg, 83%) as a white solid:

\[
\text{C}_{23}\text{H}_{34}\text{Cl}_{2}\text{F}_{2}\text{N}_{3}\text{O}_{6}
\]

mp 179 \(^\circ\text{C}\)

Rf = 0.30 (10% methanol in ethyl acetate)

IR (KBr) \(\nu\) 3525, 3305 (\(\nu_{\text{NH}}, \text{VOH}\)), 1647 (\(\nu_{\text{C} = \text{O}}\)), 1544 (5NH), 1091, 1043 (\(\nu_{\text{C}-\text{O}}\)) cm\(^{-1}\);

\(^1\)H NMR (200 MHz, acetone-\(\Delta\)) \(\delta\) 8.05 (d, IH, \( J = 9-1 \text{ Hz} \), C\(_1\)NH), 7.06 (m, 3H, H\(_\text{A}^\text{c}, \text{CH}_2\)NHCO), 6.72 (d, 2H, \( J = 8.8 \text{ Hz} \), H\(_\text{Ac}\)), 5.19 (<<d, IH, \( J = 9.1 \text{ Hz} \), \( J_{\alpha} = 2.3 \text{ Hz} \), H-1), 4.84 (d, IH, \( J = 4.5 \text{ Hz} \), OH), 4.48 (d, IH, \( J = 4.5 \text{ Hz} \), OH), 4.09 (td, IH, \( J = 9.0 \text{ Hz} \), \( J_{2\beta} = 50.9 \text{ Hz} \), H-2), 3.80-3.68 (m, 1IH, N(CH\(_2\)\(\text{CH}_2\)Cl\(_2\)), H-3, 2H6), 3.45-3.38 (m, 5H, H-4, H-5, CH\(_2\)NH, OH), 2.47 (m, 4H, \(\text{CB}_{3\text{Ph}}\)), CO\(\text{CH}_2\)\(\text{CH}_2\)NH), 2.15 (m, 2H, CO\(\text{CH}_2\)\(\text{CH}_2\)\(\text{CH}_2\));

\(^13\)C NMR (50 MHz, MeOD) \(\delta\) 176.19, 174.58 (NHCO), 145.92 (C\(_\text{Ac}\)N), 131.73 (\(\text{C}_{\text{Ac}}\)\(_\text{CH}_2\)), 130.60, 113.49 (CH\(_\text{Ac}\)), 92.20 (C-2, \( J_{2\beta} = 184.8 \text{ Hz} \)), 79.71 (C-5), 78.50 (C-I, \( J_{1\beta} = 23.1 \text{ Hz} \)), 76.90 (C-3, \( J_{3\beta} = 16.8 \text{ Hz} \)), 71.13 (C-4, \( J_{4\beta} = 7.5 \text{ Hz} \)), 62.38 (C-6), 54.53 (CH\(_2\)N), 41.69 (CH\(_2\)Cl), 36.52, 35.16 (CO\(\text{OE}_2\)\(_\text{CH}_2\)NH, CO\(\text{CH}_2\)\(\text{CH}_2\)Ph), 28.87 (CH\(_2\)\(\text{CH}_2\)\(\text{CH}_2\));

MS (ESI) m/z 538.06 [M+H].
Example 17
N-f4-f4-f4-fbisi(2-chloroethyl)fl-ni. io]phenyl>butaqvo[oxy]phenyll-3.4.6-tri-
0-benzyl-2-deoxy-2-fluoro-B-D-g-HCOPyraQsylanile (34a) (Scheme 2a)

ester (32).

To a solution of 4-nitrophenol (0.152 mg, 1.09 mmol) in CH₂Cl₂ (20 mL),
chlorambucil (500 mg, 1.64 mmol), DCC (375 mg, 1.82 mmol) and DMAP (9.1 ng, 0.073
mmol) were added and stirred one day at room temperature. The solid was removed by
filtration, and the filtrate was diluted with CH₂Cl₂ (25 ml). The mixture was washed
consecutively with a 1 N aqueous solution of acetic acid (35 mL) and water (35 mL), dried
over MgSO₄, and concentrated under vacuum. The resulting residue was purified by silica
gel chromatography, using petroleum benzine:ethyl acetate (8:2) as mobile phase, to yield
32 (432 mg, 93%) as a yellow syrup:
C₂₀H₂₂Cl₂N₂O₄
M = 425.31 g mol⁻¹
Rf= 0.49 (petroleum benzine:ethyl acetate 6:4)
IR(NaCl) ν 1762 (ν C=O), 1519 (ν asNO₂), 1347 (ν sNO₂), 1206, 1112 (ν C-O) cm⁻¹;
¹H NMR (200 MHz, CDCl₃) δ 8.28 (d, 2H, J₀ = 9.2 Hz, H₆), 7.26 (d, 2H, J₀ =
H₆), 7.19 (d, 2H, J₀′ = 8.7 Hz, H₆′), 6.67 (d, 2H, J₀, H₆), 3.65 (m, 8H, N(CH₂CH₂Cl)₂),
2.67 (t, 2H, J = 7.5 Hz, CH₂Ph); 2.63 (t, 2H, J = 7.6 Hz, COCH₂); 2.06 (qt, 2H,
CH₂CH₂CH₂CH₂);
¹³C NMR (50 MHz, CDCl₃) S 169.13 (CO), 153.51 (C₆O), 143.33, 142.55
(C₆NO₂, C₆N), 128.05 (C₆CH₂), 127.82, 123.25, 120.47, 110.31 (CH₃), 51.65 (CH₃N),
38.54 (CH₂Cl), 31.92, 31.64 (CH₂Ph, COCH₂), 24.52 (CH₂CH₂CH₂).

p-4-t4-4bis(2-chloroethyl)aminophenyl! butyric acid 4-aminophenyl γl
ester (33V)

To a suspension of 10% palladium on charcoal (1.5 g) in THF/EtOH (40/50
mL) was added the nitro compound 32 (9.1 g, 21 mmol). The mixture was hydrogenated at
atmospheric pressure for one day, filtered on celite, and concentrated to yield the
compound 33 (6.6 g, 79%) as an orange oil:
C₂₀H₂₄Cl₂N₂O₂
M = 395.33 g·mol⁻¹

Rf = 0.37 (cyclohexane : ethyl acetate 6:4)

IR (NaCl) v 3453, 3373 (v NH₂), 1747 (v C=O), 1616 (δ NH₂), 1194, 947, 844, 800, 767, 745, 690, 612 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ 7.09 (d, 2H, J₀ = 8.5 Hz, H₆b), 6.83 (s, 2H, J₁ = 8.7 Hz, H₇), 6.65 (d, 4H, H₂A), 3.73-3.56 (ra, 1OH, N(CH₂CH₂Cl)₂, NH₂), 2.63 (t, 2H, J = 7.5 Hz, CH₂Ph), 2.52 (t, 2H, J = 7.4 Hz, COCH₂), 2.00 (qt, 2H, CH₂CH₂CH₂Cl);

¹³C NMR (50 MHz, CDCl₃) δ 172.73 (CO), 144.47, 144.22 (2CA₄N), 142.93 (C₆O), 130.52 (C₅CH₂), 129.85, 122.21, 115.69, 112.26 (CU₁), 53.68 (CH₂N), 40.63 (CH₂Cl), 34.05, 33.72 (CH₂Ph, COCH₂), 26.89 (CH₂CH₂CH₂).

c) N-f4-f4-(4-fbis(2-chloroethoxy)UaminolDhenvUbutanov ioxy^Dhenv π-

A solution of amino compound 33 (307 mg, 0.78 mmol) in CH₃CN (5 ml) was added to a solution of bromide 12 (400 mg, 0.78 mmol) in CH₃CN (10 ml) containing Ag₂O (770 mg, 3.32 mmol). After stirring at room temperature for 20h, the mixture was filtered on celite to remove Ag salts, and the solvent was evaporated. The crude product was purified by column chromatography on silica gel using petroleum benzine:ethyl acetate (8:2) as eluent to give the β-anomer 34a as an oil (222 mg, 35%):

C₄H₅Cl₂F₂N₆O₆

M = 829.84 g·mol⁻¹

Rf= 0.54 (cyclohexane:ethyl acetate 7:3)

IR (NaCl) v 3393 (νNH). 1750 (νC=O), 1518 (δm), 1200, 1180, 1133, 1027 (νC−O) cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 7.39-7.19 (m, 16H, H₆Ar, NH), 7.12 (d, 2H, J₀ = 8.6 Hz, H Ar), 6.91 (d, 2H, J₀ = 8.8 Hz, H Ar), 6.76 (d, 2H, J₀ = 8.8 Hz, H Ar), 4.94 (d, IH, J = 11.1 Hz, OCH₂Ph), 4.87 (d, IH, J = 10.8 Hz, OCH₂Ph), 4.80 (d, IH, J = 11.1 Hz, OCH₂Ph), 4.69 (br t, IH, J₂ = J₁N = 7.5 Hz, H-I), 4.60 (d, IH, J = 12.1 Hz, OCH₂Ph), 4.56 (d, IH, J = 10.9 Hz, OCH₂Ph), 4.52 (m, IH, -H-I), 4.50 (d, IH, J = 12.1 Hz, OCH₂Ph), 4.41 (td, IH, J₂₃ = 8.5 Hz, J₂₃ = 51.0 Hz, H-2), 3.88 (td, IH, J₃ = 8.5 Hz, J₃ = 15.0 Hz, H-3), 3.77 (dd, IH, J₃₆ = 11.0 Hz, J₆₆ = 2.0 Hz, H-6a), 3.72 (t, 5H, J = 6.9 Hz, N(CH₂CH₂Cl)₂, 3.64 (t, 4H₂J = 6.9 Hz, N(CH₂CH₂Cl)₂), 3.61 (m, 3H, H-5).
2H, J = 7.5 Hz, CH₂CH₂Ph), 2.56 (t, 2H, J = 7.4 Hz, COCH₂), 2.06 (qt, 2H, J = 7.5 Hz, 
CH₂CH₂CH₂).

Example 18

N-f^\alpha^\beta-chloroethylaminophenyllbutanoyloxy^\beta-phenyl-l-deoxy-
2-fluoro-B-D-glucopyranoSylamine (34b).

A solution of the benzylated derivative 34a (189 mg, 0.23 mmol) in EtOH/THF 
(5/2.5 irL) was stirred under hydrogen atmosphere in the presence of 10% palladium on 
charcoal (47 mg) for 18 h at room temperature. After filtration of the catalyst on eelite and 
evaporation of the solvent, the crude product was purified by silica gel chromatography 
(cyclohexane:ethyl acetate 1:9), to yield the deprotected product 34b (100 mg, 78%) as a 
white powder (α/β ratio =20/80):

C₂₉H₃₁Cl₂FN₂O₆
M = 559.46 g·mol⁻¹

IR (KBr) v 3349 (νNH·V₂O), 1750 (νO=O), 1729 (νC=O), 1455 (νCH₂), 1229, 1201, 1179, 1135, 1078, 
1012 (νC-O) cm⁻¹;

¹H NMR (200 MHz, acetone-δ) δ 7.10 (d, 2H, J₆= 8.5 Hz, H₄); 6.86 (d, 2H, 
J₆’ = 9.1 Hz, HA;); 6.75 (2d, 4H, H₂A), 6.00 (d, IH, J₁₈= 8.4 Hz, NHβ); 5.76 (d, IH, J₁₈= 8.5 Hz, H₋₁β), 
4.83 (br t, IH, J₂= 5.2 Hz, H-Ia); 4.81 (br t, IH, J₂= 8.5 Hz, H₋₁β), 
4.75 (d, IH, J = 4.5 Hz, OHβ); 4.61 (d, IH, J = 4.4 Hz, OHα); 4.41 (d, IH, J = 4.0 Hz, 
OHβ), 4.38 (d, IH, J = 5.0 Hz, OHα); 4.13 (td; 4H, J₂= 8.7 Hz, J₂= 5.18 Hz, H₋₁β), 
4.01 (m, IH, H₋₁β), 3.82-3.38 (m, 13H, N(CH₂CH₂CH₂)₂, H₋₄, H₋₅, 2H₋₆, OH), 2.60 (t, 2H, 
J = 7.5 Hz, CH₂Ph), 2.50 (t, 2H, J = 7.3 Hz, COCH₂), 1.94 (qt, 2H, J = 7.4 Hz, 
CH₂CH₂CH₂): 

¹³C NMR (50 MHz, acetonMs): 172.74 (CO), 145.65, 145.00 (2C₆N), 143.91 
(C₆O), 130.98 (CA₆C₆H₂), 130.41, 122.94, 114.84, 113.06 (CHα), 92.84 (C-2, J₂= 184.7 
Hz), 83.67 (C-I, J₁F = 20.2 Hz), 77.92 (C-5), 77.01 (C-3, J₂F = 16.9 Hz), 71.73 (C-4, J₂F = 7.7 Hz), 62.53 (C₆), 53.86 (NCH₂), 41.59 (CH₂Cl), 34.54, 33.93 (CH₂Ph, COCH₂), 27.71 
(CH₂CH₂CH₂):

MS (ESI) m/z 559.10 [M+H].
Example 19

\[ \text{N-f4-} (3.4.6\text{-tri-0-acetyl-2-deoxy-2-fluoro-}\beta\text{-D-glucoDyranosvIoxy}) \text{DhenvH-}
\]
\[ 4-f4\text{-rbis (2-chloroethyl )amlP } \beta \text{DhenvHbutanam } \text{de (37a)} \] (see scheme 2a).

\[ \text{a) 4-nitrophenyl } \]
\[ 3.4.6\text{-tri-Q-acetylU2-deoxy-2-fluoro-B-D-}
\]
\[ \text{glucopyranoside (35).} \]

A solution of 4-nitrophenol (1.88 g, 13.5 mmol) in CH\(_3\)CN (25 mL) was added to a solution of bromide 6 (5 g, 13.5 mmol) in CH\(_3\)CN (75 mL) containing Ag\(_2\)O (4 g, 17.3 mmol). After stirring at room temperature for 23 h, the mixture was filtered on celite to remove Ag salts, and the solvent was evaporated. The crude product was purified by column chromatography on silica gel using cyclohexane:ethyl acetate (7:3) as eluent, thus affording the \(\beta\)-anomer 35 as a white solid (4.59 g, 79%).

\[ \text{CigH}_{10}\text{FNO}_{10} \]
\[ M = 429.36 \text{ g.mol}^{-1} \]
\[ \text{mp 142-143°C} \]
\[ \text{RF= 0.35 (petroleum benzineethyl acetate 7:3)} \]
\[ \text{IR (KBr) } \nu 1755 (\nu_c=\text{cm}^{-1}), 1526 (\nu_o), \text{1347 } (\nu_c), 1231, 1076 (\nu_c c m^{-1}); \]
\[ ^1\text{H NMR (200 MHz ; CDCl}_3) \delta 8.23 (d, 2H, J_n = 9,2 Hz, H-zH), 7.14 (d, 2H, H-Ar), \]
\[ 5.46 \text{ (td, IH, } J_{5,3} = J_{3,4} = 9.2 \text{ Hz, } J_3F = 14.6 \text{ Hz, H-3)}, 5.30 \text{ (dd, IH, } J_{1}F = 3.1 \text{ Hz, } J_{1,2} \]
\[ \approx 7.6 \text{ Hz, H-I) } \delta 5.12 \text{ (t, } J_{1,2} \approx 9.7 \text{ Hz, H-4)}, 4.63 \text{ (ddd, IH, } J_{2,9} = 50.4 \text{ Hz, H-2), 4.31}
\]
\[ \text{ (dd, IH, } J_{6,5b} = 12.4 \text{ Hz, } J_{5,6} = 5.4 \text{ Hz, H-6a}), 4.17 \text{ (dd, } IR, J_{5,6b} = 2.4 \text{ Hz, H-6b), 3.97}
\]
\[ \text{ (ddd, IH, H-5), 2.13, 2.09, 2.07 (each s, 3x3H, OAc);} \]
\[ ^{13}\text{C NMR (50 MHz, CDCl}_3) \delta 170.48, 170.03, 169.59 \text{ (COCH}_3), 161.13
\]
\[ \text{(C=O), 143.57 } (\text{CA}_{\text{O}}), 125.94, 116.95 \text{ (CA}_{\text{H}}), 97.98 \text{ (C-I, } J_{1,2} = 23.6 \text{ Hz), 88.96 (C-2, }
\]
\[ J_{2,9} = 191.6 \text{ Hz), 72.57 (C-5), 72.47 (C-3, } J_{3,4} = 19.9 \text{ Hz), 67.94 (C-4, } J_{4,5} = 7.3 \text{ Hz), 61.83}
\]
\[ \text{(C-6), 20.66 (CH}_3). \]

\[ \text{b) 4-aniinophenyl } \]
\[ 3.4.6\text{-tri-0-acetyl-2-deoyy-2-fluoro-f } \beta\text{-D-}
\]
\[ \text{glucopyranoside (36).} \]

A solution of the nitro derivative 35 (4.20 g, 9.78 ninioi) in THF/EtOH (50/50 mL) was stirred under hydrogen atmosphere in the presence of 10% palladium on charcoal
(550 mg) for 23 h at room temperature. Filtration of the catalyst on celite and evaporation of the solvent yield the amino product 36 (3.90 g, 100%) as a beige powder:

$$\text{C}_{18}\text{H}_{22}\text{FNO}_8$$

$$M = 399.37 \text{ g mol}^{-1}$$

5 mg 109-110°C

IR (KBr) $\nu$ 3326 (v N H), >1757 (v COOCH), 1221, 1069, 1044 (v C=O)

I R (KBr) v 3466 (v N NH), 3376 (v N NH2), 1753 (v COOH), 1224, 1067, 1039 (v C=O) cm$^{-1}$;

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 6.92 (d, 2H, $J_0 = 8.9$ Hz, H$_{2}$), 6.62 (d, 2H, H$_{3}$), 5.38 (td, 1H, $J_{3,4} = J_{2,3} = 9.3$ Hz, J$_{2,3} = 14.5$ Hz, H-3), 5.09 (t, IH, $J_{4,5} = 9.7$ Hz, H-4), 4.96 (dd, IH, $J_{1,4.F} = 3.0$ Hz, $J_{1,2} = 7.7$ Hz, H-1), 4.52 (ddd, IH, $J_{2,3} = 50.4$ Hz, H-2), 4.30 (dd, IH, $J_{6a,6b} = 12.3$ Hz, J$_{5,6a} = 5.2$ Hz, H-6a), 4.14 (dd, IH, $J_{5,6b} = 2.5$ Hz, H-6b), 3.79 (dd, IH, H-5), 3.10 (br s, 2H, NH$_2$), 2.11, 2.08, 2.05 (each s, 3*3H, OAO).

$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 170.69, 170.17, 169.67 (COCH$_3$), 149.69 (CA1O), 142.95 (CA1N H$_2$), 119.60, 116.02 (CA1O), 100.50 (C-I, $J_{1,4,F} = 23.1$ Hz), 89.20 (C-2, $J_{2,F} = 190.4$ Hz), 72.97 (C-3, $J_{3,4,F} = 19.8$ Hz), 72.03 (C-5), 68.33 (C-4, $J_{4,F} = 7.3$ Hz), 62.00 (C-6), 20.80, 20.69 (CH$_3$).

1H NMR (200 MHz, CDCl₃) δ 7.44 (d, 2H, J₀ = 9.0 Hz, HA), 7.23 (br s, IH, NH), 7.09 (d, 2H, J₆’ = 8.6 Hz, HA), 7.02 (d, 2H, J₆ : HA), 6.63 (d, 2H, J₀ \ H₄), 5.41 (td, IH, J₃₄ = J₂₃ = 9.2 Hz, J₁₄ = 14.5 Hz, H-3), 5.10 (t, IH, J₄₅ = 9.5 Hz, H-4), 5.07 (dd, IH, J₁₂ = 2.7 Hz, J₁₃ = 7.5 Hz, H-1), 4.56 (ddd, IH, J₂₄ = 50.4 Hz, H-2), 4.30 (dd, IH, J₅₆₈ = 5.3 Hz, J₆₈₋₆ = 12.3 Hz, H-6a), 4.15 (dd, IH, J₅₈ = 2.1 Hz, H-6b), 3.79 (ddd, IH, H-5), 3.73-3.58 (m, 8H, N(CH₃CH₂Cl)₂), 2.62 (t, 2H, J = 7.3 Hz, CH₂Ph), 2.34 (t, 2H, J = 7.3 Hz, COCH₃), 2.12, 2.08, 2.05 (each s, ≥3H, OAc), 2.11-1.95 (m, 2H, CH₂CH₂CH₂H₂);

13C NMR (50 MHz, CDCl₃) δ 171.22, 170.66, 170.13, 169.65 (COCH₃), 153.16 (C₁₋₂), 144.48 (CA₁-N), 133.94 (CA₃NH), 130.52 (CA₃CH₂), 129.83, 121.40, 118.12, 112.26 (CH₃), 99.39 (C₁), J₁₄ = 23.2 Hz, 89.09 (C-2), J₂₋₄ = 190.6 Hz), 72.78 (C-3, J₃₋₄ = 19.9 Hz), 72.10 (C-S), 68.14 (C-4, J₄₋₅ = 7.3 Hz), 61.91 (C₄), 53.66 (CH₂Cl), 40.63 (CH₂Cl₂), 36.79 (COCH₃), 34.03 (CH₂Ph), 27.21 (CH₂CH₂CH₂), 20.81, 20.79, 20.68 (CH₃);

M (ESI) m/z 685.30 [M+H]⁺.

