



PATENTS ACT 1977

APPLICANT Pierce Biotechnology, Inc. and Dyomics GmbH

ISSUE Whether patent application GB 1214580.1 complies
 with section 1(1)(b)

HEARING OFFICER C L Davies

DECISION

Introduction

- 1 Patent Application number GB 1214580.1 (“the application”) was filed by Pierce Biotechnology, Inc. and Dyomics GmbH on 15 August 2012, claiming priority from three earlier United States patent applications, 61/524,167 (filing date 16 August 2011), 61/604,232 (filing date 28 February 2012) and 61/607,737 (filing date 7 March 2012). The application was published as GB 2493843 A on 20 February 2013.
- 2 The examiner initially raised an objection based on a lack of unity of invention. Following amendment of the claims this objection was overcome by deleting the claims to the first invention and proceeding on the basis of old claim 3, now claim 1.
- 3 The examiner has found that the currently maintained claims on file lack an inventive step over WO 02/32466 A1, US 2004/241095 A1 and US 2008/233050 A1 on the basis that they relate to an arbitrary selection from the prior art as the technical effect relied upon by the Applicants is not rendered plausible by the patent specification and therefore cannot be taken into account when assessing inventive step.
- 4 The application has been through numerous rounds of substantive examination where the Applicants (via their attorneys Scott and York) have been unable to persuade the examiner that the invention involves an inventive step. As the examiner and Applicants have not been able to reach agreement on these matters, the Applicants have been offered a further opportunity to be heard, but has instead requested that a decision be issued based on the papers on file.
- 5 I confirm that, in reaching my decision, I have considered all the correspondence on file.

The invention

- 6 The application is entitled ‘Benzocyanine compounds’ and relates to compounds that are useful as labels in optical determination and detection methods. Typical application methods are based on the reaction of the compounds with biomolecules. Thus, among other embodiments, the compounds are used to measure enzyme kinetics, receptor-ligand interactions and nucleic acid hybridization kinetics *in vitro* and/or *in vivo*. The compounds are used for the pharmacological characterization of receptors and/or drugs.

The claims

- 7 This decision is based upon the most recent set of claims filed on 17 April 2013. Claim 1 relates to compounds selected from a group of ‘Markush’ structures. Claim 4 is independent and is directed to two specified compounds that fall within the scope of claim 1. Claim 5 relates to a method of labelling at least one biomolecule comprising providing a composition comprising a compound of claims 1 to 4. Claim 7 relates to a method of detecting at least one biomolecule comprising providing a composition comprising a compound of claims 1 to 4. Claim 11 relates to a kit comprising a compound of claims 1 to 4. Claim 12 to 15 are omnibus claims. Claim 1 is set out in Appendix 1.

The Law

- 8 The law regarding inventive step is set out in sections 1, and 3 of the Patents Act 1977 (“the Act”), the relevant parts of which are set out below:

1.-(1) A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say –

(a) ...

(b) it involves an inventive step;

(c) ...

and references in this Act to a patentable invention shall be construed accordingly.

.....

3. An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of section 2(2) above (and disregarding section 2(3) above).

.....

- 9 The standard test for determining inventive step is the structured approach found in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59 (*‘Windsurfing’*), as reformulated by Jacob LJ in *Pozzoli SPA v BDMO SA* [2007] EWCA Civ 588 (*‘Pozzoli’*; see paragraph 23 of the Court of Appeal’s judgment). The four steps are:

(1)(a) *Identify the notional “person skilled in the art”*

(1)(b) *Identify the relevant common general knowledge of that person;*

(2) *Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;*

(3) *Identify what, if any, differences exist between the matter cited as forming part of the “state of the art” and the inventive concept of the claim or the claim as construed;*

(4) *Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?*

Arguments and Analysis

10 The examiner has maintained that the claims on file lack an inventive step over WO 02/32466 A1, US 2004/241095 A1 and US 2008/233050 A1.

11 I shall now follow the four steps of the *Windsurfing* test, as modified by *Pozzoli*. In doing so, I will consider steps (2) and (3) together.

