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(54) **MULTI-SENSOR ARRAY COMPOUND AND METHODS OF USE THEREOF**

VERBINDUNG AUS MEHREREN SENSORARRAYS UND VERWENDUNGSVERFAHREN DAFÜR

COMPOSÉ DE RÉSEAU MULTICAPTEUR ET SES PROCÉDÉS D'UTILISATION

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Description

FIELD OF THE INVENTION

[0001] The present invention is directed to a multi-sensor array compound including at least three chromophores, at least one receptor and an anchor. Contacting the compound of this invention with an analyte (such as carbohydrate) forms a complex with unique optical signature. The unique optical signature allows differentiating between carbohydrates, diagnosing diseases associated with the carbohydrate, and encoding information in an encoding system.

BACKGROUND OF THE INVENTION

[0002] Colorimetric or fluorescent molecular sensors triggered by several input signals are applied as molecular computation and analytical devices. Such sensors can imitate the function of electronic logic gates, digital circuits; arithmetic and security systems, as well as be applied in multiplexed cellular imaging, in clever chemosensing, and as molecular tags. Such sensors require a receptor-per-target, which significantly limits their multiplicity.

[0003] In order to obtain multi-analyte detection using fluorescent or colorimetric molecular sensors cross-responsive arrays are required similar to the mammalian olfactory system. An artificial nose, typically includes two components, an array of chemical sensors and a pattern-recognizer. The array may mimic the operation of the olfactory neural system and can identify complex vapors and aromas as well as analyze disease biomarkers. State-of-the-art developments in supramolecular analytical chemistry afforded colorimetric and fluorescent molecular sensor arrays that can operate in biochemical solutions. Developing methods for verifying drug content at a point-of- care is receiving growing international attention. Unlike any other class of biosensors, such arrays can detect, identify, and discriminate among specific mixtures containing possibly hundreds of different chemical species or between structurally similar biomolecules including phosphates, steroids, saccharides, nucleotide phosphates, peptides, and proteins in a high-throughput manner.

[0004] For example, macrolides, aminoglycosides, and rifampycins are large families of antibiotics whose counterfeits are highly prevalent in the developing world. Cardiac glycosides, used for treating heart conditions, have been associated with substandard medication in developed countries and are often involved in medication errors due to their narrow therapeutic window and adverse drug interactions.

[0005] Glycans play diverse and crucial roles in several biological processes. Most plasma membrane and secretory proteins are glycosylated.

[0006] The presence and/or irregular concentrations of glycans can be a sign for various diseases such as multiple sclerosis, Crohn's disease, autoimmune disease, colitis, inflammatory bowel disease, cancer, lysosomal storage disease and celiac. Some inherited and nongenetic diseases results of alterations of the glycan structures. Sensitive, convenient and precise glycan-sensing methods provide crucial tools for the early diagnosis of diseases and successful treatments of patients. Therefore, selective sugar detection is a challenging problem. Elfeky (Current Organic Synthesis, 2011, 8(6): 872-880) discloses the use of a compound consisting of a fluorescent boronic acid bound to a diol quencher, in the detection of saccharides (and nucleotides) as they interact with the compound and bring about a fluorescence recovery reaction. He further studied the effect of pH on the sensitivity and concluded that the sensitivity drops in acidic media. Larkin et al. (New J. Chem., 2010, 34: 2922-2931) discloses a similar use of modular sensors consisting of one fluorophore and two boronic acid moieties, all connected to the same backbone and experience increase in the fluorescence intensity upon the addition of some saccharide analytes.

[0007] Although every sensor in an array may respond to a given chemical or mixture of chemicals differently, the pattern recognizer evaluates the responses and through predetermined, programmed, or learned patterns the pattern-recognizer compares the unique pattern or "fingerprints" of the measurements to stored patterns for known chemical species for identifying and quantifying of the species chemical.

[0008] Fluorescent or colorimetric molecular sensors have the ability to recognize various biologically compounds, specific and mixtures of chemicals and detect disease biomarkers. Fluorescent or colorimetric molecular sensors are among the most powerful analytical tools used in cell biology. Cell-permeable molecules that combine a receptor and a fluorophore allow one to sense specific ions or biomolecules in their native environments and to better understand their role in various cell signalling pathways.

[0009] A combinatorial fluorescent molecular sensor mimics the operation of optical cross-reactive sensor arrays (the so-called artificial "nose/tongues"). The sensor integrates different non-specific fluorescent receptors (e.g. boronic acid-dye conjugates) and utilizes photo-induced electron transfer (PET), internal charge transfer (ICT), and fluorescence resonance energy transfer (FRET) for generating distinguishable emission patterns for different carbohydrate-based drugs and their combinations. For example, Musto et al. (Curr Opin Chem Biol. 2010, 14(6): 758-66) discloses the use of pattern based colorimetric arrays from a collection of crossreactive sensors, based on the known interaction between boronic acids and diols. Schiller et al. (Anal Chim Acta. 2008, 627(2): 203-11) and Schiller et al. (Angew Chem Int Ed Engl. 2007, 46(34): 6457-9) disclose the use of a fluorescent sensor array consisting of boronic acid appended bipyrid-

inium salts and a coordinating fluorescent dye. In his studies, the addition of analyte molecules such as sugars, phosphosugars and nucleotides to a sensor array results in the departure of the salts from the dye, giving rise to enhanced fluorescent output.

[0010] Specifically, combinatorial sensing devices that, similar to small fluorescent molecules, could operate in a microscopic world might eventually be able to provide insight into the dynamics of bioanalyte combinations within cells, information that cannot be obtained from conventional fluorescent sensors.

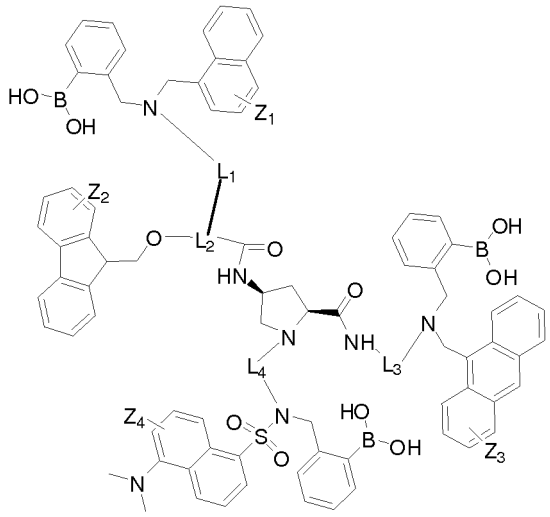
[0011] Further, a combinatorial fluorescent molecular sensor can operate as a highly efficient molecular security/encoding system. The ability of a pattern-generating molecule to process diverse sets of chemical inputs, discriminate between their concentrations and form multivalent and kinetically-stable complexes, is a powerful tool for processing a wide range of chemical 'passwords' at different lengths. Such system results in unbreakable combination locks at a molecular scale.

[0012] Similar to the electronic devices, the molecular encoding system can respond to diverse input and authorize multiple password entries.

[0013] The present application is directed to compounds for differential sensing, particularly of saccharides at the molecular-scale as well as within confined microscopic spaces such as cells.

SUMMARY OF THE INVENTION

[0014] In one embodiment, this invention is directed to a compound represented by the structure of formula III:



(III)

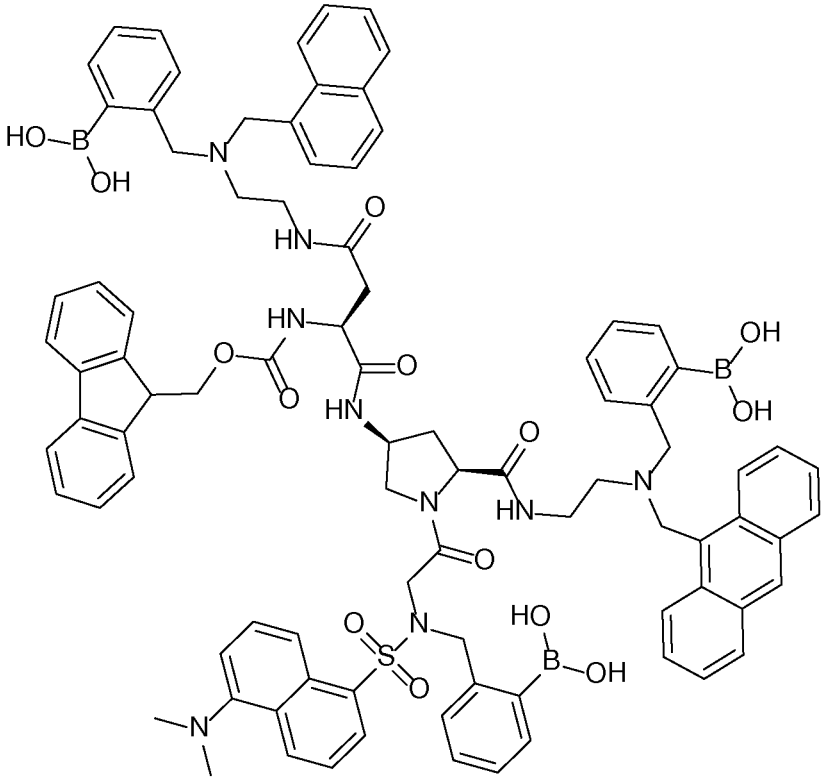
wherein

L_1, L_2, L_3, L_4 are independently a linker, wherein said linker is -alkylene-, -O-alkylene-, -NHC(O)-, -C(O)NH-, -NHC(O)X-, -C(O)NHX-, -C(O)X-, -X'NHC(O)-, -X'C(O)NH-, -X'NHC(O)X-, -X'C(O)NHX-, -X'C(O)X-, -NHX-, -NH-[amino-acid]-C(O)-, -NH-[amino-acid]-C(O)-alkylene-, -C(O)-[amino-acid]-NH-, or -C(O) -[amino-acid]-NH-alkylene-;

X and X' are independently alkylene, haloalkylene, arylene or phenylene; and

Z_1, Z_2, Z_3, Z_4 are independently hydrogen, alkyl, alkenyl, haloalkyl, aryl, O-aryl, -(CH_2)n-aryl, cycloalkyl, O-cycloalkyl, CF_3, F, I, Br, Cl, NO_2, CN, $N(R')_2$, COOH, COR', NHCOR', CONHR', $(CH_2)_nNH_2$, $(CH_2)_nNHR'$, SR', SH, OR', $(CH_2)_nOH$, $(CH_2)_nCOOH$, or OH; wherein R' is H, alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, aryl, phenyl or halogen; and n is from 0 to 8.

[0015] In one embodiment, the compound of formula III is represented by the structure of compound 1:



(1)

[0016] In one embodiment, this invention is directed to a method of differentiating between carbohydrates comprising:

- contacting a carbohydrate with a compound of formula III in a liquid medium, wherein said carbohydrate and said compound form a complex; wherein a first fluorescent dye emits at a wavelength which is the absorption wavelength of a second fluorescent dye; wherein said linker comprises nitrogen; wherein contacting said carbohydrate with said compound results in a conformational change of said compound and thereby to a unique optical signature of said complex; wherein said liquid medium is an aqueous solution; and
- measuring the optical signature of said complex;

and thereby, differentiating said carbohydrate.

[0017] In one embodiment, this invention is directed to a compound of formula III for use in a method of diagnosing a disease in a subject, wherein said diagnosis comprises detection of a carbohydrate biomarker; said method comprising:

- collecting a biological sample from a subject;
- optionally isolating components from said biological sample;
- contacting the compound of formula III with a carbohydrate comprised within said sample or within isolated component in a liquid medium; wherein said carbohydrate forms a complex with said compound; wherein contacting said compound with said carbohydrate results in a conformational change of said compound and thereby to a unique optical signature of said complex;
- measuring the optical signature of said complex;
- identifying a carbohydrate biomarker in said sample, said carbohydrate biomarker being characteristic of a disease; or measuring a change in a concentration of a carbohydrate biomarker in said sample compared to normative values, wherein said change is characteristic of a disease; thereby, diagnosing a disease in a subject.

[0018] In an embodiment, the disease is selected from hypoglycemia, prostate cancer, diabetes, syndrome X, or a glycoprotein based disease selected from multiple sclerosis, Crohn's disease, autoimmune disease, colitis, inflammatory bowel disease, cancer, lysosomal storage disease, or celiac disease.

[0019] In an embodiment, the carbohydrate is an antibiotic or a saccharide, wherein said saccharide is a monosaccharide, a disaccharide, L-Glucose, D-Glucose, D-fructose, L-fructose, D-arabinose, D-xylose, L-xylose, L-mannose, D-galactose, D-sorbitol, mannitol, dulcitol, adonitol, xylitol, L-threitol, maltitol, lactulose, D-lactose, D-maltose, D-treha-

lose or maltotriose; wherein said antibiotic is a macrolide, an aminoglycoside, a cardiac glycoside, or a rifamycin; wherein said saccharide is a component of a glycoprotein, a proteoglycan or a glycolipid or a glycan independent of a protein or lipid compound.

[0020] This invention is also directed to a method of encoding information using a compound represented by the structure of formula (III), the method comprising:

contacting said compound with between 2 and 7 analytes in a specific sequence to form a complex, wherein said complex exhibits a unique optical signature signal;
reading the unique optical signature;
associating the unique optical signature with an encoding reference specifying said analytes contacted in said specific sequence according to a predefined encoding scheme; and
storing the encoded reference keyed to the unique optical signature in a database record.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] The subject matter regarded as the invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. The invention, however, both as to organization and method of operation, together with objects, features, and advantages thereof, may best be understood by reference to the following detailed description when read with the accompanying drawings in which:

Fig. 1 depicts a synthetic scheme of a monomolecular differential sensor of compound 1.

Fig. 2 depicts a schematic illustration of the sensor function. A unique emission pattern for each saccharide can be generated due to direct optical responses of each dye, as well as conformational changes that affect fluorescence resonance energy transfer (FRET) processes among them.

Fig. 3A and 3B depict normalized excitation (Figure 3A) and emission (Figure 3B) spectra of fluorenyl-aspartic acid (Flu*), naphthalene-boronic acid (Naph*), anthracene-boronic acid (An*) and dansyl-boronic acid (Dan*) derivatives in a methanol solution. The emission spectra of Flu* and Naph* were obtained under an excitation wavelength of 270 nm using 295-1100 nm filter, whereas the emissions of An* and Dan* were recorded while exciting at 345 nm using 360-1100 nm filter.

Fig. 4 depicts fluorescence emission spectra of dansyl derivative 7 (Dan*), anthracene derivative 4 (An*) and compound 1 in methanol excited at 345nm.

Fig. 5 depicts a schematic representation of the possible FRET processes that can occur among the four fluorophores when excited at 270 nm.

Fig. 6 depicts changes in fluorescence emission spectrum of compound **1** upon addition of D-glucose, L-glucose, L-fructose, maltitol, and D-xylose. Conditions: 4.8 mM of saccharide and 3.3 μM of sensor in methanol (5% water) excited at 270 nm.

Fig. 7A-7C depict fluorescence emission spectra of compound **1** in PBS:MeOH (1:1, pH = 7.28)(Figure 7A), HEPES:MeOH (1:1, pH = 7.5) upon addition of different saccharides (48 mM) (Figure 7B) and PCA graph for the repeat experiments of five saccharides in PBS: Methanol (1:1, pH=7.28)(Figure 7C). Excitation wavelength: 270 nm.

Fig. 8 depicts a PCA mapping of emission patterns generated by various saccharides. 1) None; 2) D-glucose; 3) L-glucose; 4) D-fructose; 5) L-fructose; 6) D-arabinose; 7) D-xylose; 8) L-xylose; 9) L-mannose; 10) D-galactose; 11) D-sorbitol; 12) mannitol; 13) dulcitol; 14) adonitol; 15) xylitol; 16) L-threitol; 17) maltitol; 18) lactulose; 19) D-lactose; 20) D-maltose; 21) D-trehalose; 22) maltotriose.

Fig. 9 depicts a DFT optimized structure of compound **1.** Color scheme: Grey Stick: Molecular cavity; Black Stick: Four Dyes; Black ball: Boron; Grey ball: Oxygen ; Carbon, Nitrogen, Sulphur is not highlighted individually and Hydrogen is omitted for clarity.

Fig. 10 depicts fluorescence emission spectra of compound **1** (3 μM,) in methanol mixed with antibiotics in DMSO 100mM. Fluorescence measurements were taken in a 3 mm cuvette under an excitation wavelength of 270 nm using 295-1100 nm emission filter and 10 nm excitation and emission slit width. The spectra were recorded at a rate of 120 nm per min. The emission of the compound **1** (none) corresponds to an addition of only DMSO.

Fig. 11 depicts a principal component analysis (PCA) to distinguish between optical signatures generated by antibiotics such as macrolides, aminoglycosides, cardiac glycosides, and rifamycins, including structures of carbohydrates.

Figure 12A: Emission Spectra of compound **1** subjected to human urine loaded with different ratios of D-xylose and rifampicin. The parallel analysis of rifampicin and D-xylose levels in urine is used for diagnosing rifampicin malabsorption in patients with tuberculosis; **Figure 12B:** Fluorescence response (ΔI) pattern of different drug combinations at four different wavelength and **Figure 12C:** PCA mapping of emission experiments.

Fig. 13 depicts excitation and emission wavelengths of various commercially available red and NIR-emitting dyes

(D)/chromophores. (R= OH or $NH(CH_2)$ 2Br)

Fig. 14 depicts synthetic steps for preparing various red and NIR emitting boronic acid-dye conjugates.

Fig. 15 depicts synthetic steps for preparing a monomolecular combinatorial sensor based on *cis*-amino proline scaffold, wherein D_1 to D_4 refer to a chromophore.

Fig. 16 depicts, a) Synthetic steps for preparing Nile-DB; b) a photograph of Nile-DB prior to and after the addition of glucose; c) emission spectra generated by 400 nM of Nile-DB (red) upon addition of 5 mM D-glucose (green), D-fructose (purple), and sucrose (blue). Excitation: 530 nm.

Fig. 17 depicts emission spectra of molecule **1** (3μM) upon addition of D-glucose (G) (2.5 mM) and D-xylose (X) (25 mM) in different order (a), and at different concentrations (b). Excitation wavelength: 270 nm.

Fig. 18 schematically illustrates a unimolecular combinatorial encoding system function. Possible complexes that can be formed upon addition of two distinct saccharides (1 and 2) in different order (iv Vs. v) or at different concentrations (ii and vi vs. iii and vii), leading to differentiation between 1, 2, 11, 22, 12, 21.

Fig. 19 depicts a PCA mapping of emission patterns generated by compound **1** upon addition of D-glucose (G) and D-xylose (X) in different sequences and concentrations.

Fig. 20 provides Table 2 which includes all possible combination codes of a three state encoding system.

Fig. 21 depicts a) the structure of DC; b) the change in fluorescence spectrum of compound 1 (9 μM) upon addition of maltitol (50 mM), D-xylose (17 mM) and DC (125 μM); (c) the displacement of DC by D-xylose (X); (d) the fluorescence response (ΔI) of different two state encoding system using DC, D-xylose (X) and maltitol (M) as inputs. Excitation: 270 nm.

Fig. 22 depicts a) fluorescence spectra of compound **1** (9 μM) upon addition of maltitol (1), D-xylose (2), and DC (3) in nine different combinations; and b) the corresponding PCA plot. Excitation wavelength = 270 nm.

Fig. 23 is a block diagram of an encoding system according to certain embodiments of the present invention.

Fig. 24 depicts fluorescence emission spectra of **1** (3μM) upon a) the addition of 1^{st}: 2.5 mM D-glucose, 2^{nd}: 25 mM galactose; b) 1^{st}: 25mM galactose, 2^{nd}: 2.5 mM D-glucose; c) 1^{st}: 25mM maltitol, 2^{nd}: 2.5 mM D-fructose, d) 1^{st}: 2.5 mM D-fructose, 2^{nd}: 25 mM maltitol in methanol. Excitation wavelength: 270 nm.

Fig. 25 depicts a PCA mapping of emission patterns generated by 5 mM solution of various saccharides. 1) None; 2) D-glucose; 3) L-glucose; 4) D-fructose; 5) L-fructose; 6) D-xylose; 7) L-xylose; 8) mannitol; 9) maltitol; 10) lactulose; 11) D-maltose; 12) maltotriose.

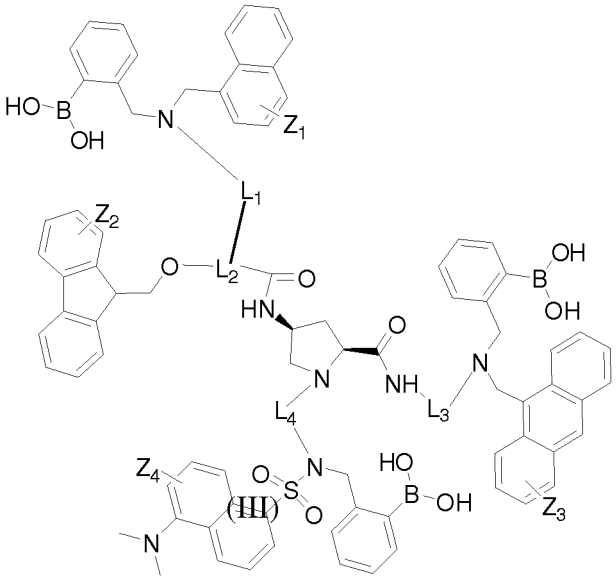
Fig. 26 depicts a PCA mapping of emission patterns generated by 50 mM maltitol (1), 17 mM D-xylose (2) and 125 μM DC (3) in twenty seven different combinations. A, B, C, D are the groups containing passwords that match each other. Group A contains 133, 331, 313, 233, 332, 323; Group B contains 113, 131, 322, 232; Group C contains 213, 123, 132, 312, 321; and Group D contains 221, 112, 211, 121.

[0022] It will be appreciated that for simplicity and clarity of illustration, elements shown in the figures have not necessarily been drawn to scale. For example, the dimensions of some of the elements may be exaggerated relative to other elements for clarity. Further, where considered appropriate, reference numerals may be repeated among the figures to indicate corresponding or analogous elements.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

[0023] In the following detailed description, numerous specific details are set forth in order to provide a thorough understanding of the invention.

[0024] In one embodiment, this invention is directed to a compound represented by the structure of formula III:

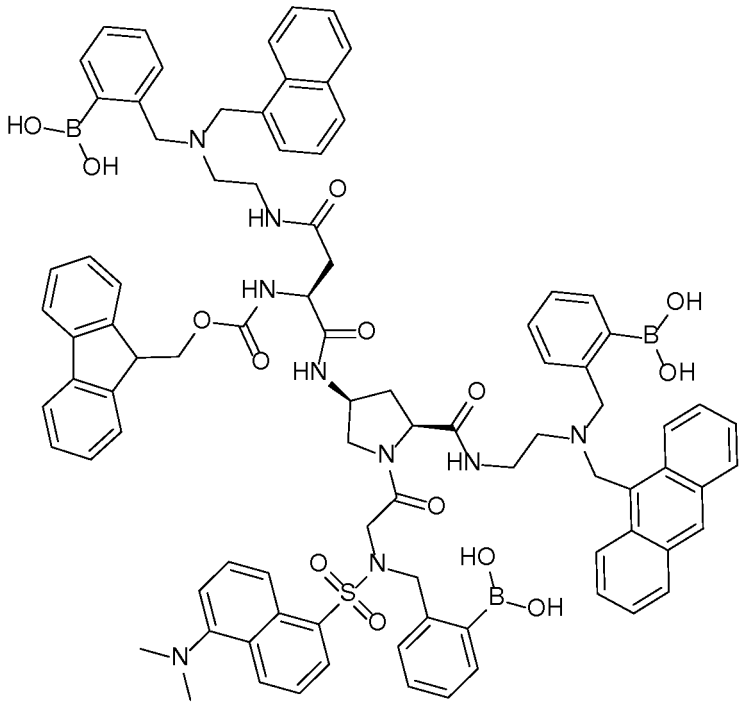


wherein

L_1, L_2, L_3, L_4 are independently a linker, wherein said linker is -alkylene-, -O-alkylene-, -NHC(O)-, -C(O)NH-, -NHC(O)X-, -C(O)NHX-, -C(O)X-, -X'NHC(O)-, -X'C(O)NH-, -X'NHC(O)X-, -X'C(O)NHX-, -X'C(O)X-, -NHX-, -NH-[amino-acid]-C(O)-, -NH-[amino-acid]-C(O)-alkylene-, -C(O)-[amino-acid]-NH-, or -C(O) -[amino-acid]-NH-alkylene-;
X and X' are independently alkylene, haloalkylene, arylene or phenylene; and
Z_1, Z_2, Z_3, Z_4 are independently hydrogen, alkyl, alkenyl, haloalkyl, aryl, O-aryl, -(CH_2)n-aryl, cycloalkyl, O-cycloalkyl, CF_3, F, I, Br, Cl, NO_2, CN, $N(R')_2$, COOH, COR', NHCOR', CONHR', $(CH_2)_nNH_2$, $(CH_2)_nNHR'$, SR', SH, OR', $(CH_2)_nOH$, $(CH_2)_nCOOH$, or OH; wherein R' is H, alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, aryl, phenyl or halogen; and
n is from 0 to 8.

[0025] Thus, the compound comprises an array of at least three fluorescent dyes, at least one boronic acid receptor and an anchor, wherein binding said receptor to an analyte forms a complex with unique optical signature.

[0026] In one embodiment, the compound of formula III is represented by the structure of compound **1:**



(1)

[0027] In one embodiment, this invention is directed to a compound and methods of use thereof. The compound of this invention includes at least three chromophores. In another embodiment the chromophore is a fluorescent dye. In another embodiment, the fluorescent dye is substituted by one to three substituents. In another embodiment the fluorescent dye is substituted by alkyl, alkenyl, haloalkyl, aryl, O-aryl, -(CH_2)n-aryl, cycloalkyl, O-cycloalkyl, CF_3, F, I, Br, Cl, NO_2, CN, $N(R')_2$, COOH, COR', NHCOR', CONHR', $(CH_2)_nNH_2$, $(CH_2)_nNHR'$, SR', SH, OR', $(CH_2)_nOH$, $(CH_2)_nCOOH$, or OH; wherein R' is H, alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, aryl, phenyl or halogen and n is between 0 to 8. In another embodiment n is between 1 to 6.

[0028] The compound of this invention includes an anchor. In an embodiment the chromophore and the receptor are covalently attached to the anchor via a linker. In another embodiment, the anchor of the compound of this invention is chiral. In another embodiment, the anchor of the compound of this invention is cis-amino-L proline. In another embodiment, the anchor of the compound of this invention is trans-amino-L proline. In another embodiment, the anchor of the compound of this invention is cis-amino-D proline or trans-amino-D proline. In another embodiment, the anchor is an aryl. In another embodiment, the anchor of the compound of this invention is proline, phenyl, bi-phenyl, naphthalene, alkyl, cyclohexane derivative, piperidine carboxylic acid derivative, cyclodextrin derivative, histidine derivative or an aminoacid.

[0029] In one embodiment, the chromophore is attached to an anchor via a linker, wherein the linker comprises nitrogen. In another embodiment, the nitrogen is in vicinity to the receptor. In another embodiment, a receptor is conjugated to a chromophore (or dye), thereby forming a receptor-dye conjugate. In another embodiment, boronic acid is conjugated to a receptor forming a boronic acid-dye conjugate. In another embodiment, the conjugation between the receptor (i.e. boronic acid) and the chromophore (i.e., dye) is via a nitrogen atom. In another embodiment, the compound of this invention includes between 3 to 4 conjugates which are linked to the anchor.

[0030] In one embodiment, the compound, encoding system and method of this invention make use of an analyte. In anembodiment, the analyte is a carbohydrate.

[0031] A "carbohydrate" analyte refers to an organic compound that consists only of carbon, hydrogen, and oxygen and optionally nitrogen with at least one hydroxyl group, in another embodiment including diol. In another embodiment a carbohydrate include 1,2 diol or a 1,3 diol or combination thereof. In another embodiment the carbohydrate is a saccharide. In another embodiment the carbohydrate is L-Glucose, D-Glucose, D-fructose, L-fructose, D-arabinose, D-xylose, L-xylose, L-mannose, D-galactose, D-sorbitol, mannitol, dulcitol, adonitol, xylitol, L-threitol, maltitol, lactulose, D-lactose, D-maltose, D-trehalose maltotriose or combination thereof. In another embodiment, the carbohydrate is a monosaccharide. In another embodiment, the carbohydrate is a disaccharide. In another embodiment, the carbohydrate is a polysaccharide. In another embodiment, the carbohydrate is a glycan. In another embodiment, the carbohydrate is a glycoprotein. In another embodiment, the carbohydrate is a proteoglycan. In another embodiment, the carbohydrate is an antibiotic. In another embodiment, the carbohydrate is a macrolide, aminoglycoside or cardiac glycoside antibiotics.

