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Modern approaches to the synthesis and prospects for the use of cyanine dyes containing functional groups in the N-substituents

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Methods for the synthesis of mono-, tri-, penta- and heptamethine cyanine dyes containing functional groups in N-substituents are considered. Approaches suitable for the preparation of both symmetrical and unsymmetrical cyanine dyes are presented. Examples of the practical use of this type of cyanine dyes as fluorescent labels and probes in biology and medicine, as well as of components of photoactive supramolecular structures, photosensitizers and photo- and electroluminescent materials are given.
The bibliography includes 106 references.

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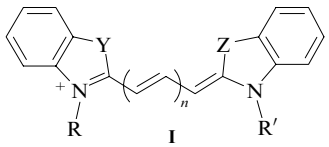
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I. Introduction

Cyanine dyes belong to a well-known class of organic dyes. Due to structural diversity of these compounds, the dyes with desired photophysical properties can be synthesized. These dyes exhibit intense fluorescence in the visible and near-IR region. Cyanine dyes are widely used as photosensitizers in photography,[1] fluorescent labels and probes,[2–6] photo- and electroluminescent materials[7–9] and optical disc recording media.[10,11] They can form supramolecular structures, dimers, J-aggregates and inclusion complexes with such cavitands as cyclodextrins and cucurbiturils.[12–18]

A number of reviews have been published regarding the synthesis and properties of cyanine dyes.[19–27] However, these reviews gave only a few examples of the preparation of dyes containing functional groups in N-substituents. Hence, the issue of our concern has not been systematically addressed.

Structures I



I

Y, Z = S, CMe_2, O, NR′, Se, CH=CH; n = 0–3;
R, R^1 are substituents containing functional groups

Meanwhile, cyanine dyes containing terminal functional groups (structures **I**) are particularly promising in biological and medical research, as well as the basis for the construction of supramolecular systems. Due to the presence of functional groups, the dyes can form stable complexes with biomolecules or can be covalently bonded to the latter. Therefore, extensive research is being conducted to develop methods for the synthesis of these dyes and their use as fluorescent labels. Cyanine dyes are chemically quite stable and exhibit long-lasting fluorescence, which changes with time only slightly. As fluorescent labels, these dyes act as molecular beacons that identify the presence or spatial arrangement of the molecule to which they are attached. In addition, since fluorescence of cyanine dyes is environ-

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mentally sensitive, these compounds can be employed as fluorescent probes, *i.e.*, as compounds, the fluorescence of which (most often fluorescence intensity or lifetime) changes upon the interaction with other molecules. Therefore, a fluorescent probe transmits information about the environment, in which it is present. It should also be noted that the introduction of charged functional groups into cyanine dyes increases their solubility in water, which is important for practical application.

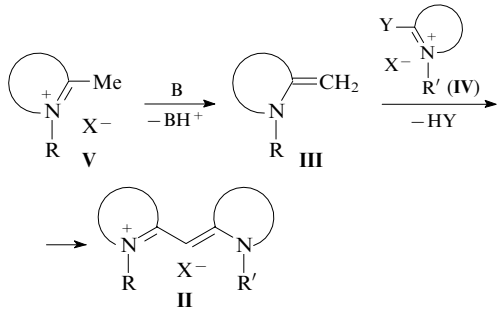
This review describes methods for the synthesis of cyanine dyes that contain various heterocyclic moieties and terminal functional groups in N-substituents having one, three, five or seven carbon atoms in the polymethine chain. Examples of interactions of such cyanine dyes with biological macromolecules and their use as photoactive components of supramolecular structures are briefly discussed.

II. Monomethine dyes

In monomethine cyanine dyes, a chromophore consists of two nitrogen-containing heterocyclic moieties linked by a methine bridge.

An approach to the synthesis of monomethine cyanines **II** (Scheme 1) is based on the reaction of a methylene base (heterocycle **III**) with heterocyclic salt **IV** containing a good leaving group Y. The methylene base is generated *in situ* from a quaternary salt of a 2- or 4-methyl derivative of heterocyclic compound **V** in the presence of a base (B) (for example, pyridine or triethylamine). The condensation occurs most easily when an alkylthio group serves as the leaving group Y.

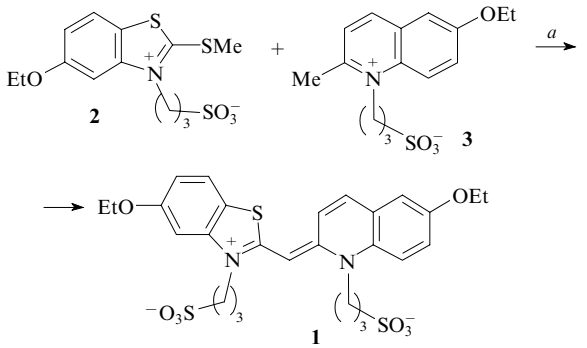
Scheme 1



The synthesis of unsymmetrical monomethine dye **1** containing two sulfopropyl substituents at the nitrogen atoms was covered by a patent.[28] The reaction of benzothiazolium betaine **2** containing the 2-methylsulfanyl group with quinolinium betaine **3** containing the reactive methyl group in position 2 affords dye **1** (Scheme 2). The reaction proceeds in the presence of triethylamine. The yield of dye **1** was not reported.

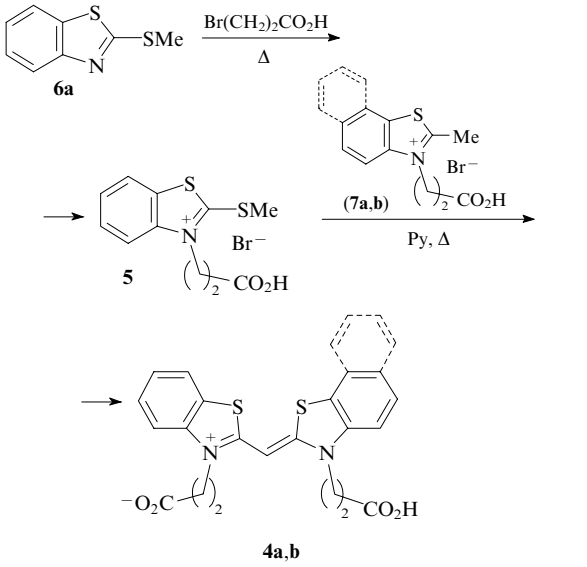
Monomethine dyes **4a**,**b** (Scheme 3) were synthesized in a similar manner.[29] The synthesis of benzothiazolium salt **5** involves the quaternization of 2-methylsulfanylbenzothiazole (**6a**) with β-bromopropionic acid to give salt **5** followed by the condensation of the latter with benzothiazolium salt **7a** or β-naphthothiazolium salt **7b**. The reaction is performed in pyridine (Py). The yields of dyes **4a**,**b** were not reported.

Scheme 2



(*a*) 1) Et_3N, EtOH, Δ; 2) NaOH

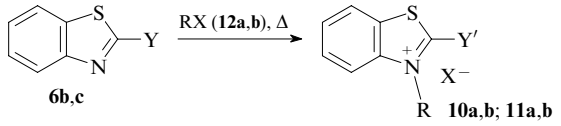
Scheme 3



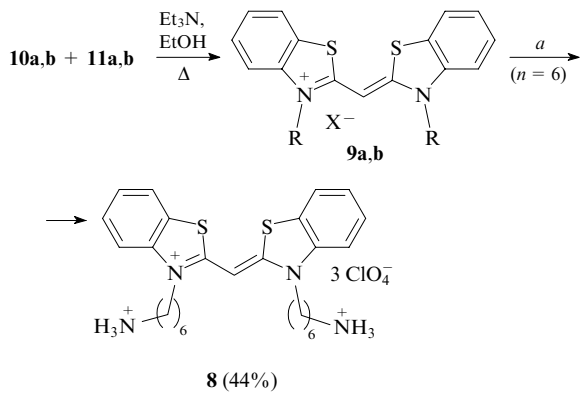
The research team headed by Gromov [30, 31] used alkylsulfanyl derivatives of benzothiazolium salts to synthesize symmetrical monomethine dye **8** containing ammonioalkyl substituents at the nitrogen atoms (Scheme 4). An attempt to synthesize a cyanine dye containing terminal ammonium groups in N-substituents by the direct condensation of quaternary salts of heterocyclic bases containing ammonioalkyl groups failed. In a basic medium, the ammonium group is deprotonated to the amino group, and the latter is involved in side reactions such as cyclization and condensation. For this reason, dyes **9a**,**b** containing phthalimide protecting groups were prepared as intermediates. This made it possible to avoid the undesirable side reactions. Quaternary benzothiazolium salts **10a**,**b** and **11a**,**b** required for the synthesis of the dyes were prepared by the quaternization of 2-sulfanylbenzothiazole (**6b**) and 2-methylbenzothiazole (**6c**), respectively, with phthalimidoalkyl derivatives **12a**,**b**. Monomethine dyes **9a**,**b** of the benzothiazole series containing phthalimidoalkyl substituents at the nitrogen atoms were synthesized by the condensation of heterocyclic salts **10a**,**b** and **11a**,**b** in ethanol in the presence of triethylamine.

Target cyanine dye **8** containing ammoniohexyl substituents at the heterocyclic nitrogen atoms was obtained after the removal of the protecting groups with a solution of

Scheme 4



R = $(CH_2)_n$NPhth; **6**: Y = SH (**b**), Me (**c**); **10**: Y′ = SR, X = TsO: *n* = 3 (**a**), 6 (**b**); **11**: Y′ = Me: X = Br, *n* = 3 (**a**); X = TsO, *n* = 6 (**b**); **12**: *n* = 3 (**a**), 6 (**b**); Ts = 4-$MeC_6H_4SO_2$, NPhth is phthalimido



8 (44%)

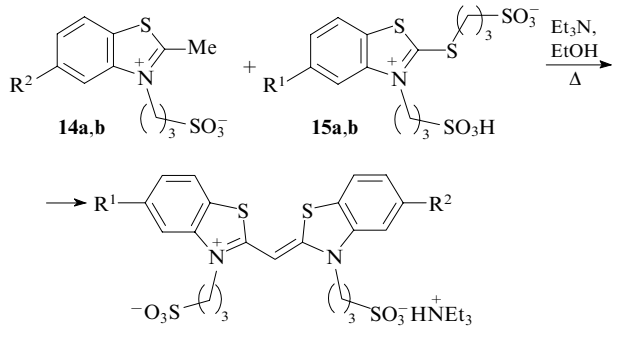
9: X = Br, *n* = 3 (**a**), X = ClO_4, *n* = 6 (**b**); (*a*) 1) $MeNH_2$, EtOH, Δ; 2) $HClO_4$

methylamine in ethanol followed by the treatment of the reaction mixture with $HClO_4$.

The formation of supramolecular complexes of dye **8** with bis(18-crown-6)stilbene was investigated. These compounds give double- and triple-decker complexes of 1 : 1 and 1 : 2 composition, in which the ammonium groups of the dye are hydrogen-bonded to the crown-ether moieties of the stilbene.[32]

The reactions with alkylsulfanyl derivatives of heterocyclic salts yielded toxic volatile alkanethiols as by-products. Gorkina *et al.*[33] proposed a modified version of this method. In this modification, the dyes are synthesized with the use of sulfoalkylsulfanyl derivatives, giving non-volatile by-products, instead of 2-alkylsulfanyl-substituted benzothiazolium salts. Monomethine dyes of the benzothiazole series **13a–c** were produced by the condensation of 2-methylbenzothiazolium betaines **14a**,**b** with 2-sulfopropylsulfanylbenzothiazolium betaines **15a**,**b** (Scheme 5). Triethylamine served as the condensing agent.

Scheme 5



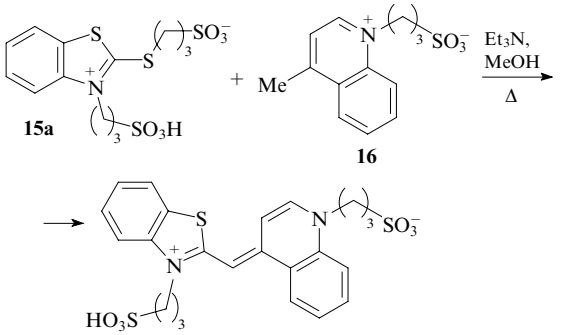
13a–c

13: $R^1 = R^2 = H$ (**a**, yield 61%); R^1 = Cl, R^2 = H (**b**, 28%); $R^1 = R^2$ = Cl (**c**, 30%); **14**: R^1 = H (**a**), Cl (**b**); **15**: R^2 = H (**a**), Cl (**b**)

Monomethine dyes can form inclusion complexes with cyclodextrins and cucurbiturils. Huang *et al.*[34] studied the complexation of monomethine dye **13a** with β-cyclodextrin (β-CD) in water.[34] It was demonstrated that hydrogen bonds and hydrophobic interactions between the guest and host molecules make the major contribution to stabilization of the inclusion complex.

A similar condensation of 4-methylquinolinium betaine **16** with 2-sulfopropylsulfanylbenzothiazolium betaine (**15a**) gave unsymmetrical dye **17** (Scheme 6).[35] Triethylamine served as the condensing agent. The yield of dye **17** was not reported.