Step 1(a): Identify the notional “person skilled in the art”

12 Neither the Applicants nor the examiner have discussed who the person skilled in the art is, but it would seem that they would have a knowledge of dye chemistry and the use of labels in biological imaging and analysis.

Step 1(b): Identify the relevant common general knowledge of that person

13 There has been no discussion of the common general knowledge. However, the Applicants have relied upon WO 2009/078970 in their arguments. The examiner has asserted that this document does not form part of the common general knowledge and this does not seem to have been contested by the Applicants. I agree with the examiner’s assessment that this document does not form part of the common general knowledge. I am not going to consider the common general knowledge any further.

Step 2: Identify the inventive concept of the claim in question or if that cannot readily be done, construe it; and

Step 3: Identify what, if any, differences exist between the matter cited as forming part of the “state of the art” and the inventive concept of the claim or the claim as construed

14 The examiner has cited three prior art documents, WO 02/32466, US 2004/241095 and US 2008/233050. Each of these documents disclose generic chemical formulae which encompass compounds falling within the scope of claim 1. The Applicants and the examiner are in agreement that the inventive concept is the selection of a subset of the general formulae provided by the prior art, specifically while the prior art discloses a large range of polyethylene glycol (PEG) group length of between 1 and

100, the applicants have claimed compounds with short side chains having a length of 1 to 6 PEG groups.

Step 4: Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

- 15 As this is a selection invention, the approach used by the Court of Appeal in *Dr Reddy's Laboratories (UK) Ltd. v Eli Lilly & Co. Ltd.* [2010] RPC 9 will be followed. The question to be asked is whether the invention makes a hitherto unknown technical contribution or is merely an arbitrary selection. If the selection is an arbitrary one, the invention is obvious. As stated at paragraph 44 in *Dr Reddy's Laboratories*, "...it regards what can fairly be regarded as a mere arbitrary selection from a class as obvious. If there is no more than arbitrary selection then there is no technical contribution provided by the patentee".
- 16 The Court of Appeal considered the law regarding selection inventions in *Generics [UK] LTD (t/a Mylan) v Yeda Research and Development co. LTD & Anor* [2013] EWCA Civ 925. The position was summarised therein by the following statements:
- "i) Article 56 of the EPC is in part based on the underlying principle that the scope of the patent monopoly must be justified by the patentee's contribution to the art;*
 - ii) if the alleged contribution is a technical effect which is not common to substantially everything covered by a claim, it cannot be used for the purposes of judging obviousness;*
 - iii) in such circumstances the claim must either be restricted to the subject matter which makes the technical contribution, or a different contribution common to the whole claim must be found;*
 - iv) a selection from the prior art which is purely arbitrary and cannot be justified by some useful technical property is likely to be held to be obvious because it does not make a real technical advance;*
 - v) a technical effect which is not rendered plausible by the patent specification may not be taken into account in assessing inventive step;*
 - vi) later evidence may be cited to support a technical effect made plausible by the specification;*
 - vii) provided the technical effect is made plausible, no further proof of the existence of the effect is to be demanded of the specification before judging obviousness by reference to the technical effect put forward."*
- 17 From statement v), it is clear that the alleged technical effect relied upon to justify a selection invention should be clearly identified or otherwise made plausible, in the specification at the time of filing. The examiner has questioned whether the technical effect relied upon by the Applicants is rendered plausible by the patent specification.
- 18 The Applicants are claiming (set out in their letter of 25 September 2013) that it was previously thought that in order to provide good hydrophilicity for molecules such as

those set out by the prior art, long PEG groups were required. However, the Applicants state that in applications such as their use as optical labels, the long PEG groups tend to block access of the reaction of such biomolecules. They state that they have discovered that a subset of this large range of PEG group length of between 1 and 100 described provides enhanced properties thereover. Specifically, the Applicants have discovered that short PEG groups having a length of 1 to 6 not only provide the desired level of solubility and hydrophilicity, but also provides higher fluorescence intensity, lower background, higher specificity for antibody conjugates, increased photostability, and greater target accessibility.