In another embodiment, the carbohydrate is ouabain, digoxin, digitoxin, erythromycin, roxithromycin, clarithromycin, azithromycin, hygromycin, amikacin, rifampicin, rifabutin, or combination thereof.

[0032] In one embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -alkylene-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -O-alkylene-. In one embodiment, the linkers of L_1, L_2, L_3, L_4 of the compound of formula III are independently -NHC(O)-. In another embodiment, the linkers of L_1, L_2, L_3, L_4 of the compound of formula III are independently -C(O)NH-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently - NHC(O)X-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -C(O)NHX-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -C(O)X-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -X'NHC(O)-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -X'C(O)NH-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -X'NHC(O)X-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -X'C(O)NHX-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -X'C(O)X-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -NHX-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -NH-[amino-acid]-C(O)-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -NH-[amino-acid]-C(O)-alkylene-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -C(O)-[amino-acid]-NH-. In another embodiment, the linkers L_1, L_2, L_3, L_4 of the compound of formula III are independently -C(O) - [amino-acid]-NH-alkylene-.

[0033] In one embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently hydrogen. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently alkyl. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently alkenyl. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently haloalkyl. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently aryl. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently O-aryl. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently -(CH_2)n-aryl. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently cycloalkyl. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently O-cycloalkyl. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently CF_3. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently F, I, Br or Cl. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently NO_2. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently CN. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently $N(R')_2$. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently COOH. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently COR'. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently NHCOR'. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently CONHR'. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently $(CH_2)_nNH_2$. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently $(CH_2)_nNHR'$. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently SR'. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently SH. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently OR'. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently $(CH_2)_nOH$. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently $(CH_2)_nCOOH$. In another embodiment, Z_1, Z_2, Z_3, Z_4 of compound of formula III are independently OH.

Definitions

[0034] In some embodiments, the term "isomer" includes, but is not limited to, optical isomers and analogs, structural isomers and analogs, conformational isomers and analogs, enantiomers, stereoisomers, diastereomers, tautomers and the like. In one embodiment, the term "isomer" is meant to encompass optical isomers of the described compounds such as enantiomers and diastereomers. It will be appreciated by those skilled in the art that the compounds of the present invention contain at least one chiral center. Accordingly, the compounds used in the methods of the present invention may exist in, and be isolated in, optically-active or racemic forms. It is to be understood that the present invention encompasses any racemic, optically-active, or stereoisomeric form, or mixtures thereof.

[0035] In one embodiment, the compounds are the pure (*R*)-isomers. In another embodiment, the compounds are the pure (*S*)-isomers. In another embodiment, the compounds are a mixture of the (*R*) and the (*S*) isomers. In another embodiment, the compounds are a racemic mixture comprising an equal amount of the (*R*) and the (*S*) isomers.

[0036] In one embodiment, the compounds of this invention are the pure (*RR*)-stereoisomers. In another embodiment, the compounds are the pure (*SS*)-stereoisomers. In another embodiment, the compounds are the pure (*RS*)-stereoisomers. In another embodiment, the compounds are the pure (*SR*)-stereoisomers. In another embodiment, the compounds are a mixture of the (*RR*), (*SS*), (*RS*) and the (*SR*) stereoisomers. In another embodiment, the compounds are a mixture of the (*RR*) and the (*RS*) diastereomers. In another embodiment, the compounds are a mixture of the (*RR*)

and the (*SR*) diastereomers. In another embodiment, the compounds are a mixture of the (*RR*) and the (*SS*) enantiomers. In another embodiment, the compounds are a mixture of the (*SS*) and the (*RS*) diastereomers. In another embodiment, the compounds are a mixture of the (*SS*) and the (*SR*) diastereomers. In another embodiment, the compounds are a mixture of the (*SR*) and the (*RS*) enantiomers. In another embodiment, the compounds are a racemic mixture comprising an equal amount of the (*RR*), (*SS*), (*RS*) and the (*SR*) stereoisomers. In another embodiment, the compounds are a racemic mixture comprising an equal amount of the (*RR*) and (*SS*) enantiomers. In another embodiment, the compounds are a racemic mixture comprising an equal amount of the (*RS*) and the (*SR*) enantiomers.

[0037] It is well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

[0038] An "alkyl" or "alkylene" group refers, in one embodiment, to a saturated aliphatic hydrocarbon, including straight-chain and branched-chain. In one embodiment, the alkyl group has 1-12 carbons. In another embodiment, the alkyl group has 1-7 carbons. In another embodiment, the alkyl group has 1-6 carbons. In another embodiment, the alkyl group has 1-4 carbons. The alkyl group may be unsubstituted or substituted by one or more groups selected from halogen, hydroxy, alkoxy, carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxyl, thio and thioalkyl.

[0039] An "alkenyl" group refers, in another embodiment, to an unsaturated hydrocarbon, including straight chain and branched chain having one or more double bond. The alkenyl group may have one double bond, two double bonds, three double bonds, etc. Examples of alkenyl groups are ethenyl, propenyl, butenyl, cyclohexenyl, etc. In one embodiment, the alkenyl group has 1-12 carbons. In another embodiment, the alkenyl group has 1-7 carbons. In another embodiment, the alkenyl group has 1-6 carbons. In another embodiment, the alkenyl group has 1-4 carbons. The alkenyl group may be unsubstituted or substituted by one or more groups selected from halogen, hydroxy, alkoxy, carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxyl, thio and thioalkyl.

[0040] A "haloalkyl" group refers to an alkyl group as defined above, which is substituted by one or more halogen atoms, in one embodiment by F, in another embodiment by Cl, in another embodiment by Br, in another embodiment by I.

[0041] A "cycloalkyl" group refers to a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are selected from halogen, haloalkyl, hydroxy, alkoxy, carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxy, thio or thioalkyl. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like.

[0042] An "aryl" group refers to an aromatic group having at least one carbocyclic aromatic group or heterocyclic aromatic group, which may be unsubstituted or substituted by one or more groups selected from halogen, haloalkyl, hydroxy, alkoxy, carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxy, thio or thioalkyl. Nonlimiting examples of aryl rings are phenyl, naphthyl, pyranyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyrazolyl, pyridinyl, furanyl, thiophenyl, thiazolyl, imidazolyl, isoxazolyl, and the like. In one embodiment, the aryl group is a 4-8 membered ring. In another embodiment, the aryl group is a 4-12 membered ring(s). In another embodiment, the aryl group is a 3-10 membered ring(s). In another embodiment, the aryl group is a 3-8 membered ring(s). In another embodiment, the aryl group is a 6 membered ring. In another embodiment, the aryl group is a 5 membered ring. In another embodiment, the aryl group is 2-4 fused ring system.

[0043] In one embodiment, this invention is directed to a compound, encoding system and methods of use thereof. In another embodiment, the compound of this invention binds to an analyte resulting in a conformational change of the compound upon the binding of the analyte to the compound of this invention, which is transmitted to the chromophore and results in an optical signature. In another embodiment, the optical signature is a fluorescent pattern. The optical signature is characteristic to the complex formed between the compound of this invention and the analyte. In another embodiment, attaching the chromophore to an anchor (such as proline) provides a flexible and chiral molecular cavity that can potentially accommodate and discriminate between a wide range of carbohydrates.

[0044] In another embodiment, the optical signature of the complex is used to identify, detect, differentiate an analyte, or diagnose a disease which is characterize by the presence of the analyte.

[0045] In another embodiment, the optical signature of the complex is used to identify, detect, differentiate a carbohydrate, or diagnose a disease which is characterize by the presence of the carbohydrate.

[0046] Binding of different analytes affects differently the optical properties of the chromophore, as well as to induce conformational changes that would result in different optical signature. In another embodiment binding of different analytes affects differently the emission of each fluorescent dye, as well as to induce conformational changes that would result in different fluorescence resonance energy transfer (FRET) processes between them. The combination of these effects provides a vast number of unique optical signatures. In one embodiment, the compound of this invention includes at least three fluorescent dyes. In another embodiment, the first fluorescent dye emits at a wavelength which is the absorption

wavelength of a second fluorescent dye. In another embodiment, the first fluorescent dye is naphthalene, fluorenyl or combination thereof, wherein said first fluorescent dye emits light at a wavelength of between 300-370 nm following excitation at 270 nm. In another embodiment, the second fluorescent dye is dansyl, anthracene or combination thereof, wherein said second fluorescent dye absorbs light at a range of between 300 to 400 nm.

[0047] In another embodiment, Figure 3 shows the excitation and emission spectra of the individual fluorescent dyes, namely, each boronic acid-dye conjugate (e.g., Naph*, An*, and Dan*) and a fluorenyl-aspartic acid derivative (Flu*). The emission spectra of naphthalene and fluorenyl overlap with the excitation spectra of anthracene and dansyl. Therefore, illuminating at 270 nm results in an emission pattern ranging across the UV-Vis spectrum due to FRET between the donors (e.g., naphthalene and fluorenyl) and acceptors (e.g., dansyl and anthracene) as well as direct excitations, mainly of naphthalene, fluorenyl, and dansyl. An additional energy transfer process that occurs to a lesser extent involves FRET between anthracene and dansyl. Because FRET largely depends on the distances between the donors and acceptors, conformational changes that are likely to occur upon carbohydrate binding is one factor that should contribute to the generation of distinct fluorescence signatures.

[0048] Another photochemical process known to significantly affect the emission of boronic acid-based sensors is photo-induced electron transfer (PET), resulting from incorporating a nitrogen atom in the vicinity of a boronic acid and a fluorophore.

[0049] A third signaling mechanism that further contributes to the discrimination ability of the compound of this invention is an internal charge transfer (ICT). In designing a differential compound an advantage of ICT over PET and FRET is that ICT can also induce a change in the emission wavelength.

[0050] In another embodiment, the optical signature of the complex provides quantitative information of the analyte in the sample or the in the liquid medium.

[0051] In one embodiment, the compound methods of this invention operate at the molecular scale, which larger analytical devices cannot address. The compound of this invention includes non-specific chromophores in a single molecular platform. The compound of this invention can discriminate between a wide range of closely related carbohydrate structures.

[0052] In one embodiment, the methods of this invention operate at the molecular scale, such that combinatorial sensing by individual molecules is feasible. The molecular diagnostic system presented here combines several recognition elements, and utilizes distinct photochemical processes that enable to analyze a wide range of pharmaceuticals in a high-throughput manner.

[0053] In one embodiment, contacting a compound of this invention with an analyte forms a complex. In another embodiment, contacting a compound of this invention with an analyte results in a conformational change of said compound and thereby to a unique optical signature of the complex.

[0054] In one embodiment, this invention is directed to a method of differentiating between carbohydrates comprising:

- contacting a carbohydrate with a compound of the invention in a liquid medium, wherein said carbohydrate and said compound form a complex; wherein a first fluorescent dye emits at a wavelength which is the absorption wavelength of a second fluorescent dye; wherein said linker comprises nitrogen; wherein contacting said carbohydrate with said compound results in a conformational change of said compound and thereby to a unique optical signature of said complex; wherein said liquid medium is an aqueous solution; and
- measuring the optical signature of said complex;

and thereby, differentiating said carbohydrate.

[0055] In one embodiment, this invention is directed to a method of differentiating between saccharides comprising:

- contacting a saccharide with a compound of the invention in a liquid medium, wherein said saccharide and said compounds form a complex; wherein contacting said saccharide with said compound results in a conformational change of said compound and thereby to a unique optical signature of said complex and
- measuring the optical signature of said complex;

and thereby, differentiating said saccharide.

[0056] Also disclosed is a method of identifying an analyte, said method comprising:

- contacting an analyte with a compound in a liquid medium, wherein said analyte and said compound form a complex; wherein said compound comprises an array of at least three chromophores, at least receptor and an anchor; wherein contacting said analyte with said compound results in a conformational change of said compound and thereby to a unique optical signature of said complex and
- measuring the optical signature of said complex;

and thereby, identifying said analyte.

[0057] Also disclosed is a method of identifying a carbohydrate, said method comprising:

- contacting a carbohydrate with a compound in a liquid medium, wherein said carbohydrate and said compound form a complex; wherein said compound comprises an array of at least three chromophores, at least one boronic acid receptor and an anchor; wherein contacting said carbohydrate with said compound results in a conformational change of said compound and thereby to a unique optical signature of said complex and
- measuring the optical signature of said complex;

and thereby, identifying said carbohydrate.

[0058] Also disclosed is a method of identifying a saccharide, said method comprising:

- contacting a saccharide with a compound in a liquid medium, wherein said saccharide and said compound form a complex; wherein said compound comprises an array of at least three chromophores, at least one boronic acid receptor and an anchor; wherein contacting said saccharide with said compound results in a conformational change of said compound and thereby to a unique optical signature of said complex and
- measuring the optical signature of said complex;

and thereby, identifying said saccharide.

[0059] In one embodiment, the methods for identifying an analyte, carbohydrate or a saccharide further comprising comparing the received optical signature with stored database of optical signatures (emission spectra) of said complex, and thereby identifying said analyte, carbohydrate or a saccharide.

[0060] Disclosed herein is a method of diagnosing a disease in a subject, wherein said diagnosis comprises detection of an analyte biomarkers; said method comprising:

- medium; wherein said carbohydrate forms a complex with said compound; wherein contacting said compound with carbohydrate results in a conformational change of said compound and thereby to a unique optical signature of said complex;
- measuring the optical signature of said complex;
- identifying a carbohydrate biomarkers in said sample, said carbohydrate biomarkers being characteristic of a disease; or measuring a change collecting a biological sample from a subject;
- optionally isolating components from said biological sample;
- contacting a compound with an analyte comprised within said sample or within isolated component in a liquid medium; wherein said analyte forms a complex with said compound; wherein said compound comprises an array of at least three chromophores, at least one receptor and an anchor; wherein contacting said compound with said analyte results in a conformational change of said compound and thereby to a unique optical signature of said complex;
- measuring the optical signature of said complex;
- identifying an analyte biomarker in said sample, said analyte biomarker being characteristic of a disease; or measuring a change in a concentration of an analyte biomarker in said sample compared to normative values, wherein said change is characteristic of a disease.

[0061] In one embodiment, this invention is directed to a compound of the invention for use in a method of diagnosing a disease in a subject, wherein said diagnosis comprises detection of a carbohydrate biomarker, said method comprising:

- collecting a biological sample from a subject;
- optionally isolating components from said biological sample;
- contacting a compound of the invention with a carbohydrate comprised within said sample or isolated component in a liquid in a concentration of a carbohydrate biomarker in said sample compared to normative values, wherein said change is characteristic of a disease.

[0062] In one embodiment, this invention is directed to a compound of the invention for use in a method of diagnosing a disease in a subject, wherein said diagnosis comprises detection of a saccharide biomarker; said method comprising:

- collecting a biological sample from a subject;
- optionally isolating components from said biological sample;
- contacting a compound of the invention with a saccharide comprised within said sample or within isolated component in a liquid medium; wherein said saccharide forms a complex with said compound; wherein contacting said compound with said saccharide results in a conformational change of said compound and thereby to a unique optical signature

of said complex;

- measuring the optical signature of said complex;
- identifying a saccharide biomarker in said sample, said saccharide biomarker being characteristic of a disease; or measuring a change in a concentration of a saccharide biomarker in said sample compared to normative values, wherein said change is characteristic of a disease;

thereby, diagnosing a disease in a subject.

[0063] In one embodiment, the methods for diagnosing a disease in a subject further comprise a step of identifying carbohydrate or saccharide biomarkers. In another embodiment, the identifying step further comprising comparing the received optical signature of the complex with stored database of optical signatures (emission spectra) of said complex, and thereby identifying said carbohydrate or saccharide biomarkers.

[0064] Also disclosed herein is a kit comprising a compound of this invention in a liquid medium. In one embodiment, said kit further comprises tools for measuring an optical signature (i.e. spectrophotometer) of a complex formed by contacting said compound with analytes, or carbohydrates, or saccharides. In another embodiment, said kit further comprises means for comparing the measured optical signature with stored database of optical signatures (emission spectra) of said complex. In one embodiment, said kit can be used for differentiating between said analytes, or said carbohydrates, or saccharides. In another embodiment, said kit can be used for identifying said analytes, or said carbohydrates, or said saccharides, and thereby diagnosing a disease in a subject.

[0065] Also disclosed herein is a kit for identifying an analyte or for differentiating between analytes comprising:

- a compound of this invention in a liquid medium; and
- a tool for measuring a unique optical signature (i.e. spectrophotometer) of a complex formed by contacting said analyte or analytes with said compound.

[0066] .Also disclosed herein is a kit for identifying a carbohydrate or for differentiating between carbohydrates comprising:

- a compound of this invention in a liquid medium, and

a tool for measuring a unique optical signature (i.e. spectrophotometer) of a complex formed by contacting said carbohydrate or carbohydrates with said compound.

[0067] Also disclosed herein is a kit for identifying a saccharide or differentiating between saccharides comprising:

- a compound of this invention in a liquid medium; and
- a tool for measuring a unique optical signature(i.e. spectrophotometer) of a complex formed by contacting said saccharide or saccharides with said compound.

[0068] It is disclosed that the kits for identifying an analyte, carbohydrate or a saccharide may further include means for comparing the received optical signature with stored database of optical signatures (emission spectra) of said complex, and thereby identifying said analyte, carbohydrate or a saccharide.

[0069] In one embodiment, the analyte is a saccharide. The term "saccharide" refers to monosaccharide, disaccharide, trisaccharide, polysaccharide, carbohydrate, sugar or glycan. The polysaccharide is linear or branched. In another embodiment, the saccharide is found free or attached to, e.g., proteins, lipids, other carbohydrates, nucleic acid, a virus, or a cell in biological samples. In another embodiment, a saccharide is a component of a glycoprotein, a glycolipid or a proteoglycan. In another embodiment, the saccharide is independent of a protein or lipid molecule. Non limiting examples of monosaccharides include galactose, glucose, mannose, N-acetylneuraminic acid, fucose, N-acetylgalactosamine, N-acetylglucosamine, xylose, iduronic acid, arabinose and glucuronic acid.

[0070] The term "glycoprotein" includes any molecule that contains both a protein component and a carbohydrate component. The carbohydrate component is commonly referred to as a "glycan." As used herein, the term glycoprotein is inclusive of a glycopeptide, a glycopolypeptide and a proteoglycan. A glycan may contain one monosaccharide, or it may contain two or more monosaccharides linked by glycosidic bonds. A glycan can include nonrepeating or repeating monosaccharides, or both.

[0071] An oligosaccharide is an oligomeric saccharide that contains two or more saccharides. The structure of an oligosaccharide is typically characterized by particular identity, order, linkage positions (including branch points), and linkage stereochemistry (α, β) of the monomers, and as a result has a defined molecular weight and composition. An oligosaccharide typically contains about 2 to about 20 or more saccharide monomers. In a polysaccharide, the identity, order, linkage positions (including branch points) and/or linkage stereochemistry can vary from molecule to molecule. Polysaccharides typically contain a larger number of monomeric components than oligosaccharides and thus have

higher molecular weights. The term "glycan" as used herein is inclusive of both oligosaccharides and polysaccharides, and includes both branched and unbranched polymers as defined herein.

[0072] In one embodiment, this invention is directed to a method of differentiating or diagnosing a carbohydrate in a liquid medium. In another embodiment, the liquid medium is an aqueous solution. In another embodiment, the liquid medium is a buffered aqueous solution. In another embodiment, the liquid medium is a biological sample.

[0073] In one embodiment, the methods include a step of measuring the optical signature of the complex. In another embodiment, the optical signature is a unique optical signature for each complex. In another embodiment, the unique optical signature provides a fluorescence pattern of said complex; and said fluorescence pattern is obtained followed irradiation of said complex at a wavelength that at least one of said fluorescent dyes is excited. In another embodiment, the fluorescence pattern indicates the presence of at least one saccharide in said medium. In one embodiment, measuring the optical signature of the formed complex refers to the emission spectra of the complex. In one embodiment, measuring the optical signature of the formed complex refers to the absorption spectra of the complex. In one embodiment, measuring the optical signature of the formed complex refers to the emission and/or absorption spectra of the complex.

[0074] In one embodiment, this invention is directed to a compound of the invention for use in a method of diagnosing a disease in a subject, wherein said diagnosis comprises detection of a carbohydrate biomarker comprising the step of collecting a biological sample from a subject. In another embodiment, the term "biological sample" refers to a serum, a blood, a plasma, a urine, a saliva, a peritoneal, a stool, a mucus, a tear, a sweat, a biopsy, a sperm or a cerebrospinal fluid sample.

[0075] In one embodiment, the method comprises the optional step of isolating components from said biological sample. In another embodiment, "isolating components" refers to isolating cells having saccharide or carbohydrate; isolating proteins from the biological samples, isolating sugars, isolating glycans, phosphates (non limiting examples include ATP, ADP, AMP, GMP), isolating phospholipids, isolating glycoprotein, a glycolipid or a proteoglycan from the biological sample.

[0076] In one embodiment, the disease to be diagnosed is a sugar disease. Non limited examples of a disease are hypoglycemia, prostate cancer, diabetes, HIV, Tuberculosis or syndrome X.

[0077] In another embodiment, the disease to be diagnosed is a glycoprotein based disease. Non limiting examples of a glycoprotein based disease is multiple sclerosis, Crohn's disease, autoimmune disease, colitis, inflammatory bowel disease, cancer, lysosomal storage disease, or celiac. Changes of structures and functions of glycoproteins have implications in cancer, inflammatory diseases such as influenza, nerve degenerative diseases, muscle degenerative diseases such as muscle dystrophy, and lifestyle-related diseases such as diabetes.

[0078] In other embodiments, the disease being diagnosed in this invention may be a cardiovascular disease (e.g., acute myocardial infarction), cerebrovascular disease (e.g., stroke), rheumatoid arthritis, chronic alcoholism or cancer (e.g., a carcinoma, lymphoma, blastoma, sarcoma, or leukemia). More particular examples of such cancers include prostate cancer, squamous cell cancer, small-cell lung cancer, non-small-cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, vulval cancer, thyroid cancer, hepatic carcinoma, gastric cancer, melanoma, and various types of head and neck cancer. The disease may also be an autoimmune disease, e.g., autoimmune hepatitis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, type I diabetes, rheumatoid arthritis, psoriasis, Hashimoto's thyroiditis, Grave's disease, Sjogren's syndrome, or scleroderma. The methods described herein may also be used to diagnose infections, e.g., viral infections, such as hepatitis C infection and human immunodeficiency virus (HIV) infection.

[0079] In another embodiment, the disease is prostate cancer.

[0080] In one embodiment, this invention is directed to a compound of the invention for use in a method of diagnosing a disease in a subject comprising identifying a saccharide biomarker in a biological sample. In another embodiment, the saccharide biomarker is a component of a glycoprotein, a glycolipid or a proteoglycan. In another embodiment, the saccharide biomarker is a monosaccharide, a disaccharide or a glycan independent of a protein or lipid molecule.

[0081] A biomarker is a molecular, biological, or physical characteristic that can be measured or otherwise evaluated as an indicator of a normal biologic process, disease state, or response to a therapeutic intervention. The biomarker of the invention is a "saccharide" or "carbohydrate" biomarker, i.e., it includes a 1,2 or 1,3-diol moiety. Saccharide biomarkers of the invention include, but are not limited to, monosaccharides, disaccharides, oligosaccharides, polysaccharides, glycans, saccharides linked to peptides (e.g., proteoglycans), saccharides linked to proteins (e.g., glycoproteins), saccharides linked to lipids (e.g., glycolipids). Saccharide biomarkers are detectable and/or measurable using a compound of this invention.

[0082] The saccharide/carbohydrate or glycoprotein biomarker may be indicative of a sugar disease or a glycoprotein disease or a condition by its presence, absence, increase in amount, decrease in amount, or differential glycosylation. Amounts of biomarker can be determined in absolute or relative terms. For example, a carbohydrate biomarker may indicate the presence of cancer or a precancerous condition simply by its presence, absence or amount compared to a

noncancerous sample or a predetermined level.

[0083] Examples of glycans that can be detected on an ovarian cancer-specific glycoprotein glycoform include erythroagglutinating phytohemagglutinin (E-PHA), Aleuria aurantia lectin (AAL) and Datura stramonium lectin (DSL). In another embodiment, non-limiting examples for diagnosing cancer or a precancerous disease include a GlcNAc β.(1,6) Man branched N-linked glycan, a GlcNAc β.(1,4) Man bisected N-linked glycan, a glycan containing α.(1,6) fucose linked to a core *N*-acetylglucosamine, and a branched N-linked glycan extended with *N*-acetyllactosamine.

[0084] Various concentrations of biomarkers and biomarker complexes may be detected and measured by the methods described herein. Biomarkers present at concentrations of between about 1-5mM, 1-100 μM, 50-100mg/mL or less than, e.g., 100 milligrams/milliliter (mg/ml), 10 mg/ml, 1 mg/ml, 100 micrograms/milliliter (μg/ml), 10 μg /ml, 1 μg /ml, 100 nanograms/milliliter (ng/ml), 10 ng/ml, 1 ng/ml, may be detected in the biological sample, and the concentration may be measured.

[0085] In one embodiment, the method of diagnosing a disease in a subject comprises measuring a change in a concentration of a saccharide biomarker compared to normative values, wherein said change is characteristic of a disease. The term "normative value" refers to the concentration range of saccharide found in a normal healthy subject. The term "normative value" refers to the control.

[0086] In one embodiment, this invention is directed to diagnosing a disease in a subject. In another embodiment, a subject refers to a mammal, a human, a female or a male.

[0087] The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

[0088] Unless otherwise specified, "a," "an," "the," and "at least one" are used interchangeably and mean one or more than one.

[0089] Disclosed herein is an encoding system for encoding information using a compound of the present invention.

[0090] Thus, disclosed herein is an encoding system for encoding information using a complex of a compound represented by the structure of formula (III), and between 2 and 7 analytes in a specific sequence, wherein said complex exhibits a unique optical signature signal; said encoding system comprising:

a data processor;
a non-transitory database storage device for storing a plurality of database records;
a chemical process interface, for controlling chemical processes binding analytes to the compound; and
a spectroscopic interface, for reading unique optical signatures of the complex.

[0091] In certain embodiment, n is from 1 to 6.

[0092] In one embodiments, L_1, L_2, L_3, L_4 are independently -alkylene-, -NHC(O)-, -C(O)NH-, -NHC(O)X-, -C(O)NHX-, -C(O)X-, -X'NHC(O)X-, or -X'C(O)NHX-. In another embodiment, L_1 and L_2 are independently NHC(O)-, -C(O)NH- -NHC(O)X-, or -C(O)NHX and L_3, L_4 are independently -alkylene- or -C(O)X-.

[0093] In certain embodiments, said compound is represented by structure 1.

[0094] In one embodiment, said analytes are between 2 and 7 analytes. In another embodiment, 2 or 3 analytes.

[0095] In another embodiment, said between 2 and 7 analytes can be any number of analytes. For example, between 2 and 7 analytes. In another embodiment, 2 analytes, 3 analytes, 4 analytes, 5 analytes, 6 analytes, or 7 analytes.

[0096] In one embodiment, said analytes are a carbohydrate. In another embodiment, said carbohydrate is L-Glucose, D-Glucose, D-fructose, L-fructose, D-arabinose, D-xylose, L-xylose, L-mannose, D-galactose, D-sorbitol, mannitol, dulcitol, adonitol, xylitol, L-threitol, maltitol, lactulose, D-lactose, D-maltose, D-trehalose, or maltotriose.

[0097] In one embodiment, said analytes are the same or different. In another embodiment, said analytes can be distinct from each other. In another embodiment, said analytes can include the same analytes. For example, when three analytes are included, the first two of the analytes can be the same, and the third analyte is distinct from the first two analytes.

[0098] In one embodiment, the encoding system further comprises a non-transitory program storage device for storing an application program.

[0099] In another embodiment, the encoding system further comprising a hardware controller with a logic element configured to receive an input from the processor.

[0100] The present invention is also directed to a method of encoding information using a compound represented by the structure of formula (III),
the method comprising:

a) contacting said compound with between 2 and 7 analytes in a specific sequence to form a complex, wherein said complex exhibits a unique optical signature signal;
b) reading the unique optical signature;
c) associating the unique optical signature with an encoded reference specifying said analytes contacted in said

specific sequence according to a predefined encoding scheme; and
d) storing the encoded reference keyed to the unique optical signature in a database record.

[0101] In certain embodiments, said compound is represented by structure 1.