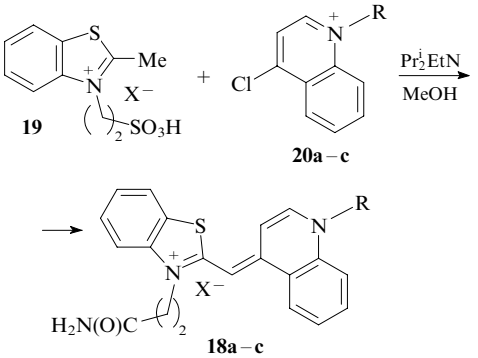
Scheme 6



17

Monomethine dyes can be synthesized using salts of heterocyclic bases containing a chlorine atom as the leaving group. This method also allows one to avoid the formation of volatile alkanethiols as by-products. Besides, more readily available 2-chloro derivatives of heterocyclic salts serve in this synthesis as the starting compounds instead of alkylsulfanyl derivatives. The method was applied to synthesize di- and tricationic monomethine dyes containing different functional groups. For instance, dicationic dyes **18a–c** were produced in methanol by the condensation of quaternary benzothiazolium salts **19** having the reactive methyl group with 4-chloroquinolinium salts **20a–c** (Scheme 7).[36–39] The reaction was performed at room temperature in the presence of the sterically hindered base diisopropyl(ethyl)amine.

Scheme 7

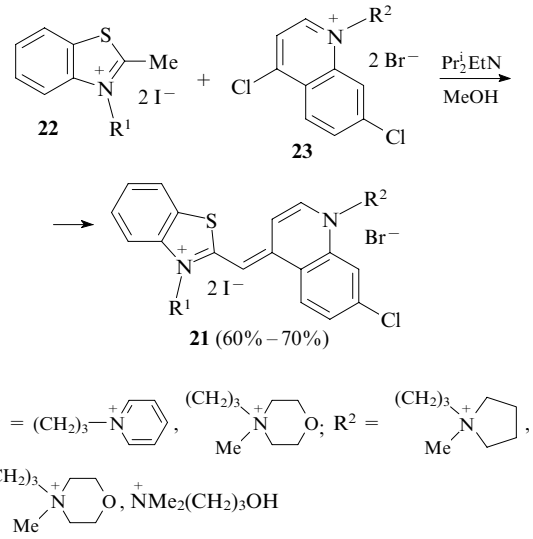


18a–c

18: R = $(CH_2)_3$– $NMe_2\,Br^-$, X = I (**a**, yield 93%); R = $(CH_2)_3$– I^-, X = ClO_4 (**b**, 77%); R = $(CH_2)_3\overset{+}{N}Et_3\,I^-$, X = I (**c**, 52%)

Tricationic dyes **21** were synthesized in a similar manner by the condensation of appropriate benzothiazolium salts **22** with quinolinium salts **23** (Scheme 8).[39]

Scheme 8

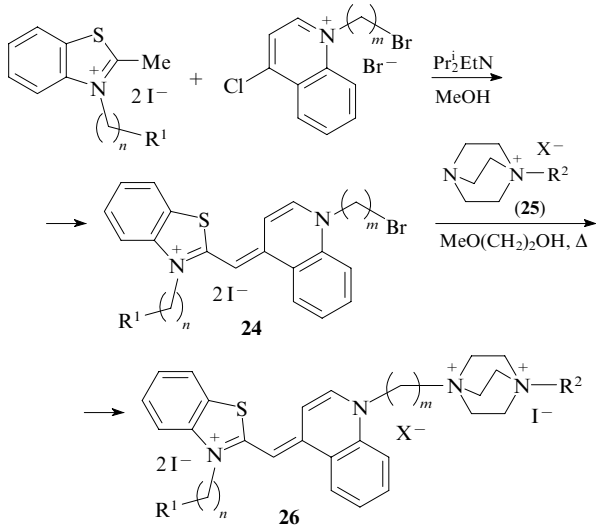


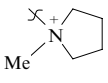
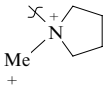
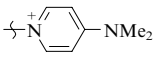
Di- and tricationic dyes **18a–c** and **21** serve as photoinitiators for free-radical polymerization of acrylates under visible light irradiation in the presence of electron donors, for example, of tetramethylammonium n-butyltriphenylborate.[39] These dyes can be applied also as fluorescent labels for nucleic acids, the binding of the dyes being noncovalent.

To increase the fluorescence quantum yield, dicationic dyes **24** containing the terminal bromine atom were synthesized according to a similar procedure. The latter atom can easily be replaced with a bicyclic N-heterocyclic moiety by means of nucleophilic substitution with compounds **25** (Scheme 9). The fluorescence quantum yield of the resulting tetracationic dyes **26** increases by hundreds of times upon binding to double-stranded DNA.[40]

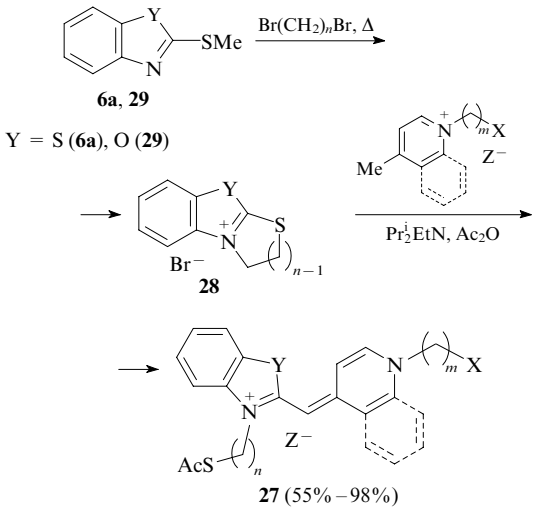
Deligeorgiev *et al.*[41,42] synthesized dyes **27** containing acetylsulfanylalkyl groups using cyclic benzothiazolium and benzoxazolium salts **28**, which were prepared by the condensation of appropriate 2-methylsulfanyl derivatives **6a** and **29** with dibromoalkanes (Scheme 10). Dyes **27** served as the starting compounds in the synthesis of homodimeric dyes **30** containing two chromophores (Scheme 11),[42] which exhibit virtually no fluorescence in the free state but which form fluorescent complexes with double-stranded DNA and, therefore, are applied as fluorescent labels.[43]

Scheme 9



n	*m*	R^1	X	R^2	Yield (%)
3	3		I	Bn	47
3	3		Br	Et	70
3	3	NEt_3^+	Br	Et	83
3	4		I	Bn	70
4	3		I	Bn	82
3	4		I	Et	85

Scheme 10

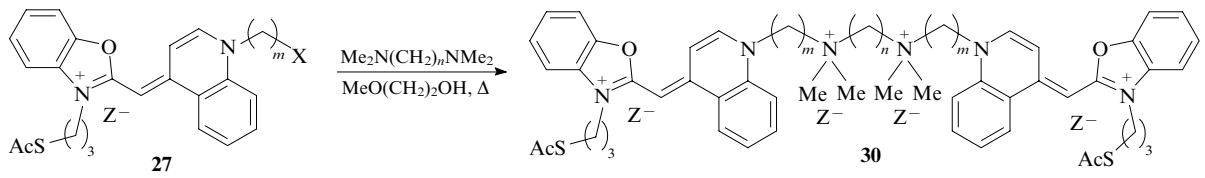


Y = O, S; X = Br, I; Z = Br, I, ClO_4; n = 2, 3; m = 3–5

Another method for the synthesis of monomethine dyes is based on the use of oximes of heterocyclic salts as electrophilic reagents. Unsymmetrical monomethine dye **31** containing two sulfopropyl N-substituents is produced by the condensation of 2-methylbenzoxazolium betaine **32** with naphthoxazolium betaine oxime **33** in acetic anhydride in the presence of triethylamine (Scheme 12).[44] The yield of compound **31** was not reported. This dye serves as a sensitizer for photographic emulsions in the near-IR region.

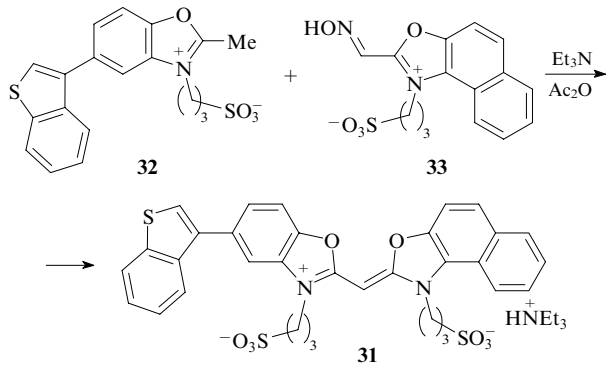
The major area of application of monomethine dyes, as well as of their homo- and heterodimeric derivatives, as fluorescent labels for DNA visualization in biological samples is based on fluorescence enhancement of these compounds as a result of their intercalation between DNA base pairs *via* stacking and electrostatic interactions.

Scheme 11



X = Br, I; Z = I, ClO_4; n = 3, 6; m = 3, 5

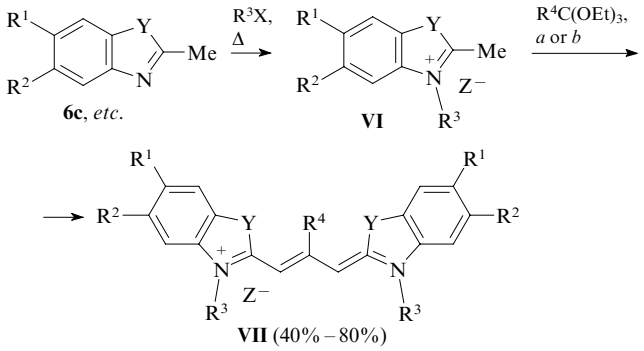
Scheme 12



III. Trimethine dyes

The approach to the synthesis of trimethine dyes involves the reaction of quaternary salts of heterocyclic bases with electrophilic reagents serving as a source of the central carbon atom of the polymethine chain of the dye. For instance, the condensation of quaternary salts of heterocyclic bases **VI** containing a reactive methyl group in position 2 with carboxylic acid orthoesters affords symmetrical trimethine dyes of the general formula **VII** (Scheme 13). The reaction is performed in pyridine or acetic anhydride in the presence of triethylamine. Quaternary salts **VI** are generated by the quaternization of appropriate heterocyclic bases (**6c** and other) with halogen derivatives or esters of *p*-toluenesulfonic acid.[29, 44 – 58]

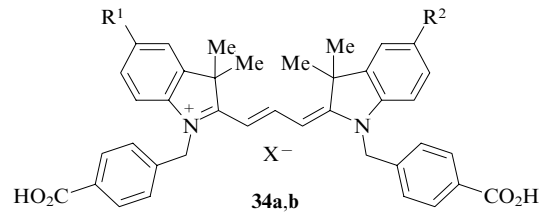
Scheme 13



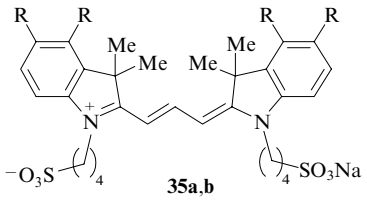
Y = O, S, Se, CMe_2, CH=CH, NEt; R^1 = H, Me, SO_3K, Br; R^2 = H, Me, Ph, Cl, CN; R^3 = $(CH_2)_nCO_2H$ (n = 1, 2, 4, 5), CH_2CO_2Et, $(CH_2)_2CO_2Et$, $(CH_2)_2CN$, $(CH_2)_2Cl$, $(CH_2)_2OAc$, CH_2Ac, $(CH_2)_3SO_2NHAc$, $(CH_2)_4SO_2NHAc$, $CH_2C(O)NHSO_2Et$, $(CH_2)_2C(O)NHSO_2Me$, $CH_2C(O)NHSO_2NMe_2$, $(CH_2)_2OH$, $(CH_2)_3OH$, $CH_2C(O)NEt_2$, $(CH_2)_3P(O)(OH)_2$, $CH_2CO_2(CH_2)_4SO_3Na$, $CH_2CH(OH)CH_2SO_3Na$, $CH_2C_6H_4CO_2H$-4, $(CH_2)_3NEt_3^+Br^-$; R^4 = H, Me, Pr^n; X, Z = Br, I, OTs; (*a*) Py, Δ; (*b*) Et_3N, Ac_2O, Δ

It was shown that dye **34a** can be employed for the fluorescence detection of DNA. Besides, this compound forms an inclusion complex with β-CD and is of interest as a component for the construction of supramolecular systems.[60] Benzindole-based trimethine dye **35a** was investigated as a reagent for fluorescence imaging in retinal surgery.[61] Dye **34b** was proposed as a photosensitizer for solar cells based on TiO_2 nanoparticles.[62] The dye was grafted to the nanoparticle surface through the terminal

Structures 34, 35



$R^1 + X^- = SO_3^-$, $R^2 = SO_3K$ (**a**, yield 40%); $R^1 = R^2 = H$, X = Cl (**b**, 60%)