Example 20
4-f4-fbis(2-chloroethyl)>aminolpheov 1]-N-f4-(2-deoxy-2 -fluoro-B-D- g.ucopyraposyloxy)ohenyllbutanftmlde (37(1)).

To a solution of acetylated compound 37a (1.37 g, 2.0 mmol) in methanol (50 mL) was added sodium methoxide (20 mg) and the mixture was stirred at room temperature for 20 h. After neutralization with IRC 50 Amberlite ion-exchange resin (HT), filtration and evaporation to dryness, a precipitate in diisopropyl ether provided compound 37b (1.1 g, 98%) as a white solid:

C₁₂₆₄₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂₁₃₁₃₂¹ ;

1H NMR (200 MHz, acetone-d₆) δ 9.07 (s, IH, NH), 7.61 (d, 2H, J₀ = 9.0 Hz, H₂₆), 7.10 (d, 2H, J₀ = 8.7 Hz, H₆₋₆), 7.03 (d, 2H, J₀ : H₆₋₆), 6.73 (d, 2H, J₂₋₃ : H₂₆), 5.19 (dd, IH, J₂₋₃ = 7.7 Hz, J₁₋₆ = 3.8 Hz, H-I), 4.88 (d, IH, J = 4.6 Hz, OH), 4.58 (d, IH, J = 4.6 Hz, OH), 4.24 (dd, IH, J₂₋₃ = 8.3 Hz, J₂₋₃ = 51.5 Hz, H-2), 3.89-3.56 (m, 14H,
N(CH₂CH₂Cl)₂, H-3, H-4, H-5, 2H-6, OH), 2.59 (t, 2H, J = 7.5 Hz, CH₂Ph), 2.36 (t, 2H, J = 7.4 Hz, COCH₂), 1.96 (qt, 2H, CH₂CH₂CH₂);

³¹C NMR (50 MHz, acetone-d₆) δ 171.45 (NHCO), 153.93 (CAr-O), 145.53 (CArN), 135.49 (CArNH), 131.43 (GCH₂), 130.37, 121.26, 117.68, 113.07 (CHAₓX 99.59 C-I, 9.2 Hz, J₁₂ = 14.6 Hz, H-3), 5.13 (s, 2H, CHPh), 5.12-5.03 (m, 2H, H-4, H-!), 4.55 (ddd, 1H, J₃ = J₄ = 9.2 Hz, H-3), 5.13 (s, 2H, CH₂Ph), 5.12-5.03 (m, 2H, H-4, H-!), 4.55 (ddd,

Example 21
N-f2-f4-f3.4,6-trt-Q-acetyl-2-deoxy-2-O-butyl-1-oxoethylM-U-tbis^-chloroethv
phenylHamP-lo-oxoethylM-U-tbis^-chloroethv

Example 21
N-f2-f4-f3.4,6-trt-Q-acetyl-2-deoxy-2-O-butyl-1-oxoethylM-U-tbis^-chloroethv
phenylHamP-lo-oxoethylM-U-tbis^-chloroethv

Amino derivative 36 (2.49 g, 6.24 mmol) was dissolved in anhydrous DMF (95 mL) and N-Cbz-glycine (1.44 g, 6.87 mmol), DCC (1.41 mg, 6.87 mmol), and HOBt (927 mg, 6.87 mmol) were added. The solution was stirred for 25 h at room temperature, filtered and concentrated in vacuo. The addition of ethyl acetate and a new filtration allowed the elimination of additional DCU. Evaporation of the filtrate followed by purification on silica gel (petroleum benzene:ethyl acetate 4:6) gave compound 38 (2.73 g, 74%) as a white solid:

C₂₈H₃₁F₇N₅O₇

M = 590.56 g·mol⁻¹

mp S4°C

Rf= 0.33 (petroleum benzene :ethyl acetate 4:6)

IR(KBr) ν 3326 (vNH), 1755 (vC=O), 1694 (νC-Oamf), 1510 (8NH), 1369 (S₈CH₃), 1224, 1067, 1046 (νC-O) cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ 8.44 (br s, NH, PhNH), 7.40 (d, 2H, J₀ = 9.0 Hz, HA), 7.33 (s, 5H, H₂-Ar), 6.96 (d, 2H, H₂), 5.85 (br t, 1H, CH₂NH), 5.41 (td, 1H, J₂ = 9.2 Hz, J₁₂ = 14.6 Hz, H-3), 5.13 (s, 2H, CH₂Ph), 5.12-5.03 (m, 2H, H-4, H-!), 4.55 (ddd,
IH, 3\nu = 7-8 Hz, A P = 50.4 Hz, H-2), 4.28 (dd, IH, J_{6'-6} = 12.3 Hz, J_{5,6} = 5.3 Hz, H-6a), 4.12 (dd, IH, J_{5,6} = 2.1 Hz, H-6b), 3.99 (d, 2H, J = 5.2 Has, CH$_2$NH), 3.84 (ddd, IH, J_{4,5} = 10.0 Hz, H-5), 2.1 1, 2.05, 2.04 (each s, 3\times 3H, OAc);

$^{13}$C NMR (50 MHz, CDCl$_3$) \( \delta \) 170.66, 170.16, 169.65, 167.43 (CO), 157.08 (NHQOO), 153.41 (C$_4$O), 136.08 (C$_{\text{Ar}}$CH$_2$), 133.27 (C$_{\text{Ar}}$NH), 128.71, 128.44, 128.11, 121.64, 118.00 (CHA), 99.17 (C-5, J$_{F}$ = 23.3 Hz), 89.11 (C-2, J$_{2F}$ = 190.7 Hz), 72.77 (C-3, J$_{3F}$ = 19.9 Hz), 72.06 (C-5), 68.16 (C-4, J$_{4F}$ = 7.2 Hz), 67.47 (C$_{\text{Ar}}$Ph), 61.90 (C-6), 45.43 (COQH$_2$NH$_2$) 20.76, 20.64 (CH$_3$).

**N-r4-(3.4.6-tri-0-acetyl-2-deoxy-2-fluoro-B-D-glucopyranosyloxy)**

phenyl-2-aminoacetam-de (39).

N-Cbz protected derivative 38 (2.73 mg, 4.62 \mu mol) was added, with stirring, to a suspension of ammonium formate (1.46 g, 23.1 mmol) in THF/EtOH (2/7 mL) containing 10% palladium on charcoal (545 rag). The mixture was heated at 70°C for 50 min, filtered on celite, and evaporated under reduced pressure, to provide the expected compound 39 (2.07 g, 98%) as a solid:

C$_2$H$_2$F$_2$O$_9$

M = 456.42 g/mol

mp 78°C

Rf= 0.10 (10% methanol in ethyl acetate)

IR(KBr) v 3402 (VNH), 1750 (vc-oamuk), 1682 (vc-oamuk), 1510 (SNH), 1370 (\( \delta_{\text{CH3}} \)), 1227, 1068, 1043 (V$_{\text{CO}}$) cm$^{-1}$;

$^{1}$H NMR (200 MHz, CDCl$_3$) \( \delta \) 9.46 (br s, IH, NH), 7.52 (d, 2H, J$_{\alpha}$ = 8.9 Hz, H$_{3\alpha}$), 7.00 (d, 2H, H$_{\alpha}$), 5.40 (td, IH, J$_{2,3}$ = 9.2 Hz, J$_{3,4}$ = 14.4 Hz, H-3), 5.13-5.04 (m, 2H, H-1, H-4), 4.55 (td, 1H, J$_{2,3}$ = 8.5 Hz, J$_{2,3}$ = 50.5 Hz, H-2), 4.29 (dd, 1H, J$_{6a,6b}$ = 12.3 Hz, J$_{6a,6b}$ = 5.1 Hz, H-6a), 4.13 (dd, 1H, J$_{5,6b}$ = 1.9 Hz, H-6b), 3.84 (ddd, 1H, J$_{4,5}$ = 9.6 Hz, H-5), 3.57 (br s, 2H, CH$_2$), 2.71 (ra, 2H, NH$_2$), 2.1 1, 2.07, 2.05 (each s, 3x3H, OAc);

$^{13}$C NMR (50 MHz, CDCl$_3$) \( \delta \) 153.18 (CA$_2$O), 133.53 (CA$_2$NH), 121.08, 118.03 (CH$_3$), 99.21 (C-1, J$_{1F}$ = 23.2 Hz), 89.16 (C-2, J$_{2F}$ = 190.7 Hz), 72.80 (C-3, J$_{3F}$ = 19.9 Hz), 72.05 (C-5), 68.18 (C-4, J$_{4F}$ = 7.1 Hz), 61.93 (C-6), 44.67 (COCH$_2$NH$_2$), 20.80, 20.67 (CH$_3$).
Amino derivative 38 (1.5 g, 3.28 mmol) was dissolved in anhydrous DMF (100 mL) and chlorambucil (1.10 g, 3.62 mmol), DCC (745 mg, 3.62 mmol), and HOBT (488 mg, 3.62 mmol) were added. The solution was stirred for 40 h at room temperature, filtered and concentrated in vacuo. The addition of ethyl acetate and a new filtration allowed the elimination of more than DCU. Evaporation of the filtrate followed by purification on silica gel (5:5 to 1:9 cyclohexane:ethyl acetate gradient) gave compound 40a (2 g, 82%) as a white solid:

\[
C_{34}H_{42}Cl_2F_3N_5O_{10}
\]

\[
M = 742.63 \text{ g.mol}^{-1}
\]

mp 130°C

Rf= 0.54 (cyclohexane:ethyl acetate 2:8)

IR(KBr) \nu 3307 (v_{NH}), 1755 (v_{c=O}), 1650 (v_{O-}), 1509 (\delta_{NH}), 1367 (5 CH_{3}), 1247, 1068, 1044 (v_{c-O}) cm^{-1};

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \delta 9.29 (s, IH, PhNH), 7.49 (d, 2H, J = 9.0 Hz, H_{Ar}), 7.05-6.96 (m, 4H, H_{Ar}), 6.86 (t, IH, J = 4.6 Hz, CH\(_2\)NH), 6.59 (d, 2H, J = 8.7 Hz, H_{Ar}). 2.31 (ddd, 1H, J_{123} = J_{34} = 9.2 Hz, J_{3\phi} = 14.5 Hz, H-3), 5.14-5.05 (m, 2H, H-4, H-1).

4.56 (ddd, 1H, J_{12} = 7.8 Hz, J_{2\phi} = 50.4 Hz, H-2), 4.29 (dd, 1H, J_{6a\phi6b} = 12.3 Hz, J_{6b\phi6a} = 5.3 Hz, H-6a), 4.16-4.10 (m, 3H, CH\(_2\)NH, H-6b). 3.84 (ddd, 1H, J_{1\phi5\phi} = 2.3 Hz, J_{\phi5} = 9.9 Hz, H-5), 3.73-3.56 (m, SH, N(CH\(_2\)CH\(_2\)Cl\(_2\)), 2.55 (t, 2H, J = 7.4 Hz, CH\(_2\)Ph), 2.31 (t, 2H, J = 7.3 Hz, COCH\(_3\)CH\(_2\)X2.1 i, 2.06, 2.05 (each s, 3\times3H, OAc). 1.93 (qt, 2H, CH\(_2\)CH\(_2\)CH\(_2\))

\(^13\)C NMR (50 MHz, CDCl\(_3\)) \delta 174.18, 170.64, 170.15, 169.65, 167.16 (CO), 153.33 (C\(_{Ar}\)O), 144.55 (C\(_{Ar}\)N), 133.75 (C\(_{Ar}\)NH), 130.36 (CA\(_4\)CH\(_2\)), 129.78, 121.40, 118.12, 112.32 (CH\(_a\)), 99.36 (C-I, J_{1\phi} = 23.4 Hz), 89.15 (C-2, J_{2\phi} = 190.8 Hz), 72.80 (C-3, J_{3\phi} = 19.8 Hz), 72.14 (C-5), 68.18 (C-4, J_{4\phi} = 7.3 Hz), 61.93 (C-6), 53.68 (NCH\(_2\)), 44.55 (COCH\(_2\)NH), 40.64 (CH\(_2\)Cl), 35.61 (COCH\(_2\)CH\(_2\)), 34.10 (CH\(_2\)Ph), 27.36 (CH\(_2\)CH\(_2\)CH\(_2\)), 20.81, 20.69 (CH\(_3\));

MS (ESI) m/z 742.35 [M+H]^+. 

\(c\)\(_{14}\) N-{(2-L4-(3,4,\(\theta\)-tri-O-acetyl-Z-deoxy-l-fluoro-B'D-\(\theta\)-lucodvi'anosyloxy)}

Dhenyllamo-2-oxoethylU-4-(4-tbiss(2-chloroethvDam8no1

phenUahuutanamide (40a).

\(c\)\(_{14}\) N-{(2-L4-(3,4,\(\theta\)-tri-O-acetyl-Z-deoxy-l-fluoro-B'D-\(\theta\)-lucodvi'anosyloxy)}

Dhenyllamo-2-oxoethylU-4-(4-tbiss(2-chloroethvDam8no1

phenUahuutanamide (40a).
Example 22


To a solution of acetylated compound 40a (100 mg, 0.135 mmol) in methanol (4 mL) was added sodium metJioxide (2 mg) and the mixture was stirred at room temperature for 5 h. After neutralization with IRC 50 Amberlite ion-exchange resin (HT), filtration and evaporation to dryness, a precipitation in EtOH provided compound 40b (83 mg, 100%) as a white solid:

C_{28}H_{36}Cl_{2}F_{3}N_{7}O_{7}

M = 616.51 g·H·O

rap 114°C

Rf= 0.63 (10% methanol in ethyl acetate)

IR (KBr) ν 3312 (νNH, νOH), 1684 (νC=O), 1510 (SNH), 1231, 1075 (νC-O) cm⁻¹;

¹H NMR (200 MHz, acetone-^) S 9.22 (br s, 1H, PhNHCO), 7.56 (d, 2H, J_0 = 8.9 Hz, H_A), 7.43 (br t, 1H, CH_2NHCO), 7.09 (d, 2H, J_0' = 8.6 Hz, H_A$^\delta$), 7.03 (d, 2H, J_0, H_A$^\delta$), 6.72 (d, 2H, J_0, H_A$^\delta$), 5.19 (dd, 1H, J_0, J_F = 7.9 Hz, J_0, J_F = 2.6 Hz, H-I), 4.88 (br s, 1H, OH), 4.61 (br t, 1H, OH), 4.23 (td, 1H, J_2=3 - 8.2 Hz, J_2=3 = 51.2 Hz, H-2), 4.01-3.45 (m, 16H, N(CH_2CH_2Cl)_2H-3, H-4, H-5, 2H-6, CH_2NH, OH), 2.55 (t, 2H, J = 7.6 Hz, CH_2Ph), 2.29 (t, 2H, J = 7.4 Hz, CH_2CH_2CO), 1.89 (q, 2H, CH_2CH_2CH_2);

¹³C NMR (50 MHz, acetone-^) 5 173.83, 168.37 (CO), 154.23 (C^O), 145.55 (C^A$^\delta$N), 134.78 (C^A$^\delta$NH), 131.56 (C^A$^\delta$CH_2), 130.40, 121.52, 117.73, 113.09 (C_A$^\delta$), 99.47 (C-1), 93.16 (C-2, J_2,F = 184.8 Hz), 77.82 (C-5), 76.09 (C-3, J_3,F = 16.8 Hz), 71.18 (C-4, J_4,F = 7.6 Hz), 62.27 (C-6), 53.94 (NCH_2), 44.16 (COCH_2NH), 41.65 (CH_2Cl), 35.85 (COCH_2CH_2), 34.82 (CH_2Ph), 28.40 (CH_2CH_2CH_2);

MS (ESI) m/z 616.31 [M+I]⁻.
Example 23

(3,4,6-tri-O-acetyl)-2-deoxy-2-fuoro-β-D-glucopyranosyl) 4-f-4-fbis(2-chloroethyl)ntpolphen'vi)butanamido)acetamidol1)henylcarbamate (46) see Scheme 26

\[ \text{C}_{19}H_{24}FNO}_{2} \]

M = 473.36 g·mol⁻¹;

Rdf = 44 %;

IR(KBr) ν 1779, 1740 (ν = o), 1526 (ν = O), 1346 (ν = N,O), 1241, 1079, 1040 (ν = o);

\(^1\)H NMR (200 MHz, CDCl₃) δ 8.32 (d, 2H, J = 9.1 Hz, EM), 7.44 (d, 2H, H₆), 5.75 (d, IH, A = 3.3 Hz, J₁₂ = 8.0 Hz, H-I), 5.44 (td, IH, J₂₃ = J₃₄ = 9.2 Hz, J₃ = 14.3 Hz, H-3), 5.13 (t, IH, J₆₅ = 9.8 Hz, H-4), 4.57 (ddd, IH, J₂₇ = 50.6 Hz, H-2), 4.34 (dd, IH, J₆₁₅ = 12.6 Hz, J₆₅ = 4.4 Hz, H-6a), 4.17 (dd, IH, J₅₆₈ = 2.2 Hz, H-6b), 3.93 (ddd, 1H, H-5), 2.12, 2.10, 2.06 (each s, 3x3H, OAc);

\(^13\)C NMR (50 MHz, CDCl₃) δ 170.59, 169.93, 169.56 (QOCH₃), 154.99, 150.95 (QOQMO), 145.96 (C₁₉NOR₂), 125.59, 121.84 (CHA), 95.58 (C-I, J₁-F = 24.4 Hz), 88.09 (C-2, J₂-F = 191.9 Hz), 73.19 (C-5), 72.41 (C-3, J₃₋₄ = 19.6 Hz), 67.43 (C-4, J₄₋₅ = 7.3 Hz), 61.26 (C-6), 20.79, 20.74, 20.65 (CH₃).