[0102] In one embodiment, the term "in a specific sequence" refers to "in a specific order" or "in a particular order." As indicated herein, e.g., Figure 18, contacting analytes and the compound of the invention in a different sequence would induce the formation of distinct complexes which would exhibit different optical signatures.

[0103] Also disclosed herein is a method of decoding encoded information using a compound represented by the structure of formula (III), the method comprising:

a) contacting said compound with between 2 and 7 analytes in a specific sequence to form a complex, wherein said complex exhibits a unique optical signature signal;
b) reading the unique optical signature of the compound; and
c) accessing a database record keyed to the unique optical signature to obtain a code corresponding to a complex of said analytes bound to said compound.

[0104] In certain embodiments, said compound is represented by structure 1.

[0105] In one embodiment, said contacting step comprises contacting between 2 and 7 analytes. In another embodiment, 2 or 3 analytes.

[0106] In another embodiment, said between 2 and 7 analytes can be any number of analytes. For example, between 2 and 7 analytes. In another embodiment, 2 analytes, 3 analytes, 4 analytes, 5 analytes, 6 analytes, or 7 analytes.

[0107] In one embodiment, said analytes are a carbohydrate. In another embodiment, said carbohydrate is L-Glucose, D-Glucose, D-fructose, L-fructose, D-arabinose, D-xylose, L-xylose, L-mannose, D-galactose, D-sorbitol, mannitol, dulcitol, adonitol, xylitol, L-threitol, maltitol, lactulose, D-lactose, D-maltose, D-trehalose, or maltotriose.

[0108] In one embodiment, said analytes are the same or different. In another embodiment, said analytes can be distinct from each other. In another embodiment, said analytes can include the same analytes. For example, when three analytes are included, the first two of the analytes can be the same, and the third analyte is distinct from the first two analytes.

[0109] In one embodiment, the method further comprises
inputting the code corresponding to the complex into a decision point in a program executed by a processor; and
executing a program branch of the decision point according to the code.

[0110] In another embodiment, the method further comprises inputting the code corresponding to the complex into a hardware logic element of a hardware controller.

[0111] The compound of the present invention can be used in an efficient molecular encoding system because it is able to generate unique optical "fingerprints" for a wide range of analytes and thus substantially increases the number of input "keys" that can be processed by the encoding system of this invention. Further, because pattern-generating systems are very efficient in discriminating between input concentrations, the compound of the present invention should be able to distinguish between password entries containing distinct ratios of identical inputs, for example, between 112 and 122. Moreover, the tendency of multivalent receptors to exhibit binding cooperativity and conformational dynamics as well as their ability to be entrapped in kinetically-stable states, should allow the compound of the present invention to distinguish between chemical input sequences.

[0112] The compound of the present invention can bind different saccharides in distinct stoichiometries, for example, 1:1, 1:2, or 1:3, and these saccharides can interact with it in a mono-, bi-, or trivalent configuration, thus resulting in distinct optical signatures.

[0113] The molecular encoding system of the present invention can be a two state, or three state, or four state, or five state, or six state, or seven state, or more than seven state molecular encoding system. In one embodiment, the molecular encoding system can be a two state molecular encoding system. In another embodiment, the molecular encoding system can be a three state molecular encoding system. In another embodiment, the molecular encoding system can be a four state molecular encoding system. By way of example, when the molecular encoding systems of the present invention is a two state molecular encoding system that respond to different sequences of saccharide pairs, the saccharide pairs can be D-glucose (G) and D-xylose (X), or D-glucose (G) and galactose (L), or D-fructose (F) and maltitol (M). It is the feature of the present invention that the distinct optical signatures can be observed for passwords GX/XG, GL/LG, and FM/MF as described in Example 8. The state of the encoding system is determined by the number of inputs. For example input of D-glucose (G) and D-xylose (X), is a two state molecular encoding system.

[0114] The molecular encoding systems of the present invention can distinguish between passwords containing different inputs or different ratios of the same input. For example, the compound of the present invention, e.g., compound **1,** recognizes X, G, XX, and GG as distinct code entries.

[0115] The method enables a unimolecular security system to be 'programmed' to authorize multiple password com-

binations, as well as passwords assembled from diverse input keys. The later can be selected from a vast library of structurally similar saccharides that are transparent in the visible region; hence, their structure and concentration levels cannot be straightforwardly determined. The security system becomes exceedingly complicated when fluorescence-signaling provides the system with ultimate steganography for breaking such a security system. Specifically, it requires prior knowledge of code entries, as well as access to a molecular-scale security device and to invisible and randomly-selected chemical inputs. An additional layer of protection comes from the fact that the system utilizes both password- and pattern-recognition for user authentication. Thus, unlike electronic encoding systems or biometric locks that rely on a single defense mechanism, the molecular devices can ensure that even if the combination codes or the entry 'keys' are exposed, the system remains secure.

[0116] In one embodiment, the encoding system of this invention is as presented in Figure 23 wherein a data processor **101** is connected to a non-transitory database storage device **103** and to a non-transitory program storage device **105** for storing application program **107.** A chemical process interface **111** provides output control from processor **101** over chemical processes that modify molecular logic elements **115** to represent different data states {these are the "molecular logic elements"). A spectroscopic interface **113** provides input sensing to processor **101** according to the unique optical signature of molecular logic elements **115.**

[0117] As disclosed herein, in an embodiment, to initialize a database for use, processor **101** stores database records **121** in storage device **105** according to a code field **123** whose code values are according to a predefined encoding scheme and which correspond to the order of analyte binding of molecular logic elements **115** as described herein, which is keyed in database records **121** to a unique optical signature field **125.**

[0118] In use, molecular logic elements **115** express their binding history {e.g., first binds analyte A, then binds analyte C -- } by their unique optical signature, which is input to processor 101 via spectroscopic interface **113.** Processor then looks up the corresponding code in database records **121.** In an embodiment the code is input into a software decision point **131** in application program **107.** Decision point **131** follows a point **133** in program execution and has multiple branches, illustrated in this non-limiting example as program branches **135, 137,** and **139.** The branch taken by program execution depends on the code input into decision point **131.** In a related embodiment, a hardware controller **141** contains a hardware logic element **143** (illustrated in this non-limiting example as a gate), and the code is input into an input **145.** An additional input for another signal is shown as an input **147.** Logic element **143** has an output **149** for controlling a function of controller **141** according to the code.

[0119] As described above, the state of molecular logic elements **115** can thereby influence the execution of application program **107** and/or control devices via hardware controller **141.**

[0120] Although not limited in this regard, discussions utilizing terms such as, for example, "processing," "computing," "calculating," "determining," "establishing", "analyzing", "checking", "receiving", "comparing", or the like, refer to operation(s) and/or process(es) of a computer, a computing platform, a computing system, or other electronic computing device, that manipulates and/or transforms data represented as physical (e.g., electronic) quantities within the computer's registers and/or memories into other data similarly represented as physical quantities within the computer's registers and/or memories or other information non-transitory storage medium, transmission or display devices that may store instructions to perform operations and/or processes.

[0121] Embodiments may use terms such as, "processor", "computer", "apparatus", "system", "sub-system", "module", "unit", "device" (in single or plural form) for performing the operations herein. This may be specially-constructed for the desired purposes, or may comprise a general purpose computer selectively activated or reconfigured by a computer program stored in the computer.

[0122] Some embodiments may be provided in a computer program product that may include a non-transitory machine-readable medium, stored thereon instructions, which may be used to program a computer, or other programmable devices, to perform methods as disclosed herein. Embodiments may include an article such as a computer or processor non-transitory readable medium, or a computer or processor non-transitory storage medium, such as for example a memory, a disk drive, or a USB flash memory, encoding, including or storing instructions, e.g., computer-executable instructions, which when executed by a processor or controller, carry out methods disclosed herein. The storage medium may include, but is not limited to, any type of disk including floppy disks, optical disks, compact disk read-only memories (CD-ROMs), rewritable compact disk (CD-RWs), and magneto-optical disks, semiconductor devices such as read-only memories (ROMs), random access memories (RAMs), such as a dynamic RAM (DRAM), erasable programmable read-only memories (EPROMs), flash memories, electrically erasable programmable read-only memories (EEPROMs), magnetic or optical cards, or any other type of non-transitory media suitable for storing electronic instructions that are capable of being conveyed via a computer system bus.

[0123] A system may also include components such as, but not limited to, a plurality of central processing units (CPU) or any other suitable multi-purpose or specific processors or controllers, a plurality of input units, a plurality of output units, a plurality of memory units, and a plurality of storage units. A system may additionally include other suitable hardware components and/or software components. In some embodiments, a system may include or may be, for example, a personal computer, a desktop computer, a mobile computer, a laptop computer, a notebook computer, a terminal, a

workstation, a server computer, a tablet computer, a network device, or any other suitable computing device. Unless explicitly stated, the method embodiments described herein are not constrained to a particular order or sequence. Additionally, some of the described method embodiments or elements thereof can occur or be performed at the same point in time.

[0124] Although embodiments of the invention are not limited in this regard, the terms "plurality" and "a plurality" as used herein may include, for example, "multiple" or "two or more". The terms "plurality" or "a plurality" may be used throughout the specification to describe two or more components, devices, elements, units, parameters, or the like. Unless explicitly stated, the method embodiments described herein are not constrained to a particular order or sequence. Additionally, some of the described method embodiments or elements thereof can occur or be performed simultaneously, at the same point in time, or concurrently.

[0125] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention.

EXAMPLES

EXAMPLE 1

Synthesis of Compound 1

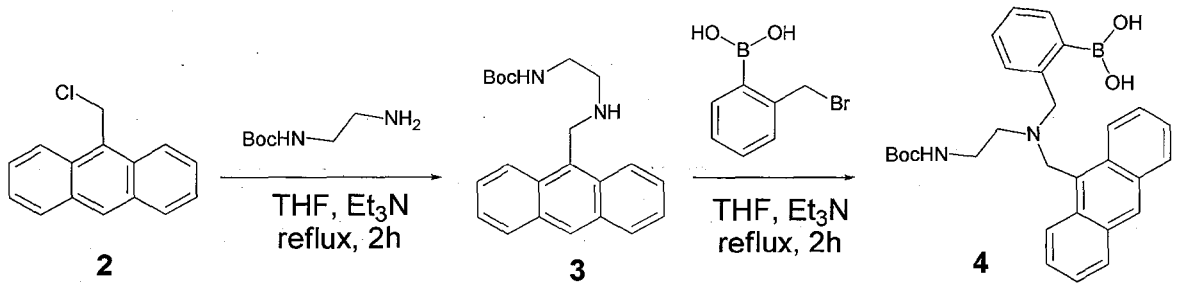
Material and methods:

[0126] Chemicals, saccharides, spectroscopic grade solvent, and anhydrous solvents for synthesis were obtained from Sigma Aldrich, and were used without further purification. Fmoc-Asp-O^{t}Bu was purchased from Nova-Biochem. Compound 6 was prepared according to literature procedures (Chen, X. Y., Koch, S.; Uhlenbrock, K.; Weise, K.; Das, D., Gremer, L.; Brunsveld, L.; Wittinghofer, A.; Winter, R.; Triola, G.; Waldmann, H., Angew. Chem. Int. Ed. 2010, 49, 6090-6095). Anhydrous solvents were transferred using an oven-dried syringe. Flasks were oven dried under a stream of argon. The Teledyne combiflash was used to purify all the synthetic intermediates. Reverse phase HPLC separations were performed with a Spectra series P200 HPLC system equipped with variable wavelength absorbance detector and a pre-packed Vydac C-18 column. The purity of fractions was ascertained by analytical reverse phase HPLC using a prepacked Chromolith™ Performance RP-18e column. The ^{1}H NMR spectra of all compounds were recorded on a Bruker Avance 300 MHz spectrometer and the spectrum of the final compound was recorded on Bruker Avance 400MHz NMR spectrometer. Mass spectra were recorded on a Waters Micromass LC-Q-TOF micro spectrometer. Fluorescent measurements were performed on a VarianTechnology International Fluorimeter. Quartz cuvettes were used for the fluorescence measurements. Principal component analysis of the emission spectra was performed using XLSTAT version 2011.4.03 (32 bit).

[0127] Compound 1 is synthesized as presented in Figure 1.

Synthesis of compound **3:**

[0128]



[0129] To a stirred solution of N-Boc-ethylenediamine (0.55 g, 3.43 mmol) in dry THF (15 mL) were added 9-chloromethylanthracene **2** (0.04g, 1.76 mmol) and triethylamine (0.45 mL, 3.11 mmol) under argon. The reaction mixture was refluxed at 90 °C for 2.5 h. The solution was then separated from the solid formed during the reaction and was evaporated to dryness. The crude reaction mass was subjected to combi-flash column chromatography (silica gel, 2% methanol in DCM) to afford **3** (0.4 g) as yellow solid in 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$) 1.43 (9H, s), 2.98 (2H, t, *J* = 6 Hz), 3.30 (2H, m, br), 4.73 (2H, s), 4.98 (1H, br), 7.44-7.56 (4H, m), 8.0 (2H, d, *J* = 9 Hz), 8.31 (2H, d, *J* = 9 Hz),

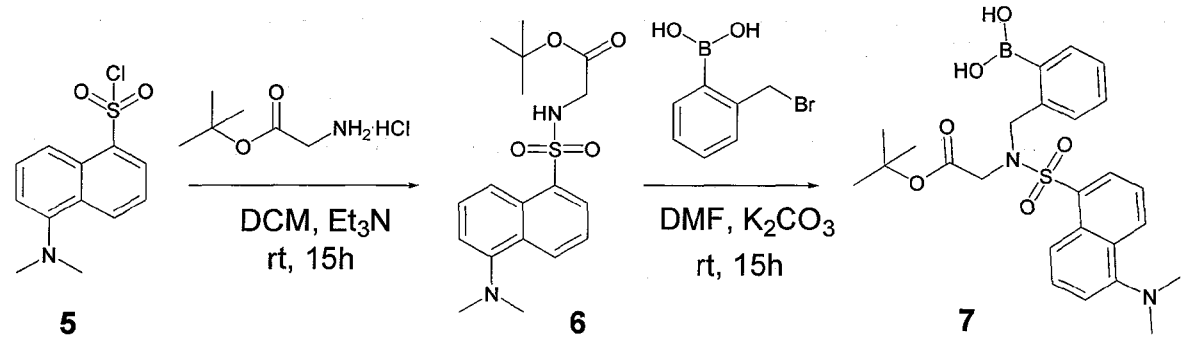
8.41 (1H, s); MS (ESI+): *m/z* (%) = 541.17 (100) $[M+H]^+$, 563.11 (15) $[M+Na]^+$

Synthesis of compound **4:**

[0130] Compound **3** (0.36 g, 1.05 mmol), 2-bromomethyl phenyl boronic acid (0.33 g, 1.5 mmol) and triethylamine (0.29 mL, 2 mmol) were mixed in dry THF (20 mL) and the reaction mixture was refluxed at 90 °C for 2 h. The liquid was separated from the solid using pipette and evaporated to dryness. The crude reaction mass was subjected to combi-flash column chromatography (silica gel, 2% methanol in DCM) to afford **4** (0.32 g) in 63% yield. ^{1}H NMR (300 MHz, $CDCl_3$) 1.23 (9H, s), 2.63 (2H, t, br), 3.10 (2H, t, br), 3.90 (2H, s), 4.50 (2H, s), 7.35 (3H, s), 7.39-7.46 (4H, m), 7.85 (1H, s, br), 7.93-7.96 (2H, m), 8.06 (2H, d, br), 8.38 (1H, s); MS (ESI+): *m/z* (%) = 485.19 (35) $[M+H]^+$, 499.20 (40) $[M+H-H_2O+MeOH]^+$, 507.12 (100) $[M+Na]^+$, 521.20 (70) $[M-H_2O+MeOH+Na]^+$

Synthesis of compound 7:

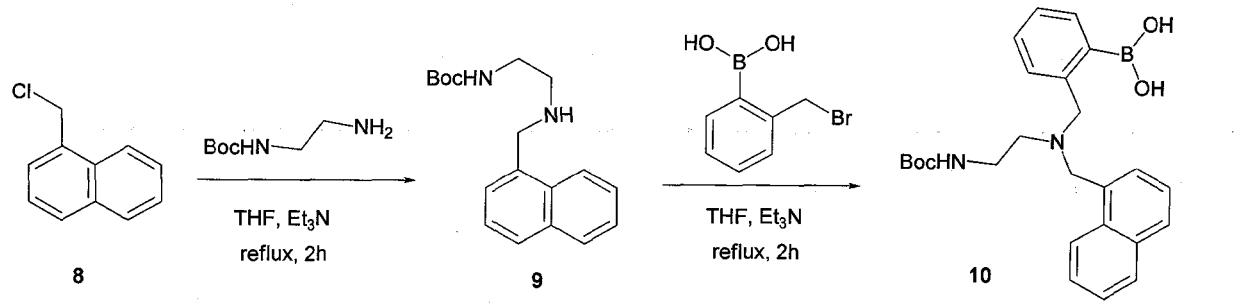
[0131]



[0132] To sulphonamide **6** (0.36 g, 1.05 mmol) in anhydrous DMF (20 mL) were added 2-bromomethyl phenyl boronic acid (0.33 g, 1.5 mmol) and K_2CO_3 (0.29 mg, 2 mmol) under argon. The reaction mixture was stirred at room temperature for 15 h. The solvent was evaporated and the residue was dissolved in ethyl acetate (50 mL) and washed twice with water (50 mL) followed by brine (20 mL). The organic layer was dried over anhydrous sodium sulphate and evaporated to dryness. The crude reaction mass was subjected to combi-flash column chromatography (silica gel, 2% MeOH in DCM) to furnish 7 (0.32 g) in 80% yield (based on starting material recovery). ^{1}H NMR (300 MHz, CD_3OD) 1.14 (9H, s), 3.14 (6H, s), 3.87 (2H, s), 4.73 (2H, s), 7.10 (1H, d, *J* = 6 Hz), 7.22-7.32 (2H, m), 7.35 (1H, d, *J* = 6 Hz), 7.63 (1H, d, *J* = 9 Hz), 7.69-7.76 (2H, m), 8.36 (1H, d, *J* = 6 Hz), 8.58 (1H, d, *J* = 9 Hz) 8.68 (1H, d, *J* = 9 Hz); MS (ESI+): *m/z* (%) = 549.09 (100) $[M-2H_2O+2MeOH+Na]^+$, 1075.20 (20) $[2(M-2H_2O+2MeOH)+Na]^+$

Synthesis of compound 9:

[0133]



[0134] To a flame dried, argon purged flask with condenser were added N-Boc-ethylenediamine (0.27 g, 1.7 mmol), 1-chloromethylnaphthalene **8** (0.3 g, 1.7 mmol) and triethylamine (0.47 mL, 3.4 mmol) in dry THF (10 mL). The solution was stirred for 10 h at 90 °C. Upon completion, the reaction mixture was cooled to room temperature and the solution

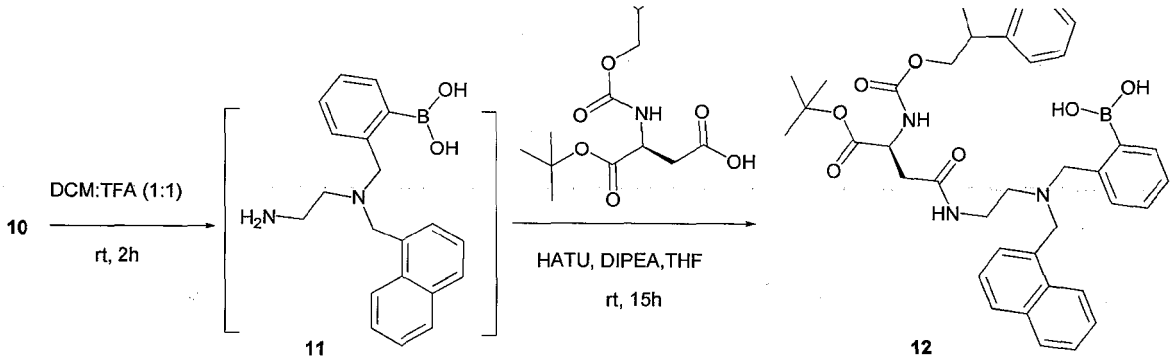
was separated from the solid using pippette. The organic layer was removed *in vacuo.* The crude reaction mass was subjected to combi-flash column chromatography (silica gel, 2% MeOH in DCM) to obtain 9 (0.3 g) as a white solid in 55% yield. ^{1}H NMR (300MHz, $CDCl_3$) 1.42 (9H, s), 2.85 (2H, t, *J* = 7.5 MHz), 3.26 (2H, m, br), 4.23 (2H, s), 4.97 (1H, s, br), 7.41-7.53 (4H, m), 7.77 (1H, d, *J* = 6 Hz), 7.86 (1H, d, *J* = 6 Hz), 8.10 (1H, d, *J* = 6Hz); MS (ESI+): *m*/*z* (%) = 301.24 (100) $[M+H]^+$, 601.40 (95) $[2M+H]^+$, 623.40 (35) $[2M+Na]^+$.

Synthesis of compound 10:

[0135] To a stirred solution of **9** (0.3 g, 0.9 mmol) in dry THF (20 mL) were added 2-bromomethyl phenyl boronic acid (0.32 g, 1.5 mmol) and triethylamine (0.28 mL, 2 mmol) under argon. The solution was refluxed for 6 h at 90 °C. Upon completion of the reaction, the reaction mixture was cooled to room temperature and the solution was separated from the solid using pippette. The organic layer was evaporated and the crude reaction mass was subjected to combi-flash column chromatography (silica gel, 2% MeOH in DCM) to obtain **10** (0.32 g) as a white solid in 69% yield. ^{1}H NMR (300 MHz, CD_3OD) 1.37 (9H, s), 2.80 (2H, t, *J* = 6 Hz), 3.27 (2H, t, *J* = 6 Hz), 4.05 (2H, s), 4.27 (2H, s), 7.29-7.36 (3H, m), 7.46-7.51 (3H, m), 7.56 (1H, s, br), 7.61 (1H, d, *J* = 9 Hz), 7.87-7.91 (2H, m), 7.94 (1H, d, *J* = 9 Hz); MS (ESI+): *m*/*z* (%) = 435.29 (35) $[M+H]^+$, 449.30 (100) $[M+H-H_2O+MeOH]^+$, 463.31 (55) $[M+H-2H_2O+2MeOH]^+$, 471.28 (20) $[M-H_2O+MeOH+Na]^+$, 485.31 (75) $[M-2H_2O+2MeOH+Na]^+$

Synthesis of compound 12:

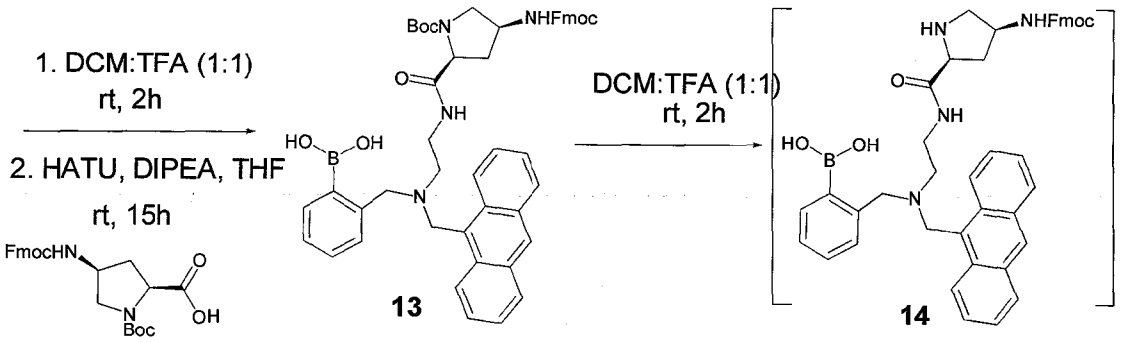
[0136]



[0137] To a solution of **10** (0.2 g, 0.46 mmol) in DCM (1 mL) was added trifluoroacetic acid (1 mL) and the reaction was stirred for 2 h at room temperature. After completion of the reaction, the solvent was evaporated for 5 h under high vacuum. The crude solid **11** was dissolved in dry THF (10 mL) and the solution was basified to pH~7-8 with DIPEA (0.18 mL, 0.92 mmol). In the following step, N-α-Fmoc-L-aspartic acid α-t-butylester (0.19 g, 0.46 mmol) and HATU (0.17g, 0.46 mmol) were added and the reaction mixture was stirred at room temperature for 15 h under argon. The solvent was evaporated and the crude mass was subjected to combi-flash column chromatography (silica gel, 3% MeOH in DCM) to furnish **12** (0.2 g) in 60% yield. ^{1}H NMR (300MHz, CD_3OD) 1.41 (9H, s), 2.21-2.37 (2H, m), 3.24 (2H, s), 3.44 (2H, t, br), 4.20 (1H, t, *J* = 7.5 Hz), 4.31-4.39 (3H, m), 4.64 (2H, s, br), 4.90 (2H, s), 7.28-7.34 (2H, m), 7.39-7.44 (2H, m), 7.49-7.57 (6H, m), 7.60-7.65 (2H, m), 7.79-7.83 (5H, m), 7.94-7.97 (1H, m), 8.03 (1H, d, *J* = 9 Hz); MS (ESI+): *m*/*z* (%) = 728.44 (10) $[M+H]^+$, 742.45 (60) $[M+H-H_2O+MeOH]^+$, 756.46 (60) $[M+H-2H_2O+2MeOH]^+$, 764.38 (55) $[M-H_2O+MeOH+Na]^+$, 778.39 (100) $[M-2H_2O+2MeOH+Na]^+$

Synthesis of compound 13:

[0138]



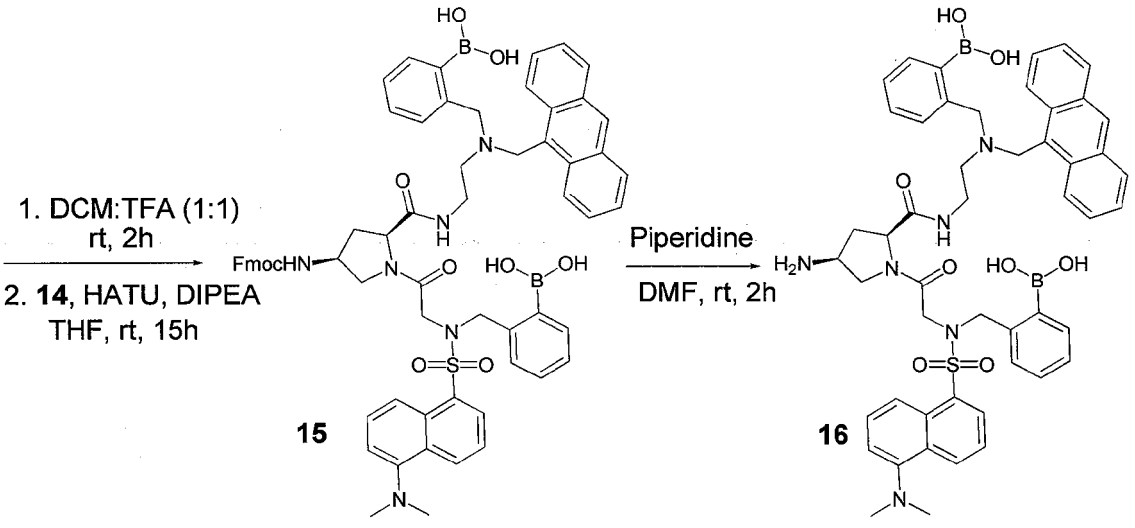
[0139] Compound **4** (0.22 g, 0.45 mmol) was dissolved in DCM (1mL) and the solution was cooled to 0 °C. Trifluoroacetic acid was dripped into the solution and the reaction was slowly warmed to room temperature. After 2 h, the solvent was evaporated and the residue was dried for 5 h under high vacuum. The crude solid was dissolved in THF (10 mL) and the solution was basified to pH~7-8 with DIPEA (0.17 mL, 0.90 mmol). In the following step, N-Boc-cis-4-N-Fmoc-amino-L-proline (0.20 g, 0.45 mmol) and HATU (0.17 g, 0.45 mmol) were added and the reaction mixture was stirred at room temperature for 15 h under argon. The solvent was removed in *vacuo* and the crude mass was subjected to combi-flash column chromatography (silica gel, 3% MeOH in DCM) to afford **13** (0.2 g) in 54% yield. ^{1}H NMR (300 MHz, CD_3OD) 1.20 (9H, s), 1.96-2.06 (2H, m), 2.62 (2H, s), 3.13 (2H, m, br), 3.33 (1H, s), 3.56-3.62 (2H, m), 3.78-3.82 (1H, d, br), 3.88 (1H, s, br), 4.00-4.04 (1H, t, br), 4.10-4.15 (1H, t, br), 4.35 (2H, m), 4.45 (2H, s), 7.24-7.43 (11H, m), 7.59 (2H, d, *J*= 9 Hz), 7.59 (1H, br), 7.72 (2H, d, *J*= 9 Hz), 7.89 (2H, d, *J*= 6 Hz), 8.11 (2H, d, *J*= 6 Hz), 8.31 (1H, s); MS (ESI+): *m/z* (%) = 819.46 (5) $[M+H]^+$, 833.47 (20) $[M+H-H_2O+MeOH]^+$, 847.48 (15) $[M+H-2H_2O+2MeOH]^+$, 855.46 (25) $[M-H_2O+MeOH+Na]^+$, 869.47 (100) $[M-2H_2O+2MeOH+Na]^+$

Synthesis of compound 14:

[0140] Trifluoroacetic acid (0.5 mL) was added dropwise to a solution of **13** (0.12 g, 0.165 mmol) in DCM (0.5 mL). The reaction was stirred at room temperature for 2 h. After consumption of the starting material, the solvents were removed under reduced pressure. The reaction mixture was dried for 5 h under high vacuum to afford **14** (0.07 g) in quantitative yield.