- 19 In order to support their argument that the alleged technical benefit was plausible, the Applicants have highlighted two reasons (set out in their letter of 19 December 2013):

“Reason 1: The specification does support each of (a) high specificity, (b) low background, and (c) increased target accessibility exhibited by the claimed compounds”

“Reason 2: The specification does support the enhanced photostability exhibited by the claimed compounds”

- 20 I will deal with Reason 2 first.

- 21 The Applicants have highlighted paragraph 5 on page 1 of the specification as originally filed as providing basis for an inventive step. The passage reads:

“...The compounds have high hydrophilicity, high molar absorbance, high photostability, and high storage stability...”

On the 25 September 2013, the Applicants provided later evidence (“Evidence”) in the form of experimental data that shows Compound A (the inventive compound) exhibiting higher photostability compared to a prior art dye, CF680.

- 22 The examiner dismissed Reason 2 in his examination report of 20 February 2014 and I agree with the examiner’s assessment. The statement on page 1 paragraph 5 of the description is limited to the compounds having high photostability. There is no indication in the specification that the claimed compounds with short PEG chain lengths have superior photostability to the prior compounds with longer PEG chain lengths. As such, while this statement does make the high photostability of the claimed compounds plausible, it does not provide basis for a valid selection as there is no indication that shorter PEG groups leads to greater photostability. The Applicants’ Evidence suggests that short PEG groups may enhance photostability as is allowed by statement vi) in *Generics*. However, statements v) and vi) of *Generics* make it clear that the monopoly sought must be made plausible by the specification, i.e. justified by the patentee’s contribution to the art at the earliest date. As such, this later filed evidence does not provide basis for the selection as there is no indication in the specification as filed that such a selection shows the alleged technical benefit. To allow later filed evidence in this case would be to allow the Applicants to benefit from discoveries after the relevant date. This is clearly not allowable. Therefore, I agree with the examiner that Reason 2 does not provide basis for an inventive step.

- 23 Turning now to Reason 1, the Applicants refer to example 9 which they state shows the claimed compounds show higher specificity than the prior art compounds. The relevant passages read:

“There was very little non-specific binding observed with V08-15173-GAM and 679 Compound 1/1-GAM. Company A Compound-GAM and Company B Compound-GAM conjugates showed high non-specific binding starting from 5X molar excess.” (page 217, last paragraph, example 9)

“Company A Compound showed much higher non-specific binding compared to V08-15173 and 679 Compound 1/1, with non-specific binding appearing at the 2.5X condition for Company A Compound.” (page 219, first paragraph, example 9)

This is the crux of the disagreement between the examiner and the Applicants. The examiner acknowledges that the claimed compound V08-15173 shows greater specificity than prior art Company A Compound. However, the examiner’s objection is that as the structure of Company A Compound is not shown in the specification, the nature of the comparison between the claimed compounds and the prior art would not be apparent to the skilled worker. Therefore, the examiner concludes that the technical effect being relied upon is not made plausible by the specification.

- 24 The Applicants and the examiner are in agreement that Company A compound is Biotium’s CF680 and that the skilled worker could determine this by consulting the first table in Example 6 of US 61/604232 (one of the priority documents) and comparing it with Example 6 of the present specification. The Applicants assert that the skilled person can readily determine the structure of CF680, based on information in the priority document, Biotium’s product literature and Biotium’s patent application WO 2009/078970.
- 25 I agree that it is apparent from the priority document that Company A compound is Biotium’s CF680. However, neither the specification of the present application nor that of the priority document state the PEG group length of this compound. Indeed, in the final table on page 208 of Example 6 of the present specification, the PEG length of Company A compound is listed as “?”. The Applicants and examiner are in disagreement as to whether, at the priority date of the application, the person skilled in the art would have been able to determine the structure of CF680. The Applicants submit that the skilled worker would have determined the structure of CF680 because it would have been obvious for the skilled person to obtain that information.
- 26 The Applicants and the examiner agree that the skilled person would have first considered the product literature for CF680 and conclude that this does not state the structure of the compound. The Applicants have stated that by considering Biotium’s patent applications it can be seen that WO 2009/078970 compares Dylight 680, Cy5.5 and Alexa Fluor 680 with Dye No. 32 therein and that these are the same competitor compounds that are compared with CF680 in Biotium’s product literature. As such, the Applicants conclude that CF680 is Dye No. 32 of WO 2009/078970 and further notes that the molecular weight for Dye No. 32 of 3210 is in close agreement with the published molecular weight of 3241 for CF680. The Applicants’ position is that the skilled person can therefore readily determine the structure of CF680 and indeed, they themselves have done this. The examiner contends that the imagination