To a solution of compound 9 (4.4 g, 14.3 mmol) in THF (70 mL), cooled to 0°C were added 4-nitrophenylichloroformate (2.87 g, 14.2 mmol) and Et₂N (2.4 mL, 17.3 mmol) and stirring was maintained at room temperature for 24 h. A white solid which precipitated was filtered and dissolved in ethyl acetate (150 mL). This organic layer was washed with water (4×40 mL) and brine (60 mL). After drying over MgSO₄, and concentration under reduced pressure, a solid corresponding to the β-anomer of compound 41 (1.5 g, 3.17 mmol) was obtained. The former filtrate was chromatographed on silica gel with cyclohexane:ethyl acetate 6:4 as eluent to offer carbonate as a mixture of α- and β-anomers. A supplementary fraction of β-anomer could be obtained by crystallization in diisopropryl ether:

\[ \text{C}_{19}H_{24}FNO}_{2} \]

M = 473.36 g·mol⁻¹;

Rdf = 44 %;

IR(KBr) ν 1779, 1740 (ν = o), 1526 (ν = O), 1346 (ν = N,O), 1241, 1079, 1040 (ν = o);
b) Benzyl 2-(4-nitroDhenylamino>-2-oxoetbylcarbamat<e>i (42) was
prepared according to the procedure described for compound 18c, starting from Cbz-
glycine (1.5 g, 7.17 mmol) and/?-nitroaniline (1.11 g, 8.03 mmol). Purification on a
column of silica gel (cyclohexane-ethyl acetate 4:6) provided compound 42 (1.35 g, 57%)
as a dark yellow solid:

\[ \text{C}_{18} \text{H}_{13} \text{N}_{3} \text{O}_{5}; \]
\[ M = 329.31 \text{ g.mol}^{-1}; \]
\[ \text{Rf} = 0.67 \text{ (cyclohexane-ethyl acetate 4:6);} \]
\[ \text{IR (KBr) } \nu 3327, 3285 \nu(\text{NH}), 1678 \nu(\text{C}=\text{O}), 1519 \nu\text{asN}=\nu \text{O}_2), 1344 \nu\text{vN} \text{O}_2 \nu(\text{NH})\]

\[ ^1\text{H NMR (200 MHz, acetone-d}^6) \begin{align*}
&\delta 9.84 \text{ (br s, IH, NHPh), } 8.22 \text{ (d, 2H, } J = 9.2 \\
&\text{Hz, H } A_1), 7.91 \text{ (d, 2H, H } A_2), 7.39-7.29 \text{ (m, 5H, Ph), } 6.79 \text{ (br t, IH, CH}_2\text{NH), } 5.12 \text{ (s, 2H, OCH}_2\text{Ph), } 4.06 \text{ (d, 2H, } J = 6.1 \text{ Hz, CH}_2\text{NH);} \\
&\text{IR (KBr) } \nu 3327, 3285 \nu(\text{NH}), 1678 \nu(\text{C}=\text{O}), 1519 \nu\text{asN}=\nu \text{O}_2), 1344 \nu\text{vN} \text{O}_2 \nu(\text{NH})\]

\[ ^1\text{C NMR (100 MHz, DMSO-d}^6) \begin{align*}
&\delta 169.63 \nu(\text{NHCO}), 157.71 \nu(\text{NHCOO}), 145.77 \nu(\text{NH}), 143.99 \nu(\text{C}_\text{Ph} \text{N}), 138.08 (\text{C}_\text{Ph} \text{O}), 129.24, 128.71, 125.61, 119.87 (\text{CH}_2\text{NH}), 67.06 (\text{OCH}_2\text{Ph}), 45.76 (\text{COCH}_2\text{NH}). \\
&\text{c) 2-amino-\text{N}^\text{\textendash}(4-Dttroqhe \text{pyr}>acetaroide hydrolbromid}e (43)

To a stirred suspension of 42 (0.502 g, 1.52 mmol) in acetic acid (3 mL) was
added dropwise 2.6 mL (15.1 mmol) of 33% hydrogen bromide in acetic acid. The
resulting solution was allowed under stirring for 2h45, then added slowly to 30 mL cold
ether. The white solid formed was filtered off and washed with ether to yield compound 43
(0.365 g, 87%) as a white solid:

\[ \text{C}_{18} \text{H}_{19} \text{NO}, \text{HBr; } \]
\[ M = 276.09 \text{ g.mol}^{-1}; \]
\[ \text{IR (KBr) } \nu 3030 \nu(\text{NH}), 2595 \nu(\text{NH}), 1691 \nu(\text{C}=\text{O}), 1577 \nu\text{asN}=\nu \text{O}_2), 1346 \nu\text{vN} \text{O}_2 \nu(\text{NH})\]

\[ ^1\text{H NMR (200 MHz, D}_2\text{O) } \begin{align*}
&\delta 8.18 \text{ (d, 2H, } J = 8.9 \text{ Hz, H } A_1), 7.64 \text{ (d, 2H, } H A_2), 4.04 \text{ (s, 2H, C}_2\text{H}_2\text{CO)}; \\
&\text{IR (KBr) } \nu 3030 \nu(\text{NH}), 2595 \nu(\text{NH}), 1691 \nu(\text{C}=\text{O}), 1577 \nu\text{asN}=\nu \text{O}_2), 1346 \nu\text{vN} \text{O}_2 \nu(\text{NH})\]

\[ ^1\text{C NMR (100 MHz, DMSO-d}^6) \begin{align*}
&\delta 165.79 \nu(\text{NHCO}), 144.18 (\text{C}_\text{Ph} \text{N}), 142.64 (\text{C}_\text{Ph} \text{O}), 125.11, 118.92 (\text{CH}_2\text{NH}), 41.31 (\text{CH}_2\text{NH}_2). \\

d) 4-[4’’bis(2-chlorocth γ \))amlnolphenvH--V-r2-f4- \)nitrophenvlaininoJr2-

0X9$\beta$y1)bwtanamröe (44) was prepared according to the procedure described for compound 18c, starting from chlorambucil (300 mg, 0.986 mmol) and 43 (305 ing, 1.09 mmol) beforehand treated with 0.23 mL of NEt$_3$ at ambient temperature. After evaporation of the reaction mixture, the residue was suspended in saturated aqueous Na$_2$CO$_3$ (20 mL) and extracted twice with EtOAc. During this extraction, an insoluble compound is filtered off. The organic extracts were combined, washed twice with water, dried over MgSO$_4$, and concentrated under reduced pressure to offer a white powder. Both solid were combined and washed with ether. After drying, compound 44 (435 mg, 92%) was obtained as a white powder, analytically pure, and used without other purification for the following stage:

$$C_{22}H_{28}Cl_2N_4O_2;$$

M = 451.40 g/mol$^{-1}$;

Rf= 0.60 (cyclohexane:ethyl acetate 1:9);

IR (KBr) v 3394, 3280, 3250, 3225 (VNH), 1702, 1643 (v00), 1508 (6NH, V$_{\alpha}$NO$_2$), 1337 (V$_{\gamma}$NO$_2$) cm$^{-1}$;

$^1$H NMR (200 MHz, DMSO-$_d$) δ 10.66 (br s, IH, NHPPh), 8.23 (d, 3H, $J_0 = 8.9$ Hz, H$_A$, NH), 7.84 (d, 2H, $J_\gamma = 8.1$ Hz, H$_A$), 6.66 (d, 2H, $J_\gamma = 8.9$ Hz, H$_A$), 3.93 (d, 2H, $J = 5.4$ Hz, CH$_2$NH), 3.70 (s, 8H, N(CH$_2$CH$_2$Cl)$_2$), 2.47 (t, 2H, $J = 6.9$ Hz, CH$_2$Ph), 2.17 (t, 2H, $J = 6.8$ Hz, COCH$_2$), 1.76 (qt, 2H, CH$_2$CH$_2$CH$_2$);

$^{13}$C NMR (50 MHz, CDC$_1$_$d$) δ 172.66, 169.01 (CO), 145.10, 144.40 (2CA$_2$N), 142.14 (C$_A$NO$_2$), 129.98 (CA$_4$C$_2$), 129.31, 125.00, 118.71, 111.91 (CBM), 52.23 (CH$_2$N), 42.87 (COCH$_2$NH), 41.15 (CH$_2$Cl), 34.54, 33.52 (CH$_2$CH$_2$CH$_2$), 27.28 (CH$_2$CH$_2$CH$_2$).

e) In$\beta$-f4-anthaQPhenylar oinoV2-oxoethyl-4-f4-rbisf2-

chloroethy \)amniophypytittntaitamde (45) was prepared starting from the nitro compound 44 by reduction with hydrogen and Pd/C according to the procedure described for compound 19a. The crude product was purified by column chromatography on silica gel using cyclohexane:ethyl acetate (1:9) as eluent to yield the compound 45 (291 mg, 88%) as a solid:

$$C_{22}H_{28}Cl_2N_4O_2;$$

M = 451.40 g/mol$^{-1}$;
Rf = 0.25 (cyclohexane:ethyl acetate 9:1);
IR (KBr) v 3377, 3307 (VNH), 1686, 1630 (νo_o), 1517 (6NH) cm⁻¹;
1H NMR (200 MHz, acetone-δ) δ 8.88 (br s, IH, NH), 7.30 (d, 3H, J = 8.9 Hz, NH, HAT), 7.09 (d, 2H, J = 8.7 Hz, H A1), 6.72 (d, 2H, H A2), 6.60 (d, 2H, J = 4.45 Hz, H A3);
(br s, 2H, NH₂), 3.95 (d, 2H, J = 5.7 Hz, CH₂NH), 3.83-3.66 (m, SH, N(CH₂CH₂Cl)₂), 2.55 (t, 2H, J = 7.6 Hz, CH₂Ph), 2.28 (t, 2H, J = 7.4 Hz, COCH₂CH₂), 1.88 (qt, 2H, CH₂CH₂CH₂);

13C NMR (50 MHz, DMSO-δ) δ 172.44, 166.90 (CO), 144.39, 144.18 (C A*NH₂, CA N), 130.02, 128.41 (CA CH₂, CA'NH), 129.33, 120.88, 114.12, 111.90 (CH A);

52.25 (CH₂N), 42.49 (COCH₂NH), 41.17 (CH₂Cl), 34.67, 33.59 (CH₂CH₂O₂H₂), 27.33 (CH₂CH₂CH₂).

f) (3,4,6-tri-0-acetyl-2-deoxy-2-fluoro-β-D-glucopyra αosyl) 4,12-(4-(4-\(\text{tbisC2-centroethyl \text{~>~ amino|phenyl} butanamido>acetamidophenylcarbamate}\) (46)

To a solution of compound 41 (340 mg, 0.718 ramol) in DMF (20 mL), were added compound 45 (230 mg, 0.598 mmol) and Et₃N (132 µL, 0.950 mmol) and stirring was maintained at room temperature for 20h. After evaporation of the volatiles, the crude product was chromatographed on silica gel using cyclohexane:ethyl acetate (3:7) as eluent to give the title compound 46 (β) (175 mg, 37%) as a white powder:

C₃₅H₄₃Cl₂F₃O₁₄;
M = 785.65 g mol⁻¹;
Rf = 0.53 (cyclohexane:ethyl acetate 2:8);
IR (KBr) ν 3350 (VNH). 1752, 1653 (νc = o), 1519 (6NH), 1221, 1071, 1037 (νc = o) cm⁻¹;
1H NMR (200 MHz, CDCl₃) δ 8.91 (br s, IH, NH), 7.47 (d, 2H, J = 8.6 Hz, H A₂);
5.85 (dd, 1H, J₁₂ = 8.1 Hz, J₂F = 2.9 Hz, H-I), 5.43 (td, 1H, J₂3 = 9.3 Hz, J₃F = 14.4 Hz, H-3), 5.10 (t, 1H, J₄5 = 9.7 Hz, H-4), 4.51 (ddd, 1H, J₂F = 50.6 Hz, H-2), 4.34 (dd, 1H, J₆₇ = 12.7 Hz, J₅₆ = 3.9 Hz, H-6a), 4.15-4.10 (m, 3H, CH₂NH, H-6b), 3.92 (m, 8H, N(CH₂CH₂Cl)₂), 2.56 (t, 2H, J = 7.3 Hz, CH₂Ph), 2.30 (t, 2H, J = 7.3 Hz, COCH₂), 2.11, 2.06, 2.05 (each s, 3x3H, OAc), 1.95 (qt, 2H, CH₂CH₂CH₂).
\[ ^{13}C\text{ NMR (}50\text{ MHz, CDCl}_3\text{) }\delta 171.63\text{ (CO), 144.66, 143.87, 143.54 (C}_A\text{N,}
\]
\[ C_{A^r}\text{N}_2\text{O}_2, C_{A^r}\text{NH), 130.18 (C}_A\text{C}_2\text{H}_2), 129.85, 125.24, 119.05, 112.38 (C}_A\text{Ph), 53.69 (NCH}_2\text{,}
\]
\[ 40.66 (CH}_2\text{Cl}, 36.99 (COCH}_2\text{), 33.97 (CH}_2\text{Ph), 26.86 (CH}_2\text{CH}_2\text{CH}_2\text{).} \]

---

Example 24

(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl-D-4-(4-fluoro-4-bis(2-chloroethyl)amino)phenylbutanamido)phenylearbamate (49) (see scheme 2e)

a) 4-(4-fluoro-4-bis(2-chloroethyl)aminophenyl)-N-(4-nitrophenyl)butanamide (47) was prepared according to the procedure described for compound 18c, starting from chlorambucil (0.5 g, 1.64 mmol) and p-nitroaniline (240 mg, 1.74 mmol). Purification by chromatography on alumina (cyclohexanetethyl acetate 7:3) yielded compound 47 (170 mg, 24 %) as a yellow powder;

\[ \text{C}_{20}\text{H}_{25}\text{Cl}_2\text{N}_3\text{O}_3;}
\]
\[ M = 424.33 \text{ g.mol}^{-1};
\]
\[ \text{Rf} = 0.53 \text{ (cyclohexane:ethy acetate 6:4);}
\]
\[ \text{IR (KBr) v} 3331 \text{ (v}_\text{NH}), 1681 \text{ (v COO)}, 1520 \text{ (v}_\text{NO}_2\text{), 1508 (v O-H), 1349 (v COO)}\text{ cm}^{-1};
\]
\[ ^1H\text{ NMR (200 MHz, CDCl}_3\text{) }\delta 8.16 \text{ (d, 3H, J} = 9.0 \text{ Hz, H}_A\text{NH), 7.73 \text{ (d, 2H, J} = 9.0 \text{ Hz, H}_A\text{NH), 7.05 \text{ (d, 2H, J} = 8.5 \text{ Hz, H}_A\text{NH), 6.59 \text{ (d, 2H, J} = 8.5 \text{ Hz, H}_A\text{NH), 3.72-3.55 \text{ (m, 8H, N(CH}_2\text{CH}_2\text{Cl)}_2\text{), 2.60 \text{ (t, 2H, J} = 7.3 \text{ Hz, CH}_2\text{Ph), 2.43 \text{ (t, 2H, J} = 7.4 \text{ Hz, COCH}_2\text{), 2.01 \text{ (q, 2H, CH}_2\text{CH}_2\text{CH}_2)}\text{).}
\]
b) 4-(4-aminophenyl)-4-(4-tbis(2-chloroethyl)amino)phenylbutanamido (49)

After reduction in the same conditions as those used for the nitro compound 19a, the amine 48 (250 mg, 75%) was obtained as a light yellow solid after purification by silica gel chromatography, using cyclohexane/ethyl acetate (4:6) as eluent:

\[ \text{C}_{20}\text{H}_{22}\text{Cl}_{2}\text{N}_{3}\text{O} \; \]
\[ M = 394.34 \text{ g mol}^{-1}; \]
\[ RF = 0.32 \text{ (cyclohexane:ethyl acetate 4:6);} \]
\[ ^1H \text{ NMR (200 MHz, CDCl}_3) \delta 7.24 \text{ (d, 2H, } J_{\text{NN}} = 8.4 \text{ Hz, } H_{\text{Ar}}), 7.08 \text{ (d, 3H, } J_{\text{NN}} = 8.7 \text{ Hz, } H_{\text{Ar}}, \text{ NH}). \]
\[ 6.62 \text{ (2d, 2x2H, } J_{\text{NN}}, J_{\text{NN}'}, H_{\text{Ar}}) 3.74-3.56 \text{ (m, 8H, N(CH}_2\text{CH}_2\text{Cl})_2), 2.60 \text{ (t, 2H, } J = 7.3 \text{ Hz, CH}_2\text{Ph), 2.30 \text{ (t, 2H, } J = 7.4 \text{ Hz, COCH}_2)_1.99 \text{ (qt, 2H, CH}_2\text{CH}_2\text{CH}_2);} \]
\[ ^13C \text{ NMR (50 MHz, CDCl}_3) \delta 170.98 \text{ (CO), 144.47, 134.33 (CA}_N\text{, C}_A\text{NH}_2), 130.71 \text{ (C}_A\text{CH}_2), 129.84 \text{ (CHA)}, 129.39 \text{ (CA}_N\text{), 122.10, 115.48, 112.30 (CHA), 53.70 (NCH}_2), 40.67 \text{ (CH}_2\text{Cl), 36.75 (COCH}_2)_3, 34.11 \text{ (CH}_2\text{Ph), 27.34 (CH}_2\text{CH}_2\text{CH}_2).} \]

c) 4-(4-(4-tbis(2-chloroethyl)aminophenyl)butanamido)phenylcarbamate (49) was prepared according to the procedure described for compound 46, starting from amine 48 (100 mg, 0.254 mmol) and carbonate 41 as a α/β mixture (118 mg, 0.249 mmol). Chromatography on silica gel using CH\(_2\text{Cl}_2\)/ethyl acetate (9:1) as eluent gave compound 49 (β) (77 mg, 42 %) as a white powder:

\[ 0.33H\text{OCl}_2\text{FN}_3\text{Oid; } \]
\[ M = 728.60 \text{ g mol}^{-1}; \]
\[ RF = 0.46 \text{ (cyclohexane:ethyl acetate 5:5);} \]
\[ ^1H \text{ NMR (200 MHz, CDCl}_3) \delta 7.43 \text{ (d, 3H, } J_{\text{NN}} = 8.8 \text{ Hz, } H_{\text{Ar}}, \text{ NH), 7.31 \text{ (d, 2H, } J_{\text{NN}} = 7.24 \text{ (br s, IH, NH), 7.07 \text{ (d, 2H, } J_{\text{NN}} = 8.5 \text{ Hz, HA}), 6.61 \text{ (d, 2H, } J_{\text{NN}} = 8.8 \text{ Hz, HA}), 5.83 \text{ (dd, IH, } J_{\text{NN}} = 8.1 \text{ Hz, } J_{\text{NN}} = 2.9 \text{ Hz, H-I), 5.41 \text{ (td, IH, } J_{\text{NN}} = 9.2 \text{ Hz, } J_{\text{NN}} = 14.3 \text{ Hz, H-3), 5.09 \text{ (t, IH, } J_{\text{NN}} = 9.7 \text{ Hz, H-4), 4.48 \text{ (td, IH, } J_{\text{NN}} = 50.8 \text{ Hz, H-2), 4.33 \text{ (dd, IH, } J_{\text{NN}} = 12.8 \text{ Hz, } J_{\text{NN}} = 4.3 \text{ Hz, H-6a), 4.10 \text{ (dd, IH, } J_{\text{NN}} = 3.1 \text{ Hz, H-6b), 3.89 \text{ (ddd, IH, } H-S),} \]

(49)
3.74-3.56 (m, 8H, N(CH₂CH₂Cl)₂), 2.60 (t, 2H, J = 7.3 Hz, CH₃Ph), 2.33 (t, 2H, J = 7.4 Hz, COCH₂), 2.10-1.96 (m, HH, OAc, CH₂CH₂CH₂);

31C NMR (50 MHz, CDCl₃) δ 171.43 (NHCO), 170.71, 170.00, 169.70 (COCH₃), 150.92 (CONH), 144.51 (C₂N), 134.40, 133.17 (C₃NH), 130.52 (QMCU₂), 129.79, 120.95, 119.90, 112.32 (CH₂), 92.49 (C-I, JHF = 23.8 Hz), 88.27 (C-2, J₂F = 191.3 Hz), 72.83 (C-3, J₃F = 19.0 Hz), 72.65 (C-5), 67.74 (C-4, J₄F = 7.4 Hz), 6L44 (C-6), 53.65 (NCH₂), 40.67 (CH₂Cl), 36.77 (COCH₂), 34.08 (OCH₂Ph), 27.18 (CH₂CH₂CH₂), 20.74, 20.63 (CH₂);

MS (ESI) m/z 728.25 [M+1]+ (Exact Mass: 728.20)

Example 25

R3A.β-tri-O-acetyl^-deoxy-1-fluoro-B-D-glucoPyranosv 1) 2-f4-(4-(4-fbls(2-Cloroethyl^amino)phenyllbuta α-amido^phe βylaminol-Z-oxoethylcarbamate (52) (see Scheme 2e)

a) (3>4.6-sri^-?-acyl-2-deoa:v-2-fluor 0β^-D-plucopyranosv 1) 2-(4-

NitrDhenylamtnoV2-oxoethylcarbamate (SO) was prepared according to the procedure described for compound 46, starting from amine hydrobromide 43 (0.3 g, 1.09 mmol) and carbonate 41 (p) (0.51 g, 1.08 inmol). Chromatography on silica gel using cyclohexane: ethyl acetate (4:6) as eluent provided compound 50 (β) (0.510 g, 89%) as a white powder:

C₂H₂F₃N₃O₃;

M = 529.43 g·mol⁻¹;

Rf= 0.40 (cyclohexane: ethyl acetate 4:6);

IR (KBr) ν 3349 (vNH), 1747 (vC=O), 1558 (δCH₂), 1513 (vCH₂), 1345 (vCH₃), 1236, 1074, 1038 (vC=O) cm⁻¹;

1H NMR (200 MHz, CDCl₃) δ 8.50 (s, IH, NHPH), 8.22 (d, 2H, J = 9.2 Hz, H₃), 7.72 (d, 2H, H₄), 6.89-5.83 (m, 2H, J₁₂ = 8.2 Hz, J₃-F = 3.0 Hz, H-I, NHCH₂), 5.46 (td, IH, J₂₃ = J₃₄ = 9.3 Hz, J₅₆ = 14.1 Hz, H-3), 5.10 (t, 1H, J₄₅ = 9.5 Hz, H-4), 4.46 (td, IH, J₅₆ = 50.9 Hz, H-2), 4.31 (dd, IH, J₆₇ = 12.7 Hz, J₅₆ = 4.1 Hz, H-6a), 4.18-4.07 (m, 3H, J₃, J₃₄ = 5.7 Hz, H-6b, NHCH₂), 3.92 (ddd, IH, J₅₆ = 2.2 Hz, H-5), 2.12, 2.08, 2.05 (each s, 3*3H, OAc).
b) \(3,4,6\text{-tri-}Q\text{-acetyl-2-deoxy-2-fluoro-B-P-glucopyranosyl}\) 2-(4-
\(\text{aminoDheQylamto>2-nxoethylcarbamate}\) (51)

