International Journal of Chemistry Studies
ISSN: 2581-348X; Impact Factor: RJIF 5.44
Received: 05-09-2020; Accepted: 19-09-2020; Published: 10-10-2020
www.chemistryjournal.in
Volume 4; Issue 4; 2020; Page No. 07-09

Studies of synthesis and applications of benzothiazole containing cyanine dyes

Pankaj Kumar
Begusarai, Bihar, India

Abstract
Heterocyclic compounds are of immense interest due to their extensive occurrence in nature as well as their applicability in the pharmaceutical industry. Benzothiazole and its derivatives encompass an attractive heterocyclic class that displays practical applications ranging from mevdicine to photography and agriculture, among other things. This review focuses on the synthesis and specific applications of various benzothiazole cyanine dyes. Benzothiazole-containing heterocyclic structures are prominent throughout the literature and it is very important to acknowledge their efficacy and applicability as we discuss herein.

Keywords: benzothiazole; cyanine dyes; synthesis

Introduction

Cyanine dyes are a unique class of compounds that have a wide range of applications in numerous fields. The first member of this type was reported by Williams in 1856 [1]. The name cyano was given due to the beautiful blue (blue – kyano in Greek) color of the dye. This dye was obtained by treatment of quinoline and 4-methylquinoline with amyl iodide followed by reaction with ammonia. Vogel in 1873 found that cyanine dyes can be used to increase sensitivity of the photographic plate [2]. It was the turning point in the history of the cyanine dyes.

Cyanine dyes are a subclass of polymethine dyes. As shown in, polymethine dyes consist of two nitrogen centers joined by a conjugated chain of odd number of methine carbons or a conjugated system of double bonds. This polymethine bridge connects an electron acceptor group at one end and an electron donor group at the other. Conjugation between the electron donor and acceptor groups results in delocalization of π electrons and hence positive charge over the two nitrogen atoms.

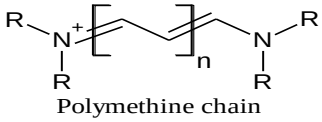

Fig 1

The monomethine and trimethine cyanine dyes usually absorb in the visible region (500–600 nm) of the electronic spectrum with each added (CH=CH) methine unit inducing a bathochromic shift of approximately 100 nm in the electronic spectrum resulting in an absorption wavelength of 700–800 nm for penta- and heptamethine cyanines. The 4-pyrilium, 4-thiopyrilium, and benz [*c, d*] indole heterocyclic end groups extend absorption/emission wavelength well into the near-infrared region, whereas the presence of the benzoxazole end group results in a hypsochromic shift in the electronic spectrum. Polymethine cyanine dyes are generally classi fied based on the nature of the end groups present on the polymethine chain. Dyes with two heterocyclic terminal groups are referred to as closed chain cyanine dyes or generally referred to as cyanines. The two heterocycles in the cyanines can either be identical or different. Hemicyanines are characterized by the presence of one heterocyclic and another non-cyclic end group. Dyes without a terminal heterocyclic moiety are defined as streptocyanines or open chain cyanines.

In the literature, it is recognized that in 1926, Koenig identified the chromophoric nature of the polymethine structure of the cyanine dye and reported the synthesis of the first chiral polymethine dye [3]. Since then many different types of cyanine dyes have been synthesized. The first bridged cyanine dye synthesis was published in 1933 where trimethine chain formed a part of cyclopentadiene ring[4]. In a review by Behera *et al*., it was discussed that some naturally occurring cyanine dyes have been isolated from *Beta vulgaris* and *Amanita muscaria* [5]. Cyanine dyes possess some characteristic properties which include structure-dependent photochemical stability, narrow absorption band, high molar absorption coefficients (~10^5 m^{-1} cm^{-1}), tendency to form aggregates in solution, and relatively high fluorescence intensity. A large number of cyanine dyes have been synthesized using different heterocycles such as indolenine, quinoline, benzoxazole, and benzothiazole.

Benzothiazoles have a planar structure, which is an essential criterion for nucleic acid binding and hence for their applications as an effective biological marker [6, 7]. The use of benzothiazole compounds as *in vivo* imaging agents for Alzheimer's disease is considered to be a major breakthrough for benzothiazole studies [8].

Synthesis and applications of benzothiazole cyanine dyes

The synthesis of the first benzothiazole cyanine dye was reported in the late 18th century [9]. It was synthesized by heating *N*-amylbenzothiazolium iodide and 2-methylbenzothiazole in the presence of ammonia. To date, a large number of symmetric and asymmetric benzothiazole cyanine dyes have been synthesized [10].

Benzothiazole cyanine dyes are commonly classified into four categories of mono-, tri-, penta-, and heptamethine

cyanine dyes. The spectral range for these dyes extends approximately between 450 and 750 nm in the electronic spectrum. In the past few years, many synthetic routes to benzothiazole cyanine dyes have been developed.