or perseverance of the Applicants cannot be attributed to the skilled worker and that as WO 2009/078970 does not form part of the common general knowledge, the skilled worker would not be expected to locate this document and then go on to identify the relevant compound within it.

- 27 I cannot conclude that it would have been clear to the skilled worker at the relevant date that Dye No. 32 is CF680. The skilled worker would need to partake in a significant amount of research and make a number of inferences in order to reach the conclusion that Dye No. 32 is CF680. Firstly, they would need to decide to scour all of Biotium's patent applications in the hope that CF680 is mentioned. Even, if they concluded that WO 2009/078970 is the most relevant document, there is no indication in this document to suggest that Dye No. 32 is CF680 apart from the statement comparing it with Dylight 680, Cy5.5 and Alexa Fluor 680. The molecular weight and other properties of Dye No. 32 are not given in WO 2009/078970. The skilled worker would have to infer that this is potentially the relevant compound based only on the fact that CF680 is compared to similar prior art compounds and then do further research to compare their properties. It is noted that while the Applicants contend that they have determined the structure of CF680, it does not appear that this was the case at the earliest date as neither the specification of the present application nor that of the priority document state the PEG length of CF680. If it was obvious for this to be determined and was the basis for the selection, it would seem reasonable to think that this would be included in the specification. While the skilled person is taken to have the capacity for routine work and experimentation, in *Valensi v BRC* [1973] R.P.C. 33, Buckley L.J. said that "...the hypothetical addressee is not a person of exceptional skill and knowledge, that he is not to be expected to exercise any invention nor any prolonged research enquiry [emphasis added], research or experiment". As such, it does not appear valid to suggest that it clear from the present application that Dye No. 32 is CF680.
- 28 The Applicants have further argued that even if the skilled worker could not determine the exact structure of CF680 that they would at least be able to determine that it contain long PEGs. The Applicants have argued that the product literature states "*Core structure-modifying elements refer to various chemical attachments to the core structure [i.e. PEGs] (added by Applicants) and are a key aspect of the CF dye invention that makes CF dyes superior to other commercial dyes*" and from this the skilled worker would be able to determine that CF680 has long PEGs. However, the product literature does not refer to PEGs specifically so there is no indication that CF680 or indeed any of the CF dyes have PEG chains never mind long PEGs. Indeed the statement highlighted by the Applicants could refer to the claimed compounds with short PEGs. As such, this does not lead to the conclusion that the CF680 must have long PEGs.
- 29 However, even if skilled worker was able to determine the structure of Company A Compound (CF680), I am still not convinced that this would provide adequate basis for the selection claimed.
- 30 The specification as filed does not enable the reader to determine the contribution to the art. The skilled worker when comparing the structures of V08-15173 and CF680 would still be required to interpret that it is the PEG length of the side chains that is the important difference, as the PEG length is not the only structural difference

between V08-15173 and CF680. The structures of the two compounds are shown in Appendix 2.