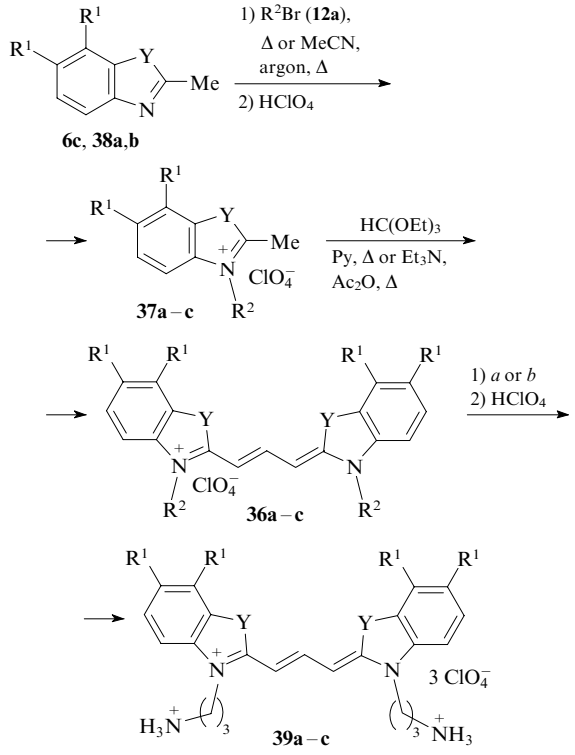


R – R is benzo (**a**, 53%), H (**b**)

carboxy groups. Dye **35b** forms an inclusion complex of 1 : 1 composition with cucurbit[7]uril (CB[7]).[12, 13, 63]

Symmetrical trimethine dyes **36a – c** containing phthalimide protecting groups can be synthesized by the condensation of quaternary salts **37a – c** with triethyl orthoformate. The reaction is performed in pyridine or acetic anhydride in the presence of triethylamine (Scheme 14). The synthesis of quaternary salts **37a – c** involves the quaternization of heterocyclic bases **6c** or **38a**,**b** with *N*-(3-bromopropyl)-phthalimide (**12a**) followed by the treatment with concentrated $HClO_4$. The phthalimide protecting groups are removed by hydrazinolysis or using other milder nucleophilic reagents, such as methylamine in ethanol. The subsequent treatment of the reaction mixture with $HClO_4$ affords symmetrical trimethine dyes **39a – c** containing terminal N-ammoniopropyl groups in yields of up to 45%.[30, 31]

Scheme 14

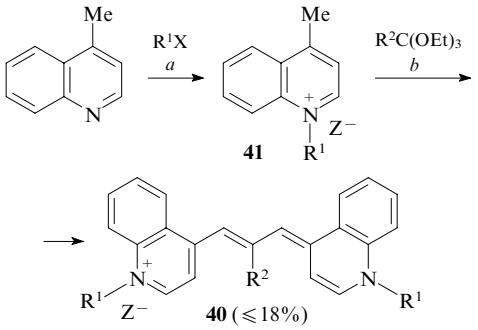


$R^2 = (CH_2)_3NPhth$; **38**: Y = CMe_2: R^1 = H (**a**), $R^1 - R^1$ is benzo (**b**); **36**, **37**, **39**: Y = S, R^1 = H (**a**, yield **39** 17%); Y = CMe_2: R^1 = H (**b**, 45%); $R^1 - R^1$ is benzo (**c**, 25%); (*a*) $MeNH_2$, EtOH, Δ; (*b*) $N_2H_4 \cdot H_2O$, $MeOH - CH_2Cl_2$

Trimethine dye **39b** of the indolenine series forms two types of supramolecular complexes with bis(18-crown-6)stilbene: bimolecular and trimolecular. In the latter complex, the dye molecule is located between two stilbene molecules. The complexation occurs through the binding of the ammonium groups of the dye to the crown-ether moieties of the stilbene.[30]

Dyes **40** were synthesized in a similar manner by the condensation with carboxylic acid orthoesters (Scheme 15). Starting salts **41** were prepared by the quaternization of 4-methylquinoline with halogen derivatives of acid, alcohol, ester, amide and so on.[44, 48 – 50]

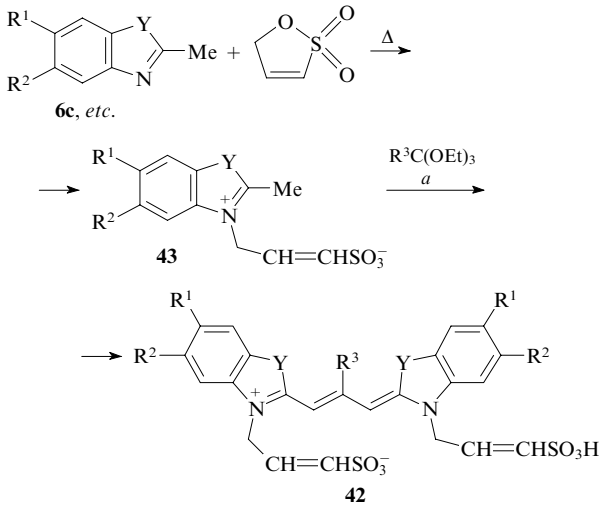
Scheme 15



R^1 = $(CH_2)_2OAc$, CH_2CO_2Et, $(CH_2)_2OH$, $CH_2C(O)NEt_2$; R^2 = H, Me; X, Z = Br, I, Cl; (*a*) 1) Δ, 2) KI, H_2O; (*b*) Py, Δ; or Et_3N, Ac_2O, Δ; or AcONa, Ac_2O, Δ

The synthesis of dyes **42** containing sulfopropenyl groups is based on the condensation of betaines **43** with carboxylic acid orthoesters (Scheme 16). Starting betaines **43** were generated by the quaternization of appropriate heterocyclic bases (**6c**, **29** and so on) with propene sultone.[64] The yields of dyes **42** were not reported.

Scheme 16



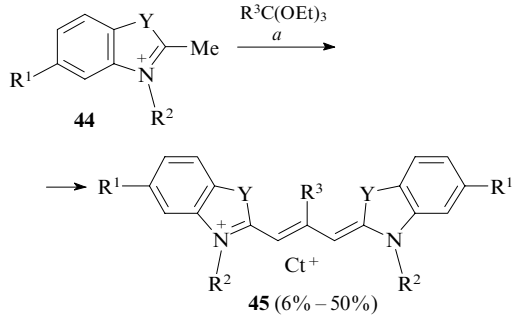
Y = S, O; R^1 = H, Me; R^2 = H, Me, Ph; R^3 = H, Me; (*a*) *m*-cresol, Δ; or Py, Et_3N, Δ; or Ac_2O, *m*-cresol, Δ

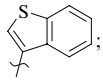
A similar condensation of quaternary salts **44** with carboxylic acid orthoesters gave symmetrical dyes **45**, which are spectral sensitizers for photographic emulsions (Scheme 17).[45, 64 – 69]

There are different modifications of the above-described method for the synthesis of trimethine dyes. Takeuchi *et al.*[70] described a method for the synthesis of trimethine dye **46** by the condensation of methylene base **47** with orthoformic ester (Scheme 18). Methylene base **47** was isolated in the individual state by alkalinization of an aqueous solution of quaternary salt **48** followed by the extraction with diethyl ether.

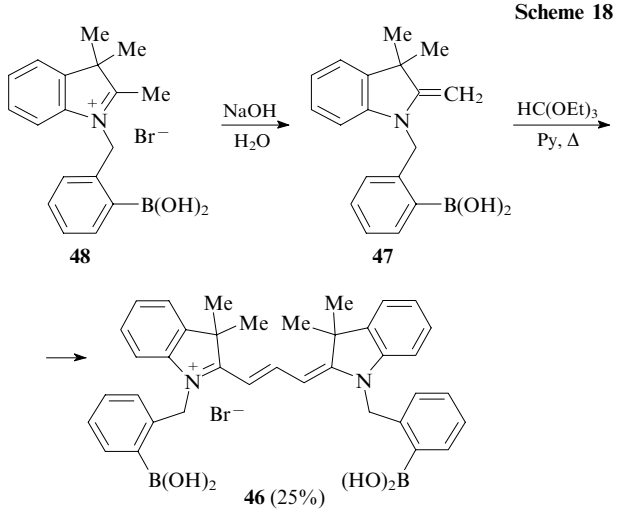
Dye **46** can be employed as a fluorescent molecular sensitizer for carbohydrates. For instance, in an alkaline medium this dye exists in anionic form **46′** and can interact with a monosaccharide molecule to form a complex of 1 : 1 composition having a cyclic structure. This results in a

Scheme 17



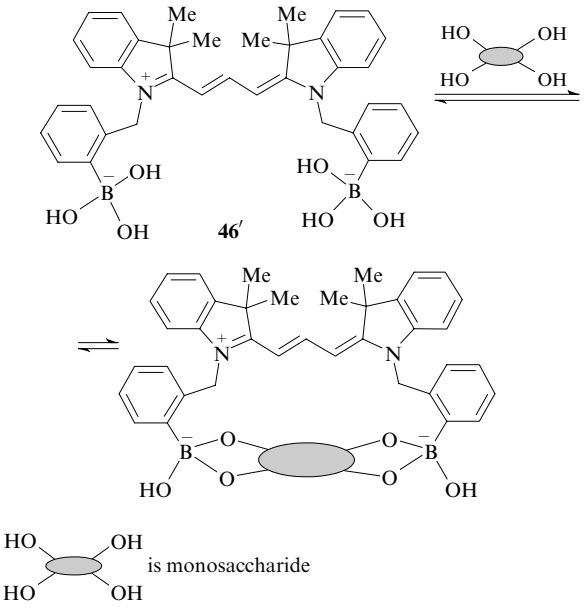
Y = S, O, CMe_2, NPh; R^1 = H, Cl, CF_3, SO_2CF_3, ;
$R^2 = (CH_2)_nSO_3^-$ (n = 2 – 4),
$CH_2CH(OH)CH_2O(CH_2)_3SO_3^-$, $CH_2C_6H_4SO_3^-$-4; R^3 = H, Me, Et;
Ct = H, Et_3NH, PyH, K, Na; (*a*) *m*-cresol, Δ; or Py, Δ; or Py, Et_3N, Δ; or Py, Et_3N, AcOH, Δ; or $PhNO_2$, Δ

Scheme 18



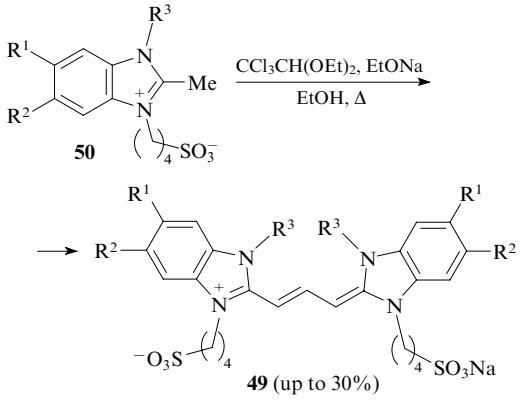
substantial increase in the fluorescence intensity of the dye due to an increase in the rigidity of its molecule in the complex (Scheme 19).

Scheme 19



In the synthesis of dyes, acetals can be used instead of orthoesters as donors of the central carbon atom of the trimethine chain. For instance, dye **49** was synthesized by the condensation of betaine **50** with chloral diacetal (Scheme 20). The reaction was performed in ethanol in the presence of sodium ethoxide as a base.[71, 72]

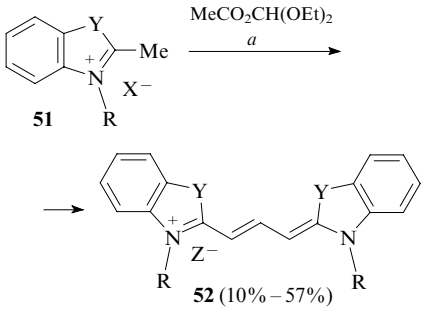
Scheme 20



R^1 = H, Cl; R^2 = Cl, CF_3, SO_2CF_3; R^3 = Me, Et

Diethoxymethyl acetate can serve as a donor of the central carbon atom of the trimethine chain (Scheme 21). This method was used to prepare a series of dyes **52** starting from quaternary salts **51**.[73, 74]

Scheme 21



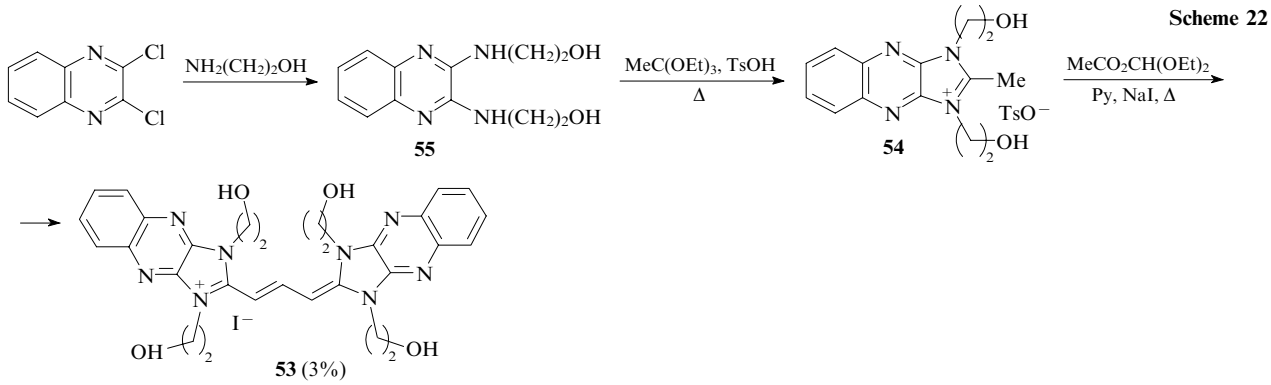
Y = S, CMe_2, ; R = $(CH_2)_2Ac$, $(CH_2)_2CH{=}NNHPh$,

$(CH_2)_2CH(OH)SO_3H$, $CH_2C_6H_3(OH)_2$-2,5, $CH_2C_6H_3(OEt)_2$-2,5;
X, Z = Br, OH, ClO_4; (*a*) Py, Δ; or 1) AcONa, Ac_2O; 2) $NaClO_4$

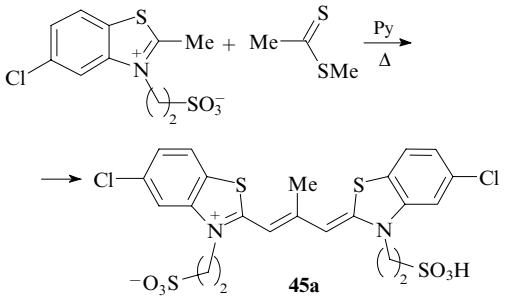
This approach was also applied to synthesize dye **53** that can serve as a photosensitizer.[75] Quaternary salt **54** is produced in two steps. First, the reaction of 2,3-dichloroquinoxaline with 2-aminoethanol gives intermediate **55**, which undergoes cyclization in the presence of diethoxymethyl acetate to form quinoxalinium salt **54** (Scheme 22).

Other appropriate electrophilic reagents, which can be involved in the condensation with a methylene base, can serve as donors of the central carbon atom in the synthesis of trimethine dyes containing a substituent in the *meso* position of the trimethine chain. For instance, methyl dithioacetate is a source of the central moiety in the synthesis of trimethine dye **45a** containing a methyl group in the *meso* position (Scheme 23).[76]

Scheme 22



Scheme 23



Another commonly accepted approach to the synthesis of trimethine dyes involves the condensation of salts of heterocyclic bases with diphenylformamidine. This method is more frequently used for the preparation of unsymmetrical dyes. In this case, the condensation product with 1 mole of one salt can be introduced into the reaction with another salt, resulting in the formation of an unsymmetrical dye containing different heterocyclic moieties.

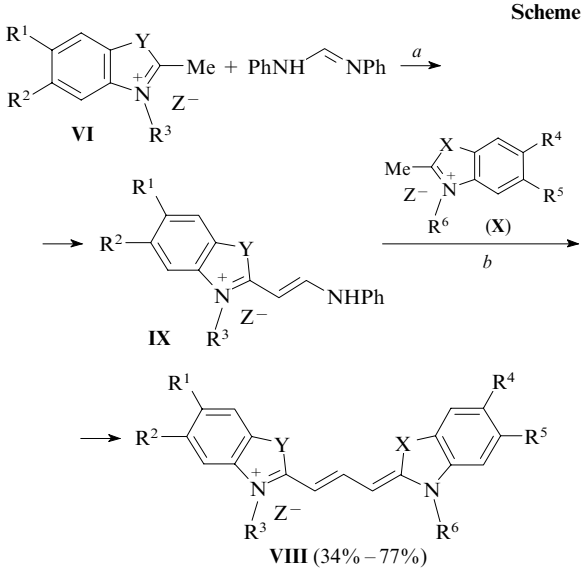
Unsymmetrical trimethine dyes of the general formula **VIII** (Scheme 24) were synthesized by the condensation of quaternary salts **VI** with diphenylformamidine giving intermediates **IX**, which were subjected to condensation with other quaternary salts of heterocyclic bases **X**.[29, 47, 70, 76 – 80] In order to prepare symmetrical dyes by this method, an excess of salt **VI** is added in the first reaction step, resulting in the direct formation of the target dyes.

Trimethine cyanine dyes are employed as fluorescent labels and probes in biology and medicine. Such compounds have to meet a number of requirements. In addition to intense fluorescence and a high extinction coefficient, these compounds should be photostable, readily soluble in water, non-toxic and contain chemically active groups for specific binding to a biomolecule. Cyanine dyes **VIII** are well-suited for this purpose. However, all cyanine dyes have a considerable drawback. Thus, these compounds tend to form dimers, resulting in fluorescence quenching. This drawback can be overcome by introducing charged substituents into the dye molecule. The sulfo group or a phosphoric acid moiety is generally used to address this issue.[78 – 80] At certain pH values of the solution, the latter moiety can bear two negative charges, which further contributes to disaggregation of the dye and increases its solubility in water.

Meguellati *et al.*[81] described the DNA-templated synthesis of trimethine dyes **56** using single-stranded DNA that can form a G-quadruplex (Scheme 25).[81] Two short peptide nucleic acid (PNA) chains complementary to terminal single-stranded DNA fragments were functionalized with moieties of indolenine derivatives. In the G-quadruplex DNA, two moieties are preorganized for the condensation reaction giving chromophore dye **56**. The course of the reaction was monitored by fluorescence spectroscopy. This approach to the formation of a chromophore dye can be used for the design of fluorescent labels for polypeptides of specified sequence.

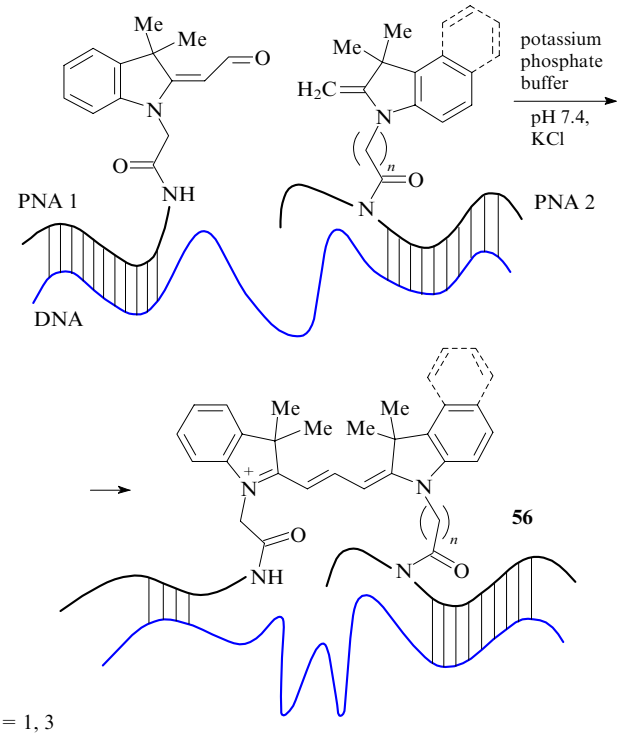
Initially, trimethine dyes have gained interest due to the development of color photography. Thus, cyanine dyes were served as sensitizers for silver halide emulsions in color photographic films. Currently, trimethine dyes are used mainly as fluorescent labels and probes in biology and medicine.

Scheme 24



Y = O, CMe_2; X = O, S, Se, CMe_2, $CMe(CH_2)_5CO_2H$, NEt;
R^1 = H, Me, OMe, $P(O)(OH)_2$, SO_3H; R^2 = H, SO_3H;
R^3 = $(CH_2)_2CO_2H$, $(CH_2)_5CO_2H$, $(CH_2)_3SO_3H$, $(CH_2)_4SO_3H$, $(CH_2)_4SO_2NHAc$; R^4 = H, Me, Cl, $P(O)(OH)_2$, SO_3H; R^5 = H, Me, Cl, SO_3H; R^6 = $(CH_2)_2CO_2H$, $(CH_2)_5CO_2H$, $CH_2C_6H_4CO_2H$-4, $(CH_2)_3SO_3H$, $(CH_2)_4SO_3H$; Z = Br, I, OH; (*a*) Ac_2O, Δ; or DMF, Δ; or AcOH, Δ; or Ac_2O, AcOH, Δ; or Py, Ac_2O, Δ; (*b*) Py, Δ; or Et_3N, Ac_2O, Δ; or Py, Ac_2O, Δ; or AcOH, Ac_2O, Py, Δ; or AcOH, Δ

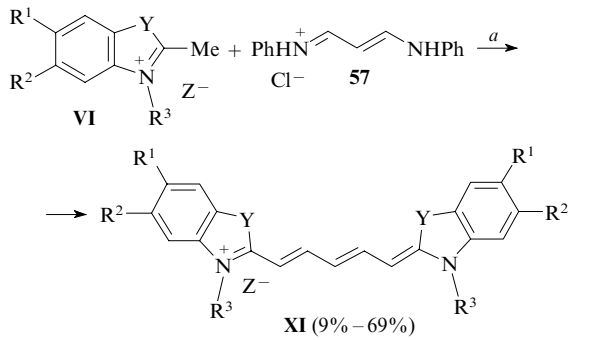
Scheme 25



IV. Pentamethine dyes

One method commonly used for the synthesis of pentamethine dyes involves the condensation of a salt of heterocyclic base **VI** containing a reactive methyl group with malondialdehyde dianil hydrochloride (**57**). This method was applied for the synthesis of a series of symmetrical pentamethine dyes of the general formula **XI** (Scheme 26), which serve as sensitizers and fluorescent labels. Quaternary salt **VI** is condensed with dianil hydrochloride **57** in the presence of a base.[29, 47–49, 57, 58, 78, 82]

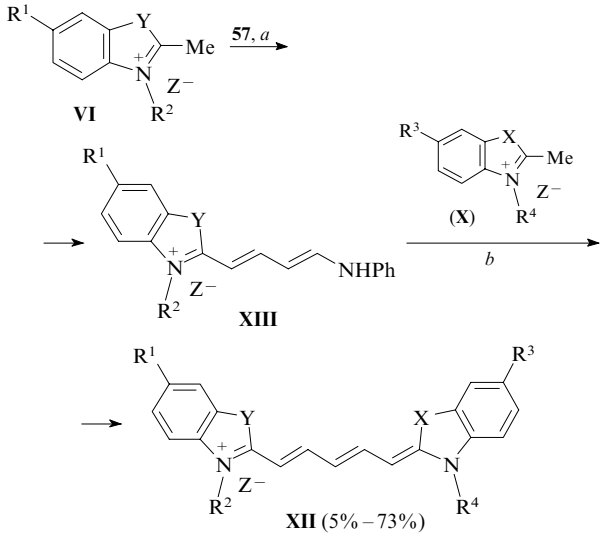
Scheme 26



Y = S, CMe_2; R^1 = H, $P(O)(OH)_2$, SO_3^-; R^2 = H, Cl; R^3 = $(CH_2)_2CO_2H$, $(CH_2)_5CO_2H$, $CH_2C_6H_4CO_2H$-4, $(CH_2)_2OH$, $(CH_2)_4SO_3H$, $(CH_2)_4SO_2NHAc$; $R^3 + Z^- = CH_2C_6H_4SO_3^-$-4; Z = Br, I, OH; (*a*) piperidine, Δ; or Et_3N, Ac_2O, Δ; or Et_3N, EtOH, Δ; or Et_3N, Py, Δ; or Py, Ac_2O, Δ; or AcONa, Ac_2O, Δ

Malondialdehyde dianil hydrochloride (**57**) is suitable for the synthesis of both symmetrical and unsymmetrical pentamethine dyes. The synthesis of unsymmetrical pentamethine dyes of the general formula **XII** (Scheme 27) involves the condensation of a salt of heterocyclic base **VI** with dianil hydrochloride **57** giving intermediate **XIII** followed by the condensation of the latter with another salt **X**.[58, 76, 77, 83–86]

Scheme 27

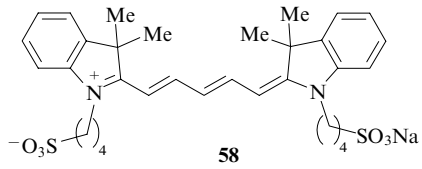


Y = CMe_2, $CMe(CH_2)_5CO_2H$, $CMe(CH_2)_4SO_3H$; X = S, CMe_2, $CMe(CH_2)_5CO_2H$, $CMe(CH_2)_4SO_3H$; R^1 = H, SO_3H; $R^1 + Z^- = SO_3^-$; R^2 = $(CH_2)_4CO_2H$, $(CH_2)_5CO_2H$, $(CH_2)_3SO_3H$, $(CH_2)_4SO_3H$, $(CH_2)_4$(2-Th); R^3 = H, CO_2H, SO_3H, $P(O)(OH)_2$; R^4 = $(CH_2)_5CO_2H$, $(CH_2)_3SO_3H$, $(CH_2)_4SO_3H$; Z = Br, I, OH; Th is thienyl; (*a*) AcOH, Ac_2O, Δ; or AcOH, Δ; or Et_3N, Ac_2O, Δ; (*b*) Py, Ac_2O, Δ; or Py, Ac_2O, N_2, Δ; or Et_3N, Ac_2O, Δ; or AcONa, AcOH, Ac_2O, Δ; or Py, AcOH, Ac_2O, Δ

Pentamethine dyes of type **XII** are used in biological studies as fluorescent labels and probes.[58, 76–78, 83–85] A large number of sulfo groups in the dye molecule increases its solubility in water and reduces its tendency to aggregate.