Monomethine benzothiazole cyanine dyes typically absorb in the visible region (450–470 nm) of the electronic spectrum depending on the substituents attached to the benzothiazole core structure. These dyes are characterized by a narrow absorption peak and high fluorescence intensity.

They are best known for their nucleic acid binding properties. The oldest method for the synthesis of the monomethine cyanine dyes involves condensation of an *N*-alkyl-2-(methylthio) benzothiazolium salt with another alkylated heterocycle with an activated methyl group [11]. This method was adopted for the synthesis of *β*-cyclodextrin functionalized benzothiazole cyanine dye [12]. *β*-Cyclodextrin possesses both a hydrophobic cavity and hydrophilic surface and is used for molecular recognition as a drug delivery agent in pharmaceutics [13]. The medicines containing vitamins are generally unstable to light, heat, and oxygen, whereas the formation of inclusion complexes of vitamins with *β*-cyclodextrin enhances the stability, solubility, and bioavailability of the drug [14]. Analysis of such inclusion interactions of vitamins are commonly conducted by means of spectrophotometric titration using external agents such as dyes as spectral probes. The incorporation of the dye molecule as host compound provides an option to easily recognize colorless guest molecules by direct titration.

The synthetic procedure shown above involves a major drawback of producing methyl mercaptan, which is a toxic pollutant. Researchers have overcome this problem by developing a new procedure that uses 2-iminoben zothiazoline instead of 2-methylthiobenzothiazolium salt [15].

This method can be used to synthesize symmetric and asymmetric cyanine dyes. In this procedure, cyanine dyes are prepared by melting 2-iminobenzothiazoline with quaternary heterocyclic salt containing 2- or 4-methyl groups, as depicted in Equation 2.

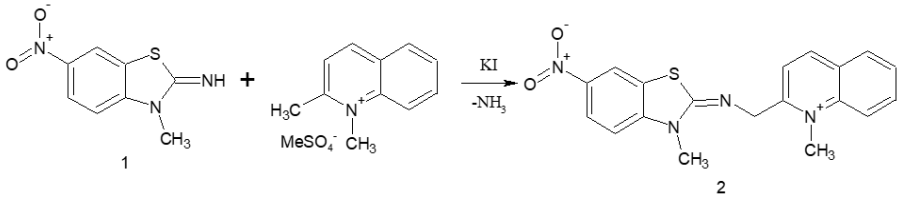

Fig 2

Deligeorgiev *et al*. described a novel procedure for the synthesis of benzothiazole monocyanines, which involves heating a sulfobetaine salt of *N*-alkylbenzothiazolium compound with the quaternary salt of a heterocyclic compound containing a reactive methyl group, as illustrated [16]. These reactions are usually carried out without solvent by heating the mixture to approximately 150–200°C. An alternative route to less thermostable compounds involves heating a solution in polar solvent. This synthetic procedure is characterized by high yields and short reaction times.

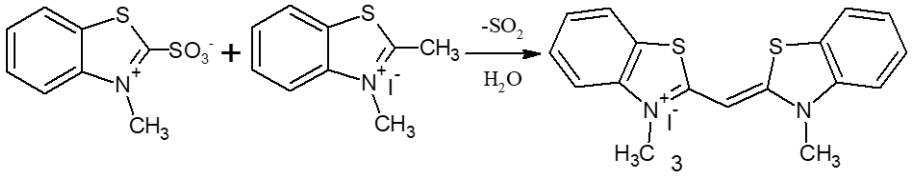

Fig 3

Another approach towards the synthesis of monomethine cyanine dyes involves condensation of *N*-alkyl-2-methylbenzothiazolium salt with 2-or 4-chloropyridinium or quinolinium substrate in a basic medium [17]. This synthetic procedure has been used to synthesize dicationic and tricationic benzothiazole cyanine dyes. In this particular case, the increased cationic charge helps increase water solubility of the dye.

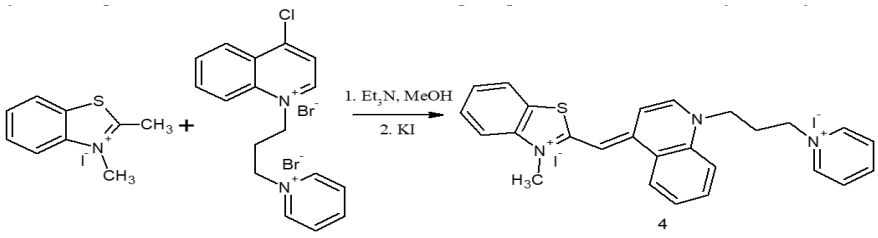

Fig 4

Compounds 2–4 are structural analogs of the thiazole orange dye which is used extensively for the purpose of nucleic acid detection, flow cytometry, and gel electrophoresis [18]. Typically, monomethine cyanine dyes display almost negligible fluorescence in aqueous solutions but show multifold fluorescence enhancement upon binding to nucleic acids. This phenomenon can be used to detect nucleic acids in the solution up to certain nanomolar