After reduction in the same conditions as those used for the nitro compound
19a, the amine 51 (440 mg, 93%) was obtained starting from compound 50 (500 ing, 0.944
mmol) and after filtration on celite, as a solid which was used in the next step without
further purification:

\[
\text{C}_{21}\text{H}_{28}\text{FN}_{3}\text{O}_{6};
\]

\[
\text{M} = 499.45 \text{g.mol}^{-1};
\]

\[
\text{Rf} = 0.38 \text{(cyclohexane:ethyl acetate 2:8)};
\]

IR (KBr) \(\nu\) 3367 (\(\text{NH}\)), 1747, 1681 (\(\nu\text{C=O}\)), 1516 (\(\delta\text{NH}\)), 1237, 1074, 1037 (\(\nu\text{C-O}\))
\(\text{cm}^{-1}\

\(1\text{H NMR} (200 \text{MHz, CDCl}_3) \delta 8.02 (s, \text{IH, NHPh}), 7.22 (d, 2\text{H}, J_0 = 8.5 \text{Hz},
\text{HAT}), 6.62 (d, 2\text{H}, J_0 = 8.5 \text{Hz}, \text{HAT}), 6.11 (\text{br t, IH, } J = 5.2 \text{Hz}, \text{NHCH}_2), 5.81 (\text{dd, IH, } J = 8.0 \text{Hz},
\text{J}_{1,2} = 3.0 \text{Hz}, \text{H-I}), 5.42 (\text{td, IH, } J_{2,3} = J_{3,4} = 9.3 \text{Hz}, J_{3,4} = 14.2 \text{Hz}, \text{H-3}), 5.08 (\text{t, IH, } M, s = 9.7
\text{Hz}_2\text{H-4}), 4.45 (\text{td, IH, } J_{2,3} = 50.4 \text{Hz}, \text{H-2}), 4.28 (\text{dd, IH, } J_{6,6a} = 12.5 \text{Hz}, J_{5,6} = 3.9 \text{Hz}, \text{H-6a}),
4.08 (\text{dd, IH, } J_{5,6} = 1.8 \text{Hz}, \text{H-6b}), 3.98 (\text{d, 2H, NHCH}), 3.86 (\text{ddd, IH, H-5}), 3.14
(\text{br s, 2H, NK}_2), 2.10, 2.06, 2.03 (\text{each s, 3x3H, OAc});
\]

\(13\text{C NMR} (50 \text{MHz, CDCl}_3) \delta 170.73, 170.09, 169.66 (\text{OCH}_2), 166.09
(\text{CONH}), 154.15 (\text{OCONH}), 143.99 (C_{\beta}\text{NH}_2), 128.37 (C_{\alpha}\text{NH}), 122.42, 115.54 (\text{CHA}_{\beta},
20 \text{92.85 (C-I, } J_{1,2} = 23.7 \text{Hz}), 88.34 (C-2, J_{2,3} = 191.0 \text{Hz}), 72.84 (C-3, J_{3,4} = 19.7 \text{Hz}). 72.65
(C-5), 67.74 (C-4, \text{A}_{2,4} = 7.3 \text{Hz}), 61.45 (C-6), 45.08 (\text{NHCH}_2), 20.80, 20.67 (\text{CH}_3).
\]

c) \(3,4,6\text{-tri-0-acet-}L\text{-2-deQy-2-fluoro-B-D-glucopyranosyl}\) 2-(4-
\(\text{fbij5f2-chloroethyl)aminolphenylbutaiamido\) phenylam} \text{nol-2-oxoethyl)carbamate}

\(52\) was prepared according to the procedure described for compound 18c, starting from
chlorambucil (244 mg, 0.802 mmol) and amine 51 (200 mg, 0.400 mmol). Purification by
chromatography on silica gel (cyclohexane:ethyl acetate 4:6) provided compound 52 (270
mg, 86 %) as a solid:

\[
\text{C}_{35}\text{H}_{47}\text{Cl}_2\text{FN}_4\text{O}_6;
\]

\[
\text{M} = 785.65 \text{g.mol}^{-1};
\]

\[
\text{Rf} = 0.37 \text{(cyclohexane:ethyl acetate 4:6)};
\]
IR (KBr) ν 3350 (vNH), 1750, 1676 (vC =O), 1517 (5NH), 1236, 1074, 1037 (vC =O) cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ 8.30 (s, IH, NH), 7.56 (s, IH, NH), 7.31 (s, 4H, HAT), 7.07 (d, 2H, J= 8.6 Hz, HAr), 6.61 (d, 2H, J= 8.6 Hz, HAr), 6.12 (br t, IH, J = 5.2 Hz, NHCH₂), 5.81 (dd, IH, J₁₂ = 8.0 Hz, J₁₂ = 2.9 Hz, H-1), 5.40 (td, IH, J₂₃ = J₂₄ = 9.2 Hz, J₃₄ = 14.1 Hz, H-3), 5.08 (t, IH, J₃₄ = 9.7 Hz, H-4), 4.45 (td, IH, J₂₄ = 50.9 Hz, H-2), 4.29 (dd, IH, J₆₇ = 12.4 Hz, J₅₆ = 4.1 Hz, H-6a), 4.14-4.00 (m, 3H₃ NHCl, H-6b), 3.88 (m, IH, H₂), 3.73-3.56 (m, 8H, N(CH₂CH₂Cl)₂), 2.60 (t, 2H, J = 7.3 Hz, CH₂Ph), 2.35 (t, 2H, J = 7.0 Hz, COCH₂), 2.10-1.96 (m, HH, OAc₅ CH₂CH₂CH₂);

¹³C NMR (50 MHz, CDCl₃) δ 171.88 (PhNHCO), 170.79, 170.13, 169.68 (C=CH₃), 166.86 (CH₂ONH), 154.24 (OCONH) 5 144.53 (C=N), 134.40, 133.79 (CA(NH), 130.47 (CA,CH₂), 129.81, 121.51, 121.21 112.29 (CH₂), 92.79 (C-I, J₉ = 24.1 Hz), 88.35 (C-2, J₉ = 191.1 Hz), 72.77 (C-3, J₃₄ = 20.8 Hz), 72.56 (C-S), 67.69 (C-4, J₄ = 6.8 Hz), 61.44 (C-6), 53.65 (NCH₂), 44.94 (NHCH₂), 40.68 (CH₂Cl), 36.71 (COCH₂CH₂), 34.11 (CH₂Ph) 5 27.24 (CH₂CH₂CH₂), 20.79, 20.66 (CH₃);

MS (ESI) m/z 785.60 [M+H]⁺ (Exact Mass: 785.24).

Example 26

4-(3-f4,4,6-tri-0-acetv1-2-deoxy-2-fluoro-β-D-fluoc-†yranosyl)ureidoViV-f3)

(44AX,NDbisf2-chloroethylDamlolphenvtiDroDyl)butanamide(58> (see Scheme 2f)

a) AIM 4-isovcanatobutyrlic acid (54)

To a solution of glutaric anhydride (1.68, 14.7 mmol) in allyl alcohol (10 raL) were added NEt₃ (2 inL, 14.4 mmol) and a catalytic amount of DMAP. After 5h at room temperature, the reaction mixture was diluted with ethyl acetate and washed successively with an aqueous solution of 1 N KHSO₄ and brine, followed by drying over anhydrous Na₂SO₄. Evaporation of allyl alcohol provided glutaric acid monoUylester 53 (2.5 g, 99 %) as an oil:

IR (CCl₄) ν 2948 (νOH), 1712 (νC =O) cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ 9.87 (br s, IH, OH), 5.92 (tdd, IH, V = 5.7 Hz, 3J₅₆ = 10.3 Hz, 2J₉₁₀ = 17.2 Hz, OCH₂CH=CH₂), 5.32 (qd, 4J₅₆ = 2J = 1.5 Hz, 5OCH₂CH=CH₃), 5.25 (qd, 4J₅₆ = 1.3 Hz, OCH₂CH=CH₃), 4.59 (td, 2H,
OCH₂CH=CH₂, 2.45, 2.44 (t, 2H, J = 13 Hz, CH₂CH₂CH₂), 1.97 (qt, 2H, CH₂CH₂CH₂);
13C NMR (50 MHz, CDCl₃) δ 179.17 (COOH), 172.71 (CO), 132.19 (CH₂C₂H), 118.49 (=CH₂), 65.34 (OCH₂), 33.20, 33.09 (CU₂Cu₂QHi), 19.89 (CH₂CH₂CH₂).

To a stirred solution of glutaric acid nionoallylester 53 (2.17 g, 12.6 romol) in dry CH₂Cl₂ (40 mL) were added NEt₃ (2.1 raL, 15.1 mmol) and diphenylphosphoiiylazide (3.3 mL, 15.2 romol). After stirring at room temperature for 16 h, the reaction mixture was heated at 60-70°C for 3 h resulting in crude isocyanate 54 (23 % purity) after Curtius rearrangement: CsH₂NO₃; M = 169.18 g/mol; 1H NMR (200MHz, CDCl₃) δ 8.93 (tdd, IH, V = 5.8 Hz, 3Jc₂H = 10.3 Hz, 3AA₂AB = 17.2 Hz, OCH₂CH-CH₂), 5.32 (qd, 4Jd₂ = 3J = 1.5 Hz, OCH₂CH-CH₂), 5.25 (qd, % ars = 1.3 Hz, OCH₂CH=CH₂), 4.60 (td, 2H, OCH₂CH=CH₂), 3.41 (t, 2H, J = 6.5 Hz, CH₂NCO), 2.46 (t, 2H, J = 6.4 Hz, CH₂COO), 1.94 (qt, 2H, CH₂CH₂CH₂).

b) 1H-(3,4,6-tri-O-acetyl-2-deoxy-2-f uoro-β-D-glucoDyranosyl)-N₂-f4-nealButanoatehydro (55) was prepared according to the procedure described for compound 17a, starting from amino-sugar 8 (307 mg, 1 romol) and crude isocyanate 54 (600 nag). Purification by column chromatography on silica gel with ethyl acetate-cyclohexane (5:5) as developing solvent gave compound 55 (252 mg, 53 %) as a colourless oil:

C₂₀H₁₉F₃N₂O₁₀;
M = 476.46 g.ruol⁻¹;
Rf= 0.29 (ethyl acetate-cyclohexane 6:4);
IR(NaCl) ν 3368 (νₘ), 1746 (νc=O), 1557 (SNH), 1232, 1065, 1030 (νCO) cm⁻¹:

1H NMR (200 MHz, CDCl₃) δ 6.47 (br d, IH, J = 8.9 Hz, CH₂N), 5.92 (tdd, IH, J = 5.7 Hz, 3Jc₂H = 10.4 Hz, 3J₄₈ = 17.2 Hz, OCH₂CH=CH₂), 5.63 (br t, IH, J = 5.2 Hz, CONHCH₂), 5.46-5.22 (m, 4H, OCH₂CH=CH₂, H-1, H-3), 5.02 (t, IH, J₃₄₅ = JAS = 9.7 Hz, H-4), 4.59 (m, 2H, 4Jc₂H = 4J₄₈ = 1.2 Hz, OCH₂CH=CH₂), 4.33 (td, IH, Jₚₜ = J₃₋₈ = 9.1 Hz, J₂₋₄ = 50.5 Hz, H-2), 4.34 (dd, IH, J₆₋₆₈ = 12.5 Hz, J₅₋₆₈ = 3.9 Hz, H-6a), 4.06 (dd, IH, J₅₋₈ = 1.2 Hz, H-6b), 3.87 (m, IH, H-5), 3.24 (br q, 2H, J = 6.1 Hz, NHCH₂), 2.41 (t, 2H, J = 7.1 Hz, CH₂CO), 2.07, 2.06, 2.04 (each s, 3x3H, OAc), 1.83 (qt, 2H, CH₂CH₂CH₂).
13C NMR (50 MHz, CDCl3) δ 173.49 (COO), 170.77, 169.93, 169.91 (QOCH3), 157.22 (NHCONH), 132.06 (CH2CH=COCH3), 128.04 (CH2), 118.46 (=CH2), 88.45 (C-2, / J= 190.0 Hz), 79.44 (C-1, J= 22.0 Hz), 73.64 (C-3, / J= 19.3 Hz), 73.03 (C-5), 68.08 (C-4, J= 6.8 Hz), 65.38 (OCH3), 61.69 (C-6), 39.61 (NHCH2), 31.43 (CH2CO), 25.12 (CH2CH2CH2), 190.0 (NHCONH), 185.4 (COOH), 174.31 (COO), 173.49 (COO), 170.77, 169.93, 169.91 (QOCH3), 157.22 (NHCONH), 132.06 (CH2CH=COCH3), 128.04 (CH2), 118.46 (=CH2), 88.45 (C-2, / J= 190.0 Hz), 79.44 (C-1, J= 22.0 Hz), 73.64 (C-3, / J= 19.3 Hz), 73.03 (C-5), 68.08 (C-4, J= 6.8 Hz), 65.38 (OCH3), 61.69 (C-6), 39.61 (NHCH2), 31.43 (CH2CO), 25.12 (CH2CH2CH2).
d) \(3-(4-\text{[bis(2-chloroethyl')aminolphen γ Upropyiaj[i-ne (57]}

A solution of chlorambucil (700 mg, 2.30 mmol) in acetone (2 mL) was stirred under ice-cooling for 10 min before addition of NEt₃ (0.38 mL, 2.74 mmol) and ethylechloroformate (0.26 mL, 2.72 mmol) successively. Thirty minutes later at 0°C, a solution of sodium azide (0.30 g, 4.62 mmol) in 2 mL water was added. Stirring is maintained, at 0°C, for 1 h, then ice water was added to terminate the reaction. The thus-obtained mixture was extracted with toluene (3x50 mL). The combined, dried, organic layers were heated under reflux for 2.5 h. After evaporation of the solvent wider reduced pressure, 20 mL of HCl SN was added, followed by heating under reflux for 20 min. After cooling, the reaction mixture was adjusted to pH 8 with concentrated aqueous ammonia, diluted with water, followed by extraction with ethyl acetate (3x100 mL). The combined extracts were washed respectively with water and brine, dried over anhydrous Na₂SO₄ and concentrated to afford compound 57 (610 mg, 96%) as a crude light yellow oil, which was used in the next step without further purification:

\[ \text{C}_{11}\text{H}_{20}\text{Cl}_{2}\text{N}_{2}; \]

\[ \text{M} = 275.22 \text{ g.mol}^{-1}; \]

\[ \text{RF} = 0.37 \text{ (CH}_{2}\text{Cl}_{2};\text{ethanol 8:2);} \]

\[ \text{IR (NaCl) v 3364 (vMNHz), 3292 (v}_{\text{NH}}\text{H}_{2}, 1520 (6N}_{\text{H}}\text{H}) \text{ cm}^{-1}; \]

\[ ^{1}\text{H NMR (200 MHz,CDCl}_{3} \text{) δ 7.08 (d, 2H, J = 8.7 Hz, H}_{\text{CH}}\text{); 6.62 (d, 2H, H}_{\text{A}}\text{).} \]

\[ 3.75-3.57 \text{ (m, 8H, N(CH}_{2}\text{Cl}_{2} \text{)}_{2}); 2.57 \text{ (s, 2H, J = 7.1 Hz, NH}_{2}\text{CH}_{2}); 2.56 \text{ (t, 2H, J = 7.7 Hz, CH}_{2}\text{Ph); 1.90 (s, 2H, H}_{\text{A}}\text{); 1.74 (qt, 2H, J = 7.4 Hz, CH}_{2}\text{H}_{\text{A}}\text{CH}_{2};} \]

\[ ^{13}\text{C NMR (50 MHz, CDCl}_{3} \text{) δ 129.77, 112.39 (CHA); 53.71 (NCH}_{2}); 40.70 \text{ (CH}_{2}\text{Cl); 39.50 (NH}_{2}\text{CH}_{2}); 31.51 (CH}_{2}\text{Ph); 29.47 (CH}_{2}\text{CH}_{2}\text{CH}_{2};} \]

e) \(4-(3-f3.4,6-tri-O-flcetyl-2-deoxy-2-fluoro-B-D-glucopyranosv \text{ ureidoV}

\[ \text{N-(γ-f3.4,6-tris(2-chloroethyl'amino)propylbutanamide (58) was prepared} \]

according to the procedure described for compound 18c, starting from acid 56 (110 mg, 0.253 mmol) and amine 57 (79 mg, 0.288 mmol). Chromatography on silica gel (2:8 cyclohexane:ethyl acetate to pure ethyl acetate, followed by ethyl acetate:methanol 95:5) gave expected compound 58 (76 mg, 43%):

\[ \text{C}_{96}\text{H}_{12}\text{Cl}_{2}\text{F}_{2}\text{N}_{2}\text{O}_{5}; \]

\[ \text{M} = 693.59 \text{ g.mol}^{-1}; \]
Rf= 0.45 (ewyl acetate:methanol 95:5);
IR (NaCl) v 3326 (v N\H), 1747, 1634 (\C=O), 1574, 1519 (\delta N\H), 1259, 1028 (v C-\O).

The resulting residue was purified by silica gel chromatography, using petroleum benzine:ethyl

Example 27

\textit{\textbf{N-14-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-1-\textsubscript{\textbeta}D-glucopyranosyl \gamma-carboav 1)\textit{phenH4-(4-fbis(2-chloroethyl)W \pi inq}phenv))}

bmtanamide (61) (see Scheme 2f

a) 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-1-(4-nitrobenzoyl)-(\textsubscript{\textbeta}D-glucopyranose (59)

To a stirred solution of compound 9 (238 mg, 0.77 mmol) and NEt\textsubscript{3} (130 \textmu L, 0.93 mmol) in anhydrous \textit{CH\textsubscript{2}Cl\textsubscript{2}} (9 mL) cooled in an ice bath, was added dropwise a solution of 4-nitrobenzoyl chloride (151 mg, 0.81 minol) in anhydrous \textit{CH\textsubscript{2}Cl\textsubscript{2}} (3 inL). The mixture was stirred at room temperature for 7h30. The reaction was quenched with 2 mL of methanol. After evaporation, the residue was diluted with \textit{CH\textsubscript{2}Cl\textsubscript{2}} and washed consecutively with water, 1N aqueous HCl, saturated aqueous NaHC\textsubscript{O}3 and water. Then the organic layer was dried over MgSO\textsubscript{4} and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography, using petroleum benzine:ethyl
acetate (6:4) as eluent, to yield compound 59 (321 mg, 91 %) as a yellow powder (α/β ratio = 45/55):

\[
\text{C}_{19}\text{H}_{20}\text{FNNO}_{1}\;,
\]

\[
\text{M} = 457.37 \text{ g.mol}^{-1};
\]

\[
\text{Rf}= 0.34 \text{ (petroleum benzine:ethyl acetate 7:3)};
\]

IR (NaCl) v 1748 (\nu_{c\cdots n}), 1532 (\nu_{\text{anNO}}, 1267, 1237, 1078, 1035 (\nu_{c\cdots o}) \text{ cm}^{-1};

^1H \text{ NMR} (200 \text{ MHz, CDCl}_3) \delta 8.39-8.25 \text{ (m, SH, H}_{\text{Ar}} \alpha+\beta), 6.69 \text{ (d, IH, J}_{1\beta} = 3.9 \text{ Hz, H-1} \alpha), 6.07 \text{ (dd, IH, J}_{1\beta} = 8.0 \text{ Hz, J}_{1\beta} = 3.1 \text{ Hz, H-1} \beta), 5.70 \text{ (td, IH, J}_{2\alpha} = J_{3\beta} = 9.2 \text{ Hz, J}_{3\beta} = 14.3 \text{ Hz} J_5 \text{ H-3} \beta), 5.19, 5.16 \text{ (t, IH, J}_{1\beta} = 9.8 \text{ Hz, H-4} \alpha/\beta), 4.83 \text{ (ddd, IH, J}_{2\beta} = 48.1 \text{ Hz, H-2} \alpha), 4.68 \text{ (td, IH, J}_{2\beta} = 50.8 \text{ Hz, H-2} \beta), 4.39-4.29 \text{ (ar, 2H, H-6a} \alpha+\beta), 4.25-4.06 \text{ (m, 3H, H-6b} \alpha+\beta, H-5\alpha), 4.02 \text{ (ddd, IH, J}_{3\alpha} = 4.4 \text{ Hz, } J_{5\alpha} = 2.2 \text{ Hz, H-5} \beta), 2.14, 2.13, 2.09, 2.08 \text{ (each s, OAc} \alpha+\beta);