Synthesis of compound 15:

[0141]



[0142] To compound 7 (0.08 g, 0.165 mmol) in DCM (0.5 mL) was added trifluoroacetic acid (0.5 mL) at room temperature. The reaction mixture was stirred for 2 h. Upon completion, the solvent was evaporated for 5 h under high vacuum and the crude solid was re-dissolved in dry THF (10 mL). The stirred solution was basified with DIPEA (0.06

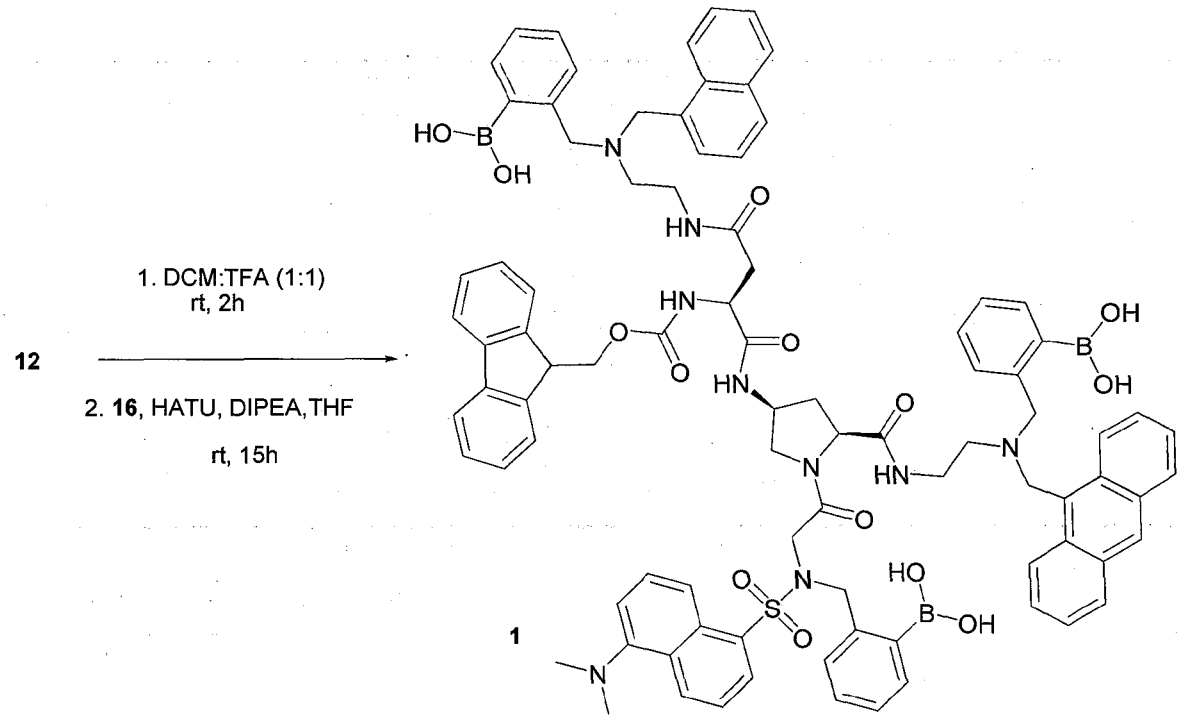
mL, 0.33 mmol) to obtain pH~7-8 followed by the addition of **14** (0.07 g, 0.165 mmol) and HATU (0.06g, 0.165 mmol) under argon. After 15 h, the solvent was removed under vacuum and the crude mass was subjected to combi-flash column chromatography (silica gel, 3% MeOH in DCM) to obtain a light yellowish solid 15 (0.07 g) in 37% yield. ^{1}H NMR (300 MHz, CD_3OD) 2.60 (2H, s), 2.82 (6H, s), 3.07-3.19 (3H, m), 3.37(1H, s), 3.71 (1H, s, br), 3.83 (2H, d, br), 3.65-3.75 (1H, m), 3.98 (2H, s, br), 4.03 (2H, d, br), 4.33 (2H, s, br), 4.46-4.64 (5H, m, br), 6.84-6.91 (1H, m), 6.95-7.15 (2H, m), 7.19 (2H, d, *J* = 6 Hz), 7.25-7.45 (12H, m), 7.47-7.56 (4H, m), 7.71-7.77 (2H, m), 7.91 (2H, d, *J* = 9 Hz), 8.12-8.15 (2H, d, br), 8.27-8.35 (3H, m), 8.51 (1H, d, *J* = 9 Hz); MS (ESI+): *m/z* (%) = 1165 (10) $[M+Na]^+$, 622.32 (45) $[M-4H_2O+4MeOH+2Na]^{+2}$, 1207.21 (20) $[M-3H_2O+3MeOH+Na]^+$, 1221.27 (100) $[M-4H_2O+4MeOH+Na]^+$

Synthesis of compound 16:

[0143] The bisboronic acid **15** (0.05 g) was dissolved in a solution of 20% piperidine in DMF (1.5 mL). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed at 40 °C using high vacuum and the crude reaction mass was purified by reverse phase HPLC. A binary gradient was made taking solution A (0.1% TFA in H_2O) and solution B (0.1% TFA in acetonitrile: H_2O; 3:1, v:v). The gradient used in HPLC was 15% B to 80% B over 80 min. The column effluents were monitored by UV absorbance at 220 nm. The purity of fractions were checked by reverse phase analytical HPLC with 10-100% B over 10 min with a flow rate of 3 ml/min. Pure fractions were collected and lyophilized to afford a light yellowish amine 16 (0.025g) in 78% yield (HPLC purity = 100%, Retention time = 8.42 min). ^{1}H NMR (300 MHz, CD_3OD) 2.02 (2H, d, *J* = 15 Hz), 2.45-2.50 (2H, m), 2.90 (1H, s), 2.95 (6H, s), 3.47 (2H, s, br), 3.71 (4H, s, br), 3.98-4.04 (2H, m), 4.33 (2H, m), 4.50 (2H, d, *J* = 12 Hz), 4.65 (1H, s, br), 5.43 (2H, s), 6.53 (1H, d, *J* = 9 Hz), 6.96 (1H, t, *J* = 7.5 Hz), 7.18 (1H, t, *J*= 9 Hz), 7.25 (1H, d, *J*= 9 Hz), 7.36 (1H, d, *J* = 9 Hz), 7.49-7.62 (9H, m), 7.84 (1H, br), 8.02 (1H, br), 8.12 (2H, d, *J* = 9 Hz), 8.34 (2H, t, *J* = 9 Hz), 8.59 (2H, d, *J* = 9 Hz), 8.69 (1H, s); MS (ESI+): *m/z* (%) = 489.31 (40) $[M+2H-4H_2O+4MeOH]^{+2}$, 500.40 (65) $[M+H-4H_2O+4MeOH+Na]^{+2}$, 963.53 (45) $[M+H-3H_2O+3MeOH]^+$, 977.47 (100) $[M+H-4H_2O+4MeOH]^+$

Synthesis of compound 1:

[0144]



[0145] To an oven dried argon purged flask were added t-butylester 12 (0.025 g, 0.029 mmol) in DCM (0.5 mL) and trifluoroacetic acid (0.5 mL). The reaction mixture was stirred for 2 h at room temperature. Upon completion, the solvent was evaporated for 5 h in high vacuum and redissolved in dry THF (10 mL). The solution was basified to pH~7-8 with DIPEA (0.02 mL, 0.11 mmol), then amine **16** (0.07 g, 0.165 mmol) and HATU (0.011g, 0.029 mmol) were added. The reaction was stirred at room temperature for 12 h under an argon atmosphere. The solvent was evaporated and the

crude mass was purified by reverse phase HPLC. A binary gradient was made taking solution A (0.1% TFA in H_2O) and solution B (0.1% TFA in acetonitrile: H_2O; 3:1, v:v). The gradient used in HPLC was 40% B to 100% B over 80 min. The column effluents were monitored by UV absorbance at 220 nm. The purity of fractions were checked by reverse phase analytical HPLC with 10-100% B over 10 min with a flow rate of 3 ml/min. Pure fractions were collected and lyophilized to afford a light yellowish solid 1 (0.004g) in 8.3% yield (HPLC purity = 98.7%, Retention time = 11.1 min). ^{1}H NMR (400 MHz, CD_3OD) 2.19-2.30 (2H, m), 2.32-2.43 (2H, m), 2.49-2.65 (2H, m), 2.89 (6H, s), 3.20 (1H, br), 3.36 (3H, s, br), 3.45 (1H, s), 3.48-3.50 (1H, m), 3.55-3.65 (1H, m, br), 3.94 (2H, dd, *J* = 5.1, 12.1 Hz), 4.08 (2H, t, *J* = 7.1 Hz), 4.15-4.16 (2H, m), 4.24-4.29 (3H, m), 4.32-4.36 (3H, m), 4.39-4.47 (3H, m), 4.58 (2H, d, br), 4.68 (2H, s, br), 6.62 (1H, t, *J* = 7.2 Hz), 6.88 (1H, t, *J* = 8.3 Hz), 6.99 (1H, t, *J* = 7.5 Hz), 7.14-7.18 (3H, m), 7.20-7.31 (5H, m), 7.45-7.53 (15H, m), 7.66-7.68 (2H, m, br), 7.67 (1H, d, *J*= 7.5 Hz), 7.73-7.77 (2H, br), 7.75 (1H, t, *J*= 7.1 Hz), 7.89 (2H, d, *J* = 8.6 Hz), 7.95 (2H, d, *J* = 8.3 Hz), 8.09 (2H, d, *J* = 7.7 Hz), 8.39 (2H, t, *J* = 10 Hz), 8.56 (1H, d, *J* = 8.6 Hz), 8.66 (1H, s); MS (ESI+): *m*/*z* (%) = 787.90 (10) $[M+2H]^{+2}$, 794.80 (40) $[M+2H-H_2O+MeOH]^{+2}$, 815.91 (75) $[M+2H-4H_2O+4MeOH]^{+2}$, 822.82 (70) $[M+2H-5H_2O+5MeOH]^{+2}$, 829.73 (20) $[(M+2H-6H_2O+6MeOH]^{+2}$, 1575.36 (5) $[M+H]^+$, 1588.60 (5) $[M+H-H_2O+MeOH]^+$, 1602.54 (5) $[M+H-2H_2O+2MeOH]^+$, 1616.60 (5) $[M+H-3H_2O+3MeOH]^+$, 1630.48 (10) $[M+H-4H_2O+4MeOH]^+$, 1644.67 (10) $[M+H-5H_2O+5MeOH]^+$, 1658.55 (5) $[M+H-6H_2O+6MeOH]^+$. Exact mass: $[M+H-5H_2O+5MeOH]^+$ $C_{94}H_{101}B_3N_9O_{14}S$ calc. 1644.7468; found 1644.7496

EXAMPLE 2

Fluorescence measurements of molecular differential sensor of compound 1 with saccharides

[0146] A solution of compound **1** (3 μM, 60 μL) in PBS:MeOH (1:1, pH = 7.28) (Figure 7a), HEPES:MeOH (1:1, pH = 7.5) (Figure 7b), or methanol (Figure 6) was mixed with a solution of a saccharide in water (1M or 100 mM, 3μL). The solution mixture was allowed to equilibrate for 6 min. Fluorescence measurements were taken in a 3 mm cuvette using 295-1100 nm emission filter and 10 nm excitation and emission slit width. The spectra were recorded at a rate of 120 nm per min. In all spectra, the emission of the pure sensor (none) corresponds to an addition of only water.

[0147] Figures 6 and 7 present fluorescence emission spectra of compound **1** upon addition of several saccharides. The binding of compound **1** and each saccharide provide a unique fingerprint (optical signature).

[0148] Exciting compound **1** at 270 nm (Figure 4) resulted in fluorescence emission across the UV-Vis spectrum owing to to intramolecular FRET processes. Adding L-glucose led to enhancement in both anthracene (58%) and dansyl (18%) emissions as well as to a hypsochromic shift in dansyl fluorescence. Almost no change was observed in the UV region. D-glucose generated a pattern similar to that of L-glucose in the naphthalene, fluorenyl, and antharacene emission regions; however, it induced a much stronger increase in dansyl emission (51 %). In contrast, the pattern generated by L-fructose differs from D-glucose mainly in the UV region where a 30% enhancement in naphthalene's fluorescence intensity was observed. Finally, maltitol and Dxylose can be easily distinguished from the other three saccharides because they induced the largest change in the emission of naphthalene (54%) and anthracene (85%), respectively.

EXAMPLE 3

PCA of molecular differential sensor of compound 1 with saccharides

[0149] The fluorescence emission for compound **1** with different saccharides **(48** mM) in PBS buffer:MeOH (1:1, pH = 7.28) were performed and analyzed using principal component analysis (PCA) (Figure 7c). Each cluster represents multiple trials for each saccharide.

[0150] Principal component analysis (PCA) was used to distinguish between these patterns as well as between optical signatures generated by other saccharides under the same conditions (Figure 8). To ensure reproducibility, each experiment was repeated four times. The PCA plot showed a clear differentiation between a variety of structurally similar sugars, including ring-forming monosaccarides (2-10), linear sugar alcohols (i.e. reduced monosaccharides) (11-17), disaccharides (18-21), and a trisaccharide (22). Therefore, these results confirm the feasibility of discriminating between numerous closely related analytes using a single fluorescent molecular sensor.

EXAMPLE 4

Excitation and emission of dyes

[0151] Figure 3A-3B present the excitation (Figure 3A) and emission (Figure 3B) spectra of the individual fluorescent dyes, namely, each boronic acid-dye pair (e.g., Naph*, An*, and Dan*) and a fluorenyl-aspartic acid derivative (Flu*). The emission spectra of naphthalene and fluorenyl overlap with the excitation spectra of antharacene and dansyl.

Therefore, illuminating at 270 nm resulted in an emission pattern ranging across the UV-Vis spectrum (Figure 5) due to FRET between the donors (e.g., naphthalene and fluorenyl) and acceptors (e.g.,dansyl and anthracene) as well as direct excitations, mainly of naphthalene, fluorenyl, and dansyl. An additional energy transfer process that occured to a lesser extent involved FRET between anthracene and dansyl (see Figure 4).

[0152] Solution of *N*-α-Fmoc-L-aspartic acid α-t-butylester (Flu*), naphthalene boronic acid derivative **10** (Naph*), anthracene boronic acid derivative **4** (An*), dansyl boronic derivative **7** (Dan*) in methanol were prepared. The excitation spectra of Flu*, Naph*, An*, Dan* were recorded while setting the emission wavelengths to 307 nm, 330 nm, 416 nm (using 360-1100 nm filter) and 521 nm (using 360-1100 nm filter), respectively. The emission spectra of Flu* and Naph* were obtained under an excitation wavelength of 270 nm using 295-1100 nm filter, whereas the emissions of An* and Dan* were recorded while exciting at 345 nm using 350-1100 nm filter. (Figure 3B) The slit widths were set to 10 nm for both excitation and emission measurements. The spectra were scanned at a rate of 120 nm per min.

Fluorescence Resonance Energy Transfer (FRET) between anthracene and dansyl:

[0153] An equal solution concentration (3.35 μM) of anthracene boronic acid derivative **4** (An*), dansyl boronic derivative 7 (Dan*) and compound **1** in methanol were prepared. The fluorescence spectra of each sample (60 μL) were measured under an excitation wavelength of 345 nm. The enhanced fluorescence emission of the dansyl moiety (540 nm), accompanied by a reduction of emission intensity for the anthracene moiety (385 nm) in compound **1** indicates of FRET between anthracene and dansyl (Figure 4).

EXAMPLE 5

Computational Structure of Compound 1

[0154] All electronic structure calculations were carried out using GAUSSIAN09 REVISION C.01. Two classes of electronic structure methods were used. Geometries were initially optimized using the semiempirical parameter model 6 (PM6). PM6 should be sufficient to provide qualitative relative energies. Selected geometries were then reoptimized using density functional theory (DFT). For the geometry optimizations, the Perdew-Burke-Ernzerhof (PBE) functional was used. Energies were then calculated with Adamo and Barone's hybrid version of this functional (PBE0, also denoted as PBEh or PBE1PBE). Density fitting basis sets (DFBS), as implemented in GAUSSIAN09, were employed in order to improve the computational efficiency of the calculation. Because the use of DFBSs precludes the use of a hybrid DFT exchange-correlation functional, they were used in conjunction with the PBE functional for the geometry optimizations. Due to the rather large size of the system, in order to make the geometry optimizations tractable, the Stuttgart-Dresden effective core potential-basis set was used on all atoms (denoted as SDDall, excluding hydrogen). The single-point energies employed Pople's 6-31G(d,p) basis set. Bulk solvation effects were approximated in the single-point energy calculations using Marenich and Truhlar's solvation model dispersion (SMD), which is an empirical reparamterization of the polarizable continuum model (PCM), specifically the integral equation formalism model (IEF-PCM); methanol was used as the solvent. The accuracy of the DFT methods was improved by adding the empirical dispersion correction as recommended by Grimme. The older version (DFTD2) is available, with analytical gradients and Hessians, in GAUSSIAN09 and was used during geometry optimizations and frequency calculations; the GAUSSIAN09 was locally modified to allow for its use for any DFT functional rather than just the limited set included in the commercially available version. The newer, and more accurate, DFTD3 version, which includes parameters for most of the periodic table, was used as an *a posteriori* correction to the PBE0 energies obtained from GAUSSIAN09; the code written by Grimme was used. All DFT-optimized structures were characterized as minima by having zero imaginary frequencies; small imaginary frequency (<10i cm^{-1}) were ignored as artifacts of the large size and flexible nature of the system.

[0155] To assess the possibility of such intra-molecular interactions, the structure of compound **1** was simulated using density functional theory (DFT) in a solvent continuum model. The modeling showed that the compound forms a flexible and structurally preorganized cavity in which the three phenyl boronic acids project toward the same direction (Figure 9). Importantly, the structure was maintained via intra-molecular hydrogen bonds and π-stacking involving the three phenyl boronic acids. For example, the phenyl boronic acid neighboring the dansyl group formed π-interactions with the adjacent aromatic ring (Figure 9), whereas its hydroxyl groups were hydrogen bonded to an amide and an amine on the neighboring arm as well as to a nearby carbonyl.

EXAMPLE 6

Fluorescence measurements of molecular differential sensor of compound 1 with antibiotics

[0156] A solution of molecule 1 (3 μM, 60 μL) in methanol was mixed with a solution of a drug in DMSO (100 mM,

3μL). The solution mixture was allowed to equilibrate for 6 min. Fluorescence measurements were taken in a 3 mm cuvette under an excitation wavelength of 270 nm using 295-1100 nm emission filter and 10 nm excitation and emission slit width. The spectra were recorded at a rate of 120 nm per min. The emission of the pure sensor (none) corresponds to an addition of only DMSO.

[0157] Principal component analysis (PCA) was applied to distinguish between these patterns as well as between optical signatures generated by other macrolides, aminoglycosides, cardiac glycosides, and rifamycins (Figure 11). Unknown samples were then taken from the training set and PCA was effectively applied to identify their content with an accuracy of 97%.

[0158] In such studies, patients are administered a normal dose of rifampicin (e.g. 300 mg) and a much larger amount of the saccharide (e.g. 5 g), as part of a standard D-xylose test used for assessing the absorptive capacity of the intestines.

[0159] To test whether the compound of this invention can distinguish between various drug concentrations and combinations within medicinally relevant samples, 1 was subjected to human urine loaded with different ratios of D-xylose and rifampicin. As shown in Figure 12A, urine samples with just D-xylose or rifampicin induced markedly distinct changes in the emission patterns. Notably, addition of the first resulted in a substantial increase in antharacene fluorescence, whereas the second mainly led to a reduction in dansyl's emission. Similar measurements were performed with urine samples consisting of different antibiotic-saccharide mixtures and PCA was used to differentiate between the patterns generated at the anthracene and dansyl emission region (Figure 12C). The robustness of the molecular diagnostic system was confirmed by its ability to identify urine-drug samples with a 95% success rate.

EXAMPLE 7

Preparation of Compound 32 and Other Boronic Acid-Dye Conjugates

[0160] Using the above protocols for preparing various boronic acid-dye conjugates and for attaching them to a single Cis-amino L-proline scaffold, a wide range of boronic acid-dye pairs will initially be prepared from commercially available, carboxy-modified dyes, which emit in the red and NIR spectral regions (Figure 13, R = OH, $NH(CH_2)_2Br$ or halide). Lanthanide complexes can also be synthesized to extend the spectral range of the emission patterns. Figure 14 shows how N-hydroxysuccinimide (NHS) esters (compounds 22 and 27) of a wide range of boronic acid-dye conjugates can be straightforwardly prepared. Figure 15 shows how the same boronic acid-dye conjugates (compounds **29, 30** and **31**) are used for preparing compound **32** (Figure 15).

[0161] The boronic acid-dye conjugates are linked to the Cis amino L-proline via amide bonds. D_1, D_2, D_3 and D_4 of Figure 15 refer to dyes/chromophores of this inventions. Specifically the dyes as depicted in Figure 13.

EXAMPLE 8

Two State Molecular Encoding System

[0162] A series of two state molecular encoding system that respond to different sequences of saccharide pairs, such as D-glucose (G) and D-xylose (X), D-glucose (G) and galactose (L), as well as D-fructose (F) and maltitol (M) (Figure 17a and Figure 24) were prepared. The distinct optical signatures observed for inputs GX and XG (Figure 17a), GL and LG, and FM and MF (Figure 24) is an example for an encoding system of this invention using 2-input analytes. Figure 18 exemplifies how the strong binding of the first saccharide (i.e., saccharide 1 or 2) to two of the three boronic acids (i.e., complexes ii and iii) followed by a weaker binding of the second saccharide can impose the formation of a metastable complex (i.e., complex iv or v) whose conversion to the thermodynamic product occurs over a prolonged reaction time.

[0163] The encoding system of this invention differentiate between 'passwords' of different inputs (i.e analytes) or different ratios/concentrations of the same input (Figure 17b). The different emission patterns obtained upon addition of each saccharide (X=D-xylose or G=D-glucose), followed by a second addition of the same input signal (XX or GG), confirm that compound 1 can recognize X, G, XX, and GG as distinct code entries. Figure 18 illustrates how such changes could result in distinguishable emission pattern. Specifically, passwords (i.e inputs) 1, 2, 11, 22, 12, 21 can be differentiated because different saccharides (i.e., 1 or 2) induce the formation of distinct complexes (i.e., ii and vi or iii and vii), while their concentration affects the ratio between them. Principal component analysis (PCA) (Figure 19) of the complete spectral data (Figures 17a and 17b) proves that an individual fluorescent molecule discriminated between all possible combinations of 1- and 2-code entries, namely, X, G, XX, GG, XG and GX, akin to an equivalent electronic device.

EXAMPLE 9

Three State Molecular Encoding System Consisting of Different Combination of 3-Inputs

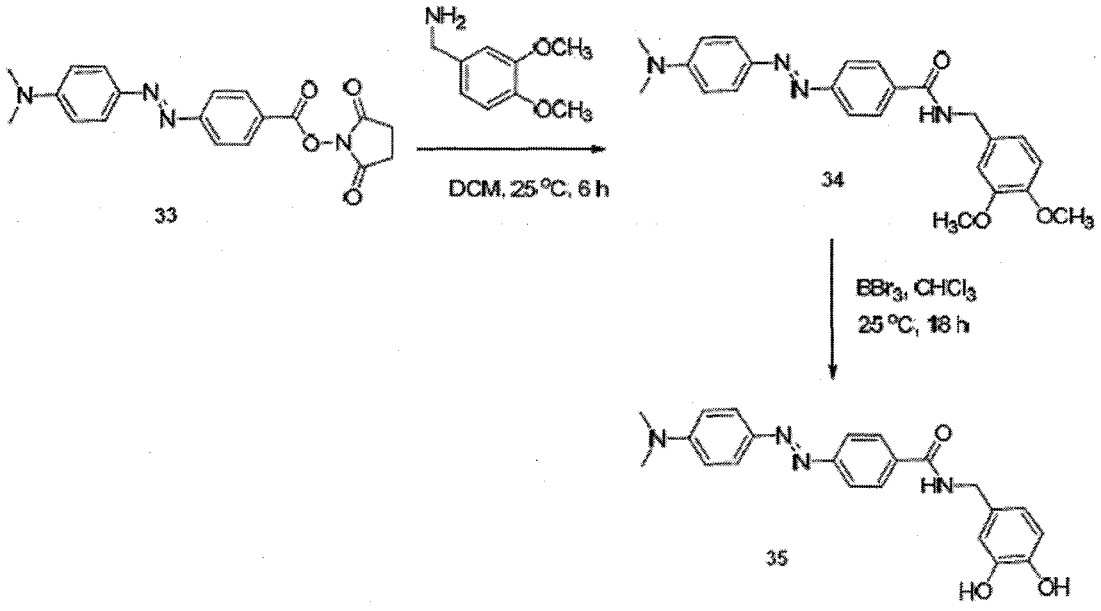
[0164] Figure 20 includes 27 code entries, and many of them should be readily differentiated by the encoding system of this invention. In Figure 20, each digit (1, 2 or 3) represents a different chemical input and the 27 combinations are divided to 10 password groups (Figure 20, groups a-j) that differ either in the type of inputs 'keys' or in the ratio between them. Because compound 1 can effectively differentiate between different chemical inputs and between distinct input concentrations (Figure 17b), many of the passwords (inputs) that belong to different groups (a-j) should be distinguished. In addition, the ability of compound 1 to discriminate between input sequences (Figure 17a and Figure 26) should allow it to differentiate passwords within each group (e.g. groups d-i). For example, passwords (11)2 and 2(11) in group should induce the formation of distinct optical fingerprints.

[0165] To efficiently discriminate between groups a-j (Figure 20), chemical inputs and different concentrations that, individually, induce the most distinguishable changes to the emission signal was first screened. In addition to testing 12 different saccharides (Figure 26), a new chemical input that integrates catechol and dabcyl functionalities (Figure 21a, DC) was synthesized (Example 10). The strong affinity of catechol to boronic acids and the ability of dabcyl to quench the emission of various fluorphores enables DC to compete with the binding of various saccharides, as well as to generate markedly distinct emission patterns. As shown in Figure 21b, maltitol, D-xylose, and DC, which were selected from this screen, generated entirely different patterns and the addition of DC has indeed led to fluorescence quenching across the UV-Vis spectrum. Moreover, the fluorescence emission was resorted upon adding competing saccharides (Figure 21c) and the resulting optical fingerprints were dependent on the order of addition (Figure 21d).

EXAMPLE 10

Synthesis of Compound 35 (Dabcyl Catechol (DC))

[0166]



Synthesis of compound 34:

[0167] To a stirred solution of DABCYL-NHS **33** (0.25 g, 0.068 mmol) in dry DCM (1.5 mL) was added 3,4-Dimethoxy benzylamine (0.011g, 0.068 mmol) under argon. The reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated and the crude reaction mass was subjected to combi-flash column chromatography (silica gel, 1% methanol in DCM) to afford **34** (0.20 g) as red solid in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) 3.10 (6H, s), 3.87 (6H, s), 4.59 (2H, d, J = 6 Hz), 6.48 (1H, s, br), 6.75 (2H, d, J = 9 Hz), 6.84 (1H, d, J = 9 Hz), 6.90 (2H, s), 7.87 (6H, s); MS (ESI+): m/z (%) = 419.31 (100) $[M+H]^+$, 441.31 (75) $[M+Na]^+$, 859.52 (60) $[2M+Na]^+$, 1277.80 (25) $[3M+Na]^+$.