concentrations. The cationic monomethine cyanine dye molecules with planar aromatic rings typically intercalate within the two adjacent base pairs of DNA. It has been observed that increasing cationic charges on the dye molecule results in improved binding to the negatively charged nucleic acids. Homodimeric cyanine dye **5** interacts with nucleic acids by bis-intercalation and electrostatic interaction, which provides extra stabilization to the dye-nucleic acid complex. Remarkably, cyanine dye **5** exhibits approximately a 40-nm difference between fluorescence maxima in the presence of single-stranded DNA and double-stranded DNA, which could make it useful to differentiate between both species in solution.

A novel method for the synthesis of monomeric asymmetric benzothiazole derivatives, such as in following scheme, containing mercapto and thioacetyl substituents has been reported [19].

Compound 7could be further modified as suggested by Ishiguro *et al.* by linking the mercapto group to oligonucleotides [20]. This method would facilitate *in vitro* transcription and gene expression studies. The synthetic methodology is depicted in scheme. The preparation of the dye intermediate **6** was carried out by heating under reflux a mixture of 2-methylmercaptobenzothiazole with 1,3-dibromopropane for 2 h. Compound **6** was then allowed to react with 1,4-dimethylquinolinium iodide to furnish dye **7** in 95% overall yield.

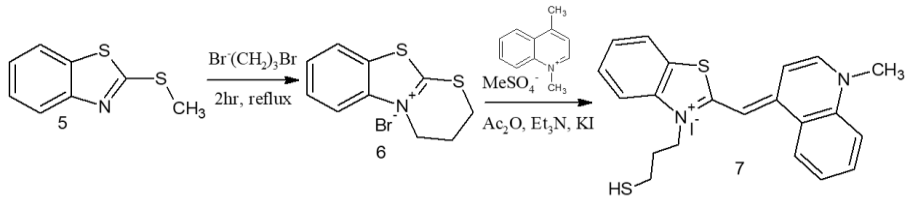

Fig 5

References

1. Williams C, Trans R. Soc. Edinb. 1856; 21:377.
2. Hamer F. Mainly introductory. Ed. John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2008, 1-31.
3. Armitage B. Cyanine dye-nucleic acid interactions.- Springer: Berlin. 2008; 14:11-29.
4. Katritzky A, Fan WQ, Li QLJ. Heterocycl. Chem. 1988; 25:1311-1314.
5. Behera G, Behera P, Mishra B. A review. J. Surface Sci. Technol. 2007; 23:1-31.
6. Kovalska V, Volkova K, Losytskyy M, Tolmachev O, Balanda A, Yarmoluk S, *et al.* Spectrochim. Acta A Mol. Biomol. Spectr. 2006; 65:271-277.
7. Kaloyanova S, Trusova V, Gorbenko G, Deligeorgiev TJ. Photochem. Photobiol. A Chem. 2011; 217:147-156.
8. lunk W, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt D, *et al.* -Ann. Neurol. 2004; 55:306-319.
9. Mills W, LIV J. Chem. Soc. Trans. 1922; 121:455-466.
10. Ogul'chansky T, Losytskyy M, Kovalska V, Yashchuk V, Yarmoluk S. - Acta A Mol. Biomol. Spectrosc. 2001; 57:1525-1532.
11. Volkova K, Kovalska V, Balanda A, Losytskyy M, Golub A, Vermeij R, *et al.* Bioorg. Med. Chem. 2008; 16:1452-1459.
12. Deligeorgiev T, Kaloyanova S, Vaquero J. Recent Patents Mater. Sci. 2009; 2:1-26.
13. Brooker L, Keyes G, Williams W. Color and constitution. VJ. Am. Chem. Soc.1942; 64:199-210.
14. Zhao JL, Lv Y, Ren HJ, Sun W, Liu Q, Fu YL, *et al.* Dyes Pigments. 2013; 96:180-188.
15. Del Valle E. Proc. Biochem. 2004; 39:1033-1046.
16. Zhu X, Sun J, Wu J. Talanta. 2007; 72:237-242.
17. Deligeorgiev T, Gadjev N, Drexhage KH, Sabnis R. Dyes Pigments. 1995; 29:315-322.
18. Deligeorgiev T, Zaneva D, Katerinopoulos H, Kolev V. Dyes Pigments. 1999; 41:49-54.
19. Deligeorgiev T, Zaneva D, Kim S, Sabnis R. Dyes Pigments. 1998; 37:205-211.
20. Timtcheva I, Maximova V, Deligeorgiev T, Gadjev N, Drexhage K, Petkova I. J. Photochem. Photobiol. B Biol. 2000; 58:130-135.