- 31 While the Applicants have argued in their letter of 22 December 2015 that they clearly contrast short vs long PEGs throughout the patent specification, this does not appear to be the case. There is no discussion in the specification to suggest the technical benefit of shorter PEG chain length. While the specification discloses a number of compounds that have a short PEG length it does not contrast this with those that have a larger PEG length. As there is no clear contrast between compounds of short PEG length to those with long PEG length, the specification as filed does not enable the reader to determine the contribution to the art. Furthermore, the Applicants have only contrasted one compound with short PEGs, V08-15173 with one prior art compound CF680 and there is nothing in the specification as filed to suggest that all of the compounds of the particular subgroup claimed show the alleged technical benefit over those compounds falling outside of the claimed selection. It is therefore considered that the alleged technical effect of the claimed selection is not made plausible by the patent specification. Following the statement v) in *Generics*, a technical effect which is not rendered plausible by the patent specification may not be taken into account in assessing inventive step. Therefore, the claimed selection of compounds is considered to be arbitrary and the invention is considered to lack an inventive step.

Decision

- 32 I have found that claims 1 to 15 lack an inventive step as required by section 1(1)(b) over WO 02/32466 A1, US 2004/241095 A1 and US 2008/233050 A1 on the basis that the claims relate to an arbitrary selection from the prior art, as the technical effect relied upon by the Applicants is not rendered plausible by the patent specification. Therefore, the alleged technical effect cannot be taken into account when assessing inventive step. I therefore refuse this application under section 18(3).

Appeal

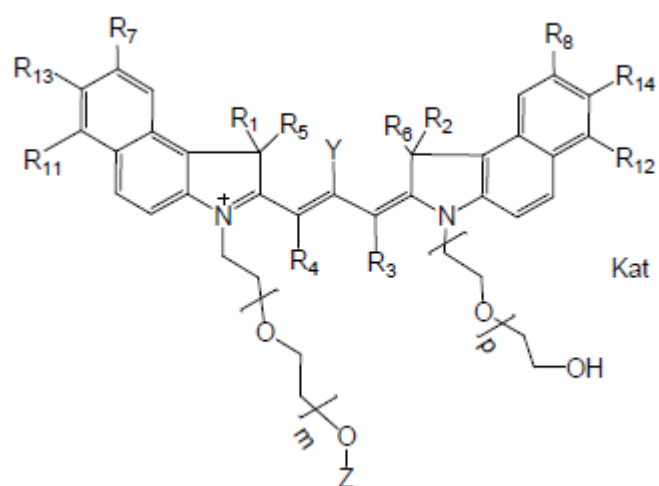
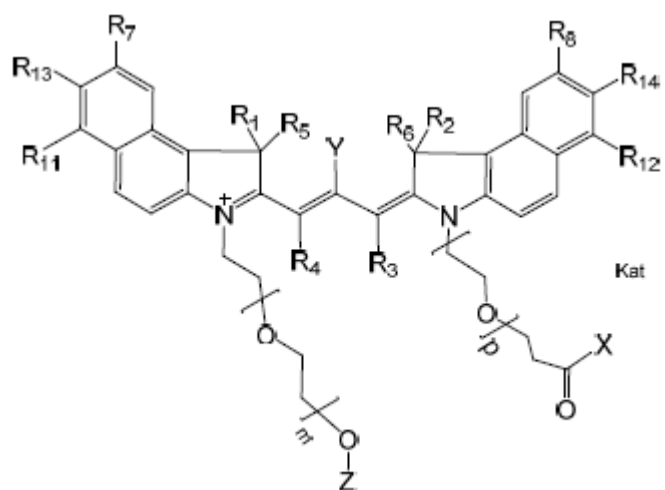
- 33 Any appeal must be lodged within 28 days