Synthesis of compound 35:

[0168] To a stirred solution of **34** (0.20 g, 0.047 mmol) in dry DCM (1.5 mL) was added boron tribromide (0.1g, 0.4 mmol, 400μL of 1M solution of BBr_3) under argon at 0 °C. The solution was warmed to room temperature and then stirred for 18 h. The reaction was diluted with DCM (25 mL) and washed with saturated solution of $NaHCO_3$ (2 x 5 mL). The organic layer was washed with brine (5 mL) and dried over anhydrous Na_2CO_3. The solvent was evaporated and the crude reaction mass was subjected to combi-flash column chromatography (silica gel, 4% methanol in DCM) to afford **35** (0.014 g) as red solid in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) 3.10 (6H, s), 4.45 (2H, s), 6.67-6.75 (2H, m), 6.80 (3H, d, *J* = 9 Hz), 7.81-7.85 (4H, m), 7.94 (2H, d, *J* = 9 Hz) ; MS (ESI+): *m*/*z* (%) = 391.28 (65) $[M+H]^+$, 413.28 (45) $[M+Na]^+$, 803.49 (40) $[2M+Na]^+$.

EXAMPLE 11

Three-State Molecular Encoding System

[0169] A three state encoding system of this invention was prepared using of 1. maltitol, 2. D-xylose, and 3. DC as input signals. Figure 22a shows some of the patterns generated by 'inputs 1 to 3. Pattern analysis of all 27 combinations (Figure 20) reveals that nine 3-digit passwords can be authorized by the unimolecular security system (Figure 22b). The feasibility of distinguishing 4-digit code entries such as, 1111, 2222, and 3333, was also demonstrated (Figure 26). Because patterns generated from repeats of identical chemical inputs are unique; these 4-digit 'passwords' should also be distinguished from the 81 possible 4-digit combination codes (i.e, 3^4= 81).

EXAMPLE 12

Fluorescence Measurements

Analysis of Two State Passwords

[0170] Saccharides (1.5 μL) were added to a solution of **1** (3 μM, 60 μL) in methanol (Figure 17). The mixture was allowed to equilibrate for 6 min after each saccharide addition. Fluorescence measurements were taken in a 3 mm cuvette using an excitation wavelength of 270 nm, an emission filter of 295-1100 nm and excitation and emission slit width of 10 nm. The spectra were recorded at a rate of 120 nm per min. A solution of 1 M D-xylose and 100 mM of D-glucose were used for measurements of two input passwords (Figures 17 and 19). The emission of the pure sensor (none) corresponds to addition of pure water.

Analysis of Saccharide and Three State Passwords

[0171] A solution of a saccharide or analyte (1 μL) was added to a solution of 1 (3 μM, 60 μL) in methanol (Figure 21b). The mixture was allowed to equilibrate for 6 min after each addition. Fluorescence measurements were taken in a 3 mm cuvette using an excitation wavelength of 270 nm, 295-1100 nm emission filter and 10 nm excitation and emission slit width. A solution of 3 M Maltitol in water, 1 M D-glucose in water and 7.7 mM DC in methanol were used for the measurements of three input passwords (Figures 21 and 22). The spectra were recorded at a rate of 120 nm per min. The emission of the pure sensor (none) corresponds to addition of pure water.

Saccharide detection

[0172] A solution of a saccharide (3 μL, 100 mM) was added to a solution of 1 (3 μM, 60 μL) in methanol (Figure 25). The mixture was allowed to equilibrate for 6 min. Fluorescence measurements were taken in a 3 mm cuvette under an excitation wavelength of 270 nm using 295-1100 nm emission filter and 10 nm excitation and emission slit width. The spectra were recorded at a rate of 120 nm per min. The emission of the pure sensor (none) corresponds to an addition of only water.

EXAMPLE 13

Principal Component Analysis (PCA)

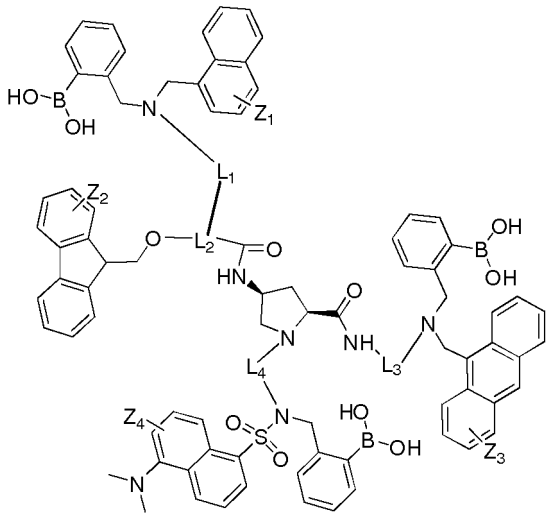
[0173] The fluorescence experiments were performed in four replicates for all the saccharides and PCA was applied to distinguish between patterns generated by the fluorescence intensities at wavelengths ranging from 295 nm to 700

nm (Figure 25).

[0174] Similarly, differentiation between D-xylose and D-glucose combinations and concentrations (Figure 19) was achieved by analyzing emission intensities at seven different wavelengths (e.g. 304 nm, 326 nm, 397 nm, 421 nm, 449 nm, 496 nm and 527 nm). The analysis of three input passwords was done at eight different wavelengths (e.g. 305 nm, 325 nm, 395 nm, 420 nm, 445 nm, 520 nm, 530 nm and 540 nm). Principal component analysis of the emission spectra was performed using XLSTAT version 2013.1.01 (32 bit).

Claims

1. A compound represented by the structure of formula III:

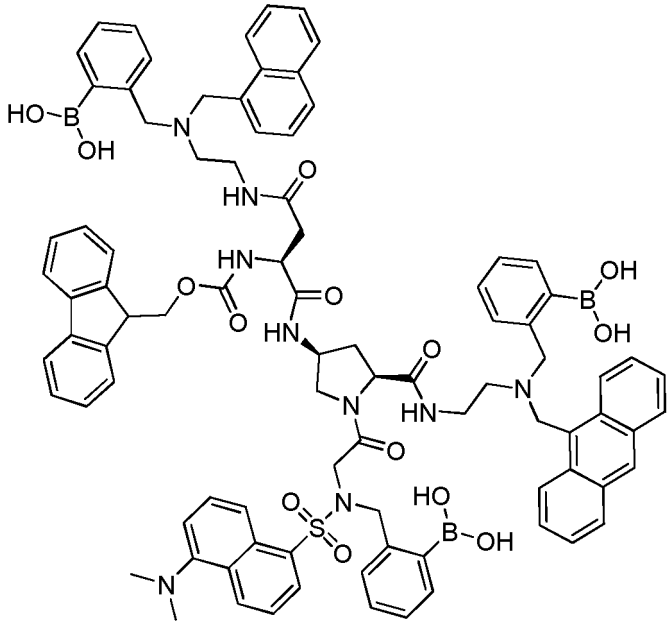


(III)

wherein

L_1, L_2, L_3, L_4 are independently a linker, wherein said linker is -alkylene-, -O-alkylene-, -NHC(O)-, -C(O)NH-, -NHC(O)X-, -C(O)NHX-, -C(O)X-, -X'NHC(O)-, -X'C(O)NH-, -X'NHC(O)X-, -X'C(O)NHX-, -X'C(O)X-, -NHX-, -NH-[amino-acid]-C(O)-, -NH-[amino-acid]-C(O)-alkylene-, -C(O)-[amino-acid]-NH-, or -C(O) -[amino-acid]-NH-alkylene-;
X and X' are independently alkylene, haloalkylene, arylene or phenylene; and
Z_1, Z_2, Z_3, Z_4 are independently hydrogen, alkyl, alkenyl, haloalkyl, aryl, O-aryl, -(CH_2)n-aryl, cycloalkyl, O-cycloalkyl, CF_3, F, I, Br, Cl, NO_2, CN, $N(R')_2$, COOH, COR', NHCOR', CONHR', $(CH_2)_nNH_2$, $(CH_2)_nNHR'$, SR', SH, OR', $(CH_2)_nOH$, $(CH_2)_nCOOH$, or OH; wherein R' is H, alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, aryl, phenyl or halogen; and
n is from 0 to 8.

2. The compound of claim 1, wherein said compound is represented by the structure of formula (1):



(1)

3. A method of differentiating between carbohydrates comprising:

• contacting a carbohydrate with a compound of any of claims 1 or 2 in a liquid medium, wherein said carbohydrate and said compound form a complex; wherein a first fluorescent dye emits at a wavelength which is the absorption wavelength of a second fluorescent dye; wherein said linker comprises nitrogen; wherein contacting said carbohydrate with said compound results in a conformational change of said compound and thereby to a unique optical signature of said complex; wherein said liquid medium is an aqueous solution; and
• measuring the optical signature of said complex;

and thereby, differentiating said carbohydrate.

4. The compound of any of claims 1 or 2 for use in a method of diagnosing a disease in a subject, wherein said diagnosis comprises detection of an carbohydrate biomarker; said method comprising:

• collecting a biological sample from a subject;
• optionally, isolating components from said biological sample;
• contacting the compound of any of claims 1 or 2 with a carbohydrate comprised within said sample or isolated component in a liquid medium; wherein said carbohydrate forms a complex with said compound; wherein contacting said compound with said carbohydrate results in a conformational change of said compound and thereby to a unique optical signature of said complex;
• measuring the optical signature of said complex;
• identifying a carbohydrate biomarker in said sample, said carbohydrate biomarker being characteristic of a disease; or measuring a change in a concentration of a carbohydrate biomarker in said sample compared to normative values, wherein said change is characteristic of a disease;

thereby diagnosing a disease in a subject,
wherein, optionally, said disease is selected from hypoglycemia, prostate cancer, diabetes, syndrome X, or a glycoprotein based disease selected from multiple sclerosis, Crohn's disease, autoimmune disease, colitis, inflammatory bowel disease, cancer, lysosomal storage disease, or celiac disease.

5. The method of claim 3 or the compound for use of claim 4, wherein said carbohydrate is an antibiotic or a saccharide, wherein said saccharide is a monosaccharide, a disaccharide, L-Glucose, D-Glucose, D-fructose, L-fructose, D-arabinose, D-xylose, L-xylose, L-mannose, D-galactose, D-sorbitol, mannitol, dulcitol, adonitol, xylitol, L-threitol, maltitol, lactulose, D-lactose, D-maltose, D-trehalose or maltotriose; wherein said antibiotic is a macrolide, an aminoglycoside, a cardiac glycoside, or a rifamycin; wherein said saccharide is a component of a glycoprotein, a

proteoglycan or a glycolipid or a glycan independent of a protein or lipid compound.

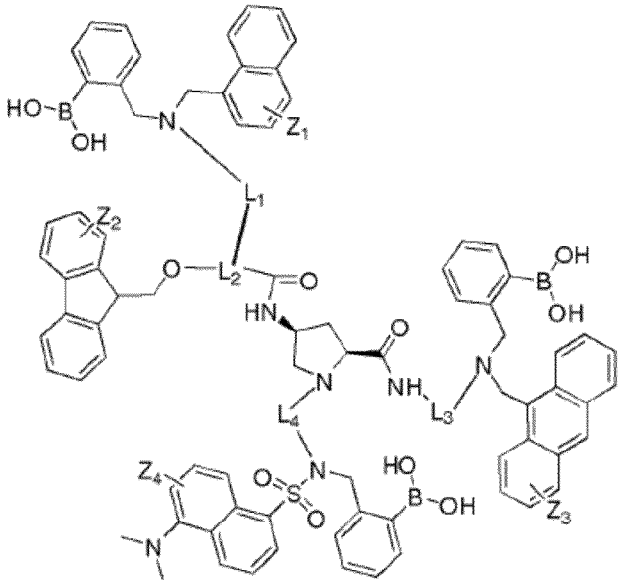
6. A method of encoding information using a compound of any of claims 1 or 2, comprising:

a. contacting said compound with between 2 and 7 analytes in a specific sequence to form a complex, wherein said complex exhibits a unique optical signature signal;
b. reading the unique optical signature;
c. associating the unique optical signature with an encoding reference specifying said analytes contacted in said specific sequence according to a predefined encoding scheme; and
d. storing the encoded reference keyed to the unique optical signature in a database record.

7. The method of claim 6, wherein said analytes are the same or different comprising L-Glucose, D-Glucose, D-fructose, L-fructose, D-arabinose, D-xylose, L-xylose, L-mannose, D-galactose, D-sorbitol, mannitol, dulcitol, adonitol, xylitol, L-threitol, maltitol, lactulose, D-lactose, D-maltose, D-trehalose, or maltotriose.

Patentansprüche

1. Verbindung, dargestellt durch die Strukturformel III:

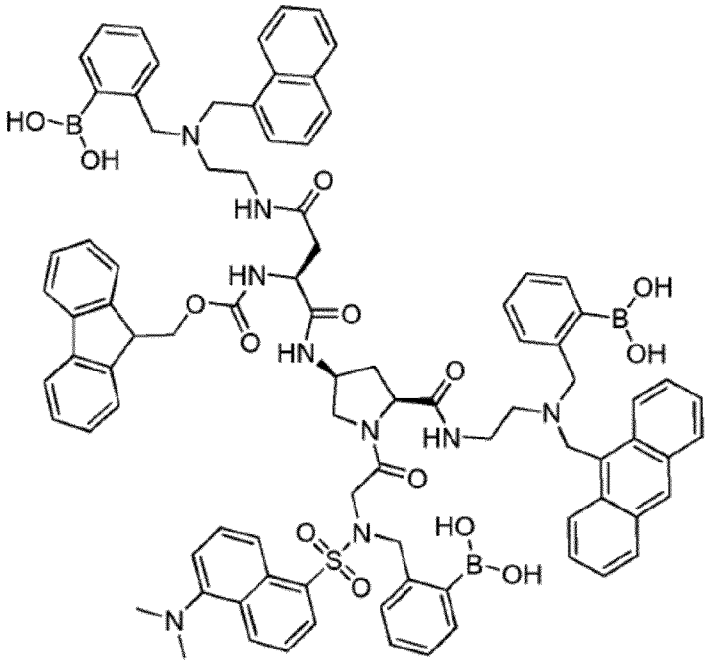


(III)

wobei

L_1, L_2, L_3, L_4 jeweils unabhängig ein Linker sind, wobei der Linker -Alkylen-, -O-Alkylen-, -NHC(O-, -C(O)NH-, -NHC(O)X-, - C(O)NHX-, -C(O)X-, -X'NHC(O)-, -X'C(O)NH-, -X'NHC(O)X-, - X'C(O)NHX-, -X'C(O)X-, -NHX-, -NH-[Aminosäure]-C(O)-, -NH-[Aminosäure]-C(O)-alkylen-, -C(O)-[Aminosäure]-NH- oder -C(O)-[Aminosäure] -NH-alkylen- ist;
X und X' jeweils unabhängig Alkylen, Halogenalkylen, Arylen oder Phenylen sind; und
Z_1, Z_1, Z_3, Z_4 jeweils unabhängig Wasserstoff, Alkyl, Alkenyl, Halogenalkyl, Aryl, O-Aryl, -(CH_2)n-Aryl, Cycloalkyl, 0-Cycloalkyl, CF_3, F, I, Br, Cl, NO_2, CN, $N(R')_2$, COOH, COR',
NHCOR', CONHR', $(CH_2)_nNH_2$, $(CH_2)_nNHR'$, SR', SH, OR', $(CH_2)_nOH$, $(CH_2)_nCOOH$ oder OH sind; wobei R' H, Alkyl, Halogenalkyl, Dihalogenalkyl, Trihalogenalkyl, Aryl, Phenyl oder Halogen ist;
und
n von 0 bis 8 ist.

2. Verbindung nach Anspruch 1, wobei die Verbindung durch die Strukturformel (1) dargestellt ist:



(1)

3. Verfahren zur Unterscheidung zwischen Kohlenhydraten, umfassend:

- Inkontaktbringen eines Kohlenhydrats mit einer Verbindung nach einem der Ansprüche 1 oder 2 in einem flüssigen Medium, wobei das Kohlenhydrat und die Verbindung einen Komplex bilden; wobei ein erster Fluoreszenzfarbstoff bei einer Wellenlänge emittiert, welche die Absorptionswellenlänge eines zweiten Fluoreszenzfarbstoffs ist; wobei der Linker Stickstoff umfasst; wobei ein Inkontaktbringen des Kohlenhydrats mit der Verbindung zu einer Konformationsänderung der Verbindung und dadurch zu einer eindeutigen optischen Signatur des Komplexes führt; wobei das flüssige Medium eine wässrige Lösung ist; und
- Messen der optischen Signatur des Komplexes;

und dadurch Unterscheiden des Kohlenhydrats.

4. Verbindung nach einem der Ansprüche 1 oder 2 zur Verwendung bei einem Verfahren zur Diagnosestellung einer Krankheit bei einem Subjekt, wobei die Diagnose den Nachweis eines Kohlenhydrat-Biomarkers umfasst; wobei das Verfahren Folgendes umfasst:

- Entnehmen einer biologischen Probe von einem Subjekt;
- wahlweise Isolieren von Komponenten aus der biologischen Probe;
- Inkontaktbringen der Verbindung nach einem der Ansprüche 1 oder 2 mit einem in der Probe enthaltenen Kohlenhydrat oder einer isolierten Komponente in einem flüssigen Medium; wobei das Kohlenhydrat einen Komplex mit der Verbindung bildet; wobei das Inkontaktbringen der Verbindung mit dem Kohlenhydrat zu einer Konformationsänderung der Verbindung und dadurch zu einer eindeutigen optischen Signatur des Komplexes führt;
- Messen der optischen Signatur des Komplexes;
- Identifizieren eines Kohlenhydrat-Biomarkers in der Probe, wobei der Kohlenhydrat-Biomarker für eine Krankheit charakteristisch ist; oder Messen einer Änderung einer Konzentration eines Kohlenhydrat-Biomarkers in der Probe im Vergleich zu normativen Werten, wobei die Veränderung für eine Krankheit charakteristisch ist;

wodurch eine Krankheit bei einem Subjekt diagnostiziert wird,
wobei die Krankheit wahlweise von Hypoglykämie, Prostatakrebs, Diabetes, Syndrom X, oder einer Glykoprotein-basierten Krankheit, ausgewählt von Multipler Sklerose, Morbus Crohn, Autoimmunkrankheit, Colitis, entzündlicher

Darmerkrankung, Krebs, lysosomaler Speicherkrankheit oder Zöliakie ausgewählt ist.

5. Verfahren nach Anspruch 3 oder Verbindung zur Verwendung nach Anspruch 4, wobei das Kohlenhydrat ein Antibiotikum oder ein Saccharid ist, wobei das Saccharid ein Monosaccharid, ein Disaccharid, L-Glucose, D-Glucose, D-Fructose, L-Fructose, D-Arabinose, D-Xylose, L-Xylose, L-Mannose, D-Galactose, D-Sorbit, Mannit, Dulcit, Adonit, Xylit, L-Threit, Maltit, Lactulose, D-Lactose, D-Maltose, D-Trehalose oder Maltotriose ist; wobei das Antibiotikum ein Makrolid, ein Aminoglycosid, ein Herzglykosid oder ein Rifamycin ist; wobei das Saccharid eine Komponente eines Glycoproteins, eines Proteoglycans oder eines Glycolipids oder eines Glycans unabhängig von einem Protein oder einer Lipidverbindung ist.

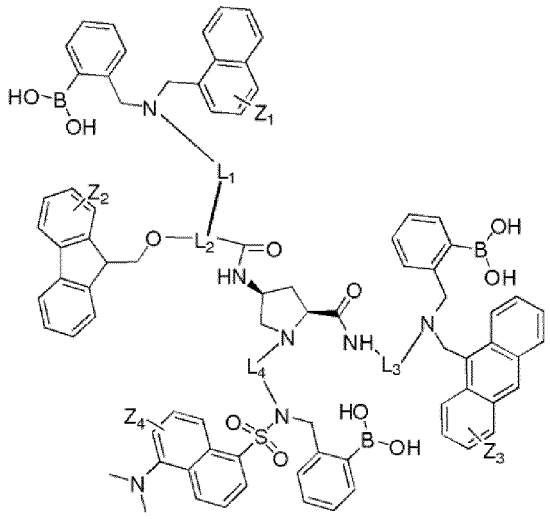
6. Verfahren zum Codieren von Information unter Verwendung einer Verbindung nach einem der Ansprüche 1 oder 2, umfassend:

a. Inkontaktbringen der Verbindung mit zwischen 2 und 7 Analyten in einer bestimmten Reihenfolge, um einen Komplex zu bilden, wobei der Komplex ein eindeutiges optisches Signatursignal zeigt;
b. Lesen der eindeutigen optischen Signatur;
c. Zuordnen der eindeutigen optischen Signatur zu einer Codierreferenz, welche die Analyten spezifiziert, die in der bestimmten Reihenfolge gemäß einem vordefinierten Codierungsschema kontaktiert wurden; und
d. Speichern der codierten Referenz, die mit der eindeutigen optischen Signatur in einem Datenbanksatz eingestimmt ist.

7. Verfahren nach Anspruch 6, wobei die Analyten gleich oder verschieden sind und L-Glucose, D-Glucose, D-Fructose, L-Fructose, D-Arabinose, D-Xylose, L-Xylose, L-Mannose, D-Galactose, D-Sorbit, Mannit, Dulcit, Adonit, Xylit, L-Threit, Maltit, Lactulose, D-Lactose, D-Maltose, D-Trehalose oder Maltotriose umfassen.

Revendications

1. Composé représenté par la structure de formule III :



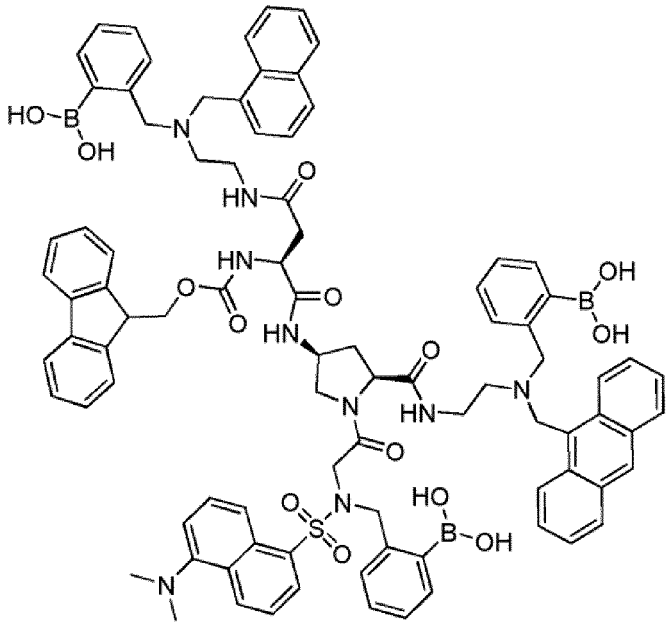
(III)

dans lequel

Li, L2, L3, L4 sont indépendamment un lieur, dans lequel ledit lieur est -alkylène-, O-alkylène-, -NHC(O)-, -C(O)NH-, -NHC(O)X-, -C(O)NHX-, -C(O)X-, X'NHC(O)-, -X'C(O)NH-, - X'NHC(O)X-, -X'C(O)NHX-, -X'C(O)X-, -NHX-, NH-[aminoacide]-C(O)-, -NH-[aminoacide]-C(O)-alkylène-, -C(O)-[aminoacide]-NH- ou C(O)-[aminoa-

cide]-NH-alkylène-;
X et X' sont indépendamment un groupe alkylène, haloalkylène, arylène ou phénylène; et
Z1, Z2, Z3, Z4 sont indépendamment hydrogène, alkyle, alcényle, haloalkyle, aryle, O-aryle, (CH_2)N-aryle, cycloalkyle, O-cycloalkyle, CF_3, F, I, Br, Cl, NO_2, CN, $N(R')_2$, COOH, COR', NHCOR', CONHR', $(CH_2)_nNH_2$, $(CH_2)_nNHR'$, SR', SH, OR', $(CH_2)_nOH$, $(CH_2)_nCOOH$ ou OH; où R' est H, alkyle, haloalkyle, dihaloalkyle, trihaloalkyle, aryle, phényle ou halogène; et
n va de 0 à 8.

2. Composé selon la revendication 1, dans lequel ledit composé est représenté par la structure de la formule (1) :



(1)

3. Procédé de différenciation entre des hydrates de carbone comprenant :

• la mise en contact d'un hydrate de carbone avec un composé selon l'une quelconque des revendications 1 ou 2 dans un milieu liquide, dans lequel ledit hydrate de carbone et ledit composé forment un complexe; dans lequel un premier colorant fluorescent émet à une longueur d'onde qui est la longueur d'onde d'absorption d'un second colorant fluorescent; dans lequel ledit lieur comprend de l'azote; dans lequel la mise en contact dudit hydrate de carbone avec ledit composé conduit à un changement conformationnel dudit composé et donc à une signature optique unique dudit complexe; dans lequel ledit milieu liquide est une solution aqueuse; et
• la mesure de la signature optique dudit complexe;

et ainsi, différencier ledit hydrate de carbone.

4. Composé selon l'une quelconque des revendications 1 ou 2, destiné à être utilisé dans une méthode de diagnostic d'une maladie chez un sujet, dans lequel ledit diagnostic comprend la détection d'un biomarqueur glucidique; ledit procédé comprenant :

• de recueillir un échantillon biologique d'un sujet;
• éventuellement, d'isoler des composants dudit échantillon biologique;
• de mettre en contact du composé de l'une quelconque des revendications 1 ou 2 avec un hydrate de carbone compris dans ledit échantillon ou un composant isolé dans un milieu liquide; dans lequel ledit hydrate de carbone forme un complexe avec ledit composé; dans lequel la mise en contact dudit composé avec ledit hydrate de carbone conduit à un changement conformationnel dudit composé et donc à une signature optique unique dudit complexe;
• de mesurer la signature optique dudit complexe;
• d'identifier un biomarqueur glucidique dans ledit échantillon, ledit biomarqueur glucidique étant caractéristique

d'une maladie; ou de mesurer une variation d'une concentration d'un biomarqueur glucidique dans ledit échantillon par rapport à des valeurs normatives, dans lequel ledit changement est caractéristique d'une maladie;

diagnostiquant ainsi une maladie chez un sujet,
dans laquelle, optionnellement, ladite maladie est choisie parmi l'hypoglycémie, le cancer de la prostate, le diabète, le syndrome X ou une maladie à base de glycoprotéine choisie parmi la sclérose en plaques, la maladie de Crohn, la maladie auto-immune, la colite, les maladies inflammatoires intestinales, un cancer, une maladie lysosomale ou une maladie coeliaque.

5. Procédé selon la revendication 3 ou composé pour l'utilisation selon la revendication 4, dans lequel ledit hydrate de carbone est un antibiotique ou un saccharide, dans lequel ledit saccharide est un monosaccharide, un disaccharide, le L-Glucose, le D-Glucose, le D-fructose, le L-fructose, le D-arabinose, le D-xylose, le L-xylose, le L-mannose, D-galactose, D-sorbitol, mannitol, dulcitol, adonitol, xylitol, L-thréitol, maltitol, lactulose, D-lactose, D-maltose, D-trehalose ou maltotriose; dans lequel ledit antibiotique est un macrolide, un aminoglycoside, un glycoside cardiaque ou une rifamycine; dans lequel ledit saccharide est un composant d'une glycoprotéine, d'un protéoglycane ou d'un glycolipide ou d'un glycane indépendant d'une protéine ou d'un composé lipidique.

6. Procédé de codage d'informations utilisant un composé selon l'une quelconque des revendications 1 ou 2, comprenant :

a. la mise en contact dudit composé avec entre 2 et 7 analytes dans une séquence spécifique pour former un complexe, dans lequel ledit complexe présente un signal de signature optique unique;
b. la lecture de la signature optique unique;
c. l'association de la signature optique unique à une référence de codage spécifiant lesdits analytes mis en contact dans ladite séquence spécifique selon un schéma de codage prédéfini ; et
d. le stockage de la référence codée associée à la signature optique unique dans un enregistrement de base de données.

7. Procédé selon la revendication 6, dans lequel lesdits analytes sont identiques ou différents comprenant du L-Glucose, du D-Glucose, du D-fructose, du L-fructose, du D-arabinose, du D-xylose, du L-xylose, du L-mannose, du D-galactose D-sorbitol, mannitol, dulcitol, adonitol, xylitol, L-thréitol, maltitol, lactulose, D-lactose, D-maltose, D-trehalose ou maltotriose.