Dye **58** containing sulfobutyl groups forms a 1 : 2 inclusion complex with cucurbituril CB[7]. In this complex, two CB[7] molecules are bound to one dye molecule. The formation of the complex is accompanied by an almost twofold increase in the fluorescence quantum yield.[12, 13]

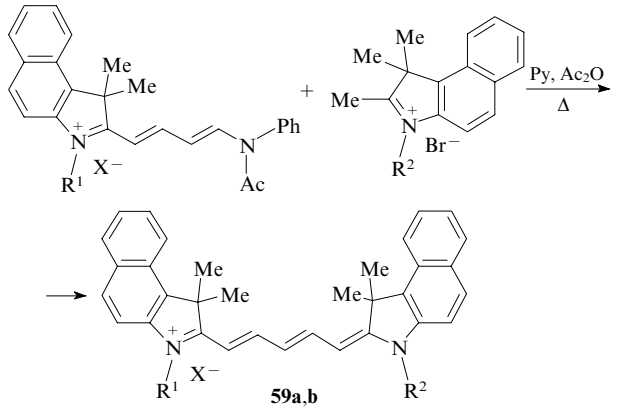
Structure 58



The above-described method was applied for the synthesis of water-soluble unsymmetrical pentamethine dyes **59a** (see Ref. 82) and **59b** (see Ref. 83) based on benzindole (Scheme 28). The fluorescence band maxima of these compounds are in the near-IR region. These dyes hold promise as fluorescent labels for DNA sequencing.[87–89]

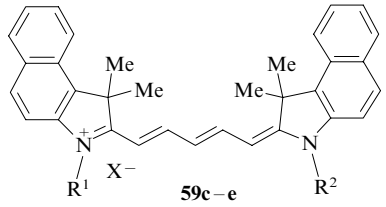
The diversity of dyes having different physicochemical properties is achieved by varying the substituents. However, in some cases, the reagents and conditions used for the synthesis of cyanine dyes are incompatible with reactive groups. In these cases, appropriate protecting groups are employed, and the already synthesized dye is functionalized. Thus, the phthalimide protecting group in dye **59b** is

Scheme 28

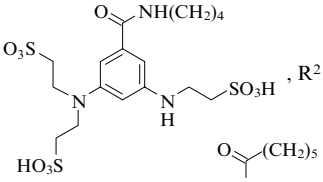


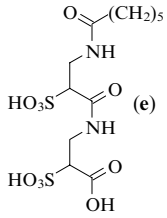
$R^1 + X^- = (CH_2)_3SO_3^-$, $R^2 = (CH_2)_5CO_2H$ (**a**, yield 80%);
$R^1 = (CH_2)_5CO_2H$, $R^2 = (CH_2)_4NPhth$, X = Br (**b**, 82%)

Structures 59c–e



$R^1 = (CH_2)_4\overset{+}{N}H_3\ CF_3CO_2^-$, $R^2 = (CH_2)_5CO_2H$, $X = CF_3CO_2^-$ (**c**);

$R^1 + X^- =$  , $R^2 = (CH_2)_5CO_2H$ (**d**);

$R^1 + X^- = (CH_2)_3SO_3^-$, $R^2 =$  (**e**)

removed with hydrazine hydrate to form dye **59c** containing the terminal ammonium group in the N-substituent. Dye **59c** was prepared as an intermediate and was used without detailed characterization. Due to the presence of the ammonium group, this dye can be further functionalized to change its hydrophobic–hydrophilic and photophysical properties. In this case, the carboxy group remains free and can form a covalent bond with a biomolecule.[87–89] This method was applied for the synthesis of dyes **59d**,**e**.

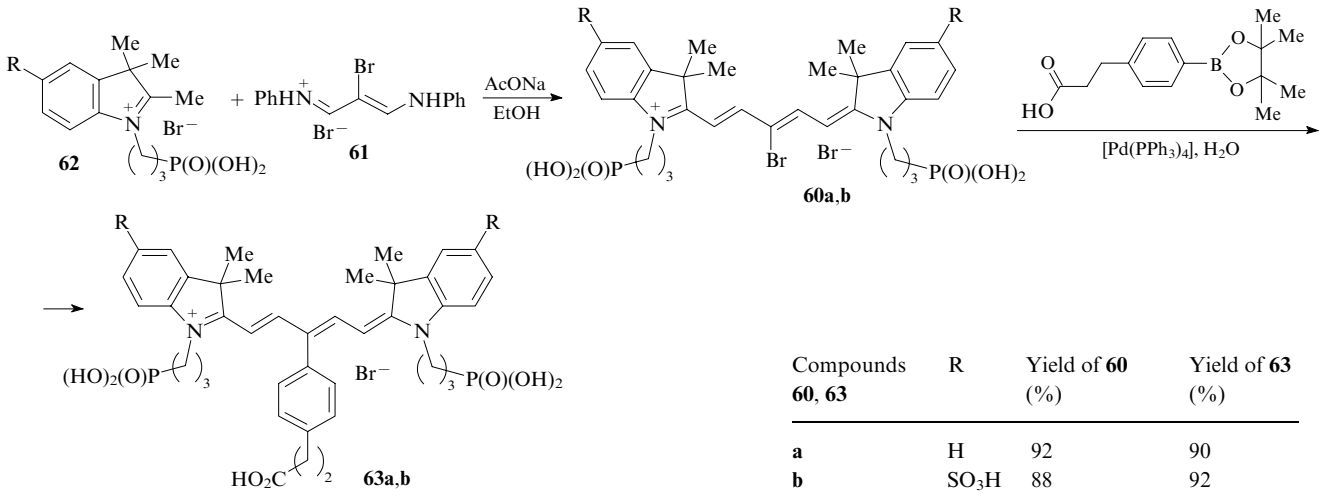
meso-Bromo-substituted pentamethine dyes **60a**,**b** (Scheme 29) can be synthesized using brominated glutaconaldehyde dianil hydrobromide **61**.[90] Quaternary salt **62** is condensed with dianil hydrobromide **61** in the presence of sodium acetate in ethanol. Then intermediates **60** are modified at the *meso* position, and the resulting dyes **63a**,**b** are used in biomedical studies as imaging agents in bone tissues.

Another approach to the synthesis of symmetrical pentamethine dyes implies the use of pyrimidine derivatives that serve as donors of a three-carbon group. Dyes **64** were produced by the condensation of quaternary salts **65a,b** with 2-methylsulfanylpyrimidinium salts **66a–c** and 2-aminopyrimidinium salts **66d** in the presence of triethylamine as the condensing agent (Scheme 30).[91]

A similar approach was used in the synthesis of symmetrical pentamethine dyes **67a**,**b** containing N-ammonioalkyl substituents in heterocyclic moieties (Scheme 31).[30,31] First, the condensation of quaternary salts **37b** or **68a**,**b** with 2-amino-1-methylpyrimidinium perchlorate gave pentamethine dyes **69a–c** containing phthalimide protecting groups as intermediates. The reaction was performed in pyridine or acetic anhydride in the presence of triethylamine. Quaternary salts **37b**, **68a**,**b** were synthesized by the quaternization of heterocyclic bases **6c**, **38a** with *N*-(3-bromopropyl)phthalimide (**12a**) or *N*-(4-bromobutyl)phthalimide (**12c**) followed by the treatment with $HClO_4$. The phthalimide protecting groups were removed by hydrazinolysis or the treatment with a solution of methylamine in ethanol. The subsequent treatment of the reaction mixture with $HClO_4$ gave pentamethine dyes **67a**,**b** containing terminal ammonium groups in yields of up to 51%.

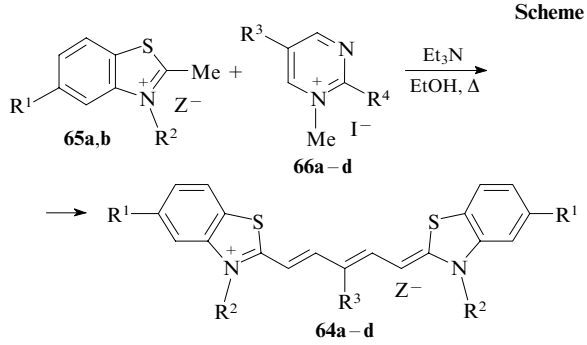
Pentamethine dyes **67a**,**b** of the indolenine series containing N-ammonioalkyl substituents interact with bis(18-

Scheme 29



Compounds **60**, **63**	R	Yield of **60** (%)	Yield of **63** (%)
a	H	92	90
b	SO_3H	88	92

Scheme 30



65: R^1 = H, R^2 = $(CH_2)_2OH$ (**a**); R^1 = Cl, R^2 = $(CH_2)_2CO_2H$ (**b**);
66: R^4 = SMe: R^3 = Me (**a**), Ph (**b**), Bu^n (**c**); R^3 = H, R^4 = NH_2 (**d**)

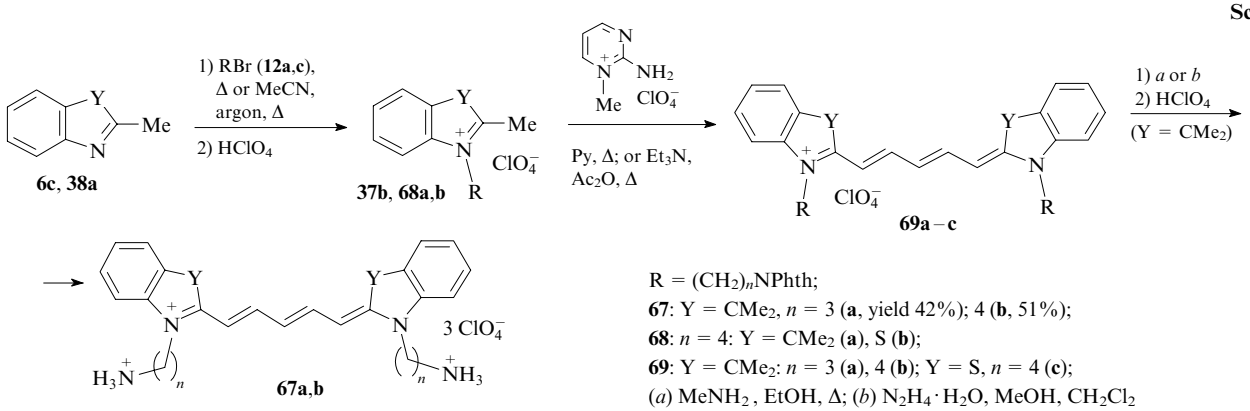
Compounds **64**	R^1	R^2	R^3	R^4	Z	Yield (%)
a	H	$(CH_2)_2OH$	Me	SMe	I	67
b	H	$(CH_2)_2OH$	Ph	SMe	I	58
c	H	$(CH_2)_2OH$	Bu^n	SMe	I	27
d	Cl	$(CH_2)_2CO_2H$	H	NH_2	OH	52

crown-6)stilbene to form not only bimolecular but also trimolecular complexes, in which the dye molecule is located between two stilbene molecules. The steric strain in the bimolecular complexes, which arises due to geometric mismatch of the distances between the binding sites of the dye and stilbene molecules, is apparently the driving force for the formation of trimolecular complexes.[32]

Symmetrical pentamethine dyes **70a–e** were synthesized by the condensation of salts of heterocyclic bases **71** with 1,3,3-trimethoxypropene (Scheme 32) in order to prepare dyes having improved photophysical characteristics.[58, 73] In this series of dyes, derivative **70a** containing sulfo groups in the benzene rings is of particular interest. This dye has a high fluorescence quantum yield and is readily soluble in water. Due to the presence of the terminal carboxy group, this compound can be transformed into the active form (succinimide ester), which is readily bound to biomolecules containing amino groups.

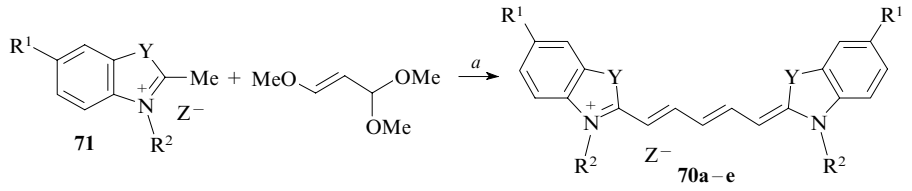
Shao *et al.*[92] described another method for the synthesis of symmetrical pentamethine dyes. Dye **72** containing a carboxybutyl group in the *meso* position was synthesized by the condensation of betaine **73** with highly reactive intermediate **74**, which was generated *in situ* by the amidoformy-

Scheme 31



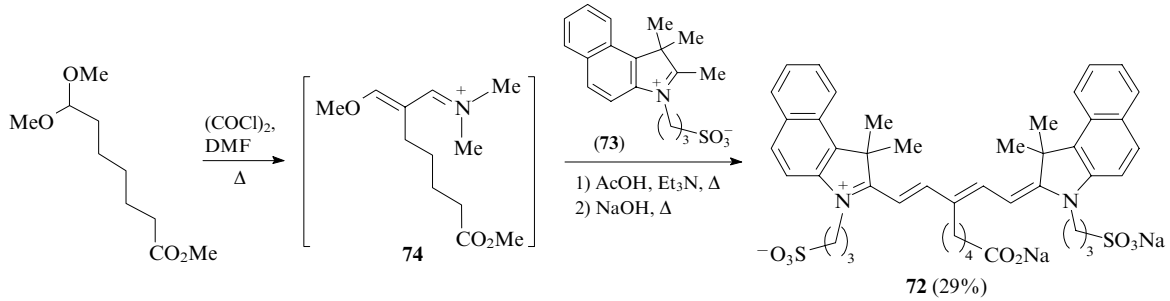
R = $(CH_2)_nNPhth$;
67: Y = CMe_2, *n* = 3 (**a**, yield 42%); 4 (**b**, 51%);
68: *n* = 4: Y = CMe_2 (**a**), S (**b**);
69: Y = CMe_2: *n* = 3 (**a**), 4 (**b**); Y = S, *n* = 4 (**c**);
(*a*) $MeNH_2$, EtOH, Δ; (*b*) $N_2H_4 \cdot H_2O$, MeOH, CH_2Cl_2

Scheme 32



71: Y = CMe_2, S, Se; Z = Br, I, ClO_4; **70**: Y = CMe_2, $R^1 + Z^- = SO_3^-$, R^2 = $(CH_2)_5CO_2H$ (**a**, yield 75%); R^1 = H, R^2 = $(CH_2)_2Ac$, Z = Br: Y = S (**b**, 29%), Se (**c**, 38%); Y = S, R^1 = H: R^2 = $(CH_2)_2CH(OEt)_2$, Z = ClO_4 (**d**, 57%); R^2 = $(CH_2)_2CH{=}NNHPh$, Z = I (**e**, 6%);
(*a*) AcOK, MeOH; or $AcNMe_2$, Δ; or MeCN, Δ; or Py, PhCN, MeCN, Δ; or 1) $AcNMe_2$, Δ; 2) $NaClO_4$, H_2O

Scheme 33



72 (29%)

lation of methyl 7,7-dimethoxyheptanoate with oxalyl chloride in DMF (Scheme 33).

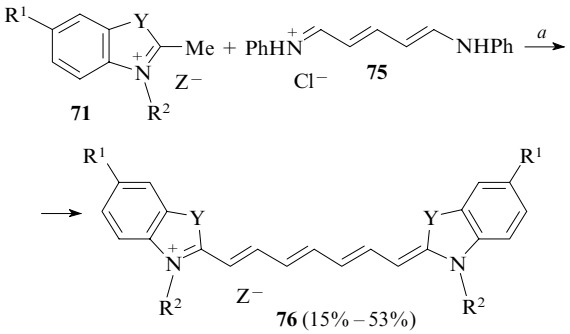
Earlier, pentamethine dyes have been used in photographic materials. Currently, their main application is in biological studies, in which the dyes serve as fluorescent labels and probes. Due to the introduction of various terminal functional groups, dyes can be bound to biomolecules through both covalent bonds and non-covalent supramolecular interactions.

V. Heptamethine dyes

The main method for the synthesis of both symmetrical and unsymmetrical heptamethine dyes involves the condensation of salts of heterocyclic bases with glutaconaldehyde dianil hydrochloride (**75**).

The condensation of betaines **71** with dianil hydrochloride **75** affords symmetrical dyes **76** (Scheme 34),[44, 93, 94] which have absorption maxima in the near-IR region, are readily soluble in water and are used as photosensitizers [58] and fluorescent labels for the detection of proteins.[93, 94]

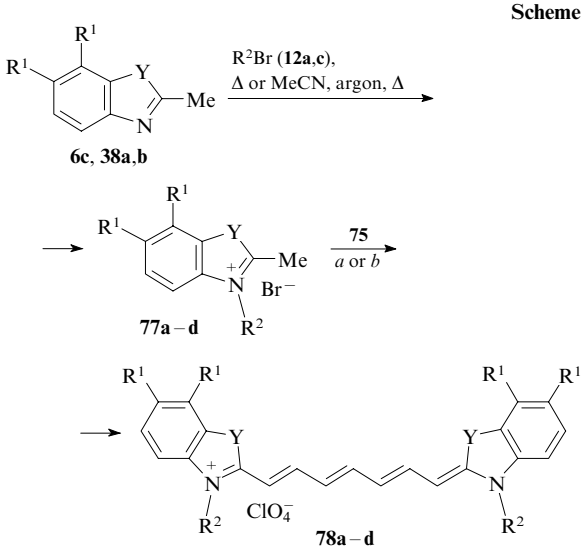
Scheme 34



Y = S, CMe_2; R^1 = H, CO_2H, SO_3H; $R^1 + Z^- = SO_3^-$;
$R^2 = (CH_2)_2OAc$, $(CH_2)_2OEt$, $(CH_2)_2CO_2Et$, $(CH_2)_5CO_2H$;
$R^2 + Z^- = (CH_2)_4SO_3^-$, $C_6H_4SO_3^-$-4; Z = Br, I;
(*a*) piperidine, EtOH, 0 °C; or piperidine, EtOH, 10 °C;
or Py, Ac_2O, Δ; or Ac_2O, AcOH, Δ

A similar condensation of quaternary heterocyclic salts **77a–d** with dianil hydrochloride **75** afforded symmetrical heptamethine dyes **78a–d** containing two phthalimidoalkyl groups at the nitrogen atoms (Scheme 35).[30] The reaction was performed in the presence of a base. Quaternary salts

Scheme 35

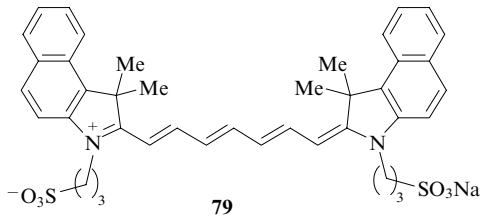


$R^2 = (CH_2)_4NPhth$; **78**: Y = S, R^1 = H: *n* = 3 (**a**, yield 53%), 4 (**b**, 63%); Y = CMe_2, *n* = 3: R^1 = H (**c**, 87%), $R^1 - R^1$ is benzo (**d**, 45%); (*a*) 1) piperidine, MeOH, −10 °C; 2) $NaClO_4$, H_2O; (*b*) 1) Et_3N, Ac_2O, Δ; 2) $HClO_4$

77a–d were generated by the quaternization of heterocyclic bases **6c**, **38a**,**b** with phthalimide derivatives **12a**,**c**.

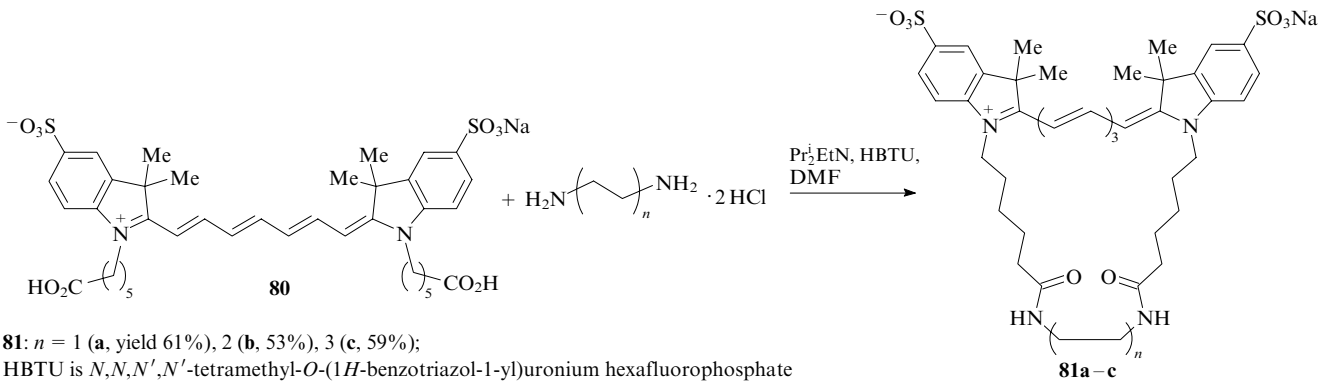
Barros *et al.*[18] studied the complexation of heptamethine dye **79** with β-cyclodextrin. In an aqueous solution, this dye is prone to dimerization. The spectrophotometric and fluorescence titration showed that compound **79** forms predominantly the 1 : 1 complex with β-CD, which is accompanied by an increase in the intensity of the absorption band of the monomer and fluorescence enhancement.

Structure 79



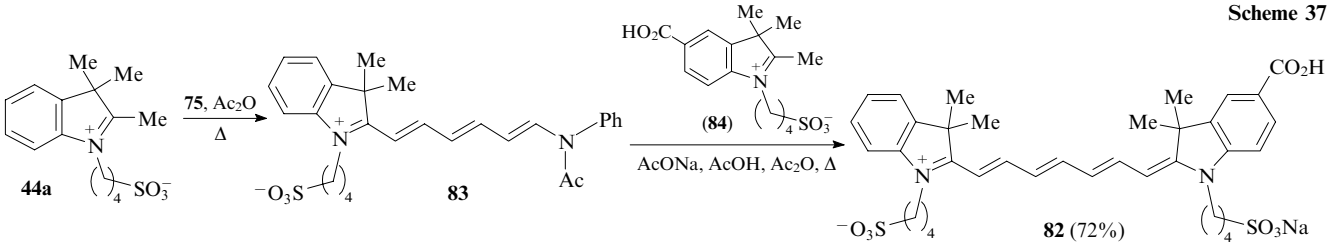
The condensation of dye **80** containing carboxypentyl groups with diaminoalkane dihydrochlorides afforded macrocyclic compounds **81a–c** (Scheme 36).[95] In dyes **81a–c**,

Scheme 36



81: *n* = 1 (**a**, yield 61%), 2 (**b**, 53%), 3 (**c**, 59%);
HBTU is *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate

Scheme 37

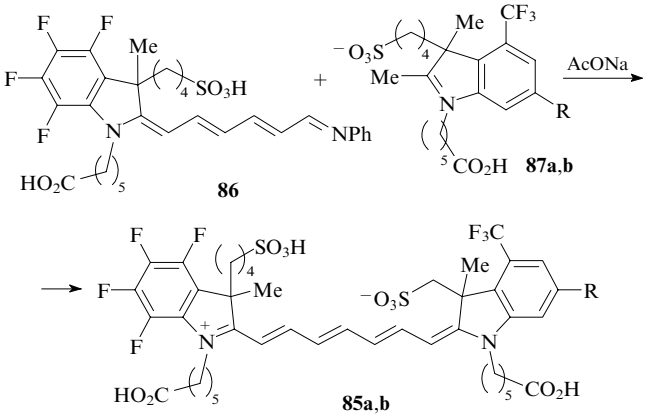


the *trans*–*cis* isomerization of the polymethine chain is hindered, resulting in an increase in their thermal stability, photostability and fluorescence intensity.

Unsymmetrical heptamethine dye **82** was synthesized by the condensation of dianil hydrochloride **75** with heterocyclic salt **44a** [Y = CMe_2, R^1 = H, R^2 = $(CH_2)_4SO_3^-$] giving intermediate **83** followed by the condensation of the latter with another heterocyclic salt **84** (Scheme 37). The resulting dye is employed as a fluorescent label for the hormone somatostatin, the binding to which occurs through an amide bond between the carboxy group of the dye and the terminal amino group of the protein.[85]

Unsymmetrical polyfluorinated dyes **85a**,**b**, which were produced from intermediate **86** and heterocyclic salts **87a**,**b** (Scheme 38), were covered by a patent.[96] Compound **86** was also synthesized using dianil hydrochloride **75**. Compounds **85a**,**b** are characterized by higher photostability and they are more prone to disaggregation compared to their unfluorinated analogues. These dyes are promising fluorescent labels in the near-IR region.

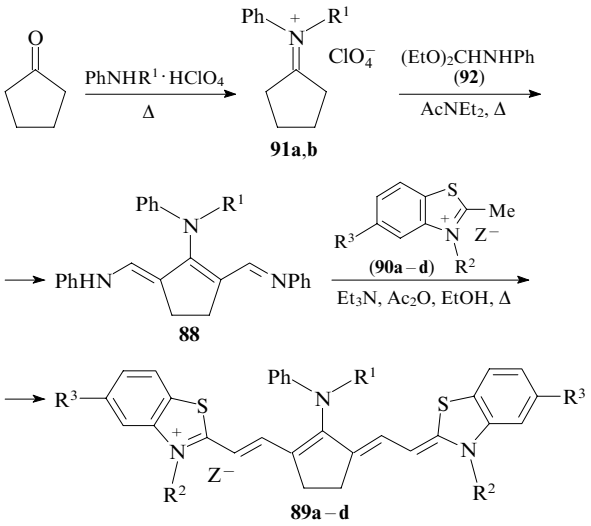
Scheme 38



R = CF_3 (**a**), H (**b**)

The main limitation for the use of heptamethine dyes compared to other cyanine dyes is associated with their relatively low photostability. The latter can be enhanced by the introduction of a structurally rigid electron-donating moiety into the polymethine chain.[97] Heptamethine dyes containing electron-donating substituents in the *meso* position of the polymethine chain are synthesized using structural analogues of glutaconaldehyde dianil, for example, compound **88**. For instance, symmetrical heptamethine dyes **89a**–**d** (Scheme 39) containing an amino group in the *meso* position[98, 99] were produced by the condensation of quaternary heterocyclic salts **90a**–**d** with dianils **88** in the presence of triethylamine. The synthesis of compounds **88** involves two steps: the reaction of cyclopentanone with methylphenyl- or diphenylamine hydroperchlorate giving iminium salts **91a**,**b** followed by the reaction of the latter with aminoacetal **92**.

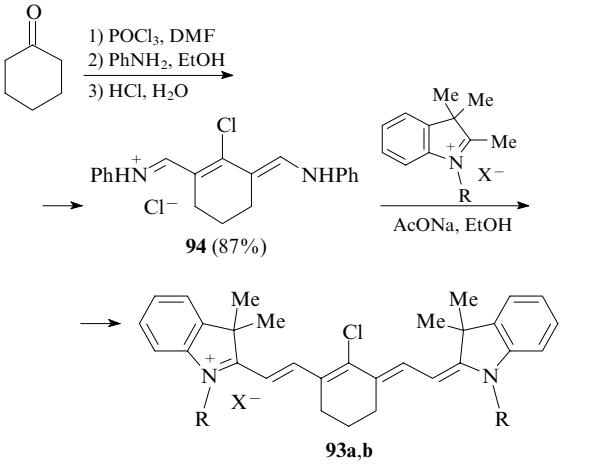
Scheme 39



89, **90**: R^1 = Ph, R^2 = $(CH_2)_3CO_2H$, $R^2 + Z^-$ = $(CH_2)_3CO_2^-$, R^3 = Cl (**a**, 63% yield of **89**); R^1 = Ph, R^2 = $(CH_2)_2OH$, R^3 = H, Z = ClO_4 (**b**, 43%); R^1 = Me, R^2 = $(CH_2)_2CO_2H$, $R^2 + Z^-$ = $(CH_2)_2CO_2^-$, R^3 = Cl (**c**, 17%); R^1 = Me, R^2 = $(CH_2)_3SO_3^-NHEt_3^+$, $R^2 + Z^-$ = $(CH_2)_3SO_3^-$, R^3 = H (**d**, 5%); **91**: R^1 = Ph (**a**), Me (**b**)

The presence of a chlorine atom in the *meso* position of the polymethine chain of heptamethine dyes **93a** (Ref. 100) and **93b** (Ref. 101) enables the introduction of various substituents by means of nucleophilic substitution.[87, 100, 101]

Scheme 40

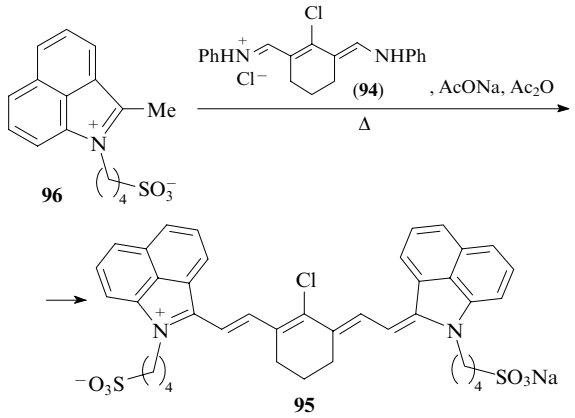


93: R + X^- = $(CH_2)_3SO_3^-$, R = $(CH_2)_3SO_3H$ (**a**, yield 52%); R = $(CH_2)_5CO_2H$, X = Br (**b**, 43%)

Water-soluble dyes **93a**,**b** were prepared by the condensation using dianil hydrochloride **94** (Scheme 40). The latter was generated from cyclohexanone by the successive treatment with $POCl_3$ in dimethylformamide, aniline in ethanol and an aqueous solution of HCl.

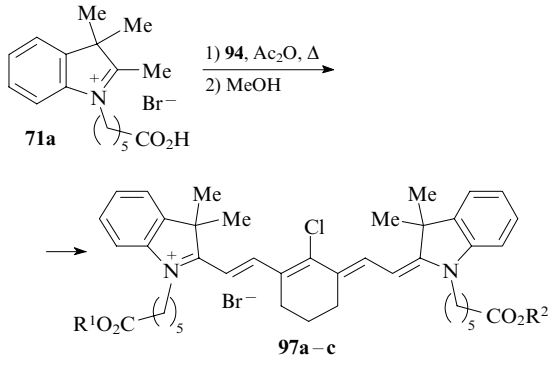
Henary *et al.*[102] reported the synthesis of benzo[*c*,*d*]indolium-based dye **95** by the similar condensation of 2-methylbenzo[*c*,*d*]indole betaine **96** with dianil hydrochloride **94** in acetic anhydride in the presence of sodium acetate (Scheme 41).

Scheme 41



This method was slightly modified to prepare unsymmetrical dyes.[103] The condensation of quaternary salt **71a** (Y = CMe_2, R^1 = H, R^2 = $(CH_2)_5CO_2H$) with dianil hydrochloride **94** followed by the treatment of the reaction mixture with methanol furnished, in addition to symmetrical dye **97a** containing two carboxyalkyl groups, dye **97b** bearing two ester groups and unsymmetrical dye **97c** with one ester group (Scheme 42). A mixture of dyes **97a**–**c** is separated by silica gel column chromatography. Since the dyes containing one or two ester groups selectively accumulate in cancer cells, they can be used for the diagnosis and imaging of cancer tissues directly, without the covalent attachment to receptor molecules.

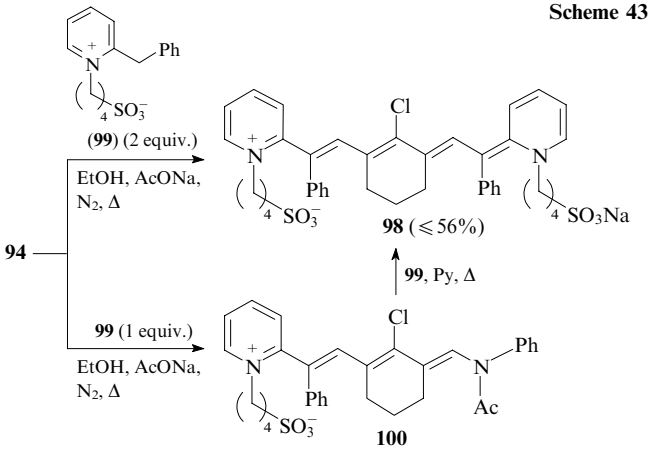
Scheme 42



97: R^1 = R^2 = H (**a**, yield 20%); Me (**b**, 15%);
R^1 = H, R^2 = Me (**c**, 30%)

Two methods were developed for the synthesis of dye **98** based on betaine **99** (Scheme 43).[104] In one method, dye **98** is synthesized by the condensation of betaine **99** (2 equiv.) with dianil hydrochloride **94** (1 equiv.) in ethanol in the presence of sodium acetate. Another approach involves two steps. In the first step, compound **100** is generated by the reaction of equimolar amounts of betaine **99** and dianil

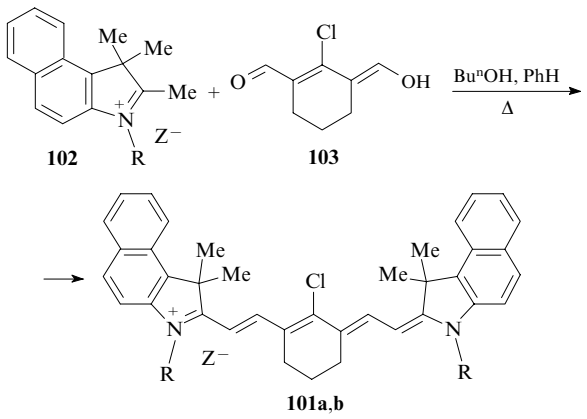
Scheme 43



hydrochloride **94** in ethanol in the presence of sodium acetate. Then intermediate **100** is introduced into the reaction with betaine **99** in pyridine. Dye **98** exhibits high antibacterial and antitumor activities.

A new method for the synthesis of *meso*-chlorinated benzindole-based heptamethine dyes **101a**,**b** (Scheme 44) and their indole-based analogues was developed by Narayanan and Patonay.[105] Quaternary salts of heterocyclic base **102** containing an activated methyl group are condensed with dialdehyde **103** in a mixture of n-butanol and benzene in the absence of a catalyst. Water that is eliminated in the course of condensation is removed by azeotropic distillation.

Scheme 44

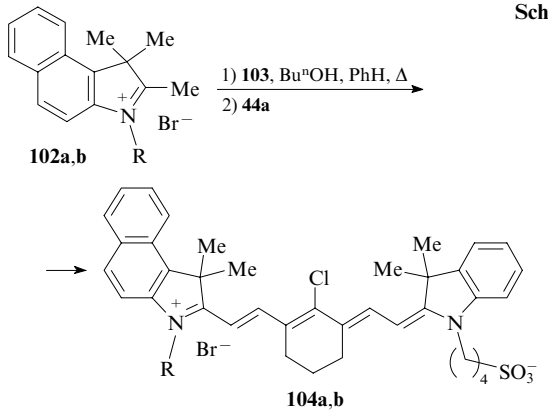


101: R + Z^- = $(CH_2)_4SO_3^-$, R = $(CH_2)_4SO_3H$ (**a**, yield 82%);
R = $(CH_2)_3NH_3^+Br^-$, Z = Br (**b**, 95%)

This method is applicable also to the synthesis of unsymmetrical dyes.[105] A mixture of quaternary salt **102a** or **102b** and dialdehyde **103** in a 1 : 1 ratio is refluxed in a mixture of n-butanol and benzene. Then betaine **44a** is introduced into the reaction, resulting in the formation of unsymmetrical dyes **104a**,**b** as the major products (Scheme 45). Therefore, this method can be used to synthesize unsymmetrical dyes without isolation of the intermediate.

Chen *et al.*[106] reported the synthesis of a series of heptamethine dyes using dialdehyde **103** as a donor of the central carbon moiety of the polymethine chain in acetic anhydride in the presence of sodium acetate (Scheme 46). The examination of photostability of dyes **105a**–**d** showed that the introduction of N-substituents containing electron-

Scheme 45

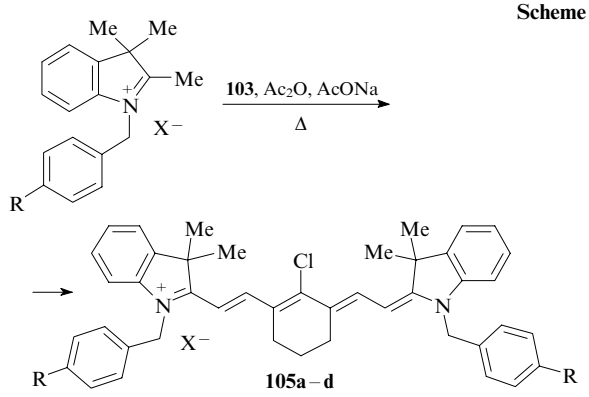


102a,b **104a,b**

R = $(CH_2)_3NH_3^+Br^-$ (**a**, yield 95%), $(CH_2)_4NPhth$ (**b**, 55%)

withdrawing groups in the benzene rings decreases the decolorization rate of the dyes.

Scheme 46



105: X = Cl: R = CO_2H (**a**, yield 52%), Me (**b**, 31%), F (**c**, 25%); R = NO_2, X = Br (**d**, 27%)

Heptamethine dyes, like the groups of cyanine dyes considered above, are used mainly as fluorescent labels and probes for biomolecules. Meanwhile, heptamethine dyes are of particular interest because their fluorescence bands generally appear in the near-IR region, in which living tissues are transparent.

VI. Conclusion

The presented review summarizes data on the methods of synthesis of mono-, tri-, penta- and heptamethine cyanine dyes containing functional groups in N-substituents. The synthesis of these dyes involves the condensation of quaternary salts of heterocyclic bases containing a reactive methyl group in position 2 or 4 with C-electrophiles.

Functional groups are introduced into N-substituents in the step of the generation of quaternary salts through quaternization of heterocyclic bases with appropriate alkylating agents or, more rarely, in the course of the formation of the heterocycles. Various cyanine dyes containing mainly sulfo-, hydroxy-, acetoxy-, acetyl- and carboxyalkyl N-substituents were synthesized by the condensation of quaternary heterocyclic salts with C-electrophiles. If the substituents are reactive towards the reactants or conditions of the synthesis of the dyes, the already synthesized dyes are functionalized. For this reason, only a few examples of the synthesis of cyanine dyes having terminal nitrogen-containing groups are documented. On the whole, this synthesis has received insufficient attention despite the fact that cyanine dyes containing terminal ammonioalkyl substituents at the nitrogen atoms of heterocyclic moieties hold promise for practical applications. Due to the ability to be covalently bound to biomolecules at the amino group, these dyes, exhibiting fluorescence in the visible and near-IR region, hold promise as fluorescent labels and probes for visualization and investigation of the properties of nucleic acids, proteins and biological membranes.

The presence of primary ammonium groups capable of hydrogen bonding provides the possibility for the self-assembly of dyes to form photoactive supramolecular complexes with various organic molecules, including biomolecules, that contain electron-donating oxygen and nitrogen atoms as heteroatoms. This interaction, due to the cooperative effect of numerous hydrogen bonds, can give rise to highly stable supramolecular complexes.

A great structural diversity of mono-, tri-, penta- and heptamethine cyanine dyes and the presence of N-substituents with various functional groups offer great opportunities for the fine tuning of the properties of photoactive supramolecular systems based on these dyes.

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References

1. I I Levkoev *Organicheskie Veshchestva v Fotograficheskikh Protsessakh (Izbr. Trudy)* [Organic Substances in Photographic Processes (Selected Works)] (Moscow: Nauka, 1982)
2. S A Soper, Q L Mattingly *J. Am. Chem. Soc.* **116** 3744 (1994)
3. L Strekowski, M Lipowska, G Patonay *J. Org. Chem.* **57** 4578 (1992)
4. G Patonay, J Salon, J Sowell, L Strekowski *Molecules* **9** 40 (2004)
5. M S T Gonçalves *Chem. Rev.* **109** 190 (2009)
6. E M S Stennett, M A Ciuba, M Levitus *Chem. Soc. Rev.* **43** 1057 (2014)
7. A V Vannikov *Ros. Khim. Zh.* **45** (5 – 6) 41 (2001)
8. Patent RF 2261890 (2003)
9. A Ehret, L Stuhl, M T Spitler *J. Phys. Chem. B* **105** 9960 (2001)
10. L A Bottomley, J E Coury, P N First *Anal. Chem.* **68** 185 (1996)
11. J Fabian, H Nakazumi, M Matsuoka *Chem. Rev.* **92** 1197 (1992)
12. W M Nau, J Mohanty *Int. J. Photoenergy* **7** 133 (2005)
13. A L Koner, W M Nau *Supramol. Chem.* **19** 55 (2007)
14. S Gadde, E K Batchelor, A E Kaifer *Chem. – Eur. J.* **15** 6025 (2009)
15. N Kh Petrov, D A Ivanov, D V Golubkov, S P Gromov, M V Alfimov *Chem. Phys. Lett.* **480** 96 (2009)
16. G V Zakharova, D A Zhizhimov, V G Avakyan, S K Sazonov, S P Gromov, A K Chibisov *High Energy Chem.* **48** 76 (2014) [*Khim. Vys. Energ.* **48** 104 (2014)]
17. G V Zakharova, D A Zhizhimov, S K Sazonov, V G Avakyan, S P Gromov, H Glrner, A K Chibisov *J. Photochem. Photobiol., A* **302** 69 (2015)
18. T C Barros, S H Toma, H E Toma, E L Bastos, M S Baptista *J. Phys. Org. Chem.* **23** 893 (2010)
19. F M Hamer *The Cyanine Dyes and Related Compounds (The Chemistry of Heterocyclic Compounds* Vol. 18) (Ed. A Weissberger) (New York: Wiley-Interscience, 1964)
20. L Berlin, O Reister, in *Methoden der Organischen Chemie (Houben-Weyl)* Vol. 5/1d (Ed. E Müller) (Stuttgart: Georg Thieme, 1972) p. 227

21. G E Ficken, in *The Chemistry of Synthetic Dyes* Vol. 4 (Ed. K Venkataramana) (Amsterdam: Elsevier, 1971) p. 211
22. D M Sturmer, in *Special Topics in Heterocyclic Chemistry* Vol. 30 (Eds A Weissberger, E C Taylor) (New York, London: Wiley-Interscience, 1977) p. 441
23. B I Shapiro *Russ. Chem. Rev.* **63** 231 (1994)
24. Z Zhu *Dyes Pigm.* **27** 77 (1995)
25. A Mishra, R K Behera, P K Behera, B K Mishra, G B Behera *Chem. Rev.* **100** 1973 (2000)
26. M Mojzych, M Henary, in *Heterocyclic Polymethine Dyes. Synthesis, Properties and Applications (Topics in Heterocyclic Chemistry* Vol. 14) (Ed. L Strekowski) (Berlin, Heidelberg: Springer-Verlag, 2008) p. 1
27. M Panigrahi, S Dash, S Patel, B K Mishra *Tetrahedron* **68** 781 (2012)
28. Patent GB 1096406 (1967)
29. Patent US 2238231 (1941)
30. Patent RF 2472822 (2013)
31. S P Gromov, M V Fomina, A S Nikiforov, A I Vedernikov, L G Kuz'mina, J A K Howard *Tetrahedron* **69** 5898 (2013)
32. M V Fomina, A S Nikiforov, A I Vedernikov, N A Kurchavov, S P Gromov *Mendeleev Commun.* **24** 295 (2014)
33. E A Gorkina, A Yu Nikolaev, A Yu Gerval'd, S K Sazonov, E Yu Bulychev *Vestn. MITKhT* **8** (1) 81 (2013)
34. W Huang, Sh Wang, H Yang, Q Gong, G Xu, J Xiang, C Chen, W Yan *J. Chem. Phys.* **117** 6614 (2002)
35. Patent WO 2005056689 (2005)
36. N I Gadjev, T G Deligeorgiev, S H Kim *Dyes Pigm.* **40** 181 (1999)
37. T Deligeorgiev, A Vasilev, K-H Drexhage *Dyes Pigm.* **73** 69 (2007)
38. T Deligeorgiev, A Vasilev, K-H Drexhage *Dyes Pigm.* **74** 320 (2007)
39. J Kabatc, J Paczkowski *Dyes Pigm.* **86** 133 (2010)
40. A Vasilev, T Deligeorgiev, S Kaloyanova, S Stoyanov, V Maximova, J J Vaquero, J Alvarez-Builla *Color. Technol.* **127** 69 (2011)
41. T Deligeorgiev, N Gadjev, A Vasilev, K-H Drexhage, S M Yarmoluk *Dyes Pigm.* **70** 185 (2006)
42. T Deligeorgiev, N Gadjev, A Vasilev, K-H Drexhage, S M Yarmoluk *Dyes Pigm.* **72** 28 (2007)
43. B A Armitage *Top. Curr. Chem.* **253** 55 (2005)
44. Patent US 2231658 (1941)
45. Patent US 6280921 (2001)
46. R E F Boto, A S Olivera, L F V Ferreira, P Almeida *Dyes Pigm.* **48** 71 (2001)
47. Patent GB 904332 (1962)
48. Patent CA 400408 (1941)
49. Patent US 2213238 (1940)
50. Patent US 2776280 (1957)
51. Patent GB 886270 (1962)
52. Patent GB 886271 (1962)
53. Patent US 3156685 (1964)
54. Patent US 3424586 (1969)
55. Patent GB 1044734 (1966)
56. Patent US 3264110 (1966)
57. L Wang, X Peng, R Zhang, J Cui, G Xu, F Wang *Dyes Pigm.* **54** 107 (2002)
58. R B Mujumdar, L A Ernst, S R Mujumdar, Ch J Lewis, A S Waggoner *Bioconjug. Chem.* **4** 105 (1993)
59. S H Sinha, E A Owens, Y Feng, Y Yang, Y Xie, Y Tu, M Henary, Y G Zheng *Eur. J. Med. Chem.* **54** 647 (2012)
60. L Q Wang, L Zhao, W W Nie, L H Zheng, J D Wang, Q R Li, J Zhai, Z W Liu, X J Peng *Chin. Chem. Lett.* **19** 739 (2008)
61. C Haritoglou, M Kernt, P Laubichler, H Langhals, K Eibl, A Varja, S Thaler, A Kampik *Graefes Arch. Clin. Exp. Ophthalmol.* **250** 829 (2012)
62. X Chen, J Guo, X Peng, M Guo, Y Xu, L Shi, C Liang, L Wang, Y Gao, S Sun, S Cai *J. Photochem. Photobiol., A* **171** 231 (2005)
63. Patent US 7511284 (2009)
64. Patent GB 1077611 (1965)
65. Patent GB 654690 (1951)
66. Patent US 2503776 (1950)
67. Patent GB 1091739 (1967)
68. Patent GB 1020295 (1966)
69. Zh-H Peng, L Qun, X-F Zhou, S Carroll, H J Geise, B-x Peng, R Dommisse, R Carleer *J. Mater. Chem.* **6** 559 (1996)
70. M Takeuchi, T Mizuno, H Shinmori, M Nakashima, S Shinkai *Tetrahedron* **52** 1195 (1996)
71. Patent GB 1020295 (1955)
72. Patent US 2912329 (1959)
73. Patent US 3854956 (1974)
74. Patent US 3649266 (1972)
75. Patent US 3431111 (1969)
76. Patent US 7511155 (2005)
77. Patent US 6977305 (2005)
78. M V Reddington *Bioconjug. Chem.* **18** 2178 (2007)
79. Y Xu, Y Liu, X Qian *J. Photochem. Photobiol., A* **190** 1 (2007)
80. F Song, L Wang, X Qiao, B Wang, S Sun, J Fan, L Zhang, X Peng *Org. Biomol. Chem.* **8** 4249 (2010)
81. K Meguellati, G Koripelly, S Ladame *Angew. Chem., Int. Ed.* **49** 2738 (2010)
82. L Wang, J Fan, X Qiao, X Peng, B Dai, B Wang, S Sun, L Zhang, Y Zhang *J. Photochem. Photobiol., A* **210** 168 (2010)
83. Patent US 20060223076 (2006)
84. Patent WO 2008139206 (2008)
85. K Licha, C Hessenius, A Becker, P Henklein, M Bauer, S Wisniewski, B Wiedenmann, W Semmler *Bioconjug. Chem.* **12** 44 (2001)
86. L I Markova, I A Fedyunyayeva, Y A Povrozin, O M Semenova, S U Khabuseva, E A Terpetschnig, L D Patsenker *Dyes Pigm.* **96** 535 (2013)
87. C Bouteiller, G Clavé, A Bernardin, B Chipon, M Massonneau, P-Y Renard, A Romieu *Bioconjug. Chem.* **18** 1303 (2007)
88. B Chipon, G Clavé, C Bouteiller, M Massonneau, P-Y Renard, A Romieu *Tetrahedron Lett.* **47** 8279 (2006)
89. A Romieu, D Brossard, M Hamon, H Outaabout, Ch Portal, P-Y Renard *Bioconjug. Chem.* **19** 279 (2008)
90. H Hyun, H Wada, K Bao, J Gravier, Y Yadav, M Laramie, M Henary, J V Frangioni, H S Choi *Angew. Chem., Int. Ed.* **53** 10668 (2014)
91. Patent GB 870633 (1961)
92. F Shao, H Yuan, L Josephson, R Weissleder, S A Hilderbrand *Dyes Pigm.* **90** 119 (2011)
93. H Wang, W-R Li, X-F Guo, H-Sh Zhang *Anal. Bioanal. Chem.* **387** 2857 (2007)
94. W-R Li, H Wang, T-X Yang, H-Sh Zhang *Anal. Bioanal. Chem.* **377** 350 (2003)
95. V E Shershov, M A Spitsyn, V E Kuznetsova, E N Timofeev, O A Ivashkina, I S Abramov, T V Nasedkina, A S Zasedatelev, A V Chudinov *Dyes Pigm.* **97** 353 (2013)
96. Patent US 20060239922 (2006)
97. F Song, X Peng, E Liu, R Zhang, X Chen, B Song *J. Photochem. Photobiol., A* **168** 53 (2004)
98. Patent US 3671648 (1972)
99. Patent US 3482978 (1969)
100. J H Flanagan Jr, Sh H Khan, S Menchen, S A Soper, R P Hammer *Bioconjug. Chem.* **8** 751 (1997)
101. Patent US 5453505 (1995)
102. M Henary, M Mojzych, M Say, L Strekowski *J. Heterocycl. Chem.* **46** 84 (2009)
103. M Henary, V Pannu, E A Owens, R Aneja *Bioorg. Med. Chem. Lett.* **22** 1242 (2012)
104. A A Fadda, R E El-Mekawy *Dyes Pigm.* **99** 512 (2013)
105. N Narayanan, G Patonay *J. Org. Chem.* **60** 2391 (1995)
106. X Chen, X Peng, A Cui, B Wang, L Wang, R Zhang *J. Photochem. Photobiol., A* **181** 79 (2006)