^13C \text{ NMR} (50 \text{ MHz} \text{ CDCl}_3) \delta 170.60, 169.35 \text{ (COCH}_3 \alpha+\beta), 162.85, 162.78

\text{(COPh} \alpha+\beta), 151.28 \text{(C}_{\text{Ar}}\text{NO}_2 \alpha+\beta), 134.14, 133.97 \text{(CA}_{\text{Ar}}\text{CO} \alpha+\beta), 131.47, 131.35, 124.03, 123.84 \text{(CH}_{\text{Ar}} \alpha+\beta), 92.49 \text{(C-1} \beta, J_{1\beta} = 24.0 \text{ Hz), 90.02 \text{(C-1} \alpha, J_{1\alpha} = 22.6 \text{ Hz), 88-34 \text{(C-2} \beta, J_{2\beta} = 190.7 \text{ Hz), 86.38 \text{(C-2} \alpha, J_{2\alpha} = 194.9 \text{ Hz), 73.18 \text{(C-5} \beta, 72.74 \text{(C-5} \beta, J_{1\beta} = 19.5 \text{ Hz), 70.59 \text{(C-3} \beta, J_{3\beta} = 19.4 \text{ Hz), 70.25 \text{(C-5} \alpha, 67.68 \text{(C-4} \alpha/\beta, J_{4\alpha/\beta} = 7.1 \text{ Hz), 67.45 \text{(C-4} \alpha/\beta, J_{4\alpha/\beta} = 7.4 \text{ Hz), 61.42, 61.34 \text{(C-6} \alpha+\beta), 20.76, 20.67 \text{(CH}_3 \alpha+\beta).}

b) \text{3,4,6-tri-O-acetyl-1-(-4-aminobenzoyl)-2-deQvy-2-F uoro-α.B-D-glucoDyranose (6O)}

After reduction in the same conditions as those used for the nitro compound 19a, the amine 60 (268 mg, 92%) was obtained starting from compound 59 (313 mg, 0.685 iranol) after filtration on celite, as a solid. The ^1H \text{ NMR analyses showed a mixture of the two anomeres (α/β ratio = 40/60) and it was used directly in the next step without further purification;}

\[
\text{C}_{19}\text{H}_{22}\text{FNNO}_{5};
\]

\[
\text{M} = 427.38 \text{ g.mol}^{-1};
\]

\[
\text{Rf}= 0.26 \text{ (petroleum benzine:ethyl acetate 6:4)};
\]
IR (NaCl) ν 3483 (v_{\text{NH}} Hz), 3384 (ν_{\text{NH}} m), 1747 (ν_{\text{C=O}}), 1603 (ν_{\text{C-H}}), 1233, 1072, 1036 (ν_{\text{C-O}}); cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ 7.91, 7.89 (d, 4H, J₀ = 8.6 Hz, H₄); 6.02 (dd, 1H, J₁,F = 3, 1 Hz, H₁); 5.69 (td, IH, J₁,F = 4.0 Hz, J₂,F = 14.4 Hz, H₃); 5.15, 5.13 (t, 1H, J₄,F = 9.7 Hz, H-4); 4.75 (ddd, 1H, J₂,F = 2.0 Hz, H-2); 4.62 (td, 1H, J₂,F = 50.7 Hz, H-2); 4.36-4.21 (m, 2H, H-6a); 4.20-4.14 (m, 2H, H-6b); 3.94 (ddd, 1H, J₅,F = 4.4 Hz, H-5); 2.11, 2.10, 2.07, 2.05 (each s, OAc α+β);

¹³C NMR (50 MHz, CDCl₃) δ 170.54, 170.16, 169.87, 169.56, 169.48 (COCH₃ α+β), 164.31, 164.17 (QOPh α+β), 152.32, 152.27 (C₆H₅NH₂ α+β), 132.34, 132.21 (CH₄ α+β), 116.99, 116.92 (C₆H₅CO α+β), 113.72, 113.58 (CH₄ α+β), 91.32 (C-1 β, J₁,F = 24.0 Hz), 88.41 (C-2 β, J₂,F = 190.5 Hz), 88.31 (C-1α, J₁,F = 21.8 Hz), 86.37 (C-2 α, J₂,F = 193.9 Hz), 72.83 (C-3 β, J₃,F = 19.7 Hz), 72.48 (C-5 β), 70.82 (C-3 α, J₃,F = 19.4 Hz), 69.37 (C-5α), 67.70 (C-4 α+β, J₄,F = 6.5 Hz), 67.51 (C-4 α+β, J₄,F = 7.5 Hz), 61.40, 61.30 (C-6 α+β), 20.63, 20.55, 20.46 (CH₃ α+β).

c) \(\text{V-f4-}(3.4.6-\text{tril-9-acetyl-2-deoxy-2-f uoro-α,B-D-}\text{elucopyranosloxy carbon vinylhepyn-4-}4\text{f4-fbis(2-chloroethylDaminolphenyKbutanamidc}(61)\text{ was prepared according to the procedure described for compound 18c, starting from chlorambucil (63 mg, 0.21 mmol) and amine 60 (80 mg, 0.19 mmol), Chromatography on silica gel (petroleum benzine;ethyl acetate 5:5) yielded compound 61 (40 mg, 30 %) as an oil (racemate):}

\[\text{C}_{33}\text{H}_{30}\text{Cl}_{2}\text{F}_{2}\text{O}_{10}\];

\[\text{M = 713.58 g mol}^{-1}\];

\[\text{RF = 0.54 (petroleum benzine; ethyl acetate 5:5)}\];

IR (NaCl) v 3351 (VNH), 1744 (voo), 1519 (δ_{\text{NH}}), 1367 (δ_{\text{C=H}}), 1243, 1078, 1037 (Vc-O); cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ 8.05, 8.04 (d, 2H, J₀ = 8.8 Hz, H₁α); 7.65, 7.62 (d, 2H, H₁α); 7.47, 7.45 (s, IH, NH α+β); 7.09, 7.08 (d, 2H, J₀ = 7.1 Hz, H₁α); 6.64-6.60 (m, SH, H₁α); 5.68 (dd, 1H, J₄,F = 3.1 Hz, H₁β).
(td, 1H, J_{2,3} = 5.45) 5.14 (td, IH, J = 9.2 Hz, H-4 α), 4.77 (dd, IH, J_{4,5} = 3.9 Hz, H-5 F)
(14.4 Hz, H-3 β), 5.16, 5.45 (td, 1H, J_{4,5} = 9.8 Hz, H-4 α), 4.77 (dd, IH, J_{4,5} = 3.9 Hz, H-5 F)
= 48.2 Hz, H-2 α), 4.64 (td, 1H, J_{2,3} = 50.7 Hz, H-2 β), 4.35-4.28 (m, 2H, H-6a γ+β), 4.21-
4.13 (m, 2H, H-6b α/β, H-5 α), 4.06 (dd, IH, J_{5,6} = 12.1 Hz, J_{5,6} = 1.7 Hz, H-6b α/β),

3.94 (dd, IH, J_{5,6} = 4.4 Hz, J_{5,6} = 2.2 Hz, H-S β), 3.75-3.56 (m, 16H, N(CH_{3}CH_{2}Cl)_{2} α+β), 2.63 (t, 4H, J = 7.2 Hz, C_{H}Ph α+β), 2.39, 2.38 (t, 2H, J = 7.4 Hz, COCH_{2} α/β), 2.12-2.00 (m, 22H, OAc α+β, CH_{2}CH_{2}CH_{2} α+β);

13C NMR (50 MHz, CDCl_{3}) δ 171.64, 170.67, 170.26, 170.01, 169.65 (CO α+β), 163.95 (QOPh α+β), 144.47, 143.34 (2C-α N α+β), 131.64, 131.50 (CH-α+β),
130.45 (CA_{H}CH_{2} α+β), 129.82 (CHAr cc-β), 123.72, 123.59 (Q_{α}CO α+β), 119.05, 118.82,
112.42 (CHAr α+β), 91.83 (C-1 β, J_{1,2} = 23.2 Hz), 88.43 (C-2 β, J_{1,2} = 190.6 Hz), 88.98 (C-16 β, J_{1,2} = 21.9 Hz), 86.45 (C-2 α, J_{1,2} = 195.1 Hz), 72.91 (C-3 β, J_{3,4} = 19.2 Hz), 72.85 (C-5 β), 70.84 (C-3 α, J_{3,4} = 19.4 Hz), 69.77 (C-5 α), 67.77 (C-4 α/β, J_{4,5} = 7.1 Hz), 67.53 (C-4 α/β, J_{4,5} = 6.6 Hz), 61.48, 61.42 (C-6a α+β), 53.69 (CH_{2}N α+β), 40.59 (CH_{2}Cl α+β),
36.97 (COCH_{2} α+β), 34.01 (CH_{2}Ph α+β), 26.92 (CH_{2}CH_{2}CH_{2} α+β), 20.76 (CH_{2} α+β);

ESI-MS : m/z = 713.42 [M+H^{+}] (exact mass = 713.20).

Example 28
7V-f34,6-tri-Q-acetvl-2-deoxy-2-f uoro-S-P-glucopyranosyl]-4-D-4-t4f4-
tbif2-chloroethalamidolnolDhenvIibuta namlndoacetain idolbenzainide (64) (sec_Scheme_2Ω)

a) benzyl 2-t4-f3.4.6-tri-Q-acetvl-2-deo \chi_{24} \alpha f uoro-o-B-D-
glucopy aosylcarbamovDphen ylaminol -2-oxoeth ylcarbamate (62) was prepared

according to the procedure described for compound 18c, starting from Cbz-glycine (215
rng. 1.03 mmol) and amine 19a (400 mg, 0.938 mmol). Chromatography on alumina (ethyl
acetate:ethanol 9:1) yielded compound 62 (290 mg, 50 %) as a white powder:
C_{32}H_{32}FN_{3}On;
M = 617.58 g/mol^{1};

{1H NMR (200 MHz, DMSO-δ)} 6 10.33 (s, IH, PhNHCO), 9.25 (d, IH, J = 8.5 Hz, H_{4β}), 7.71 (d, 2H, H_{A}), 7.61 (br t, IH, J = 6.3 Hz,
C H 2 NH), 7.37 (m, 5H, Ph), 5.74-5.51 (m, 2H, J 3F = 14.3 Hz, H-I, H-3), 5.05 (s, 2H, CH 2 Ph), 4.89 (t, IH, J 3F = 9.1 Hz, H-4), 4.67 (td, IH, J 3F = 8.9 Hz, J 2F = 50.2 Hz, H-2), 4.21-4.16 (m, 2H, 2H-6), 3.98 (m, IH, H-5), 4.18 (d, 2H, CH 2 NH), 2.05, 2.00, 1.98 (each s, 3 × 3H, OAc);

13C NMR (50 MHz, DMSO-^D) δ 170.53, 170.08, 169.88, 169.08, 166.60 (CO), 157.14 (NHCOO), 142.91 (C AHN), 137.57 (CA CCH 2 ), 129.16, 128.90, 128.34, 128.26 (CHAI), 127.93 (C ACO), 118.83 (CH AI), 88.70 (C-2, J 2F = 185.1 Hz), 77.71 (C-I, J 1F = 22.8 Hz), 73.41 (C-3, J 3F = 19.6 Hz), 72.49 (C-5), 68.36 (C-4, J 4F = 7.8 Hz), 66.04 (CH 2 Ph), 62.16 (C-6), 44.76 (COCH 2 NH), 21.06, 20.99, 20.92 (CH 3 ).

b) \[\alpha\text{-}[3,4,6-tri-0-acetyl-2-deoxy-\beta-D-glucopyranosyl]-4-[2-(2-amino-4-fluorophenyl)ethyl]aniline (64)\] was prepared according to the procedure described for compound 15a, starting from 63 (140

The deprotection of the N-Cbz protected compound 62 (390 mg, 0.631 mmol) was unaffected by hydrogenation as described for derivative 19b and yielded compound 63 (305 mg, 100%) as a white solid:

C 2 H 2 O 2 F N 2 O 2 ;
M = 483.44 g mol^{-1};
IR (KBr) ν 3446 (ν NH), 1747 (νC=O est), 1653 (νC=O amide), 1540 (δ NH), 1249, 1036 (νC-O) cm^{-1};

1H NMR (200 MHz, CDCl 3 ) δ 9.77 (br s, JH, NH), 7.80 (d, 2H J 1 = 7.7 Hz, NH, H A 0 ) 7.61 (d, 2H, H A 0 ), 5.59 (br t, IH, H-I), 5.42 (td, IH, J 3F = 9.6 Hz J 3F = 13.6 Hz, H-3), 5.07 (t, IH, J 3F = 9.6 Hz, H-4), 4.63 (td, IH J 3F = 50.4 Hz, H-2), 4.32 (br d, IH, H-6a), 4.07 (br d, IH, H-6b), 3.90 (m, IH, H-5), 3.56 (s, 2H, CH 2 NH 2 ), 2.74 (br s, 2H, NH 2 ), 2.07, 2.03 (each s, 9H, OAc);

13C NMR (50 MHz, DMSO-^D) δ 171.64, 170.01, 169.56, 169.38, 166.08 (CO), 142.16 (CArNH), 128.63 (CHA ), 127.47 (CA CCO), 118.31 (CHA*), 88.24 (C-2, J 2F = 185.9 Hz), 77.15 (C-I, J 1 = 22.8 Hz), 72.87 (C-3, J 3F = 19.3 Hz), 72.00 (C-5), 67.84 (C-4, J 4F = 7.6 Hz), 61.62 (C-6), 45.03 (COCH 2 ), 20.53, 20.46, 20.39 (CH 3 ).

c) \[\alpha\text{-}[3,4,6-tri-0-acetyl-2-deoxy-\gamma-2-fluoro-\beta-D-glucopyranosyl]-4-[2-(2-amino-4-fluorophenyl)ethyl]aniline acetamidobenzotriazanide (64)\] was prepared according to the procedure described for compound 15a, starting from 63 (140
ing, 0.290 mmol) and chlorambucil (97 mg, 0.319 mmol). Chromatography on silica gel (cyclohexanediethyl acetate 3:7), provided the title compound 64 (130 mg, 58%) as a white solid:

\[
C_{35}H_{43}Cl_2FNaO_{10};
\]

\[M = 769.64 \text{ g-mol}^{-1};\]

\[R_f = 0.64 \text{ (cyclohexane:ethyl acetate 1:9); IR(KBr) } v 3385, 1748, 1522, 1507, 1244, 1039 \text{ (voo) cm}^{-1};\]

\[\text{H NMR } (200 \text{ MHz, OMSO-}d_2) \delta 10.28 \text{ (s, } \text{IH}_3\text{PhNHCO)}, 9.23 \text{ (d, IH, } J = 8.8 \text{ Hz, C}_1\text{NH}), 8.19 \text{ (br t, IH, } J = 5.8 \text{ Hz, } \text{CH}_2\text{NH}), 7.88 \text{ (d, } 2\text{H, } J_0 = 8.9 \text{ Hz, } \text{H}_A), 7.70 \text{ (d, } 2\text{H, } J_\alpha \text{ HAT}), 7.04 \text{ (d, } 2\text{H, } J'_0 = 8.6 \text{ Hz, HAT}), 6.66 \text{ (d, } 2\text{H, } J'_0 = \text{H}_A), 5.70 \text{ (br t, IH, } H-I), 5.59 \text{ (td, IH, } J_2 = 9.3 \text{ Hz, } J_{3F} = 14.1 \text{ Hz, H-3), 4.89 \text{ (t, IH, } J_4 = 9.3 \text{ Hz, H-4), 4.66 \text{ (td, IH, } J_1 = 9.0 \text{ Hz, } J_{2F} = 50.2 \text{ Hz, H-2), 4.20-3.93 \text{ (m, } 3\text{H, } 2\text{H-6, } H-5), 3.89 \text{ (d, } 2\text{H, } \text{CH}_2\text{NH}), 3.70 \text{ (s, } 8\text{H}_1\text{N(CH}_2\text{CH}_2\text{Cl)}), 2.47 \text{ (t, } 2\text{H, } J = 8.0 \text{ Hz, } \text{CH}_2\text{Ph), 2.16 \text{ (t, } 2\text{H, } J = 7.3 \text{ Hz, } \text{COCH}_2\text{CH}_2), 2.05, 2.00, 1.98 \text{ (each s, } 3\times3\text{H}_3\text{OAc), 1.75 \text{ (qt, } 2\text{H, } \text{CH}_2\text{CH}_2\text{CH}_2)};\]

\[\text{C}^1\text{C NMR } (50 \text{ MHz, DMSO-}d_2) \delta 172.61, 169.96, 169.52, 169.34, 168.47, 166.04 \text{ (CO), 144.39 } (\text{CA}_1\text{N}), 142.32 \text{ (C}_A^\text{NH}), 129.97 \text{ (CA}_1\text{CH}_2), 129.33, 128.58 \text{ (CH}_A^\text{)}, 127.41 \text{ (CAICO), 118.30, 111.90 } (\text{CH}_A^\text{NH}), 88.23 \text{ (C-2), } J_{2F} = 185.8 \text{ Hz}, 77.09 \text{ (C-I), } J_{1} = 22.9 \text{ Hz), 72.83 \text{ (C-3), } J_{3F} = 18.9 \text{ Hz), 71.96 \text{ (C-5), 67.79 \text{ (C-4), } J_{4F} = 7.8 \text{ Hz), 61.58 \text{ (C-6), 52.23 \text{ (NCH}_2), 42.76 \text{ (CH}_2\text{NH), 41.16 \text{ (CH}_2\text{Cl), 34.58, 33.56 \text{ (CH}_2\text{CH}_2\text{CjH}_2), 27.32 \text{ (CH}_2\text{CH}_2\text{CH}_2), 20.5 \text{, 20.44, 20.37 \text{ (CH}_3).}\]

\[\text{Example 29}\]

iv-f4-f3.4,6-tri-0-acetyl-2-deoxy-2- β-uoiO-B-D-glucopyranosylol)phenyl- A^1\text{D}-3-f4-[bis(2-chloroethyl γl)aminoDhe αUDropylpropaedomamide } â€œ(67) â€œ(see Scheme 29) .

\[\text{25} \text{BD}\]

a) benzyl \[3-f4-(3.4,6-tri-0-acetyl-2-deQXV-2-fluoro- β-D- glucopyranosylol)phenylaminol-3-oxopropaOate} (65) was prepared according to the procedure described for compound \[15a\], starting from compound \[36 \text{ (0.475 g, 1.19 mmol)}\] and malonic acid monobenzyl ester (0.254 g, 1.31 mmol). Chromatography on silica gel (cyclohexane: ethyl acetate 5:5) provided compound 65 (0.420 g, 61%) as a pale yellow oil:

\[C_{28}H_{36}FNO_{11};\]
M = 575.54 g·mol⁻¹;

Rf = 0.59 (cyclohexanerethyl acetate 4:6);

IR (KBr) ν 3367 (v N), 1754 (νC=Ocatcr), 1689 (νC=Oamide), 1544 (8NII), 1370 (δCH₃), 1229, 1067, 1048 (νC=O) cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ 9.15 (s, IH, NH), 7.48 (d, 2H, J₀ = 9.0 Hz, H₆), 7.39 (s, 5H, Ph), 7.05 (d, 2H, H₂A), 5.39 (td, IH, J₅,F = 14.5 Hz, 1.23 = 9.2 Hz, H-3), 5.23 (s, 2H, OCH₂Ph), 5.09 (t, IH, J₆,F = 9.8 Hz, H-4), 5.08 (dd, 1H, J₆,F = 3.0 Hz, J₂ = 7.6 Hz, H-5), 4.56 (dd, IH, J₁,F = 5.4 Hz, H-2), 4.30 (dd, IH, J₃,F = 5.4 Hz, J₆,F = 12.3 Hz, H-6a), 4.15 (dd, 1H, J₃b,F = 2.4 Hz, H-6b), 3.85 (dd, IH, H-5), 3.52 (s, 2H, COCH₂CO), 2.10, 2.08, 2.07 (each s, 3*3H, OAc);

¹³C NMR (50 MHz, CDCl₃) δ 171.29, 170.76, 170.57, 170.30 (COO), 163.37 (NHCO), 154.17 (C₆O), 135.53 (CA,NH), 134.04 (C₆CH₂), 129.55, 129.26, 122.37, 118.84 (CH₁), 100.07 (C-I, J₁,F = 23.5 Hz), 89.78 (C-2, J₂,F = 191.0 Hz) 73.49 (C-3, J₃,F = 20.0 Hz), 72.86 (C-5), 68.90 (CM, J₄,F = 7.5 Hz), 68.42 (CH₂Ph) 62.63 (C-6), 42.15 (COCH₂CO), 21.44, 21.33 (CH₃).

3.4.6-tri-Q-acetyl-2-deoxy-2-nuoro-B-D-

GlycoDyranosyloxy-phenylamino-3-oxoproDanoic acid (66)

To a suspension of 10% palladium on charcoal (74 mg) in THF/MeOH (3/3 mL) was added benzyl ester 65 (0.370 g, 0.643 mmol). The mixture was hydrogenated at atmospheric pressure for 2 h, filtered on celite, and concentrated to yield the acid 66 (0.339 g, 100%) as a oil which was used in the next step without further purification:

C₂,H₂,FNO₁₁;

M = 485.41 g·mol⁻¹;

IR (KBr) ν 1763 (νC=Oester), 1727 (νC=Oamide), 1670 (νC=Oamide), 1558 (Sm), 1366 (δCH₃), 1233, 1080, 1068, 1040 (vouja cr) ¹;
$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 170.63, 170.26, 170.10, 169.18 (COO), 165.69 (NHCO), 154.01 (CA$_2$O), 135.02 (CA$_3$NH), 121.68, 118.01 (CHA$_3$). 99.06 (C-1, $J_{CH} = 23.0$ Hz), 90.40 (C-2, $J_{2F} = 188.5$ Hz), 73.37 (C-3, $J_{3F} = 19.5$ Hz), 72.58, (C-5), 69.13 (C-4, $J_{4F} = 7.5$ Hz), 62.64 (C-6), 20.60 (CH$_3$).

c) 4-tri-O-acetyl-2-deox-$\gamma$-2-fluoro-B-D-glucopyranosvoty 

**Dihenyll-\(\Lambda^\prime\)-r3-f 4-[b]ls (2-chloroethylaminolopheitv>proPyllpropQiediamide** (61) was prepared according to the procedure described for compound ISa, starting from acid 66 (0.150 g, 0.309 mmol) and amine 57 (0.102 g, 0.371 mmol). Chromatography on silica gel (cyclohexane:ethyl acetate 3:7) provided compound 61 (0.129 g, 56%) as an oil:

C$_{34}$H$_2$Cl$_2$F$_3$N$_3$O$_{10}$;

M $\approx$ 742.63 g.mol$^{-1}$;

RF $\approx$ 0.29 (ethanol: ethyl acetate 4:6);

IR (KBr) v 3307 (C=N), 1755 (C=Oester), 1675, 1649 (C=Oamide), 1519, 1509 (C=O).

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 9.50 (s, 1H, PhNHCO), 7.50 (d, 2H, $J_{0} = 9.0$ Hz, H$_{Ar}$), 7.05 (d, 2H, $J_{0} = 8.5$ Hz, H$_{Ar}$), 7.02 (d, 2H, $J_{0} = 6.9$ Hz, H$_{Ar}$), 6.69 (br t, 1H, NHCH$_2$), 6.61 (d, 211, $J_{0} = 6$ Hz, H$_{Ar}$), 5.41 (td, 1H, $J_{2A} = 9.2$ Hz, $J_{3F} = 14.5$ Hz, H-3), 5.09 (t, 1H, $J_{4F} = 9.6$ Hz, H-4), 5.06 (dd, 1H, $J_{1F} = 3.1$ Hz, H-1), 4.56 (dddd, 1H, $J_{2F} = 50.2$ Hz, H-2), 4.29 (ddd, 1H, $J_{5d} = 5.4$ Hz, $J_{6b} = 12.3$ Hz, H-6a), 4.14 (dd, 1H, $J_{5b} = 2.2$ Hz, H-6b), 3.85 (dddd, 2H, H-5), 3.74-3.56 (m, 8H, N(CH$_2$CH$_2$CH$_2$)$_2$), 3.31 (q, 2H, $J = 7.2$ Hz, NHCH$_2$), 3.30 (s, 2H, COCH$_2$CO), 2.57 (t, 2H, $J = 7.5$ Hz, CH$_2$Ph), 2.11, 2.08, 2.05 (each s, 3$\times$3H, OAc), 1.83 (qt, 2H, CH$_2$CH$_2$CH$_2$);

$^{15}$C NMR (SO MHz, CDCl$_3$) $\delta$ 171.28, 170.77, 170.28 (COCH$_3$), 168.44, 165.70 (NHCO), 154.08 (CA$_2$O), 145.22 (CA$_2$N), 134.24 (CA$_3$NH), 130.95 (CArCH$_2$), 130.31, 122.29, 118.75, 113.07 (CHAr), 100.00 (C-1, $J_{1F} = 23.5$ Hz), 89.78 (C-2, $J_{2F} = 191.0$ Hz), 73.47 (C-3, $J_{3F} = 20.0$ Hz), 72.51 (C-5), 68.86 (C-4, $J_{4F} = 7.5$ Hz), 62.59 (C-6), 54.34 (NCH$_2$), 44.41 (COCH$_2$CO), 41.26 (CH$_2$Cl), 40.22 (CH$_3$NH), 32.77 (CH$_2$Ph), 31.70 (CH$_2$CH$_2$CH$_2$), 21.44, 21.32 (CH$_3$).
Example 30

\[ \text{V-4-f4-(3,4,6-tri-O-acetyl-2-deoxy-2-flurorophenyl-6-phenylazo)pyranoxy} \]

\[ \\gamma H-4'-4-(4\text{-bis(2-chloroethyl)aminophenylbutamido})benzami} \]

\( (70) \)

5

a) \( \Lambda M4.\text{(3A6-tri-O-acetyl-2-deoxy-2-fluorophenylazo)pyranoxy} \)

gluopyranosvloxyphenylM-nitrophen \( \pi \)azipldec \( (68) \) was prepared according to the procedure described for compound 18a, starting from amine 36 (1.23 g, 3.08 mmol) and 4-nitrobenzoic acid (858 mg, 5.13 mmol). Chromatography on silica gel (cyclohexane:ethyl acetate 5:5) provided compound 68 (426 mg, 25%) as a white solid:

\[ \text{C}_{25}\text{H}_{27}\text{FN}_{2}\text{O}_{3}; \]

\[ M = 548.47 \text{ g.mol}^{-1}; \]

\[ \text{Rf} = 0.20 \text{ (cyclohexane:ethyl acetate 5:5);} \]

\[ \text{IR (KBr) } \nu = 3355 \text{ (vNH)}, 1759, 1744 \text{ (vc-cW), } 1672 \text{ (vc-O \text{gmid}^*), } 1515 \text{ (v_{asO}O)}, 1349 \text{ (vSNO)}, 1220, 1288, 1053, 1024 \text{ (vC-O) cm}^{-1}; \]

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\[ \text{H NMR (200 MHz, DMSO-}^d \text{ ) } \delta = 10.56 \text{ (s, IH, NH), } 8.37 \text{ (d, } 2\text{H, } J_0 = 8.9 \text{ Hz, H-AF), } 8.18 \text{ (d, } 2\text{H, } J_0' = 9.1 \text{ Hz, H-AF), } 7.94 \text{ (d, } 2\text{H, } J_0'' = 22.7 \text{ Hz, H-I1), } 7.08 \text{ (d, } 2\text{H, } J_0''' = 7.6 \text{ Hz, H-I1), } 5.57 \text{ (td, IH, } J_{23} = 9.3 \text{ Hz, H-I3), } 5.17 \text{ (dd, } 3\text{H, } J_{24} = 8.9 \text{ Hz, H-I4), } 4.70 \text{ (td, IH, } J_{34} = 51.4 \text{ Hz, H-2), } 4.30-4.05 \text{ (m, } 3\text{H, H-6), } 2.07, 2.02 \text{ (each s, } 3\text{H, OAc);} \]

\[ \text{C}_{15}\text{H}_{18}\text{O}_{3} \]

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\[ \text{C NMR (50 MHz, OMSO-C}^d \text{ ) } \delta = 169.91, 169.62, 169.33 \text{ (COCH), } 163.61 \text{ (NHCO), } 152.60 \text{ (CA)}, 149.13 \text{ (CA NO2), } 140.55 \text{ (CA CO), } 133.84 \text{ (CA NH), } 129.15, 123.54, 121.96, 116.52 \text{ (CH-AF), } 96.86 \text{ (C-I), } J_{AF} = 22.2 \text{ Hz), } 89.03 \text{ (C-2), } J_{2F} = 187.6 \text{ Hz), } 72.05 \text{ (C-3), } J_{3F} = 18.9 \text{ Hz), } 70.77 \text{ (C-5), } 67.84 \text{ (C-4), } J _{4F} = 8.1 \text{ Hz), } 61.51 \text{ (C-6) 20.36 (CH-AF).} \]

b) \( 4\text{-amino-} \text{V-f4-(3,4,6-tri-O-acetyl-2-deoxy-2-fluro-} \beta \text{-D-glucopyranosyl} \text{oxyphenyl-yl} \text{ benzami} \)

\( (69) \)

After reduction in the same conditions as those used for the nitro compound 19a, the amine 69 (416 mg, 88%) was obtained starting from compound 68 (502 mg, 0.915 mmol) and after filtration on celite, as a white solid which was used in the next step without further purification:

\[ \text{C}_{23}\text{H}_{23}\text{FN}_{2}\text{O}_{2}; \]
M = 518.49 g mol⁻¹;

Rf = 0.14 (cyclohexane:ethyl acetate 5:5);

IR (KBr) ν 3350 (νNH), 1511 (SNH) cm⁻¹;

1H NMR (200 MHz, DMSO-d₆) δ 9.74 (s, 1H, NH), 7.70 (d, 2H, J₀' = 8.5 Hz, HAT), 7.69 (d, 2H, J₀ = 9.1 Hz, H̅A), 7.01 (d, 2H, J₀, H₂A), 6.59 (d, 2H, J₀'' = 7.5 Hz, H₁A), 5.75 (s, 2H, NH₂), 5.62 (dd, IH, J₁₁₂ = 2.4 Hz, J₁₁₂₂ = 7.5 Hz, H-I), 5.56 (td, IH, J₂, J₂₃ = J₃, J₄, J₅ = 9.2 Hz, H₃, J₃, J₄ = 14.5 Hz, H-3), 4.98 (t, IH, J₄, J₅ = 9.6 Hz, H-4), 4.68 (ddd, IH, J₂₆, J₂₆ = 15.4 Hz, H-2), 4.29-4.04 (m, 3H, 2H-6, H-5), 2.06, 2.01 (each s, 9H, OAc);

13C NMR (50 MHz, DMSO-d₆) δ 169.92, 169.62, 169.34 (COCH₃), 165.08 (NHCO), 152.06, 151.77 (C₅O, C₄NH₂), 135.01 (C₄N, NH₂), 129.25, 121.47 (CH*), 121.05 (C₃O), 116.40, 112.54 (CH₃), 97.03 (C-I, J₁₁₂ = 22.7 Hz), 89.04 (C-2, J₂₆ = 187.3 Hz), 72.08 (C-3, J₃, J₄ = 18.7 Hz), 70.72 (C-5), 67.86 (C-4, J₄, J₅ = 7.4 Hz), 61.53 (C-6), 20.42, 20.37 (CH₃).

V-f4-(3,4,6-tri-6>-acetyl-2-deoxy-2-floro-B-D-glucopyranosyloxy)pheityl1-4-(4-f4-ribisf2-chloroethylOamiolDhe πvUbuitanidt)beTizarnide (70) was prepared according to the procedure described for compound 15a, starting from chlorambucil (120 mg, 0.394 mmol) and amine 69 (202 mg, 0.390 mmol). Chromatography on silica gel (cyclohexane:ethyl acetate 3:7) provided compound 70 (131 mg, 42%) as a white powder:

C₃₉H₄₄Cl₂FN₃O₆;
M = 804.69 g mol⁻¹;

Rf = 0.75 (cyclohexane:ethyl acetate 3:7);

IR (KBr) V 3325 (νNH), 1749 (νC=Osses), 1627 (yoomas), 1512 (S₉H₂), 1222, 1068, 1045 (νC=O) cm⁻¹;

1H NMR (200 MHz, acetone-6) δ 9.46 (s, 1H, NH), 9.40 (s, 1H, NH), 7.96 (d, 2H, J₀ = 8.8 Hz, H̅A), 7.81 (d, 2H, J₀'' = 9.1 Hz, H₂A), 7.78 (d, 2H, J₀, H₂A), 7.12 (d, 2H, J₀'', H₃A), 7.10 (d, 2H, J₀'''' = 8.7 Hz, H₃A), 6.73 (d, 2H, J₀''''''', H₅A), 5.63-5.47 (m, 2H, H-3, H-I), 5.09 (t, IH, J₃₄, J₄₅, J₅ = 9.5 Hz, H-4), 4.61 (ddd, IH, J₁₂ = 7.7 Hz, J₂₃, J₂₆ = 9.1 Hz, J₂₆ = 51.2 Hz, H-2), 4.34-4.07 (m, 3H, 2H-6, H-5), 3.80-3.67 (m, 8H, N(CH₂CH₂Cl)₂), 2.59 (t, 2H, J = 7.6 Hz, CH₂Ph), 2.42 (t, J = 7.3 Hz, COCH₂) ; 2.15-1.92 (m, UH, CH₂CH₂CH₂, 3*OAc).
Example 31

\( V\{4f6\rightarrow 4.6\text{-tri-0-acetyl-2-deoxy-2-fluoro-B-D-glucoDyranoiStvloxy}\} \) Dhe-iy11-

To a solution of amine 39 (400 mg, 0.876 mmol) in DMF (25 mL) cooled to 0°C, was added i-(2-chloroethyl)-3-(4-nitrophenyl)-l-nitrosourea (285 mg, 1.04 mmol) and stirring was maintained at room temperature for 2h. After evaporation under reduced pressure, the crude product was chromatographed on silica gel using cyclohexane:ethyl acetate (4:6) as eluent to give compound 71 (406 mg, 78%) as a yellow powder:

\[ \text{C}_{23}\text{H}_{22}\text{ClF}_{3}\text{N}_{4}\text{O}_{11}; \]
\[ M = 590.95 \text{ g.mol}^{-1}; \]
\[ R_f = 0.39 \text{ (cyclohexane:ethyl acetate 4:6}; \]
\[ \text{IR (KBr) } \nu 3343 \text{ (v N-H), } 1744, 1693 \text{ (v } \text{C} = \text{o}), 1510 \text{ (6NH), } 1224, 1066 \text{ (v C-o) cm}^{-1}; \]
\[ \text{H NMR (200 MHz, CDC}d\text{)} \delta 8.35 \text{ (br s, IH, PhNH), } 7.82 \text{ (br t, IH, } J = 5.1 \text{ Hz, } \text{CH}_2\text{NH), } 7.46 \text{ (d, 2H, } J_0 = 9.0 \text{ Hz, HAT), } 7.02 \text{ (d, 2H, } H_{\text{Ar}}\text{), } 5.42 \text{ (td, IH, } J_{1 \text{a}} = J_{2 \text{b}} = 9.2 \text{ Hz, } J_3\text{F} = 14.5 \text{ Hz, H-3), } 5.10 \text{ (t, IH, } J_{4 \text{a}} = 9.7 \text{ Hz, H-4), } 5.09 \text{ (dd, IH, } J_{1 \text{b}} = 7.5 \text{ Hz, } J_{xp} = 2.9 \text{ Hz, H-1), } 4.56 \text{ (ddd, IH, } J_{5 \text{ab}} = 50.4 \text{ Hz, H-2)), } 4.32-4.10 \text{ (m, } 6\text{H, 2H-6, } \text{CH}_2\text{NH), N(NO)CH}_2\text{), } 3.87 \text{ (ddd, IH, } J_{5 \text{a}a} = 5.2 \text{ Hz, } J_{5 \text{a}b} = 2.3 \text{ Hz, H-5), } 3.50 \text{ (t, 2H, } J = 6.6 \text{ Hz, } \text{CH}_2\text{Cl), } 2.12, 2.08, 2.06 \text{ (each s, } 3^*\text{3H, OAc); MS (ESI) } m/z 591.14 \text{ [M+H]}^+ \text{ (Exact Mass: 591.15).} \]

Example 32

\[ N\{3,4,6\text{-tri-0-acetyl-2-deoxy-2-fluoro-B-D-glucoyranosyl}\} 2\text{-r3-(2\text{-chlooroethylV3-nitrosourendlacetamidete} (72) \text{ see Scheme 2g) was prepared according to the procedure described for compound 71, starting from compound 19b (120 mg, 0.329 mmol) and 1-(2-chloroethyl)-3-(4-nitrophenyl)-l-nitroso urea (107 mg, 0.391 mmol). Chromatography on silica gel using cyclohexane:ethyl acetate (5:5) as eluent yielded compound 72 (70 mg, 43%) as a yellow powder:

\[ \text{C}_{17}\text{H}_{22}\text{ClF}_{3}\text{N}_{4}\text{O}_{10}; \]
\[ M = 498.84 \text{ g.mol}^{-1}; \]
\[ R_f = 0.59 \text{ (cyclohexanerethyl acetate 3:7); IR (KBr) } \nu 3350 \text{ (v N-H), } 1750 \text{ (v } \text{C} = \text{o}), 1540 \text{ (6NH), } 1233, 1069, 1038 \text{ (v C-o) cm}^{-1}; \]
**Example 33**

O\textsuperscript{\textregistered}frtri-O-acetyl\textsuperscript{\textregistered}deoxy-Z-fluoro-B-P-glucopyranosyl)4-f2-f3-(2-chloroethyl)-3-nitrosou'eldo\textsuperscript{\textregistered}aeetamido)phenylcarbamate (l€S (see Scheme 2g)

a) Benzyl 2-(4-aminophenylamiL \textsuperscript{\textregistered}o)-2-oxoethylcarbaniate (73)

To a stirred solution of compound 42 (1.19 mg, 3.61 ramol) in ethyl acetate (90 rtiL), was added SnCl\textsubscript{2}, 2H\textsubscript{2}O (4.16 g, 18.4 mmol). The suspension was heated at 70\textdegree{}C for 18h and, after cooling, poured into water, which was neutralized with a saturated aqueous NaHCO\textsubscript{3} solution, followed by two extractions with ethyl acetate. The organic layer was washed with brine, dried over MgSO\textsubscript{4} and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography, using cyclohexane:ethyl acetate (1:9) as eluent, to yield compound 73 (250 mg, 23%) as a pale rose powder:

\[ \text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3; \]
\[ M = 299.32 \text{ g/mol}^1; \]
\[ \text{Rf} = 0.35 (\text{cyclohexane:ethyl acetate 1:9}); \]
\[ \text{IR(KBr) v} 3341, 3296 (\text{vNH}), 1720, 1642 (\text{vc-o}), 1542, 1516 (\delta_{\text{N-H}}), 1248 (\text{vco}) \text{ cm}^{-1}; \]

\[ ^1\text{H NMR (200 MHz, acetone-\textsuperscript{d6})} \delta 8.89 (br s, \text{IH}, \text{NHPH}), 7.38-7.28 (m, 7H, HAT), 6.66 (d, 3H, \text{J} = 8.8 \text{ Hz, CH}_2\text{NH, H A}3), 5.10 (s, 2H, \text{CH}_2\text{Ph}), 4.49 (br s, 2H, N\text{Il}_2), 3.91 (d, 2H, \text{J} = 6.0 \text{ Hz, CH}_2\text{NH}). \]

**1H NMR** (200 MHz, CDCl\textsubscript{3}) \( \delta \) 7.74 (br t, \text{IH}, \text{J} = 5.0 \text{ Hz, CH}_2\text{NH}), 7.34 (d, \text{IH}, \text{J} = 9.1 \text{ Hz, CNH}), 5.48-5.33 (m, 2H, H-I, H-3), 5.04 (t, \text{IH}, \text{J}_{3,4} = 9.7 \text{ Hz, H-4}), 4.54-4.05 (m, 7H, H-2, H-6, CH\textsubscript{2}NH, CH\textsubscript{2}NNO), 3.89 (m, \text{IH}, \text{J}_{3,4} = 3.51 (t, 2H, \text{J} = 6.5 \text{ Hz, CH}_2\text{Cl}), 2.08, 2.07, 2.05 (each s, 3x3H, OAc);