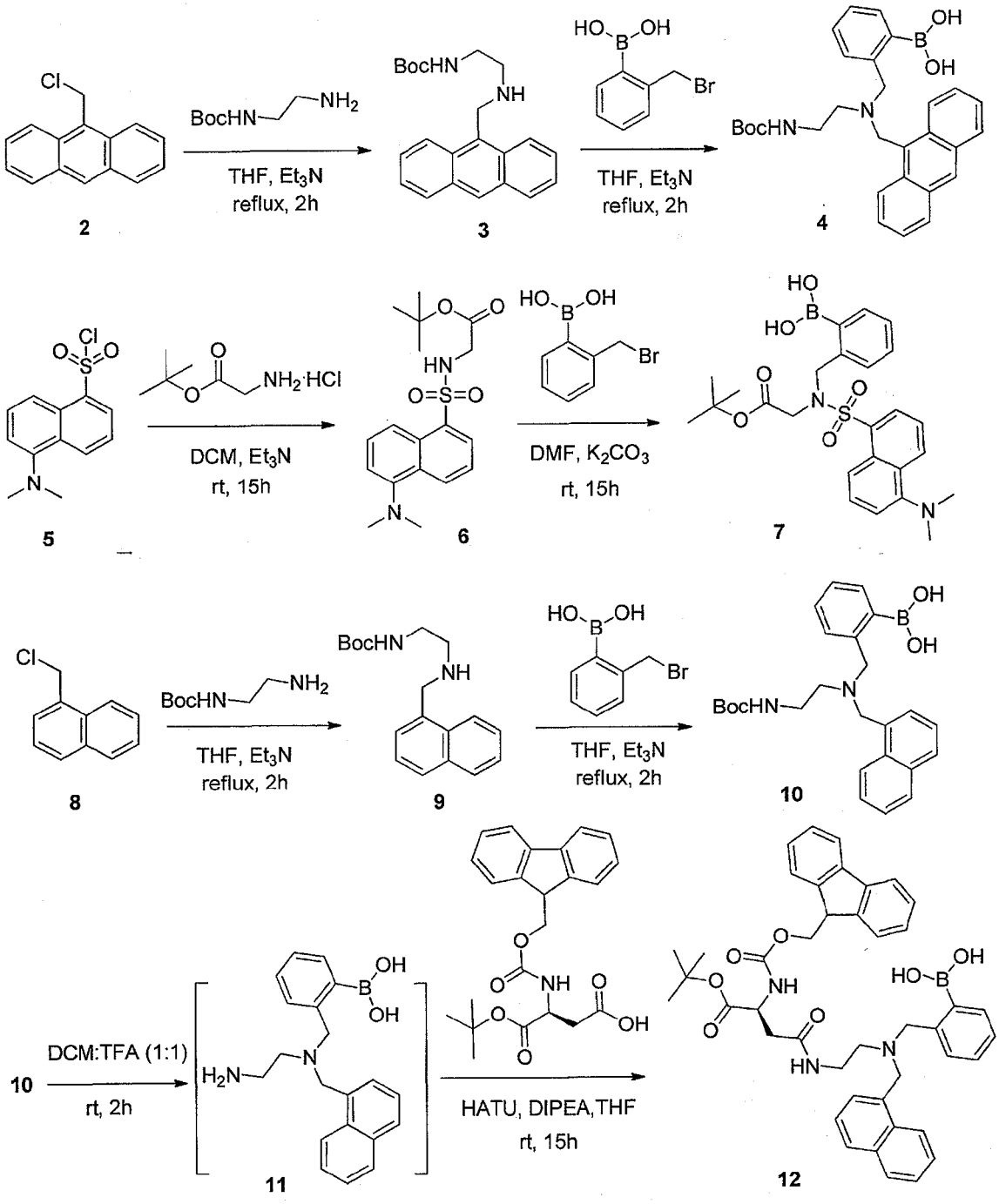

Cl
BocHN
NH2
THF, Et3N
reflux, 2h
2
3
HO
B
OH
Br
4
BocHN
NH
N
THF, Et3N
reflux, 2h
5
DCM, Et3N
rt, 15h
6
DMF, K2CO3
rt, 15h
7
8
9
10
DCM:TFA (1:1)
rt, 2h
11
HATU, DIPEA,THF
rt, 15h
12

FIGURE 1

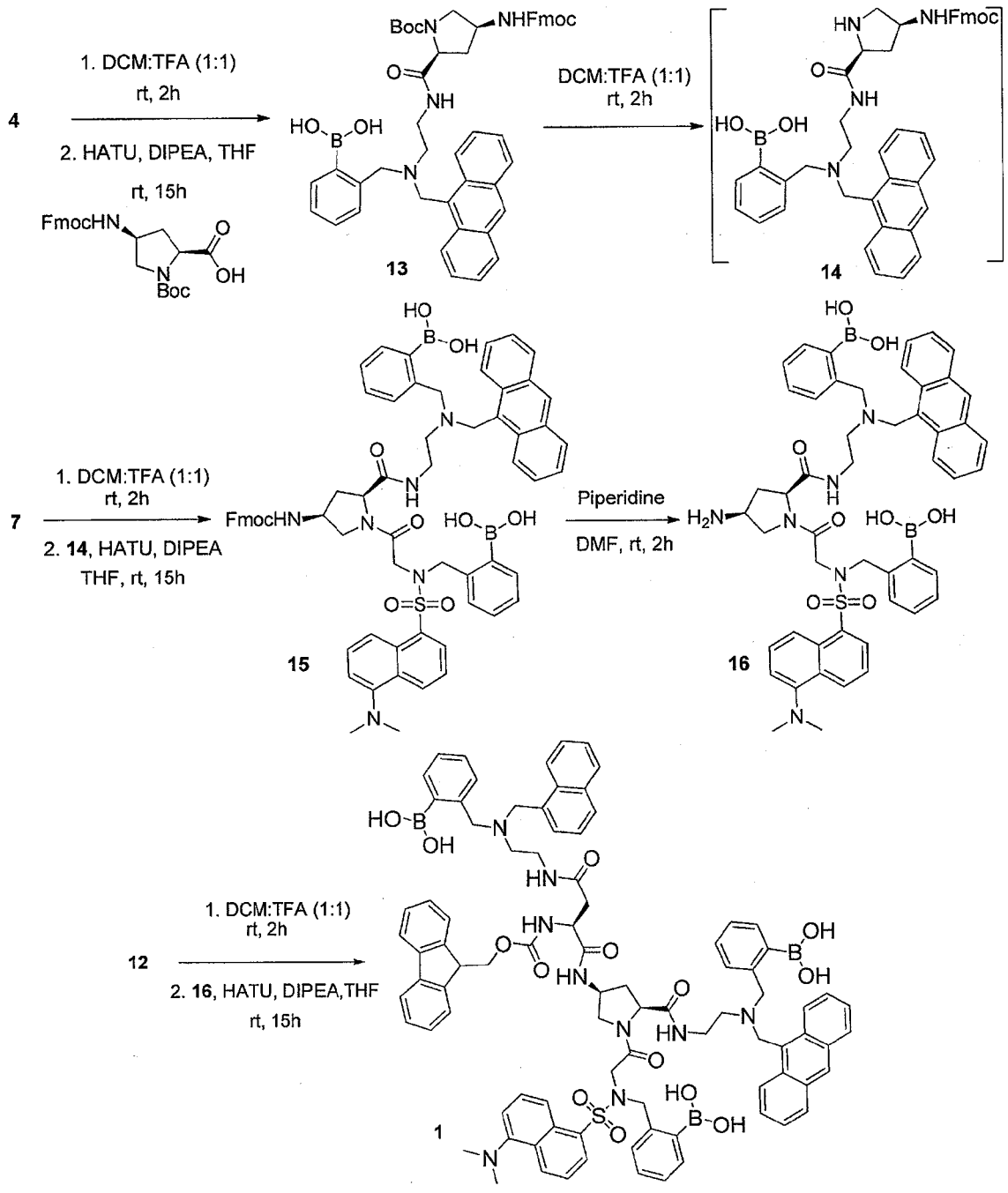


FIGURE 1-CONT.

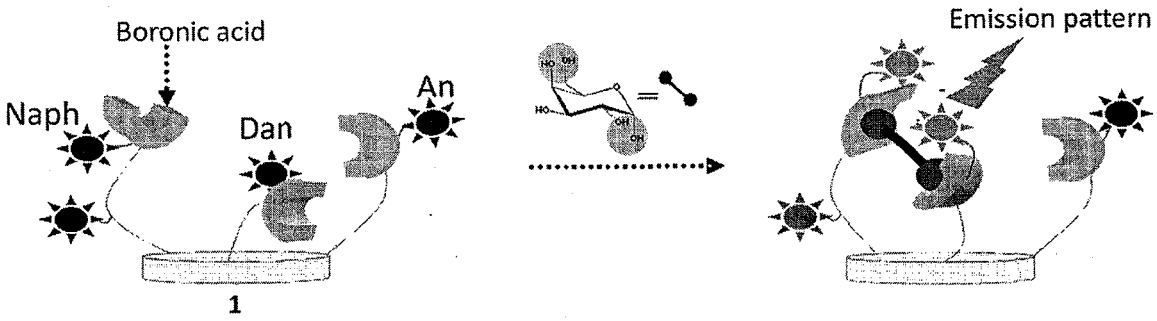
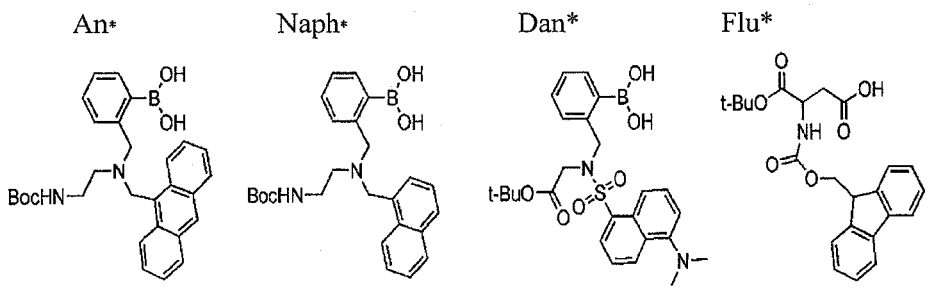


FIGURE 2


An*
Naph*
Dan*
Flu*
OH
B
OH
BocHN
N
t-BuO
O
S
NH
OH

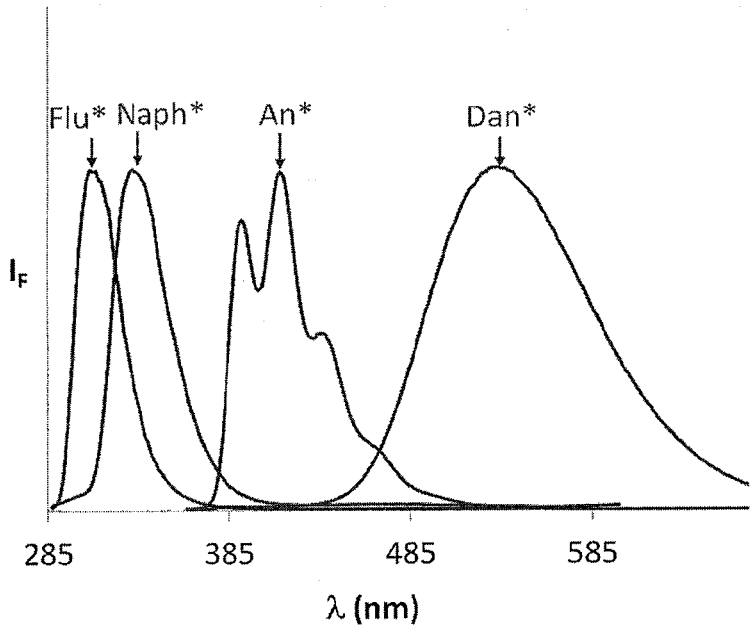

Flu*
Naph*
An*
Dan*
I_F
285
385
485
585
λ (nm)

FIGURE 3A

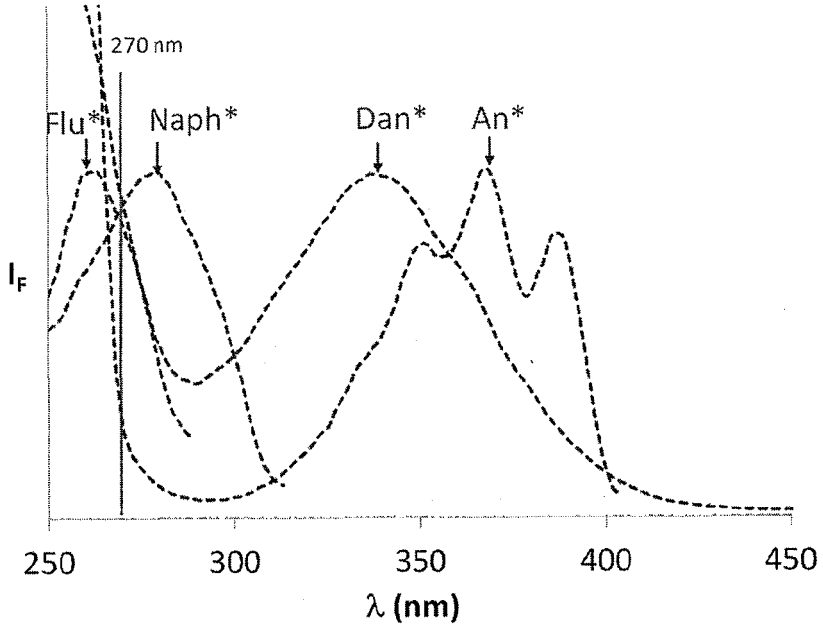


FIGURE 3B

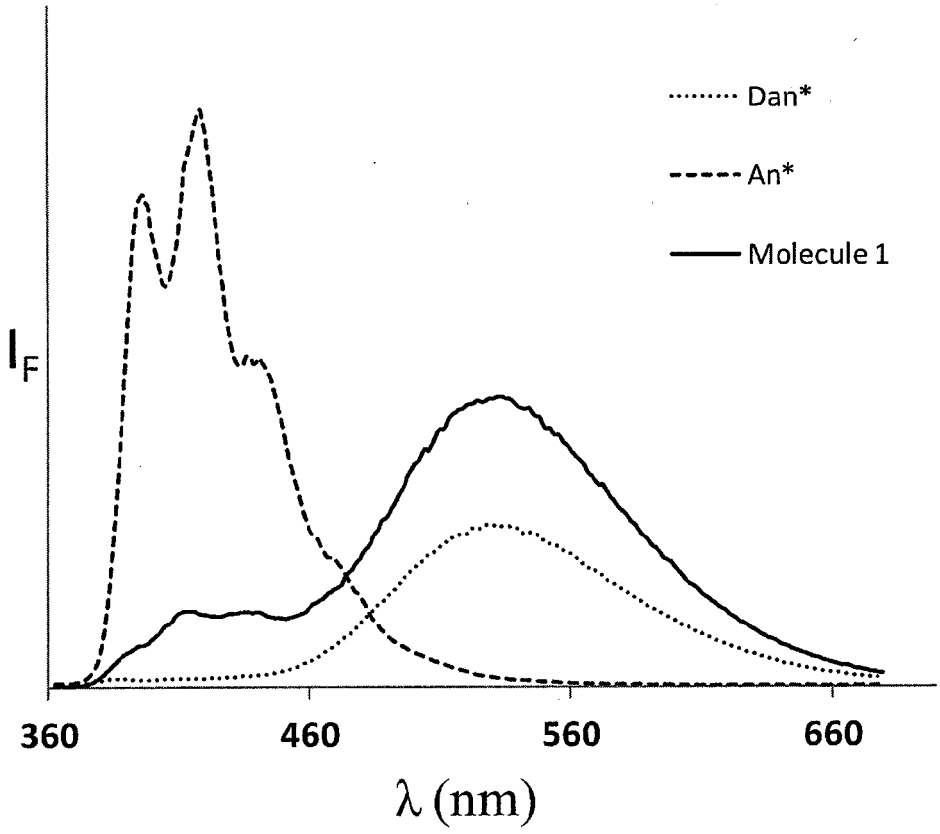


FIGURE 4

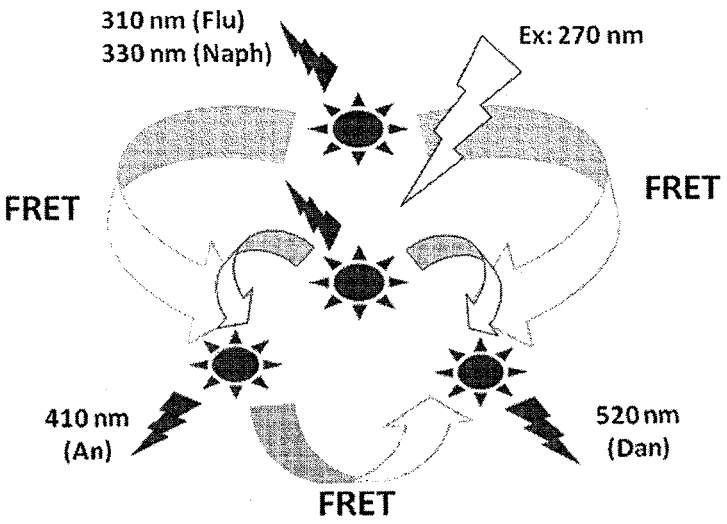


FIGURE 5

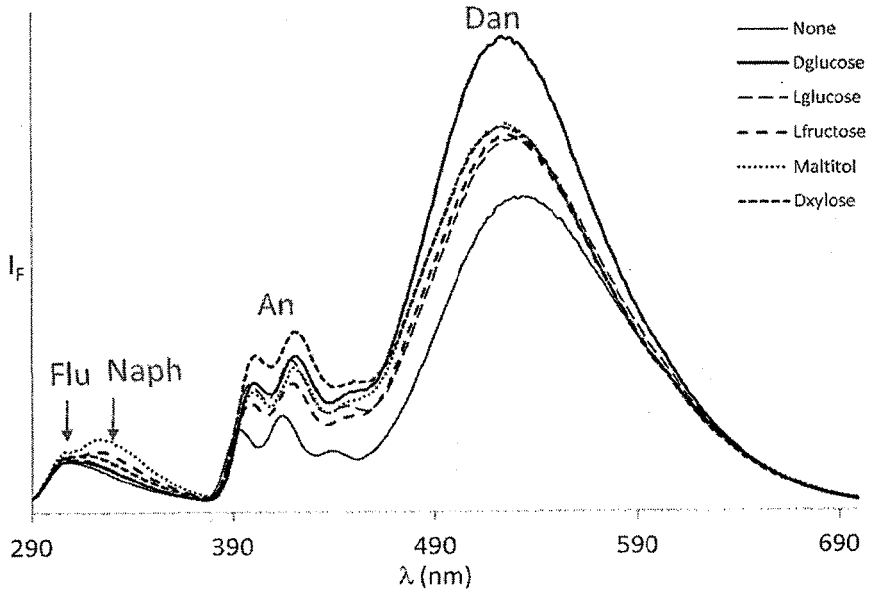


FIGURE 6

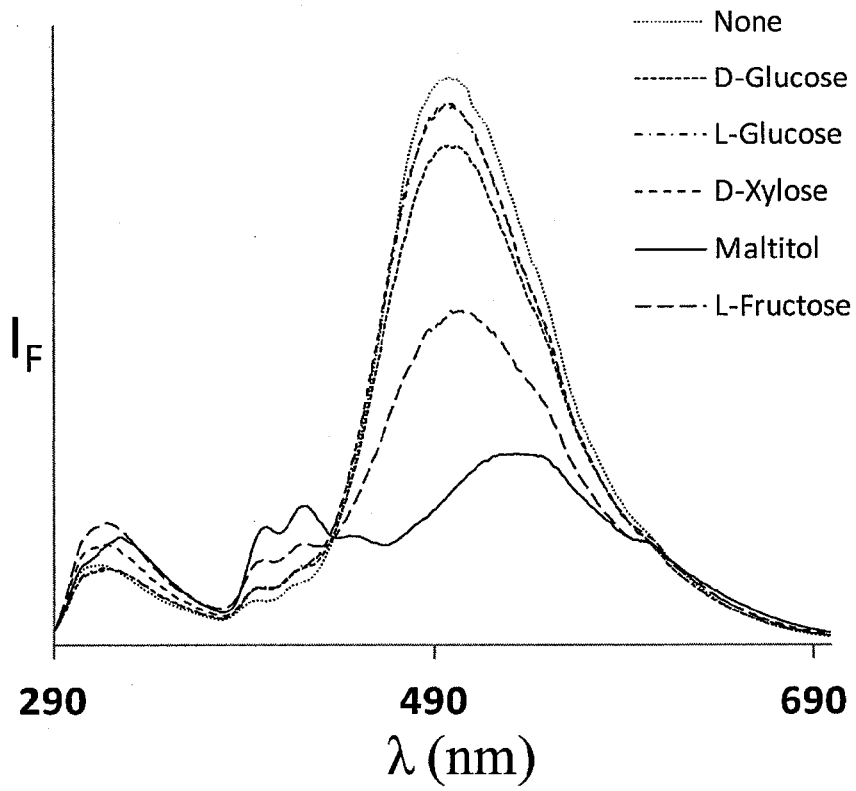


FIGURE 7A

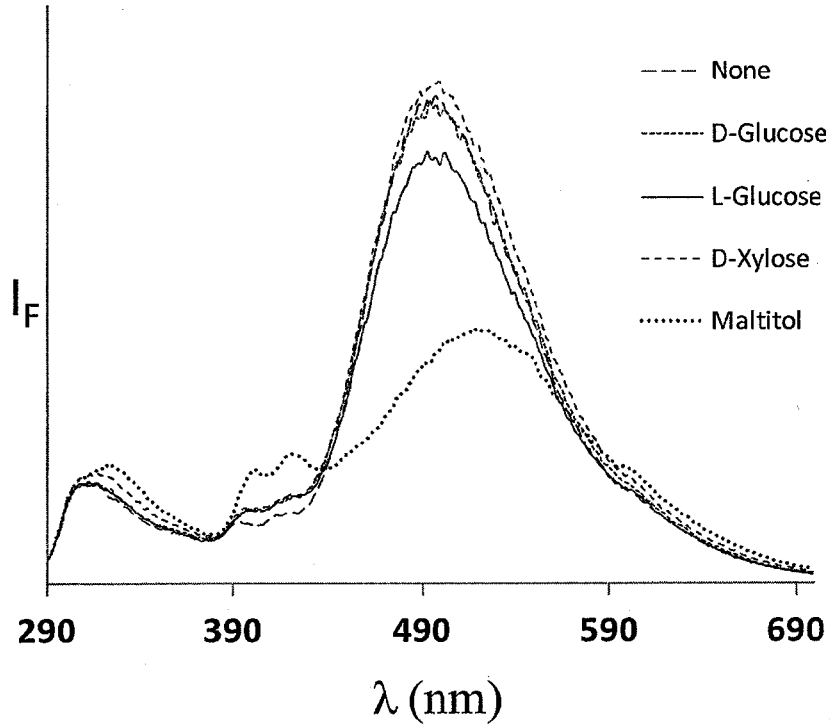


FIGURE 7B

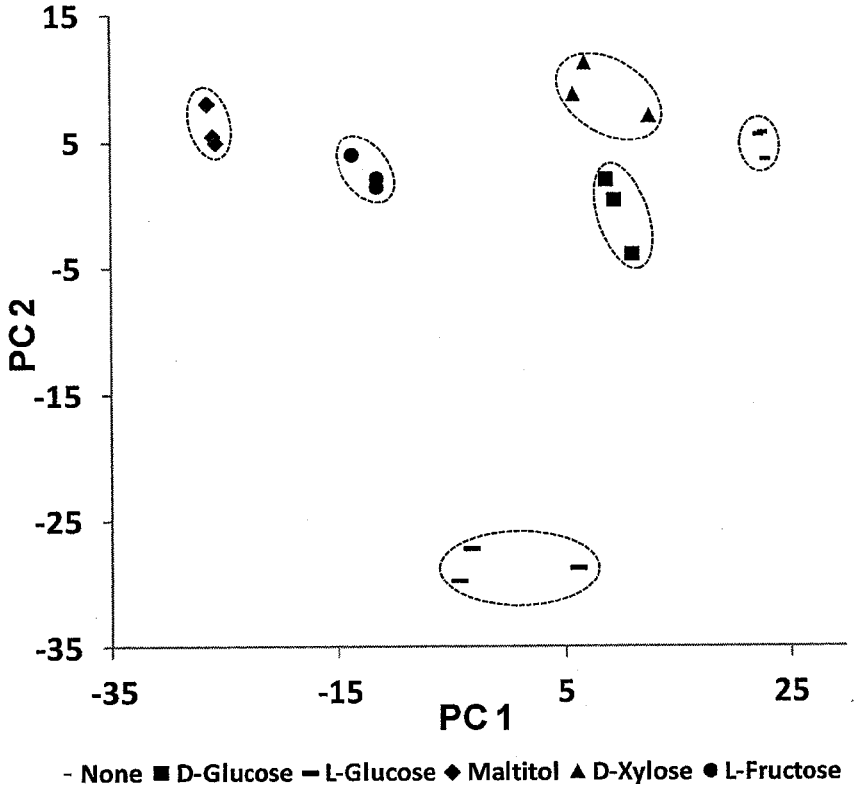

15
5
-5
-15
-25
-35
PC 2
-35
-15
5
25
PC 1
- None ■ D-Glucose ━ L-Glucose ◆ Maltitol ▲ D-Xylose ● L-Fructose