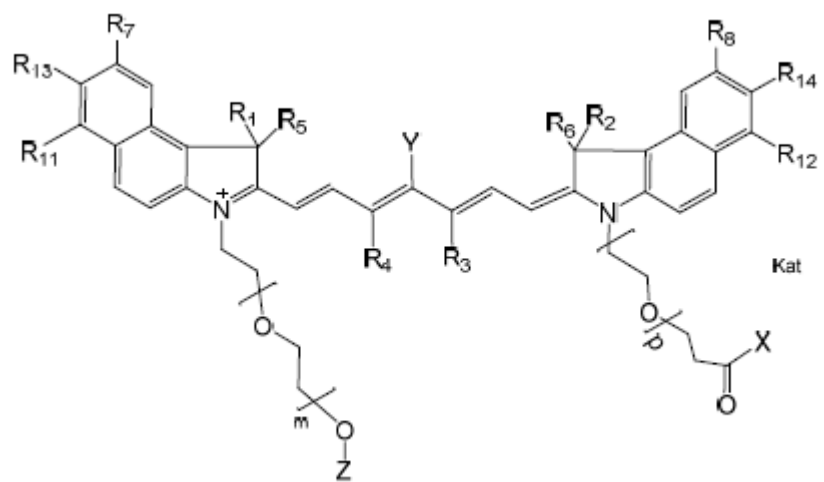
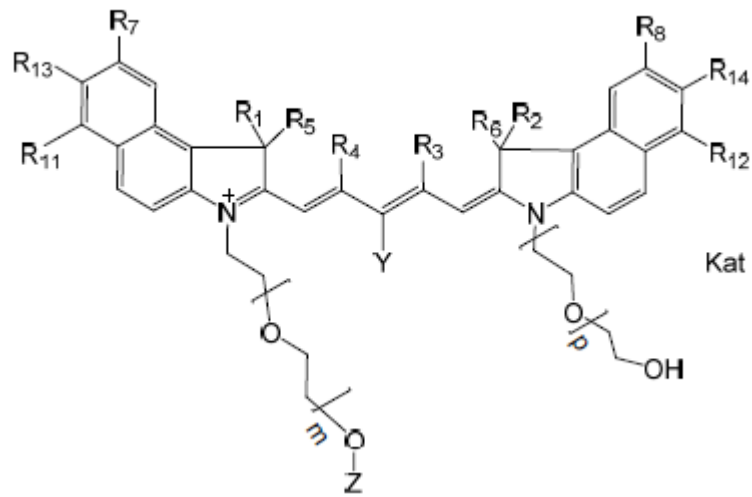
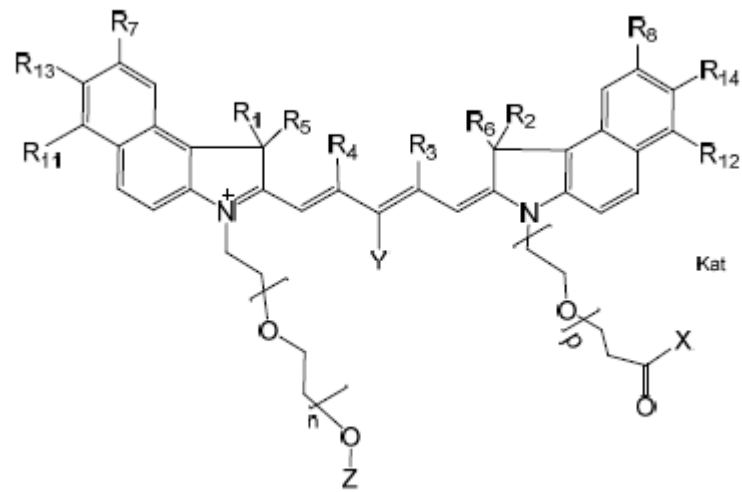
C L DAVIES