**13C NMR** (50 MHz, CDCl\textsubscript{3}) \( \delta \) 170.79, 170.03, 169.87, 168.99 (CO), 153.86 (NHCON), 88.48 (C-2, \text{J}_{2,F} = 191.2 \text{ Hz}), 77.37 (C-I), 73.96 (C-5), 73.38 (C-3, \text{J}_{3,F} = 19.3 \text{ Hz}), 67.93 (C-4, \text{J}_{4,F} = 7.1 \text{ Hz}), 61.70 (C-6), 44.14 (COCH\textsubscript{2}NH), 40.45, 39.03 (CH\textsubscript{2}C\textsubscript{H}\textsubscript{2}Cl), 20.84, 20.76, 20.70 (CH\textsubscript{3});

**MS (ESI)** m/z 499.03 [M+l] \textsuperscript{+} (Exact Mass: 499.12).
b) (3,4,6-tri-O-acetyl-l-deoxy^-fluoro-B-D-glucopyra πosyl) 4-(2-
^benz|loxycarbonvtamino)acetamido)Dhenylcarbamate (74) was prepared according to
the procedure described for compound 46, starting from amine 73 (40 mg, 0.134 mmol)
and the β carbonate 41 (66 mg, 0.139 mmol). Chromatography on silica gel using
eylhexane: ethyl acetate (3:7) as eluent provided compound 74 (30 mg, 35%) as a white
powder:

\[ \text{C}_{29} \text{H}_{32} \text{FN}_{5} \text{O}_{12}; \]
\[ M = 633.58 \text{ g.mol}^{-1}; \]
\[ \text{Rf} = 0.40 \text{ (cyclohexanciethyl acetate 3:7); IR(KBr) } \nu = 3350 \text{ (VNH), 1751} \]
\[ (\nu) \text{, } 1522 \text{ (6NH), 1224, 1070 (vc-o);} \]
\[ \^H \text{ NMR (200 MHz, acetone-}^\text{d}) \delta 9.26 \text{ (br s, IH, NH), 9.13 (br s, IH, NH),} \]
\[ 7.63 \text{ (d, 2H, } J = 9.1 \text{ Hz, H}_3); \]
\[ 7.52 \text{ (d, 2H, HAc), 7.38-7.28 \text{ (m, 5H, Ph), 6.70 (br t, IH, } J = \]
\[ 5.7 \text{ Hz, } \text{CH}_2\text{NH}, 6.07 \text{ (dd, IH, } J_{1F} = 3.2 \text{ Hz, } J_{1z} = 8.1 \text{ Hz, H-1), 5.59 (td, IH, } J_{2z} = J_{3z} = \]
\[ 9.3 \text{ Hz, } J_{4F} = 14.4 \text{ Hz, H-3), 5.11 (s, 2H, } \text{CH}_2\text{Ph), 5.07 (t, IH, } J_{4z} = 9.5 \text{ Hz, H-4), 4.53} \]
\[ (ddd, \text{ IH, } J_{2z} = 51.3 \text{ Hz, H-2), 4.28 (dd, IH, } J_{6y6z} = 11.5 \text{ Hz, } J_{5z6z} = 4.1 \text{ Hz, H-6a), 4.19-} \]
\[ 4.05 (\text{rot, 2H, H-6b, H-5), 3.99 (d, 2H, } J = 6.0 \text{ Hz, CHiNH), 2.05, 2.03, 1.99 (each s, 3x3H,} \]
\[ \text{OAc);} \]
\[ ^{11} \text{C NMR (50 MHz, acetone-}^\text{d}) \delta 170.60, 170.11, 170.03 \text{ (COCH}_3\text{), 168.39} \]
\[ (\text{NHCO), 151.93 \text{ (OCONH), 138.00 (C}_{\alpha\alpha}\text{CH}_2), 135.48, 134.74 \text{ (C}_{\alpha\beta}\text{NH), 129.12, 128.58,} \]
\[ 120.82, 119.98 \text{ (CHAc), 92.79 (C-l, } J_{1F} = 23.7 \text{ Hz), 89.57 (C-2, } J_{2F} = 188.5 \text{ Hz), 73.22 (C-} \]
\[ 3, J_{3F} = 19.4 \text{ Hz), 72.89 (C-S), 68.65 (C-4, } J_{4F} = 7.7 \text{ Hz), 66.90 (CH}_2\text{Ph), 61.32 (C-6),} \]
\[ 45.40 \text{ (COCH}_2\text{NH), 20.52 (CH}_3\text{).} \]

c) (3,4,6-tri-Q-acetyl-2-deoxy-2-fluoro-B-D-glucopyra πosyl) 4-(2-(3-(2-
ch)oroethvD-3-nitrosoureidol acetamidoophenylcarbamate (76)
Starting from the compound 74 (30 mg, 0.047 mmol), cleavage of the Cbz group by
hydrogenation as described for derivative 19b furnished the amine 75 (22 mg, 94%) as a
white solid which was directly reacted with 1-(2-chloroethyl)-3-(4-nitro phenyl)-1-
nitrosourea (20 mg, 0.073 mmol) according to the procedure described for compound 71.
Chromatography on silica gel using cyclohexanciethyl acetate (4:6) as eluent gave
compound 76 (10 mg, 35%) as a brown powder:

\[ \text{C}_{24} \text{H}_{26} \text{ClFN}_{5} \text{O}_{12}; \]
M = 633.96 g.mol\(^{-1}\);
Rf= 0.63 (cyclohexa π;ethyl acetate 3:7);
IR(KBr) \(v\) 3353 (VNH), 1751 (v\(\neq\)), 1524 (\(\delta_{\text{NH}}\)), 1223, 1071, 1039 (vCO);
\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 8.01 (br s, IH, NH), 7.83 (te, IH, \(J = 5.1\) Hz, CH\(_2\)NH), 7.43 (d, 2ft \(J = 9.0\) Hz, H\(_\text{Ar}\)), 7.31 (d, 2H, EUR), 7.01 (br s, IH, NH), 5.88 (dd, IH, \(J_{\text{N2}} = 8.0\) Hz, \(J_{\text{N1}} = 3.0\) Hz, H-I), 5.47 (td, IH, \(J_{\text{Ar3}} = J_{\text{Ar2}} = 9.3\) Hz, \(J_{\text{Ar4}} = 14.1\) Hz, H-3), 5.) 1 (t, IH, \(J_{\text{Ar6}} = 9.8\) Hz, H-4), 4.51 (td, IH, \(J_{\text{Ar2}} = 51.2\) Hz, H-2), 4.42-4.09 (in, 6H, 2H-6. 2CH\(_2\)N), 3.93 (m, IH, H-5), 3.52 (t, 2H, \(J = 6.5\) Hz 3CH\(_2\)Cl), 2.11, 2.07, 2.05 (each s, 3x3H, OAc); MS (ESI) m/z 634.03 [M-M]+ (Exact Mass: 634.16).

The table which follows illustrates the chemical structures of some compounds according to the invention.
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"Bn" means a benzyl group,
"Ac" means an acetyl group.
Example 34: Pharmacological test.

Some compounds of the invention have been the subject of pharmacological tests which have demonstrated their relevance as active substances in therapy and in particular in the treatment of cancer.

a) *In vitro* Cytotoxicity assay:

The materials and methods used for performing these pharmacological tests are as follows:

Cell cultures

Normal human fibroblasts were purchased from Promocell (Heidelberg, Germany). This frozen culture was obtained from foreskin waste from a 6-year old Caucasian male and the cells used in this work were from the seventh to twelfth passage of the culture. M4Beu, a human melanoma cell line, was established in the laboratory of Dr. J. F. Dore (INSERM, Unit 218, Lyon, France) from metastatic biopsy specimens and maintained in cell culture for almost 20 years in our lab. Breast cancer adenocarcinoma MCF 7, prostatic adenocarcinoma PC 3, colon adenocarcinoma DLD-I, lung non-small cell carcinoma A 549 , ovary adenocarcinoma PAI human cell lines and L 929 murine cell line were purchased from the European Collection of Cell Cultures (ECACC; Salisbury, United Kingdom). Murine melanoma B16 was purchased from American Type of Culture Collection (ATCC, Manassas, USA) and murine colon carcinoma cell line CT-26 was obtained from Dr I. J. Fidler (University of Texas M.D. Anderson Cancer Center, Houston).

Stock cell cultures were maintained as monolayers in 75cm² culture flasks in Glutamax Eagle's minimum essential medium with Earle's salts (MEM; Gibco BRL, Paisley, UK) supplemented with 10% fetal calf serum (Sigma, St Quentin Fallavier, France), 1 mM sodium pyruvate (Gibco), IX vitamins solution (Gibco), IX lion essential amino acids solution (Gibco) and 4 µg/ml of gentamicine (Gibco). Cells were grown at 37°C in a humidified atmosphere containing 5% CO₂.

Cells were plated at a density of 5 x 10³ cells per well in 96-well microplates (Nunclon™, Nunc, Roskilde, Denmark) in 150 µl of culture medium and were allowed to adhere for 16 h before treatment with the compound tested.

Stock solution of each compound was prepared in dimethylsulfoxide (DMSO) and kept at -20 °C. until use- The percentage of DMSO was kept at 0.5% (v/v) whichever the concentration tested. This percentage did not modify cellular growth. Fifty microliters of a 4X
solution in MEM was then added and a 48-h continuous drug exposure protocol was used. Then, the cytotoxic effect of compounds on tumour cells was tested by using Resazurin reduction test.

5 Resazurin Reduction Test
Resazurin was identified as the Alamar blue dye (O'Brien, J. et al.; European Journal of Biochemistry, 267, 5421-6, (2000)). The resazurin reduction test (RRT) was carried out according to the protocol described here. Briefly, plates were rinsed by 200 µl PBS (37° C, Gibco) using a multichannel dispenser (Labsystems, Helsinki, Finland) and emptied by overturning on absorbent toweling. Then, 150 µl of a 25 µg/ml solution of resazurin in MEM without SVF nor Phenol red was added in each well. The plates were incubated 1 h at 37° C. in an humidified atmosphere with 5% of CO₂ for fluorescence development by living cells. Fluorescence was then measured on the automated 96-well plate reader Fluoroskan Ascent FL™ (Labsystems) using an excitation wavelength of 530 run and an emission one of 590 run. The fluorescence is proportional to the number of living cells in the well and IC₅₀ (drug concentration required to decrease final cell population by 50%) was calculated from the curve of concentration-dependent cell number decrease, defined as the fluorescence in experimental wells as a percentage of that in control wells, with blank values subtracted.

Cytotoxic activity has been tested against the six human tumour cell lines breast adenocarcinoma MCF-7, colon adenocarcinoma DLD-1, ovary adenocarcinoma PAI, prostatic adenocarcinoma PC3, lung carcinoma A549, melanoma M4Beu and a primary culture of human fibroblasts.

The table 1 hereafter submits data obtained for the compounds: 17a, 20a, 21a, 22a, 31a, 37a, 40a and chlorambucil.
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</tr>
<tr>
<td>37a</td>
<td>&gt;50</td>
<td>11±4</td>
<td>11±4</td>
<td>2.9±0.4</td>
<td>31±10</td>
<td>12±4</td>
<td>12±4</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>40a</td>
<td>17±6</td>
<td>7.5±2</td>
<td>ND</td>
<td>16±5</td>
<td>9±1</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>21±9</td>
<td>4.9±0.9</td>
<td>4.9±0.9</td>
<td>3.6±0.9</td>
<td>3.6±0.9</td>
<td>3.6±0.9</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>5±0</td>
<td>5±0</td>
<td>ND</td>
<td>5±0</td>
<td>5±0</td>
<td>5±0</td>
<td>5±0</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>10±3</td>
<td>6.5±0.8</td>
<td>13±3</td>
<td>13±3</td>
<td>13±3</td>
<td>13±3</td>
<td>13±3</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>4±1</td>
<td>4±1</td>
<td>ND</td>
<td>4±1</td>
<td>4±1</td>
<td>4±1</td>
<td>4±1</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>4±1</td>
<td>4±1</td>
<td>ND</td>
<td>4±1</td>
<td>4±1</td>
<td>4±1</td>
<td>4±1</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

**IC₅₀ (µM)**

**ND:** Non-determined

Chlorambucil: 99±2 >100 43±14 47±17
As described in the table above, IC₅₀ lower than the Chlorambucil one is observed for all the acetylated compounds indicated here and whichever the cell line considered. These results underline a significant improvement of the cytotoxicity in vitro of peracetylated glucocojugated comparatively to the free molecule. Chlorambucil per se is only moderately cytotoxic in these conditions (IC₅₀ values superior to 40 µM except in PAI cells, a very sensitive cell line).

b) In vivo study of molecules 21a and 40

This in vivo study is concerned with the evaluation of the acute toxicity of the two selected molecules in mice, and their antitumour activity in murine syngeneic models of solid tumours, i.e. B16 melanoma and CT-26 colon carcinoma.

Drugs were dissolved in a mixture of dimethylacetamide (Sigma) and oleic macrogolglycerides (Labrafit® M1944Cs, Gattefossé) (10:90%, vol/vol).

Animals were handled and cared for in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996) and the European Directive EEC/86/809. Protocols were conducted under the supervision of authorized investigators in accordance with the institution recommendations for the use of laboratory animals, based on the guidelines (décret n°87-848 du 19 octobre 1987).

- Determination of the Maximum Tolerated Dose (MTD)

Initially, the Maximum Tolerated Dose (MTD) after intraperitoneal (IP) administration was determined.

For MTD determination, study was conducted on male OFl mice weighing about 30 g, 6-weeks old (Charles River, France). Groups of five to six mice received a single IP injection of each drug at variable doses according to the compound (see Tables 2, 3 and 4).

Individual dose were based on the body weight of each mouse. All the mice received a constant injection volume of 250 µL per 25 g of body weight. A group of seven control mice received die vehicle.

After IP injection, mice were weighed and observed every two days over a 2 week-period to evaluate general clinical state. For each animal, a clinical state score (CSS) was calculated based on the absence (value 0) or presence (value 1) of diarrhoea, lethargy, rough
coat and closed eyes. CSS was then calculated per group by summing individual scores. Loss of weight and mortality were also recorded.

The MTP was defined as the highest single dose that satisfy all the following criteria: zero deaths per group, maximal weight loss 15% occurring at Day 1 (24 hours after injection) and CSS value as low as possible. Within a group, when mortality was observed to be 50% of the animals, weight loss and clinical state score were not considered to be relevant.

The following tables 2 to 4 report the so-obtained results:

Table 2
MTD for drug 21a in non-tumour bearing mice after a single IP administration.

<table>
<thead>
<tr>
<th>Dose / injection (mmol/kg)</th>
<th>Number of animals</th>
<th>Number of deaths (day)</th>
<th>Diarrhoea</th>
<th>Rough coat</th>
<th>Clinical state Score (CSS)</th>
<th>Weight loss at day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.07</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0.14</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>0.18</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.21</td>
<td>5</td>
<td>1 (D1)</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>0.28</td>
<td>6</td>
<td>4 (D1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.56</td>
<td>6</td>
<td>4 (D1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.76</td>
<td>5</td>
<td>5 (D1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3
MTD for drug 40a in non-tumour bearing mice after a single IP administration.

<table>
<thead>
<tr>
<th>Dose / injection (mmol/kg)</th>
<th>Number of animals</th>
<th>Number of deaths (day)</th>
<th>Diarrhoea</th>
<th>Rough coat</th>
<th>Clinical state Score (CSS)</th>
<th>Weight loss at day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.07</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>0.14</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>0.18</td>
<td>5</td>
<td>3 (D6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.21</td>
<td>6</td>
<td>2 (D1)</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>0.28</td>
<td>6</td>
<td>3 (D6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.56</td>
<td>5</td>
<td>5 (D6,7,9,13,15)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
MTD for chlorambucil in non-tumour bearing mice after a single IP administration.

<table>
<thead>
<tr>
<th>Dose / injection (mmol/kg)</th>
<th>Number of animals</th>
<th>Number of deaths (day)</th>
<th>Clinical State Score (CSS)</th>
<th>Weight loss at day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>diarrhoea</td>
<td>rough coat</td>
</tr>
<tr>
<td>0.0175</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0.035</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>0.05</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>0.07</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>0.09</td>
<td>6</td>
<td>1 (D1)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>0.14</td>
<td>5</td>
<td>4 (D1)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

It is noticed that the two drugs and chlorambucil induce high side effects (mainly diarrhoea) occurring as early as Day 1 after IP administration for dosage equal or higher than 0.14 mmol/kg for 21a, 0.07 mmol/kg for 40a and 0.0175 mmol/kg for chlorambucil. The doses inducing 100% mortality were 0.76 mraol/kg, 0.56 mmol/kg and 0.14 mraol/kg respectively for compound 21a, 40a and chlorambucil.

According to the criteria defined above, MTD was 0.14 mmol/kg for drugs 21a and 40a and 0.05 mmol/kg for chlorambucil.

In regard to MTD values, chlorambucil glucogonjugates appeared to be less toxic than chlorambucil.

**Assessment of antitumour activity**

It is performed in tumour-bearing mice following an IP chemotherapy protocol.

Antitumour activity of both molecules and chlorambucil was assessed in B16-melanoma bearing mice (67 animals) and in CT-26 colon carcinoma bearing mice (30 animals).

To establish B16 melanoma model, 3 x 10^6 B 16F0 cells (ATCC, Manassas, USA; in vitro doubling time of 16 hours) were suspended in 100 µL of phosphate buffer solution (PBS®, Life Technologies) and injected into the subcutaneous tissue of the right flank of C57BL6J male mice, 6-weeks-old (Charles River, France) on day zero.

To establish CT-26 colon carcinoma model, 2.5 x 10^5 CT26 cells (Dr Iaiaih J. Filder of MD Anderson Cancer Center, University of Texas; in vitro doubling time of 20 hours) were suspended in 100 µL of phosphate buffer solution and injected into the subcutaneous tissue of the right flank of BALB/c male mice, 6-weeks-old (Charles River, France) on day zero.
For both molecules and both animal models, treatment was initiated eight days post tumour grafting, when the tumours had reached a measurable size, corresponding to a calculated tumour weight (CTW) of 40 and 70 mg for B16 and CT-26 models respectively.

Animals were then randomly divided in both treatment and control groups. Mice were then given three doses of the drug tested (molecule 21a/molecule 40a/chlorambucil) at four-day intervals, (i.e at Day 8, Day 12 and Day 16 after tumour inoculation) according to the Q4d x 3 schedule typically employed in discovery screening (For more details, see table 5). Two dosages have been evaluated, MTD and 0.75 MTD.

Mice were weighed and observed every two days over a 30-day-period to evaluate general clinical state. Length and width of tumours were measured every two days over a 30-day-period using a dedicated slide calliper.

The Calculated Tumour Weight (CTW) of each tumour was determined according to the formula:

\[ \text{CTW (mg)} = \frac{L \times w^2}{2} \]

with \( L = \text{length in mm} \) and \( w = \text{width in mm} \).

The table 5 thereafter discloses the protocol of treatment:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose / injection (mmol/kg)</th>
<th>Treatment schedule</th>
<th>Tumour model</th>
<th>Nb animals / groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non treated controls</td>
<td>-</td>
<td>-</td>
<td>melanoma B16</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>colon carcinoma CT-26</td>
<td>6</td>
</tr>
<tr>
<td>Solvent-treated controls (DMA/Labrafil)</td>
<td>250 ( \mu )L / 25 g-weight</td>
<td>D8, D12, D16</td>
<td>melanoma B16</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>250 ( \mu )L / 25 g-weight (g-weight)</td>
<td>D8, D12, D16</td>
<td>colon carcinoma CT-26</td>
<td>6</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>MTD = 0.05</td>
<td>D8, D12, D16</td>
<td>melanoma B16</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>0.75 MTD = 0.035</td>
<td>D8, D12, D16</td>
<td>melanoma B16</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>MTD = 0.14</td>
<td>D8, D12, D16</td>
<td>melanoma B16</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>0.75 MTD = 0.10</td>
<td>D8, D12, D16</td>
<td>melanoma B16</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>0.75 MTD = 0.10</td>
<td>D8, D12, D16</td>
<td>colon carcinoma CT-26</td>
<td>6</td>
</tr>
<tr>
<td>21a</td>
<td>MTD = 0.14</td>
<td>D8, D12, D16</td>
<td>melanoma B16</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>0.75 MTD = 0.10</td>
<td>D8, D12, D16</td>
<td>melanoma B16</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>0.75 MTD = 0.10</td>
<td>D8, D12, D16</td>
<td>colon carcinoma CT-26</td>
<td>6</td>
</tr>
<tr>
<td>40a</td>
<td>MTD = 0.14</td>
<td>D8, D12, D16</td>
<td>melanoma B16</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>0.75 MTD = 0.10</td>
<td>D8, D12, D16</td>
<td>melanoma B16</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>0.75 MTD = 0.10</td>
<td>D8, D12, D16</td>
<td>colon carcinoma CT-26</td>
<td>6</td>
</tr>
</tbody>
</table>
Considering physiopathological features of the CT26 colon carcinoma model, mainly cachexy, drugs 21a and 40a, were assessed at the lowest dosage, i.e. 0.75 MTD administered at Day 8, Day 12, Day 16.

The reference treatment chlorambucil was given at the MTD dosage according to the same schedule.

Figures 1 and 2 report the so-obtained results.

Figure 1 presents the CTW time-course obtained for the B16 melanoma model for both drugs 21a and 40a and chlorambucil administered at the MTD dosage (figure 1a) and 0.75 MTD dosage (figure 1b).

For both MTD and 0.75 MTD dosages, each of the two chlorambucil derivative drugs was observed to induce a significant tumour growth inhibition (p< 0.05, student t-test,) as compared to non-treated control group and vehicle-treated group. In contrast, chlorambucil administered at both MTD and 0.75 MTD dosages failed to induce any tumour growth inhibition.

The Figure 2 presents the CTW time-course of CT26 carcinoma model

Each of the two drugs 21a and 40a, IP administered at the 0.75 MTD dosage at Day 8, 12 and 16 was observed to induce a significant tumour growth inhibition (p< 0.05, student t-test) as compared to non-treated control group and vehicle-treated group. Chlorambucil administered at the MTD dosage according to the same schedule was observed to induce a significant tumour growth inhibition (p< 0.05, student t-test,) as compared to non-treated control group and vehicle-treated group.

For subcutaneously growing tumours, antitumour activity is often assessed by using the logio cell kill (LCK) which is calculated from the following formula:

\[ \text{LCK} = \frac{T-C}{3.32 \times Td} \]

where T is the median time (in days) required for the treatment group tumours to reach a predetermined CTW (e.g. 1000 mg).

C is the median time (in days) required for the control group tumours to reach the same CTW.

Td is the tumour volume doubling time (in days) estimated from the best fit straight line from a log-linear growth plot of the control group tumours in exponential growth.

According to the National Cancer Institute (NCI) guidelines, criteria of decision are:

- LCK < 0.7 inactive drug (-)
According to the NCI criteria decisions, drug 21a exhibited active antitumour activity on both B16 melanoma and CT26 colon carcinoma models, LCK values being around 1.1. More interesting, drug 40a exhibited highly active antitumour activity on both B16 melanoma and CT26 colon carcinoma models, LCK values being around 1.5. In contrast, chlorambucil was inactive on B16 melanoma growth inhibition, with LCK < 0.7. Considering CT26 colon carcinoma model, chlorambucil exhibited a discrete antitumour activity, LCK value being 0.79.

An increase in life span was defined by the ratio of the median survival of drug-treated mice (Mt) versus controls (Mc): a survival $M_t/M_c$ equal or higher than 125% was sought. Mean weight loss of the group was used to evaluate treatment side effects. A mean body weight loss of greater 20% was considered to indicate an excessive toxic dosage.

Life span of the animals was increased for both B16 melanoma and CT-26 colon carcinoma-bearing mice only treated with drugs 21a and 40a, and not with chlorambucil (see Table 6). Nevertheless, a high toxicity was observed for CT-26 bearing mice treated with drug 40a (maximum weight loss of 21%).

The following table 6 reports end-points for anti-tumour activity assessment.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose / inj. (mmol/kg)</th>
<th>Schedule</th>
<th>Tumour model</th>
<th>Number animals</th>
<th>LCK</th>
<th>Weight loss (% max)</th>
<th>Survival Mt/Mc</th>
<th>Antitumour Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil</td>
<td>MTD (0.05)</td>
<td>D8, D12, D16</td>
<td>B16 melanoma</td>
<td>5</td>
<td>0.24</td>
<td>13.6% (J17)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT26 colon carcinoma</td>
<td>6</td>
<td>0.79</td>
<td>13.9% (J16)</td>
<td>0.74</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>75% MTD (0.035)</td>
<td>D8, D12, D16</td>
<td>B16 melanoma</td>
<td>7</td>
<td>0.05</td>
<td>7.3% (J13)</td>
<td>0.67</td>
<td>-</td>
</tr>
<tr>
<td>21a</td>
<td>MTD (0.14)</td>
<td>D8, D12, D16</td>
<td>B16 melanoma</td>
<td>7</td>
<td>1.02</td>
<td>15.7% (J21)</td>
<td>0.74</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT26 colon carcinoma</td>
<td>5</td>
<td>1.10</td>
<td>16% (J17)</td>
<td>1.18</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>75% MTD (0.1)</td>
<td>D8, D12, D16</td>
<td>B16 melanoma</td>
<td>6</td>
<td>1.10</td>
<td>17.1% (J15)</td>
<td>1.5</td>
<td>+</td>
</tr>
<tr>
<td>40a</td>
<td>MTD (0.14)</td>
<td>D8, D12, D16</td>
<td>B16 melanoma</td>
<td>7</td>
<td>1.53</td>
<td>16.9% (J16)</td>
<td>0.8</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>75% MTD (0.1)</td>
<td>D8, D12, D16</td>
<td>B16 melanoma</td>
<td>6</td>
<td>1.81</td>
<td>13.6% (J17)</td>
<td>1.5</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT26 colon carcinoma</td>
<td>6</td>
<td>1.52</td>
<td>21.5% (J15)</td>
<td>1.29</td>
<td>++</td>
</tr>
</tbody>
</table>
Accordingly, with respect to the NCI criteria decisions, chlorambucil glucoconjugates 21a and 40a exhibited active and highly active antitumor activities respectively on both B16 melanoma and CT-26 colon carcinoma experimental models. Chlorambucil parent drug failed in exhibiting any antitumour activity on the same experimental models.

Administration of the deoxyglucose conjugates provided herein can be effected by any method that enables delivery of the conjugates to the site of the cancer or suspected cancer.

In one embodiment, delivery may be via circulation in the bloodstream. To place the conjugates in contact with cancerous tissues or cells, the methods of administration include oral, duodenal intraduodenal, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular, or infusion), topical administration, and rectal.

The amount of the conjugate administered will be dependent upon the subject being treated, the severity of the cancer, localization of the cancer, the rate of administration, the disposition of the conjugate (e.g., solubility and fluorescence intensity) and the discretion of the administrator.

However, an effective dosage is typically in the range of about 0.001 to about 100 mg per kg body weight, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this dosage would amount to about 0.05 to about 7 g/day, preferably about 0.2 to about 2.5 g/day.

In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, although such larger doses may be divided into several smaller doses for administration throughout the day.

The conjugate according to the present invention may, for example, be in a form suitable for oral administration, such as a tablet, capsule, pill, powder, sustained release formulation, solution, or suspension; for parenteral injection, such as a sterile solution, suspension or emulsion; for topical administration, such as an ointment or cream; or for rectal administration, such as a suppository.
The conjugate composition may be in unit dosage forms suitable for single administration of precise dosages and can include a conventional pharmaceutical carrier or excipient.

Exemplary parenteral administration forms include solutions or suspensions of the imaging conjugate in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water, and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients, and the like. Thus for oral administration, tablets containing various excipients, such as citric acid, may be employed together with various disintegrants such as starch, alginic acid, and certain complex silicates, and with binding agents such as sucrose, gelatin, and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate, and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the conjugate therein may be combined with various sweetening or flavoring agents, coloring matters or dyes, and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

It may prove desirable to stabilize the instant compounds e.g. to increase their shelf life and/or pharmacokinetic half-life.

Shelf-life stability may be improved by adding excipients such as; a) hydrophobic agents (e.g., glycerol); b) non-linked sugars (e.g., sucrose, mannose, sorbitol, rhamnose, xylose); c) non-linked complex carbohydrates (e.g., lactose); and/or d) bacteriostatic agents.

It may be also advantageous to co-administrate a compound according to the invention with anti-neoplastic agent, i.e. under a free form in particular as disclosed previously.
CLAIMS

1. Compound of general formula (I):

   \[ \text{R}_1 \text{O} \quad \text{OR}_1 \quad \text{X} \quad \text{Z} \quad (\text{R}_2\text{Y})_n \quad \text{Z} \quad (\text{R}_3\text{Y})_m \]

   wherein:

   - \( \text{R}_1, \text{R}_2 \) and \( \text{R}_3 \) mean, independently from the others, a hydrogen atom or an optionally substituted lower alkyl, a (C\textsubscript{1}-C\textsubscript{7}) acyl group or a benzyl,
   - \( \text{R}_4 \) is an optionally substituted and/or interrupted hydrocarbon linker,
   - \( \text{X} \) and \( \text{Y} \) are selected independently from each other from the group consisting of -NH-, -NR'-, -CO-, -NH(CO)-, -NH(CO)NH-, -NR'(CO)-, -O(CO)NH-, -O(CO)NR'-, -OC(O)NH-, -OC(O)NR'-, -SC(O)NH-, -NSO\textsubscript{3}-, -NR'SO\textsubscript{3}-, -O(CO)-, -S-S-, -OC(O)NHR''C(O)NH-, -NHC(O)R''-, -OC(O)R'', -OC(O)NH-R''-, and -NHC(O)NH-R'-'-

   and preferably are different one from the other, with \( \text{R}' \) being an optionally substituted lower alkyl group, and \( \text{R}'' \) being a (C\textsubscript{1}-C\textsubscript{3}) alkylene,

   - \( \text{Z} \) moiety represents an anti-neoplastic agent,
   - \( \text{n} \) means 0, 1 or 2,
   - and the pharmaceutically acceptable salts thereof.

2. Compound according to claim 1, wherein \( \text{R}_4 \) is of formula

   \[ -(\text{Alkylene})_m-(\text{P})_p-(\text{Alkylene})_q- \]

   or

   \[ -(\text{Alkylene})_m-(\text{P})_p-(\text{Alkylene})_q- \]

   wherein

   - \( \text{m}, \text{p} \) and \( \text{q} \) mean independently one from the others 0 or 1 with the proviso that at least one of them is different from 0,
   - \( \text{Alkylene} \) means an optionally substituted (C\textsubscript{1}-C\textsubscript{7}) alkyl group,
   - \( \text{Arylene} \) means an optionally substituted C\textsubscript{6} to C\textsubscript{10} arylene or heteroarylene, and
I means a group as proposed for X and Y as defined in claim 1.

3. Compound according to claim 1 or 2, wherein alkylene means a methylene group.

4. Compound according to claim 2 or 3, wherein P means a group selected from

5. Compound according to anyone of previous claims, wherein n is equal to zero.

6. Compound according to the previous claim, wherein X means -O(CO)-,
-NH(CO)-, -NH(CO)NH- or -NHC(O)CH₂-.

7. Compound according to anyone of claim 1 to 4, wherein n is different from zero.

8. Compound according to the previous claim, wherein R₄ comprises or is

9. Compound according to claim 7 or 8, wherein X is selected from the group consisting of -NH-, -NH(CO)-, -O-, -O(CO)-, -0(CO)NH-, -NH(CO)O- and -OC(O)NHCH₂C(O)NH.

10. Compound according to any one of claims 7 to 9, wherein Y is -NH(CO)-, - (CO)NH-, -O(CO)-, -0(CO)NH-, -NH(CO)O-, and -NHC(O)CH₂-.

11. Compound according to claim 7, wherein R₄ includes or is a (C1-C7) alkylene group and more particularly a methylene group.

12. Compound according to the previous claim, wherein X and Y represent a group selected from the group consisting of -NH-, -(CO)NH-, -NH(CO)NH- and -O(CO)-, -0(CO)NH- and -NH(CO)O-.

13. Compound according to claim 7, wherein R₄ means a radical of formula (Arylene)-P-(Alkylene), (Alkylene)-P-(Arylene) or -(Alkylene)-(P)-(Alkylene)- wherein :
- Arylene is
- Alkylene is a (C1-C3)alkylene group, and
- P is -NHCO-, -CONH-, - NR'-, -S-S- or -NH- with R' being as defined in claim 1.
14. Compound according to the previous claim, wherein Alkylene means a methylene group,
15. Compound according to any one of the previous claims, wherein \( R_1, R_2 \) and \( R_3 \) are different from hydrogen.
16. Compound according to any one of the previous claims, wherein \( R_i, R_2 \) and \( R_3 \) mean an acyl group and in particular an acetyl group.
17. Compound according to any one of the previous claims, wherein the antineoplastic agent is selected from the group consisting of cyclophosphamide, doxorubicin, vincristine, etoposide, cisplatin, ifosfamide, melphalan, chlorambucil, thiopeta, carboptati, estramustine phosphate, prednimustine, 5-fluorouracil, camptothecin, vinblastine, paclitaxel, vinorelbine, docetaxel, epothilone B or D, discodermolid, nitrosoureas like 2-chloroethyl nitrosourea, procarbazine, lomustine, caπmustine, estramustine, nucleoside like mercaptopurine, thioguanine, hydroxyurea, cytarabine, flouxuridine, fludarabine, pentostatin, cladribine, gemcitabine, and capecitabine.
18. Compound according to any one of the previous claims, wherein \( X \) and/or \( Y \) mean \(-\text{NHC(O)\text{-}}\) or \(-\text{(O)CNH\text{-}}\).
19. Compound according to any one of the previous claims, wherein the antineoplastic agent is chlorambucil or a derivative thereof.
20. Compound according to any one of the previous claims, selected from the group consisting of:
   - 3,4,6-tri-O-acetyl-1-[4-\{4-\{\text{bis(2-chloroethyl)amino\text{-}}\\text{phenyl}\}\text{butyrate}\text{-}2\text{-}\text{deoxy-2-fluoro-}\alpha\beta\text{-}\text{D-glucopyranose}
   - 3,4,6-tri-O-benzyl-1-[4-\{4-\{\text{bis(2-chloroethyl)amino\text{-}}\\text{phenyl}\}\text{butyrate}\text{-}2\text{-}\text{deoxy-2-fluoro-}\alpha\beta\text{-}\text{D-glucopyranose}
   - 1-[4-\{4-\{\text{bis(2-chloroethyl)amino\text{-}}\\text{phenyl}\}\text{butyrate}\text{-}2\text{-}\text{deoxy-2-fluoro-}\alpha\beta\text{-}\text{D-glucopyranose}
   - N\text{-}(3,4,6\text{-}\text{tri-O-acetyl-2\text{-}deoxy-2\text{-}fluoro-}\beta\text{-}\text{D-glucopyranosyl})\text{-}4\text{-}\{4\text{-}\{\text{bis(2-chloroethyl)amino\text{-}}\\text{phenyl}\}\text{butyrate}\text{-}4\text{-}\text{deoxy-2-fluoro-}\beta\text{-}\text{D-glucopyranosyl}butanamide
   - 4\text{-}\{4\text{-}\{\text{bis(2-chloroethyl)amino\text{-}}\\text{phenyl}\}\text{butyrate}\text{-}4\text{-}\text{deoxy-2-fluoro-}\beta\text{-}\text{D-glucopyranosyl}butanamide
   - \text{N\text{-}(3,4,6\text{-}\text{tri-O-acetyl-2\text{-}deoxy-2\text{-}fluoro-p\text{-}\text{D-glucopyranosyl})\text{-}N\text{'-}(3\text{-}4\text{-}\{\text{bis(2-chloroethyl)amino\text{-}}\\text{phenyl}\}\text{propyl}\)urea}
N-{3-(4-[bis(2-chloroethyl)amino]phenyl)propyl}-N'-(2-deoxy-2-fluoro-p-D-glucopyranosyl)urea.
N-(3,4,6-tri-0-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl)amine)-4-(4-[4-[bis(2-chloroethyl)amino]phenyl]butanamide
4-(4-[bis(2-chloroethyl)amino]phenyl)butanamide
N-[2-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylamino)-2-oxoethyl]-4-[4-[bis(2-chloroethyl)amino]phenyl]butanamide
N-[4-(3,4,6-tri-0-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylamino)-4-oxobuty1]-4-[4-[bis(2-chloroethyl)amino]phenyl]butanamide
N-[4-(3,4,6-tri-0-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylamino)-3-oxopropyl]-4-[4-[bis(2-chloroethyl)amino]phenyl]butanamide
N-[4-(4-[bis(2-chloroethyl)amino]phenyl)butanoyloxy)phenyl]-3,4,6-tri-0-benzyl-2-deoxy-2-fluoro-β-D-glucopyranosylamine
N-[4-(4-[bis(2-chloroethyl)amino]phenyl)butanoyloxy)phenyl]-3,4,6-tri-0-benzyl-2-deoxy-2-fluoro-β-D-glucopyranosylamine
N-[4-(4-[bis(2-chloroethyl)amino]phenyl)butanoyloxy)phenyl]-3,4,6-tri-0-benzyl-2-deoxy-2-fluoro-β-D-glucopyranosylamine
N-[4-(4-[bis(2-chloroethyl)amino]phenyl)butanoyloxy)phenyl]-3,4,6-tri-0-benzyl-2-deoxy-2-fluoro-β-D-glucopyranosylamine
4-[4-[bis(2-chloroethyl)amino]phenyl]-N-[2-(2-deoxy-2-fluoro-β-D-glucopyranosyl)benzamide
4-[4-[bis(2-chloroethyl)amino]phenyl]-N-[3-(2-deoxy-2-fluoro-β-D-glucopyranosyl)benzamide
4-[4-[bis(2-chloroethyl)amino]phenyl]-N-[3-(2-deoxy-2-fluoro-β-D-glucopyranosyl)benzamide
N-[3-(3,4,6-tri-0-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosylamino)-3-oxopropyl]-4-[4-[bis(2-chloroethyl)amino]phenyl]butanamide
N-[4-(4-[3-(4-[bis(2-chloroethyl)araino]phenyl)propyl]-N'-2-deoxy-2-fluoro-p-D-glucopyranosyl)urea.
(3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl) 4-[2-(4-[
4-[bis(2-chloroethyl)amino]phenyl]butanamido)acetamido]phenylcarbamate

(3,4,6-tri-O-acetyl-2-deoxy-2'-fluoro-β-D-glucopyranosyl) 4-[4-(4-[bis(2-
choloroethyl)amino][phe-iy][butaiamido]phenylamiino]-2-oxoethylcaxbainate

4-(3-(3,4,6-tri-O-acetyl-2-deoxy-2'-fluoro-β-D-glucopyra-
πosyl)ureido)-iV : (3-
{4-[bis(2-chloroethyl)amino][phenyl]propyl}butanamide

N-[4-(3,4,6-tri- O-acetyl-2-deoxy-2-fluoro-
α,β-D-
glucopyranosyloxy)carbonyl][phenyl]-4-[4-tbis(2-chloroethyl)amino][phenyl]butanamide

iV-[3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-
β-D-glucopyranosyl]-4-[2-(4-[bis(2-
chboroethyl)amiino][phenyl]butanamido)acetamido]benzamide

iV-[4-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-
β-D-glucopyranosyloxy)phenyl]- N'-
[3-[4-[bis(2-chloroethyl)amino][phenyl]propyl]propanediamide

iV-[4-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-
β-D-
glucopyranosyloxy)phenyl]-4-(4-[bis(2-
chloroethyl)amino][phenyl]butamido)benzamide

iV-[4-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-
β-D-glucopyranosyloxy)plienyl]-2-
[3-(2-chloroethyl)-3-nitrosoureido]acetamide

β-D-glucopyranosyl)-2-[3-(2-
chboroethyl)-3-nitrosoureido]acet 3a
tide

(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-
β-D-glucopyranosyl)-4-[2-[3-(2-
chboroethyl)-O-S-nitSOureido]acetamidolphenylcarbamate

7V-(4-[bis(2-chloroethyl)amiino][phenyl]-butanoyl]glycyl-L-phenylalanyl-L-
leucyl] (S^S^-tri-O-acetyl^3-deoxy^-fluoro-
β-D-glucopyranosy^glycynamide

4-[bis(2-ohloroetliyl)amtimio][pheiyl] - N-[4-(2-deoxy-2-fluoro-
β-D-
glucopyranosylamiino)-3-oxopropylsulfanyethyl]butanamide

and their salts.

21. Compound according to anyone of the previous claims, which is JV-[2-[4-
(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-
β-D-glucopyranosyloxy)phenyl]amiino-2-oxoethyl]-
4-[4-[bis(2-chloroethyl)amino][phenyl]butanamide.
22. Pharmaceutical composition including in a physiological acceptable vehicle, at least one compound according to any one of the previous claims.

23. A compound according to any one of claims 1 to 21, as a anti-cancer agent.

24. Use of a compound according to any one of claims 1 to 21, for preparing a pharmaceutical composition intended to the treatment of cancer.

25. Method for treatment of cancer comprising the administration to a patient in need thereof, of at least one compound of any one of claims 1 to 21, or a composition according to claim 22.