FIGURE 7C

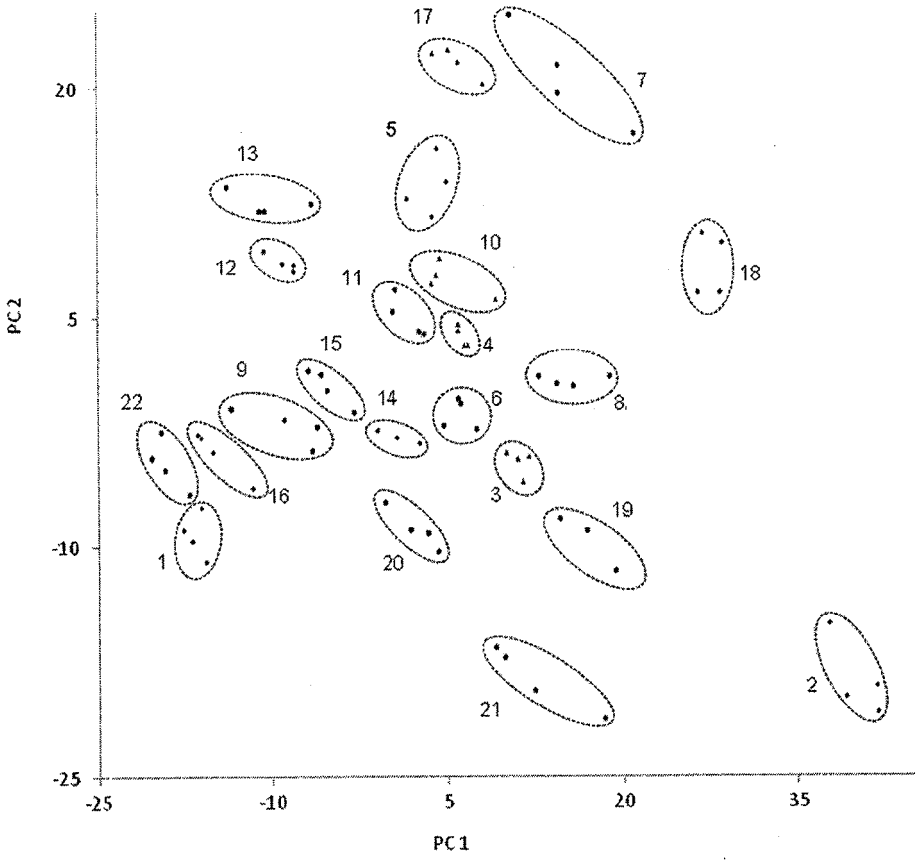

17
7
5
13
10
12
11
18
4
15
9
14
6
8
22
16
3
19
1
20
21
2
20
5
-10
-25
PC 2
-25
-10
5
20
35
PC 1

FIGURE 8

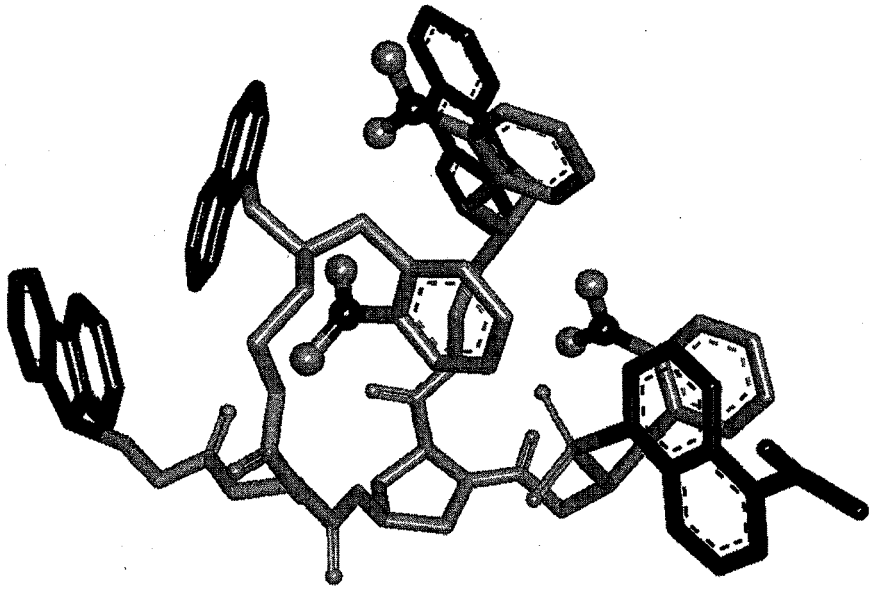


FIGURE 9

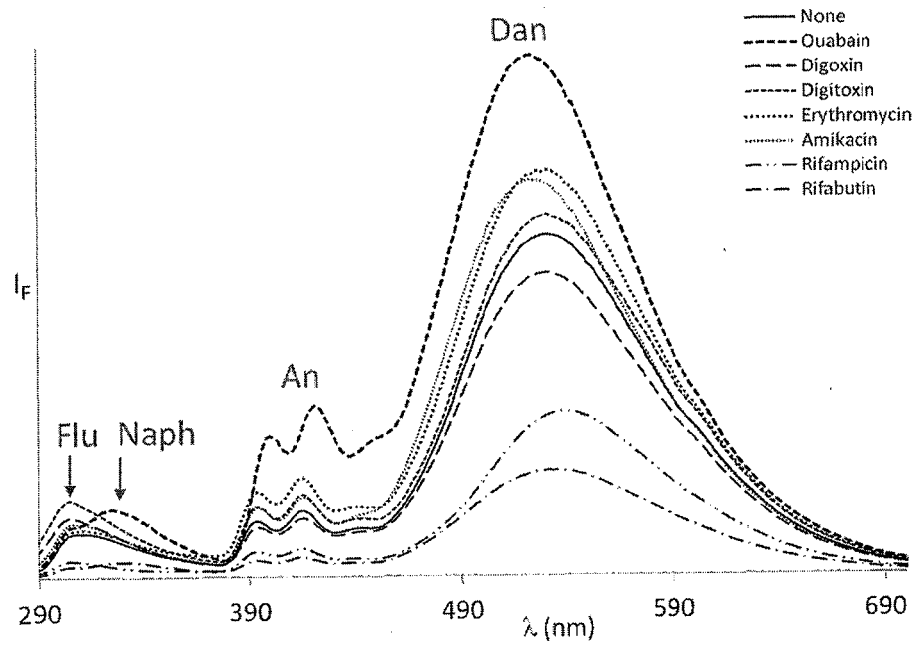
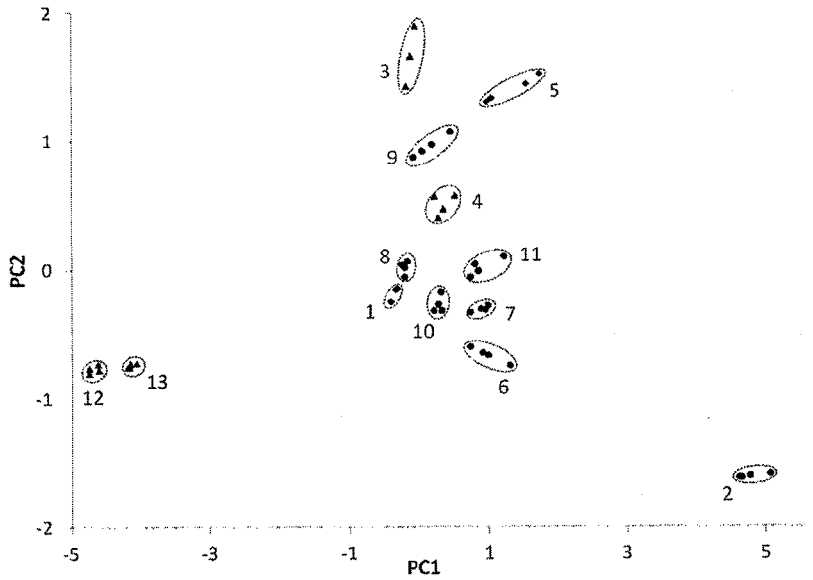
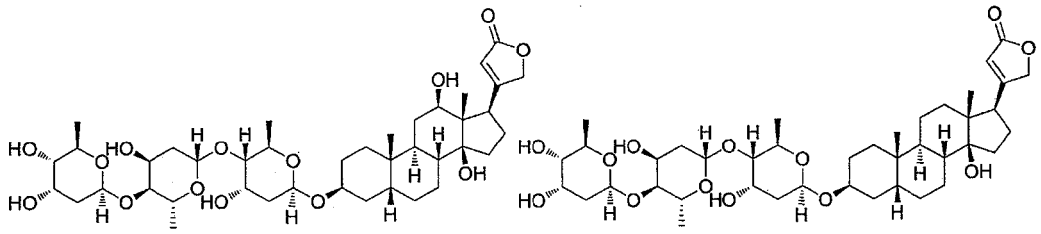


FIGURE 10



1) None; 2) Ouabain; 3) Digoxin; 4) Digoxin (2 fold); 5) Digitoxin; 6) Erythromycin; 7) Roxithromycin; 8) Clarithromycin; 9) Azithromycin; 10) Hygromycin; 11) Amikacin; 12) Rifampicin; 13) Rifabutin.

Structures of Drugs



Digoxin

Digitoxin

FIGURE 11

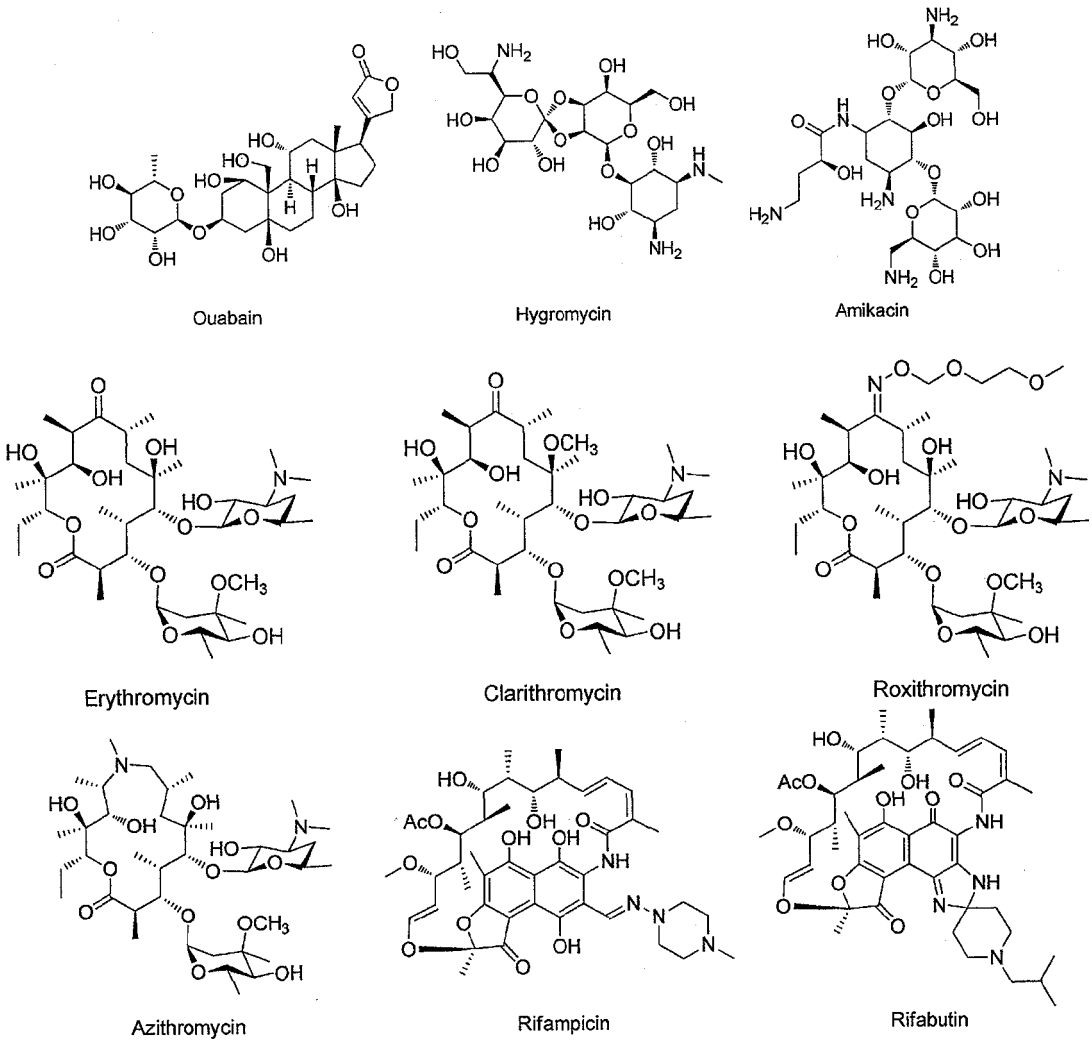


FIGURE 11-CONT

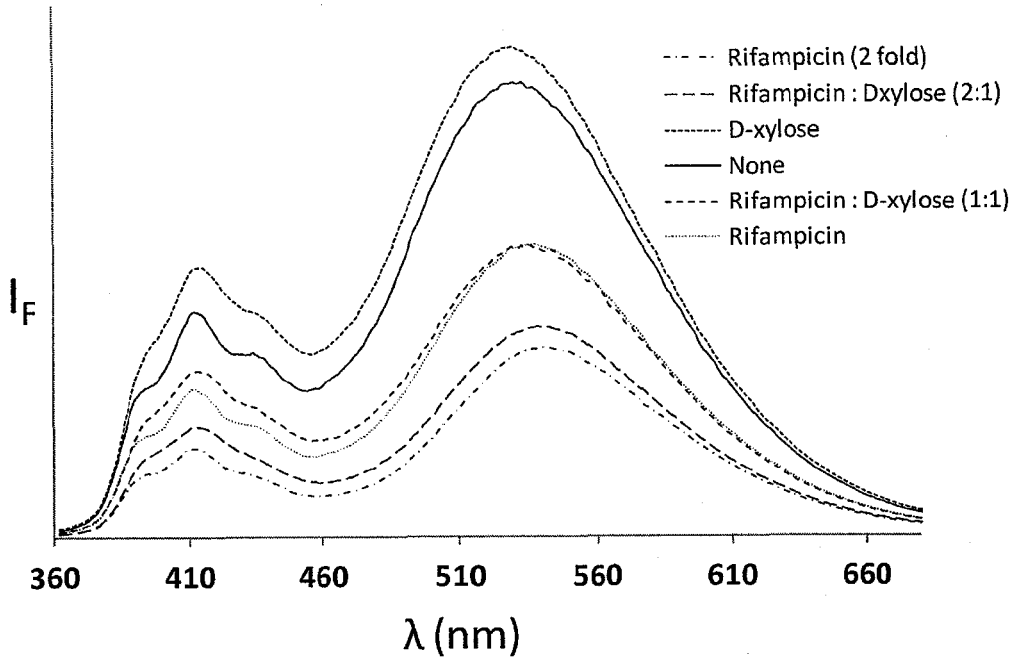


FIGURE 12A

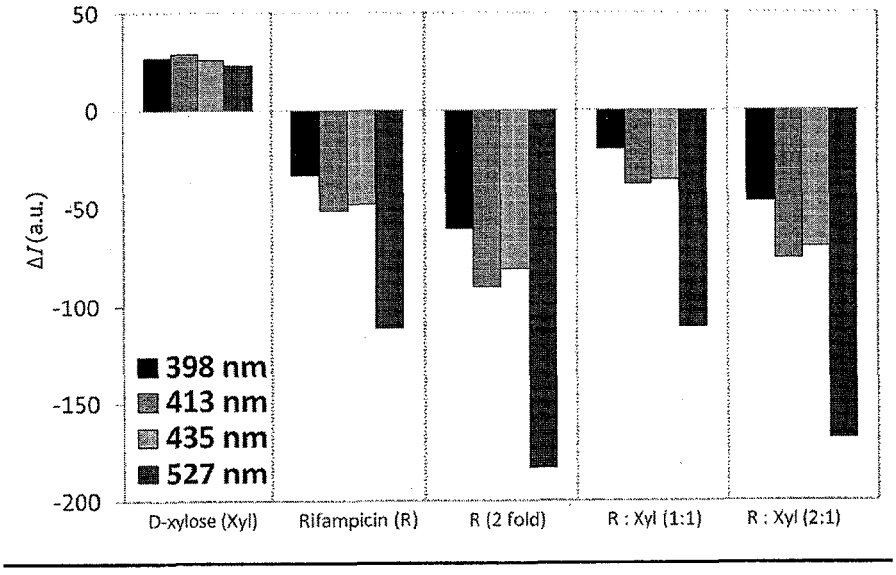
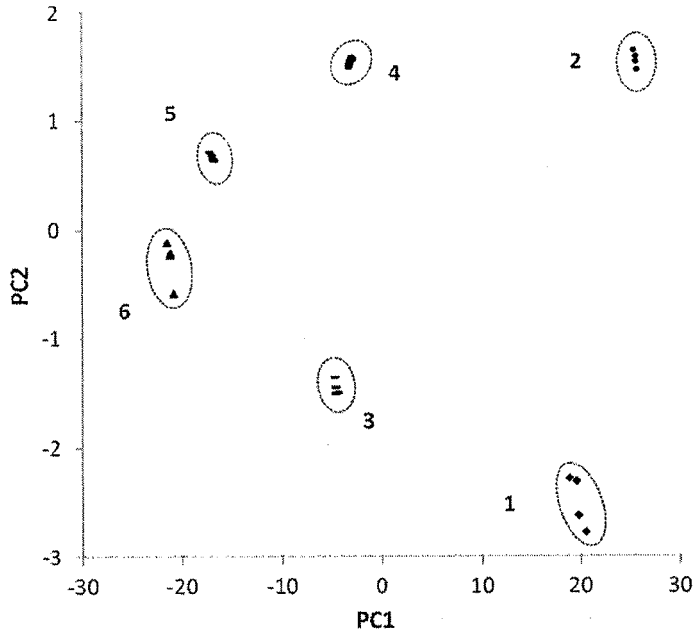


Figure 12B



1) None; 2) D-xylose; 3) Rifampicin; 4)Rifampicin:D-xylose (1:1); 5) Rifampicin:Dxylose (2:1); 6) Rifampicin (2 fold)

FIGURE 12C

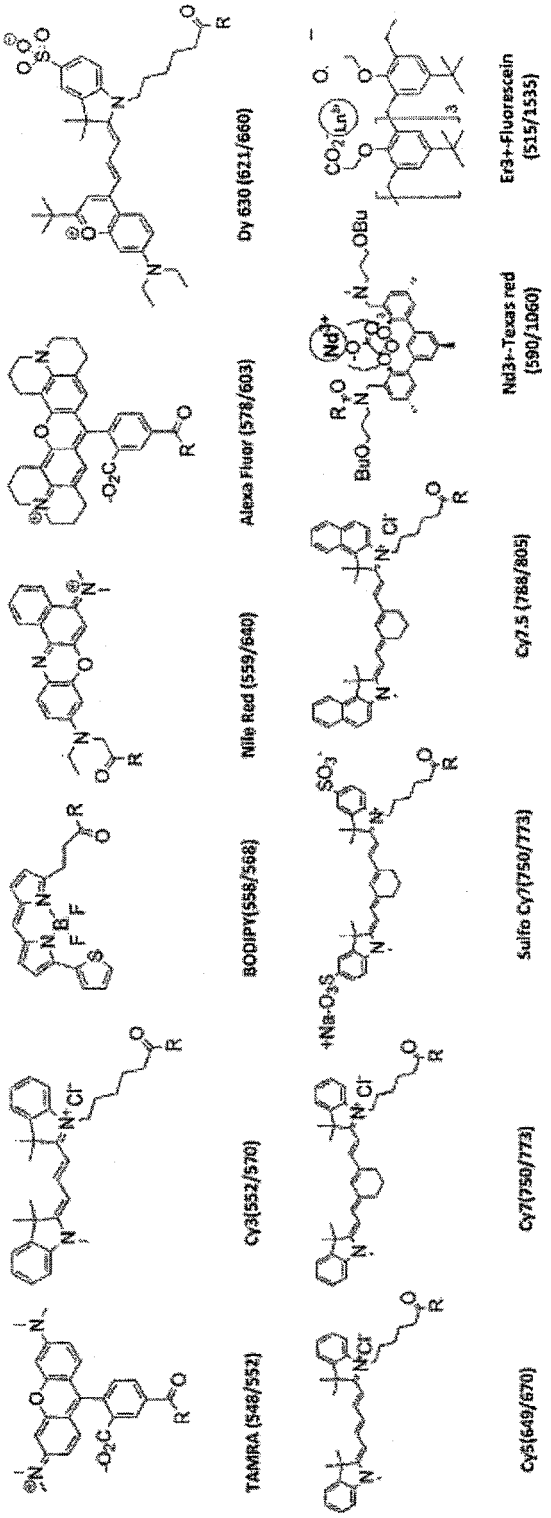

TAMRA (548/552)
Cy3(552/570)
BODIPY(558/568)
Nile Red (559/640)
Alexa Fluor (578/603)
Dy 630 (621/660)
Cy5(649/670)
Cy7(750/773)
Sulfo Cy7(750/773)
Cy7.5 (788/805)
Nd3+-Texas red (590/1060)
Er3+-Fluorescein (515/1535)

Figure 13

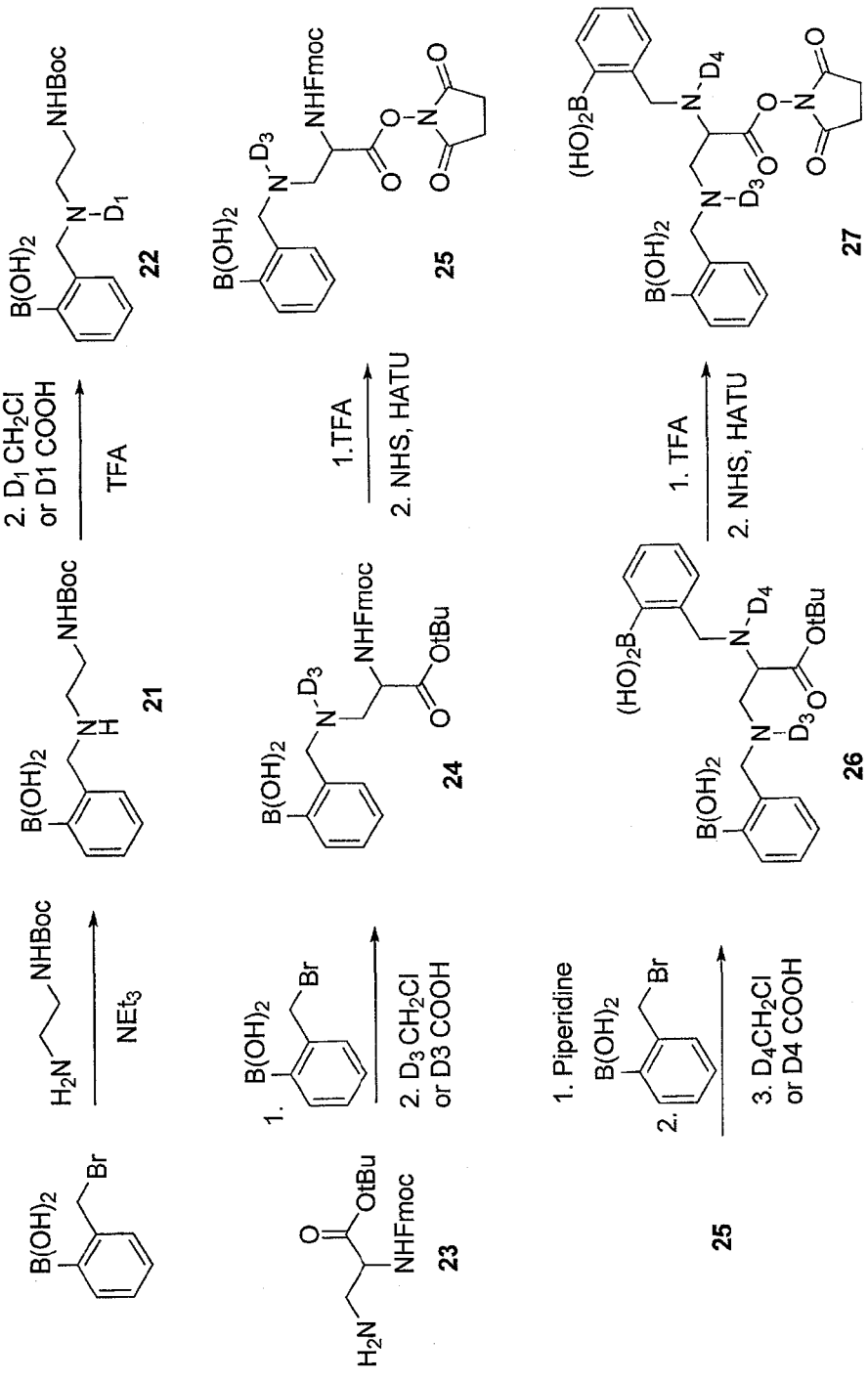

B(OH)2
Br
H2N
NHBoc
NEt3
B(OH)2
NHBoc
N
H
21
2. D1 CH2Cl
or D1 COOH
TFA
B(OH)2
NHBoc
N
D1
22
1.
B(OH)2
Br
2. D3 CH2Cl
or D3 COOH
O
OtBu
NHFmoc
H2N
23
B(OH)2
N
D3
NHFmoc
OtBu
O
24
1.TFA
2. NHS, HATU
B(OH)2
N
D3
NHFmoc
O
O
N
O
O
O
25
1. Piperidine
B(OH)2
Br
2.
3. D4CH2Cl
or D4 COOH
25
(HO)2B
N
D4
OtBu
O
N
D3
B(OH)2
26
1. TFA
2. NHS, HATU
(HO)2B
N
D4
O
O
N
O
O
O
N
D3
B(OH)2
27

Figure 14

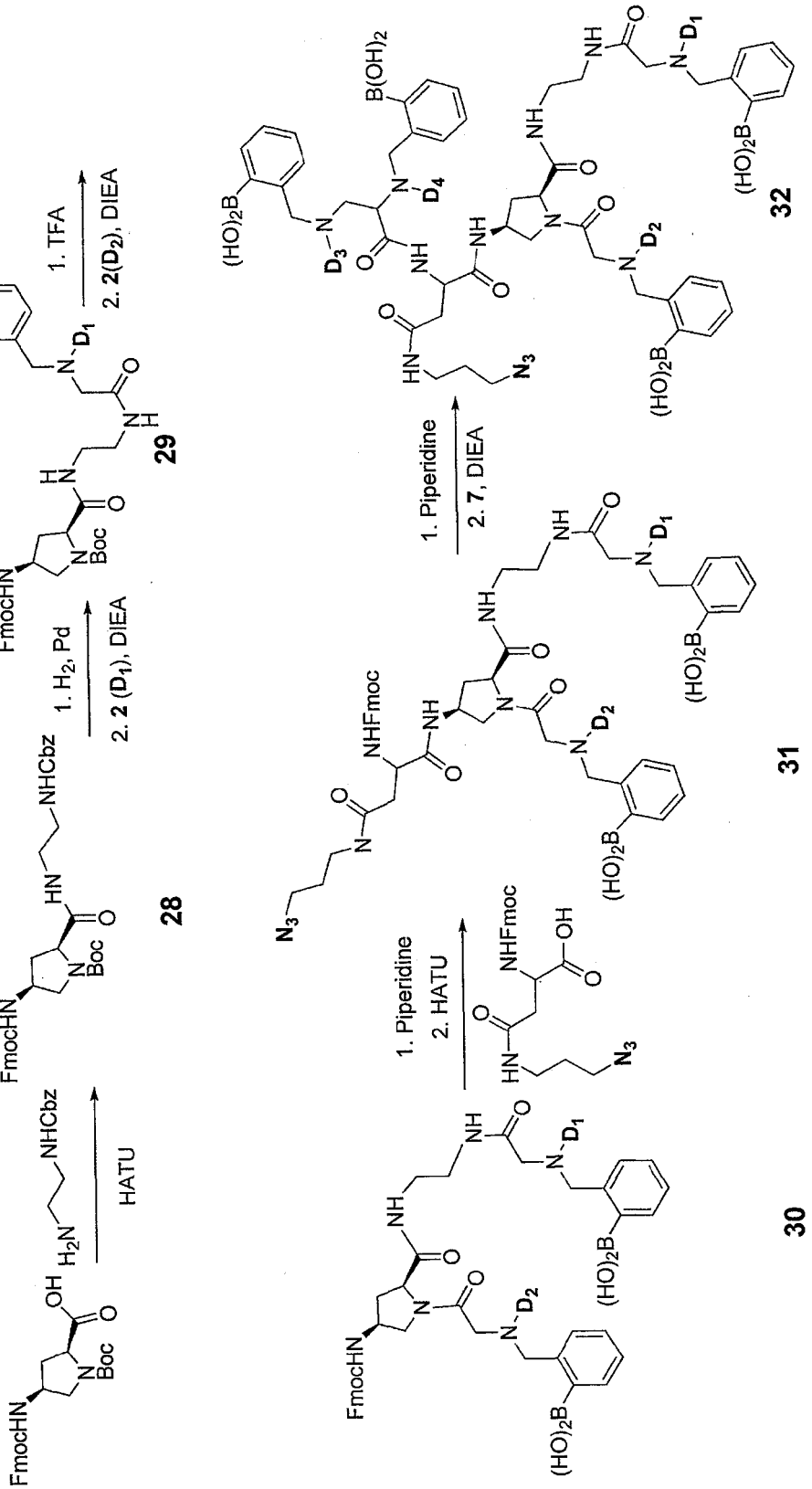

FmocHN
Boc
OH
H_2N
NHCbz
HATU
28
1. H_2, Pd
2. 2 (D_1), DIEA
29
1. TFA
2. 2(D_2), DIEA
1. Piperidine
2. HATU
30
1. Piperidine
2. 7, DIEA
31
32
$(HO)_2B$
$B(OH)_2$
N_3
NHFmoc
D_1
D_2
D_3
D_4

Figure 15

Fig. 16 (a)

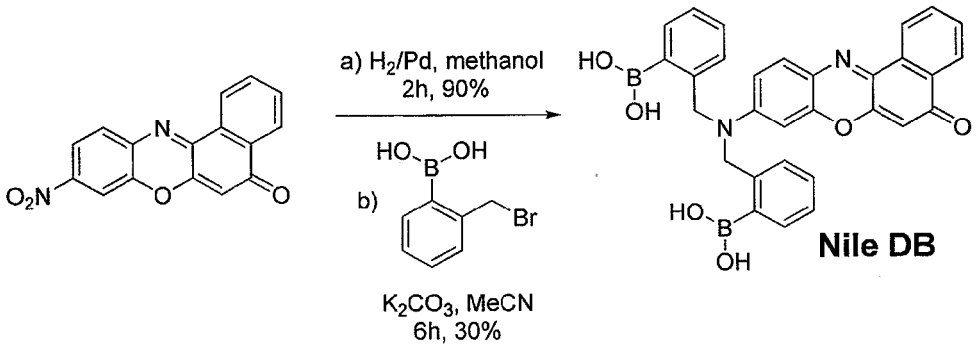
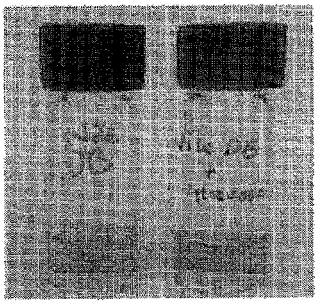
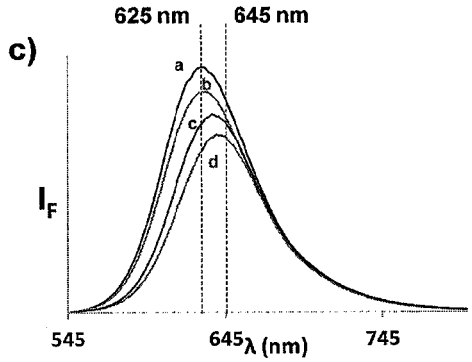


Fig. 16 (b)





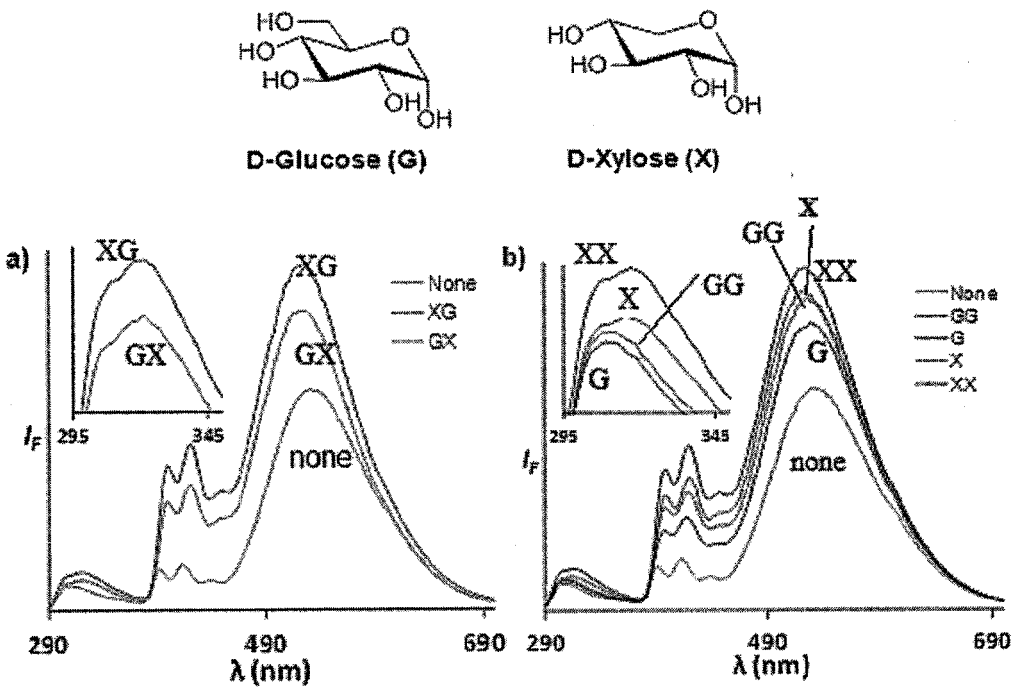


Fig. 17(a)

Fig. 17(b)

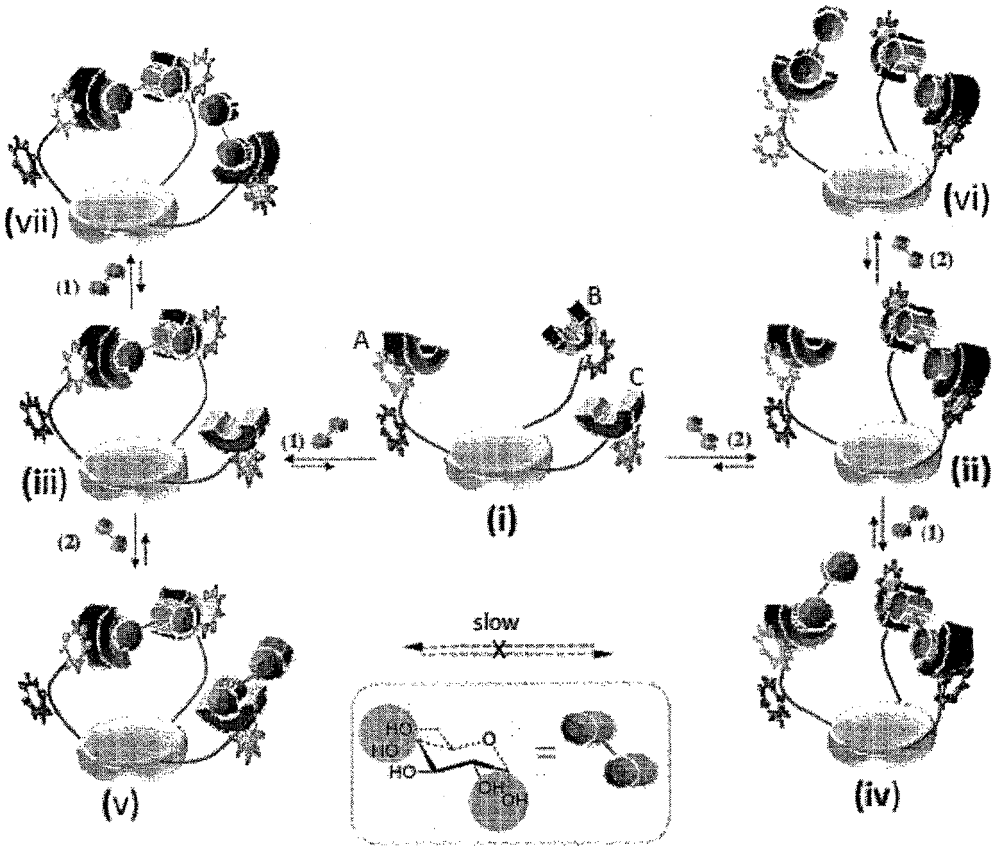


Figure 18

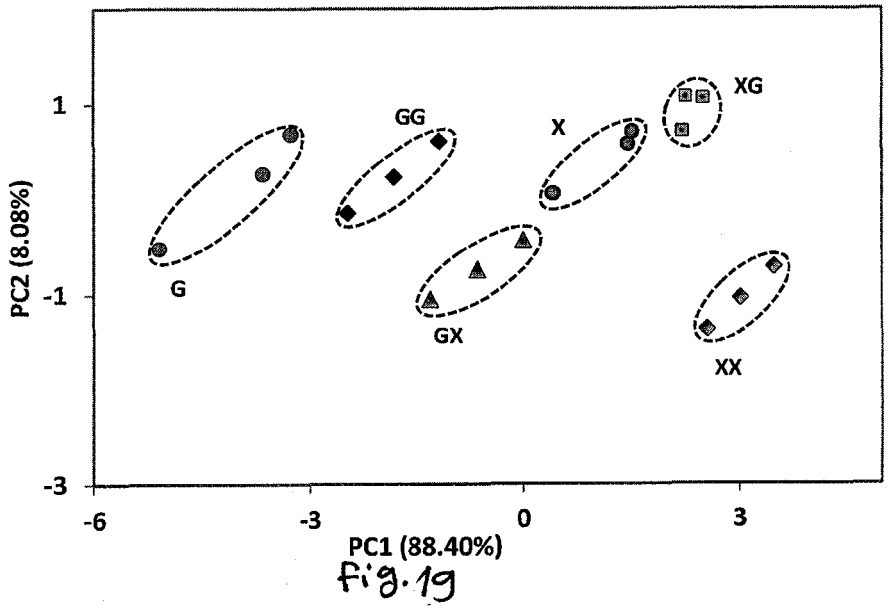


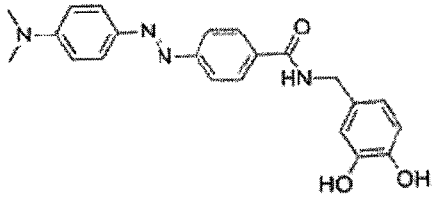
Fig. 19

Table 2: All Possible Combination Codes of a ThreeState Molecular encoding System

1 key	2-keys (1, 2)	2-keys (1, 3)	2-keys (2, 3)	3-keys (1, 2, 3)
a. 111	d. 112	e. 113	f. 223	j. 123
b. 222	121	131	232	132
c. 333	211	311	322	213
	g. 122	h. 133	i. 233	231
	212	313	323	312
	221	331	332	321

Fig. 20

Fig. 21 (a)



Dabcyl Catechol (DC)

Fig. 21 (b)

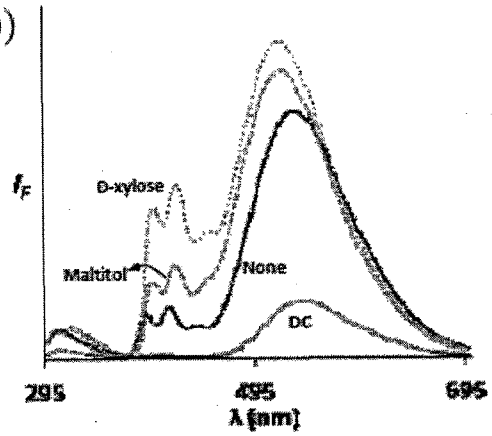


Fig. 21(c)

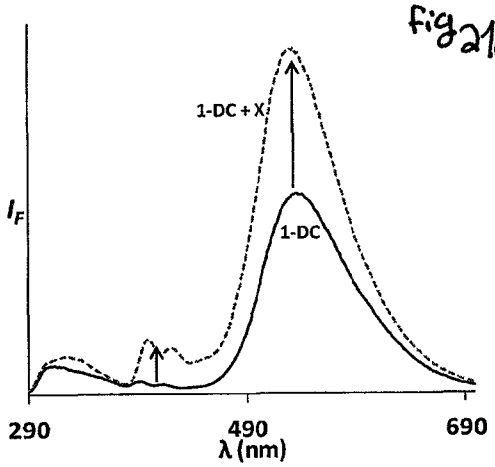


Fig 21(d)

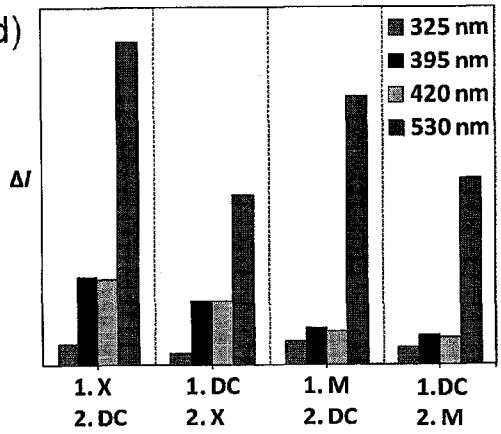


fig. 22(a)

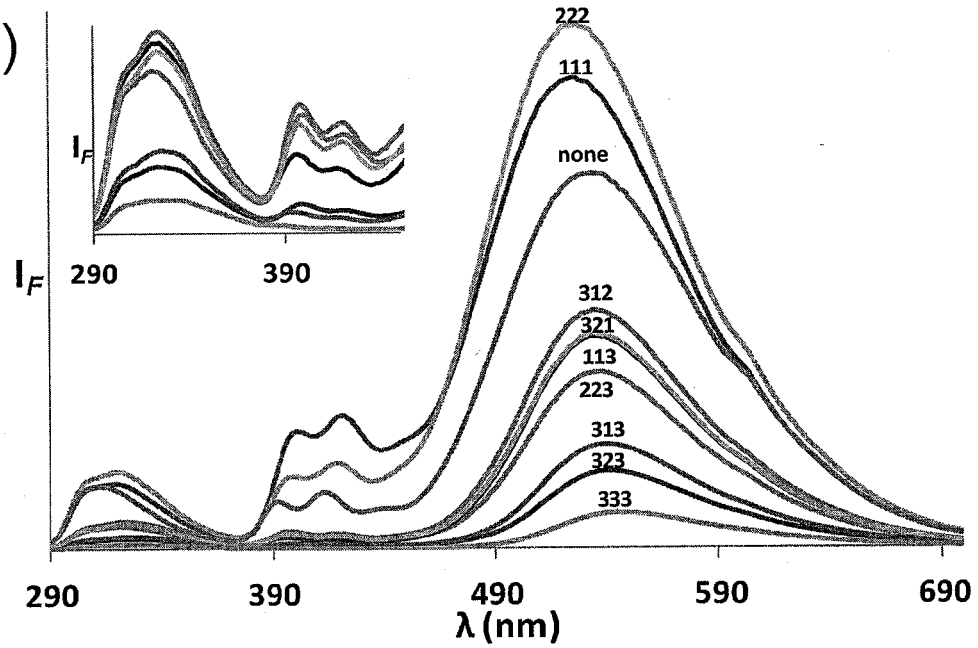
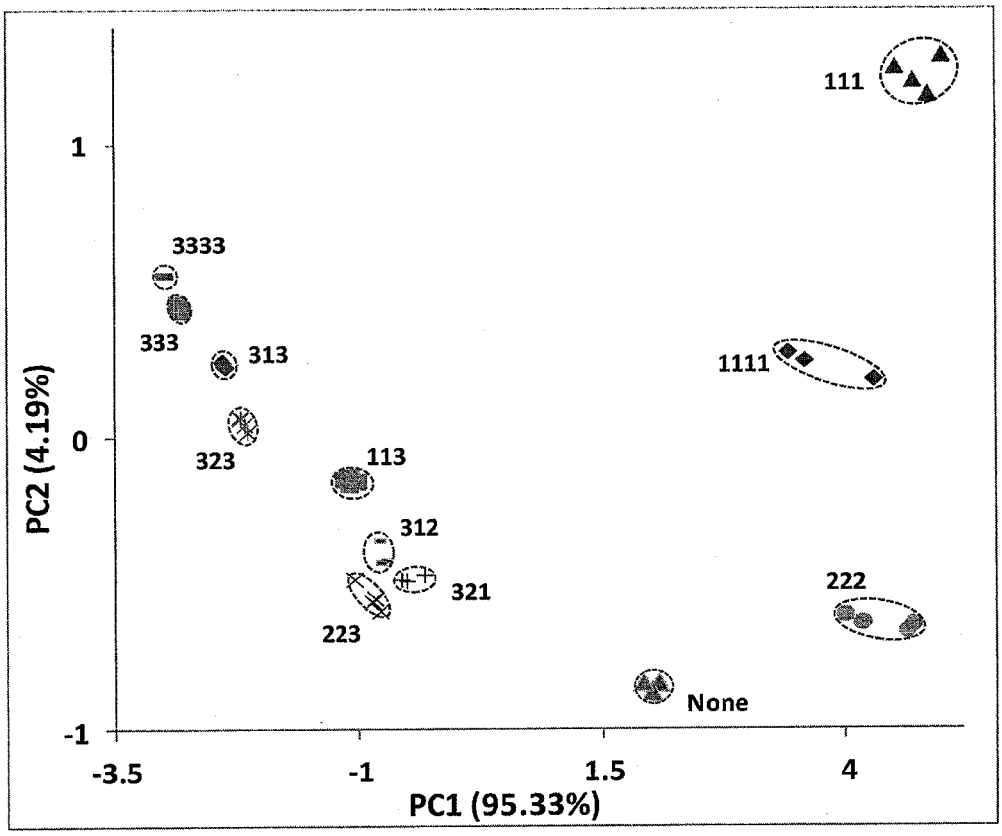


fig. 22(b)



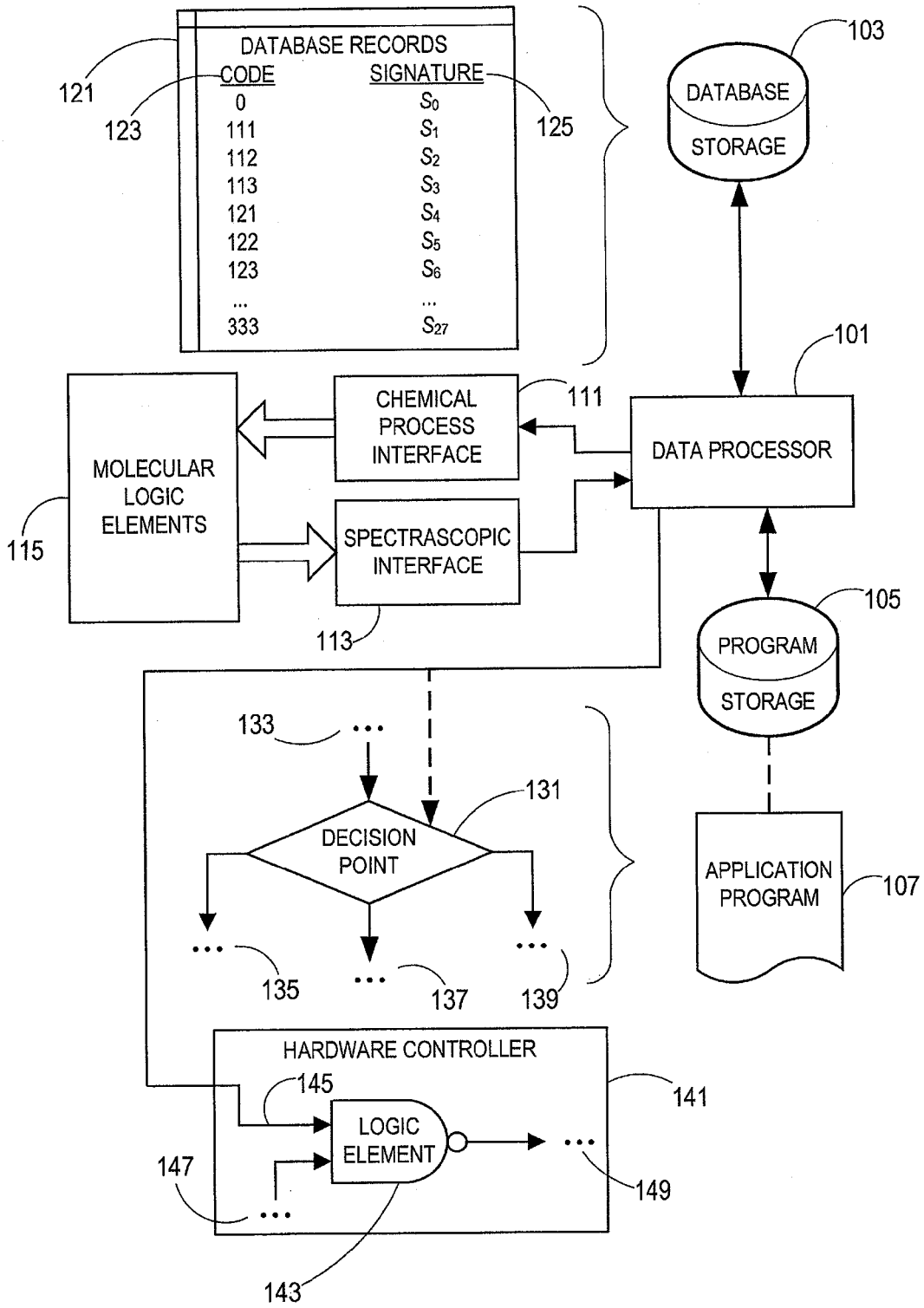

DATABASE RECORDS
CODE
SIGNATURE
0
111
112
113
121
122
123
...
333
S_0
S_1
S_2
S_3
S_4
S_5
S_6
...
S_{27}
121
123
125
103
DATABASE
STORAGE
101
DATA PROCESSOR
111
CHEMICAL PROCESS INTERFACE
MOLECULAR LOGIC ELEMENTS
115
SPECTRASCOPIC INTERFACE
113
105
PROGRAM
STORAGE
133
131
DECISION POINT
135
137
139
APPLICATION PROGRAM
107
HARDWARE CONTROLLER
145
141
LOGIC ELEMENT
147
149
143

FIGURE 23

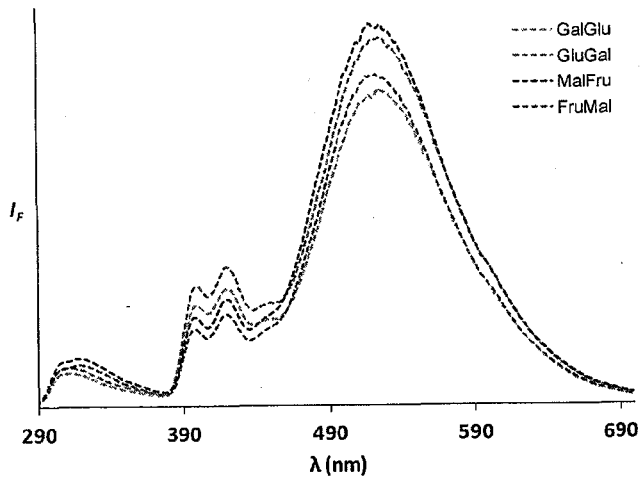


Figure 24

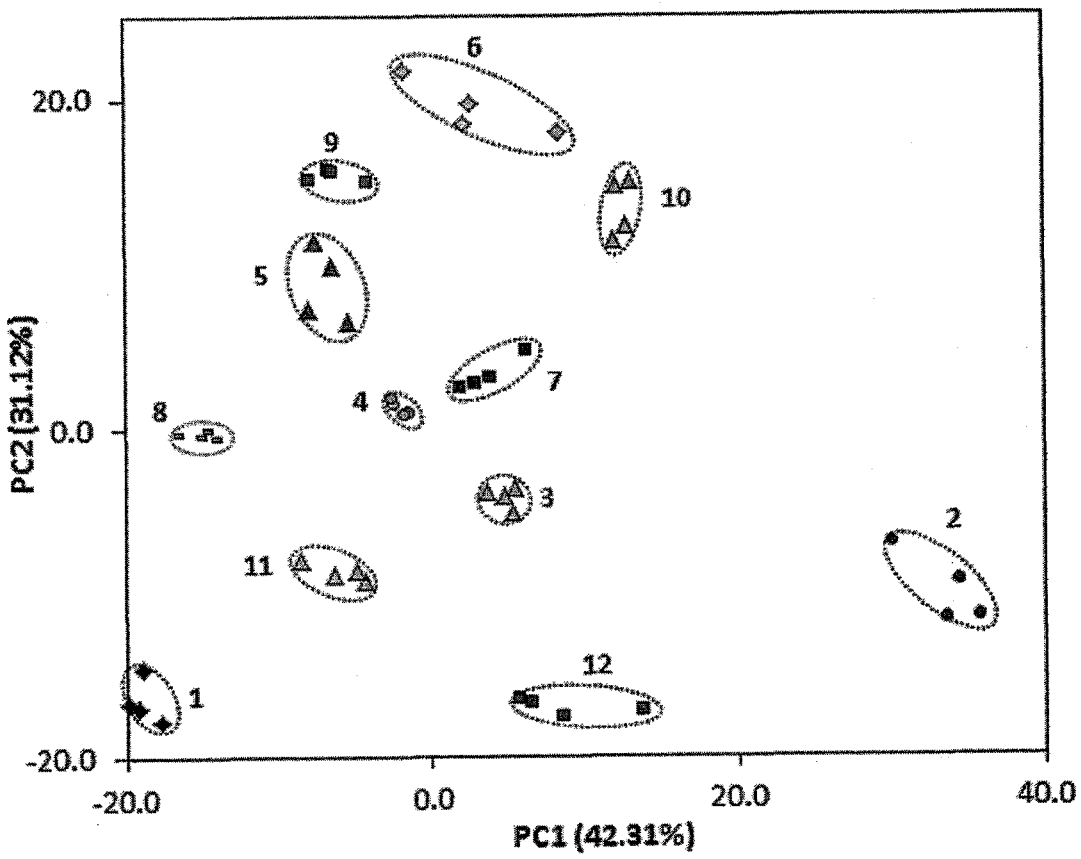


Figure 25

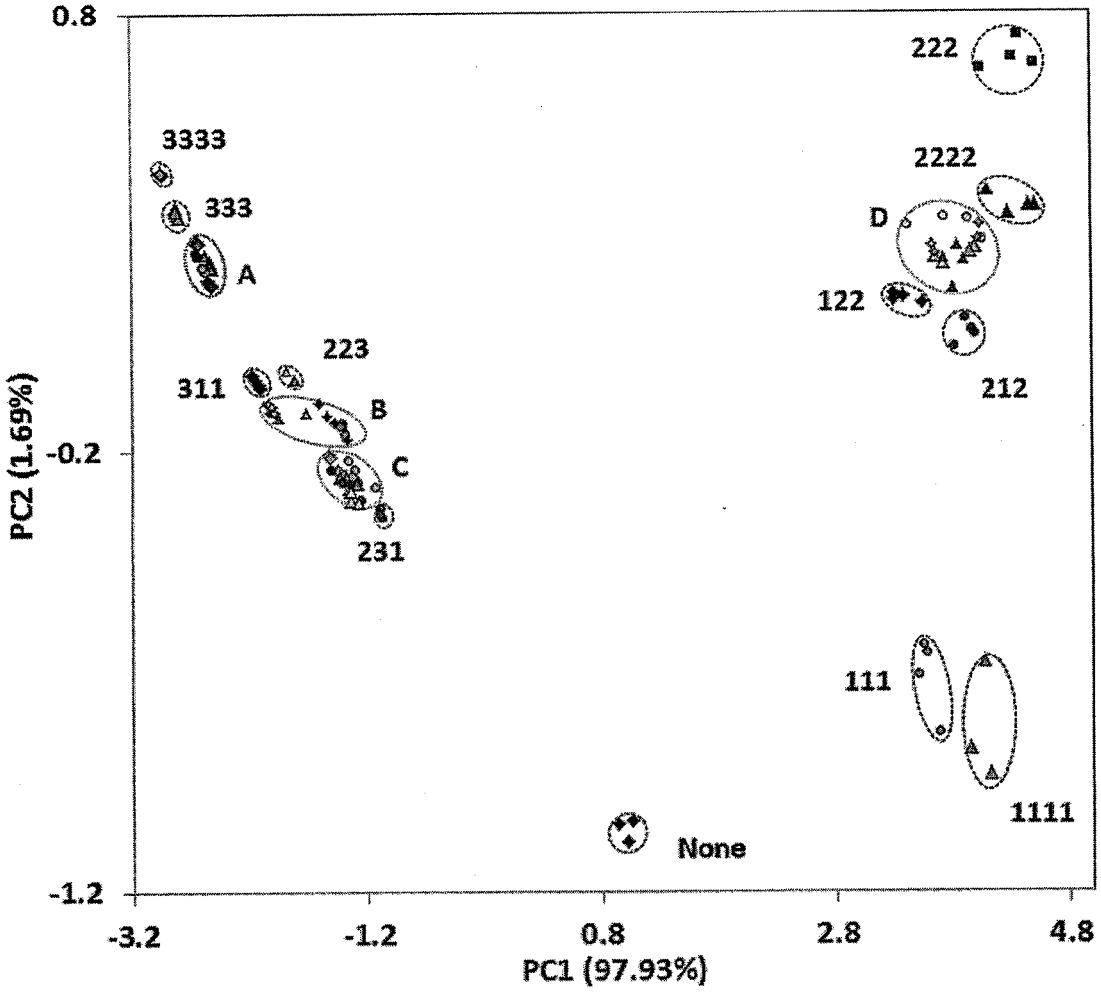

0.8
-0.2
-1.2
PC2 (1.69%)
-3.2
-1.2
0.8
2.8
4.8
PC1 (97.93%)
222
3333
2222
333
D
A
122
223
212
311
B
C
231
111
1111
None

Figure 26

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

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- **LARKIN et al.** *New J. Chem.,* 2010, vol. 34, 2922-2931 **[0006]**
- **MUSTO et al.** *Curr Opin Chem Biol.,* 2010, vol. 14 (6), 758-66 **[0009]**
- **SCHILLER et al.** *Anal Chim Acta.,* 2008, vol. 627 (2), 203-11 **[0009]**
- **SCHILLER et al.** *Angew Chem Int Ed Engl.,* 2007, vol. 46 (34), 6457-9 **[0009]**
- **CHEN, X. Y. ; KOCH, S. ; UHLENBROCK, K. ; WEISE, K. ; DAS, D. ; GREMER, L. ; BRUNSVELD, L. ; WITTINGHOFER, A. ; WINTER, R. ; TRIOLA, G.** *Angew. Chem. Int. Ed.,* 2010, vol. 49, 6090-6095 **[0126]**

专利名称(译)	多传感器阵列化合物及其使用方法		
公开(公告)号	EP2872486A1	公开(公告)日	2015-05-20
申请号	EP2013750947	申请日	2013-07-16
[标]申请(专利权)人(译)	耶达研究及发展有限公司		
申请(专利权)人(译)	烟台开发区研究与发展有限公司.		
当前申请(专利权)人(译)	烟台开发区研究与发展有限公司.		
[标]发明人	MARGULIES DAVID ROUT , BHIMSEN		
发明人	MARGULIES, DAVID ROUT , BHIMSEN		
IPC分类号	C07D211/60 A61B5/00 G01N22/00 G01J3/44		
CPC分类号	C07F5/025 C07D211/60 C09B62/44 G01N33/582 G01N2400/00 G01N2458/30 G01N2800/042 G01N2800/065 G01N2800/067 G01N2800/285		
优先权	61/671825 2012-07-16 US		
其他公开文献	EP2872486B1		
外部链接	Espacenet		

摘要(译)

本发明涉及一种多传感器阵列化合物，其包括至少三种发色团，至少一种受体和锚。使本发明化合物与分析物（如碳水化合物）接触形成具有独特光学特征的复合物。独特的光学特征允许区分碳水化合物，诊断与碳水化合物相关的疾病，以及在编码系统中编码信息。