Deputy Director, acting for the Comptroller

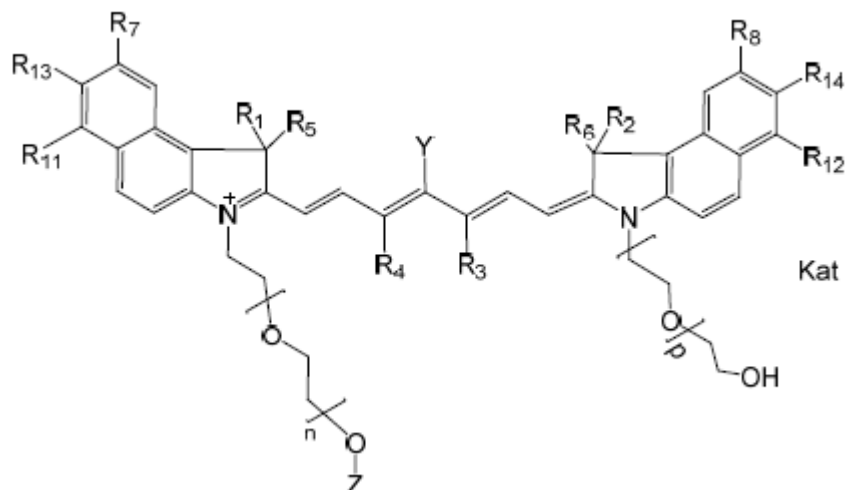
Appendix 1

1. A compound selected from the group consisting of





and



where

each of R^1 , R^2 , R^5 , and R^6 is the same or different and is independently selected from the group consisting of an aliphatic, heteroaliphatic, sulfoalkyl, heteroaliphatic with terminal SO_3 , a PEG group P-Z where P is selected from an ethylene glycol group, a diethylene glycol group, and a polyethylene glycol group, where the polyethylene glycol group is $(\text{CH}_2\text{CH}_2\text{O})_s$, where s is an interger from 3-6 inclusive, a sulfonamide group $-\text{L}-\text{SO}_2\text{NH}-\text{P}-\text{Z}$, and a caboxamide group $-\text{L}-\text{CONH}-\text{P}-\text{Z}$, where Z is selected from H, CH_3 , a CH_3 group, an alkyl group, or a heteroalkyl group;

each of R^7 , R^8 , R^{11} , R^{12} , R^{13} , and R^{14} is the same or different and is independently selected from the group consisting of H, SO_3 , a PEG group P-Z where P is selected from an ethylene glycol group, a diethylene glycol group, and a polyethylene glycol group, where the polyethylene glycol group is $(\text{CH}_2\text{CH}_2\text{O})_s$, where s is an interger from 3-6 inclusive, a sulfonamide-containing group $-\text{L}-\text{SO}_2\text{NH}-\text{P}-\text{Z}$, and a carboxamide-containing group $-\text{L}-\text{CONH}-\text{P}-\text{Z}$, where Z is selected from H, CH_3 , a CH_3 group, an alkyl group, or a heteroalkyl group;

X is selected from $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NH}-\text{NH}_2$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NHS}$ (hydroxysuccinimidyl/sulfosuccinimidyl), $-\text{O}-\text{TFP}$ (2,3,5,6-tetrafluorophenoxy), $-\text{O}-\text{STP}$ (4-sulfo-2,3,5,6-tetrafluorophenoxy), $-\text{O}-\text{benzotriazole}$, $-\text{benzotriazole}$, imidazole, azide, $-\text{O}-\text{carbodiimide}$, $-\text{NR}-\text{L}-\text{OH}$, $-\text{NR}-\text{L}-\text{O}-\text{phosphoramidite}$, $-\text{NR}-\text{L}-\text{SH}$, $-\text{NR}-\text{L}-\text{NH}_2$, $-\text{NR}-\text{L}-\text{NH}-\text{NH}_2$, $-\text{NR}-\text{L}-\text{CO}_2\text{H}$, $-\text{NR}-\text{L}-\text{CO}-\text{NHS}$, $-\text{NR}-\text{L}-\text{CO}-\text{STP}$, $-\text{NR}-\text{L}-\text{CO}-\text{TFP}$, $-\text{NR}-\text{L}-\text{CO}-\text{benzotriazole}$, $-\text{NR}-\text{L}-\text{CHO}$, $-\text{NR}-\text{L}-\text{maleimide}$, $-\text{NR}-\text{L}-\text{NH}-\text{CO}-\text{CH}_2-\text{I}$, or $-\text{NR}-\text{L}-\text{NH}-\text{CO}-\text{CH}_2-\text{Br}$ wherein R is $-\text{H}$ or an aliphatic or heteroaliphatic group;

L is selected from a divalent linear $-(\text{CH}_2)_t-$, $t = 0$ to 15), crossed, or cyclic alkyl group optionally substituted by at least one oxygen atom and/or sulfur atom;

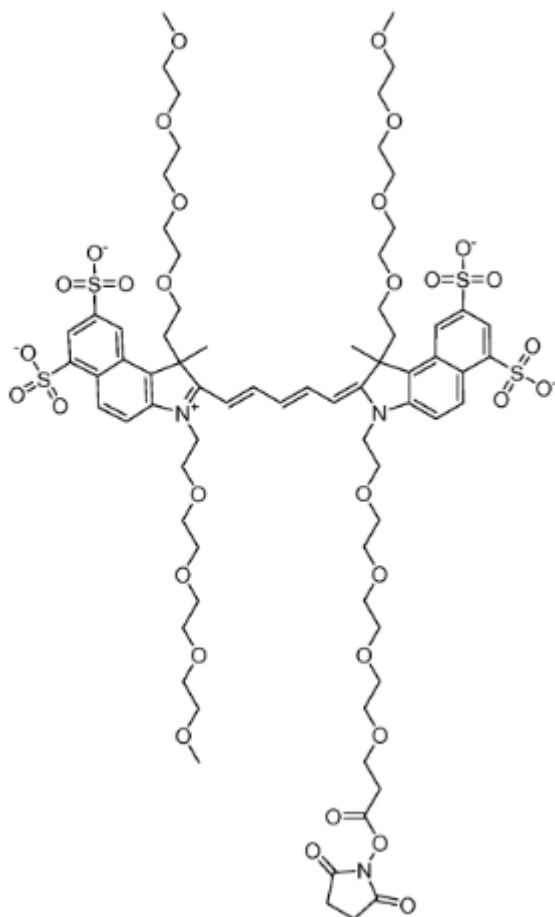
Kat is a number of Na^+ , K^+ , Ca^{2+} , ammonia, or other cation(s) needed to compensate the negative charge brought by the cyanine; m is an integer from 0 to 5 inclusive; p is an integer from 1 to 6 inclusive;

each of R^3 and R^4 is the same or different and is independently hydrogen, an aliphatic group, a heteroaliphatic group, or a PEG group P-Z where P is selected from an ethylene glycol group, a diethylene glycol group, and a polyethylene glycol group, where the polyethylene glycol group is $(\text{CH}_2\text{CH}_2\text{O})_s$, where s is an interger from 3-6 inclusive, and Z is selected from H, a CH_3 group, an alkyl group, or a heteroalkyl group; or R^3 and R^4 together form a cyclic structure where R^3 and R^4 are joined using a divalent structural element selected from the group consisting of $-(\text{CH}_2)_{q-}$, $-(\text{CH}_2)_q\text{O}(\text{CH}_2)_{q'-}$, $-(\text{CH}_2)_q\text{S}(\text{CH}_2)_{q'-}$, $-(\text{CH}_2)_q\text{CH}=\text{CH}-$, $-\text{OCH}=\text{CH}-$ where each of q and q' is the same or different and is a integer from 2 to 6 inclusive; and

Y is selected from the group consisting of hydrogen, alkyl, sulfoalkyl, fluorine, chlorine, bromine, a substituted or unsubstituted aryl-, phenoxy-, phenylmercapto function, and a PEG group P-Z where P is selected from an ethylene glycol group, a diethylene glycol group, and a polyethylene glycol group, where the polyethylene glycol group is $(\text{CH}_2\text{CH}_2\text{O})_s$, where s is an interger from 3-6 inclusive, and Z is selected from H, a CH_3 group, an alkyl group, or a heteroalkyl group.

Appendix 2

From pages 132 and 133 and claim 4 of the specification, the structure of V08-15173 is shown below:



From example 120 on page 115 of WO 2009/078970 A, the structure of Dye No. 32 is shown below:

