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Synthesis of some novel dimethine, bis-dimethine cyanine dyes and octacosamethine cyanine dyes endowed with promising biological potency against (HepG2), (Hela), (MCF-7), (MIA), (SN12C) and (H358) cell lines

Rasha E. El-Mekawy [a,*], A.A. Fadda [b]

[a] Department of Petrochemicals, Egyptian Petroleum Research Institute, Nasr City, Cairo, Egypt
[b] Department of Chemistry, Faculty of Science, Mansoura University, Mansoura, Egypt

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ABSTRACT

Successfully, one step two component synthesis of dimethine cyanine dyes, bis-dimethine cyanine dyes and icosamethine cyanine dyes **2**–**10** *via* reaction of pyridinium salt **1** with some different aldehydes hope to obtain these compounds with enhanced biological potency as antitumor agents against spontaneous liver (HepG2), cervical (Hela), breast (MCF-7), pancreas (MIA), kidney (SN12C) and lung (H358). The impact of substituted drugs on the tumor cells was reflected by means of structure activity relationship (SAR). Among these dyes, icosamethine cyanine dye **8** recorded an excellent activity toward all the tested cell lines. The newly destined drugs were identified and emphasized by spectroscopy and elemental analyses.

Fluorescent molecules have long been targets of interest for organic synthesis. The historical pursuit of these molecules stems from the merits of utilizing the properties of fluorescence as an analytical probe.[1] Fluorescence is highly sensitive allowing for large dynamic range and increased lower limits of quantitation, in relatively low concentrations.[2] The ability to tune the excitation and emission wavelengths of the fluorophore has sparked a variety of fluorophore moieties to be explored.[1] The consistency of application driven fluorophores has been a fruitful venture producing a variety of dyes, for example: fluorescein, rhodamine, and cyanine.[1] Desirable fluorophore properties include a high quantum yield, pH insensitivity, compatible excitation and emission wavelengths. Moreover, the photoinstability of cyanine dyes made them not useful for dyeing fabrics.[3] H. W. Vogel discovered that cyanine dyes were utilized in photography as photosensitizers.[3] Quickly, this feedback grow to synthesize a number of cyanine dyes which had excellent photosensitizing properties to improve silver halide photography's.[4,5] Exponentially, different classes of cyanine dyes had grown[6,7] and have been exercised in a broad assortment of implementations such as photodynamic therapy[8], nonlinear optics[9], optical data storage[10], laser materials[11,12] and in solar and photovoltaic cells.[12,13] On account of the serious biological applications of fluorescent cyanine dyes in several disciplines, the scientific researchers have a dramatic efforts to develope the demand in designing new series leading to more impacts in various life science.[5,13–18] In this strategy, we present novel different modified and coloured methine cyanine dyes based on the spectroscopic characterization with positive future of these dyes in modern sciences and advanced technologies. This research area has an exceptional significance and rapid applications in medical sciences as antitumor drugs.

Characterized cyanine dyes possessed two moieties of heterocyclic compounds which act as both electron releasing and pulling and are linked together *via* a number of methine groups in which (n + 1) π-electrons are spreaded across n atoms and may be single or odd number[19,20] yielding a resonating cation through the methine chain and a π-conjugated system. This singular merit gives chromophores a huge zone of absorption than any other known category of dye compounds. Now, the employment of pyridinium salts in organic designing is extraditing a massive interest.[21,22] Piece of our profitable strategy of evolving novel, modest and effective methods for the synthesis of modern aromatic cyanine dyes was fulfilled using readily obtainable pyridinium salts as a synthon. It is noteworthy that 1,1′-(cyclohexan-1,4-diyl)bis

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* Corresponding author at: Department of Chemistry, Faculty of Applied Science, Umm Al-Qura University, Makkah Al Mukarrama, Saudi Arabia.

E-mail address: rashachemistry1@yahoo.com (R.E. El-Mekawy).

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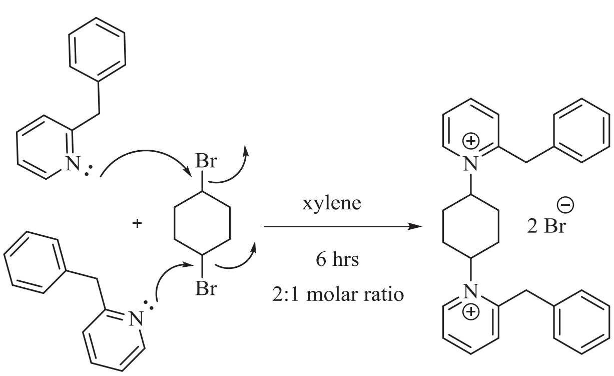
(2-benzylpyridine-1ium) dibromide (1) was synthesized by heating two moles of benzylpyridine with an appropriate amount of 1,4-dibromocyclohexane in refluxing xylene in 85% yield (Scheme 1).[23] Structure **1** was assigned on the principle of its elemental and spectral data. The ^{1}H NMR spectrum showed multiplet signals at δ 3.05 ppm due to two methine protons of $\underline{CH}$—N^+ of cyclohexyl ring, doublet signals at δ 2.14 ppm corresponding to equivalent 4 $\underline{CH_2}CH$—N^+ protons in addition to a singlet signal at δ 4.21 ppm due to two CH_2 protons of two benzyl groups. The mass spectrum of structure **1** showed a molecular ion peak at m/z (EI, 70 eV) = 422 (M^++2, -2Br, 100%) corresponding to a molecular formula $C_{30}H_{32}N_2Br_2$. Additionally, the ^{13}C NMR spectrum exhibited a more confirmation for structure **1**.

Consequently, bis-pyridinium salt **1** was used as a key intermediate in synthesizing numerous sensitive dimethine and bis-dimethine cyanine dyes **2**–**5**. It has very often been demonstrated that the refluxing of an equimolar ratio of pyridinium salt **1** with sodium 2-formylbenzenesulphonate in *N,N*-dimethylformamide containing a catalytic quantities of dry pellets of potassium hydroxide at 150 °C for 3 h resulted in the formation of dimethine cyanine dye **2**. Now, the ^{1}H NMR of compound **2** displayed two singlet signals at δ 4.50 and 5.72 ppm owing to CH_2 protons of a benzyl group and a benzal proton Ph—C=$\underline{CH}$— beside that multiplet signals at δ 7.14–7.36 ppm attributable to aromatic protons. This gave an evidence for formation of dimethinecyanine dye **2**, not bis-styryl cyanine dye or bis-dimethinecyanine dye. An alternative inferrment is mass spectroscopy which revealed a molecular ion peak at m/z (EI, 70 eV) = 619 (M^++1, -2Br, -Na, 54%) related to the molecular formula $C_{37}H_{35}N_2O_3S_2Br_2Na$. All the above data was confirmed by additional spectral information such as ^{13}C NMR which gave an agreement with them. On the other hand, compound **3** was synthesized in 56% yield by heating pyridinium salt **1** with 2-formylbenzenesulphonate in presence of *N,N*-dimethylformamide including a catalytic quantity of dry pellets of potassium hydroxide at 150 °C for 4 h in molar ratio (1:2), respectively. Alternatively, disodium 2-((*E*)-1-phenyl-2-(2-sulphonatophenyl)vinyl)-1-(4-(2-(*E*-1-phenyl-2-(2-sulphonato)vinyl)pyridine-1-ium-1-yl)-cyclohexyl)pyridine-1-ium-3-ide dibromide (**3**) was achieved by heating compound **2** with sodium 2-formylbenzenesulphonate in a catalyzed absolute ethanolic solution by few drops of pipridine in molar ratio (1:1). Significant features were achieved using ^{1}H NMR to interpret the formation of bis-styryl cyanine dye **3**. The ^{1}H NMR spectrum of structure **3** revealed a characterized singlet signal at δ 7.25 ppm related to Ph—C=$\underline{CH}$— (benzal proton) with disappearance of a singlet signal at δ 4.21 ppm owing to CH_2 proton of benzyl group. The same strategy was adopted to exhibit newly green coloured styryl cyanine dye **4** which has been synthesized by reacting with 2,3,6,7-tetrahydro-1*H*, 5*H*-pyrido[3,2,1-*ij*] quinolone-9-carbaldehyde in molar ratio (1:1) in *N,N*-dimethylformamide and few grams of potassium hydroxide. In a similar manner, novel bis-styryle cyanine dye **5** was obtained by heating salt **1** with two moles of 2,3,6,7-tetrahydro-1*H*, 5*H*-pyrido[3,2,1-*ij*]quinolone-9-carbaldehyde. Moreover, an alternative synthesis of disodium 1,1′-(cyclohexane-1,4-diyl)bis(2-((*E*)-1-phenyl-2-(2,3,6,7-tetrahydro-1*H*, 5*H*-pyrido[3,2,1-*ij*]quinolin-9-yl)vinyl)pyridine-1-iumdibromide **(5)** was depicted by refluxing compound **4** in a catalytic pipridine ethanolic solution with 2,3,6,7-tetrahydro-1*H*, 5*H*-pyrido[3,2,1-*ij*]quinolone-9-carbaldehyde in molar ratio (1:1).



Scheme 1. New features of bis-pyridinium salt **1**.

One interesting concept has been described to switch the ^{1}H NMR spectrum revealing an additional singlet signal at δ 6.58 ppm corresponding to a newly formed benzal proton (Ph—C=$\underline{CH}$—). The mass spectroscopy of structure **5** gave an additional confirmation of structure **5** which showed a molecular ion peak at m/z (EI, 70 eV) = 786 (M^+, -2 Br, 36%) according to the molecular formula $C_{58}H_{58}N_2Br_2$. The UV-*vis* spectrum showed an absorption band at λ_{max} = 478 nm (Scheme 2).

Latterly, we have improved elastic synthesis of new version of arylidene moieties incorporated novel lineaments of clear organic dye compounds and numerous routes for the planning toward higher capacity are offered. The fresh advances and chosen of these perspicuous dyes are preparation of biologically energetic porphyrin-dimethine cyanine dyes. It's just worth emphasizing here the significant and convenient method for synthesizing a new type of functionalized styryl cyanine dyes with highly conjugated porphyrin structure.

Extensive and systematic study of physical, chemical and electronic characters of porphyrin dyes and cyanine dyes too was afforded a growing interest in near future in light scattering data resulting from UV-*vis* spectra and a promising biological activity. Based on the above, a big effort was invested to prepare different derivatives of porphyrin compounds, explaining the role of derivatives in biological applications as dimethine cyanine dyes. Also, the changes of chemical structures afforded changes on absorption bands showing a different and high increase in wavelenghth. A key of understanding of the previously mentioned evidences, porphyrinodimethine cyanine dye **6** was produced by reaction of quaternary ammonium salt **1** with 1-formyl porphyrin in *N,N*-dimethylformamide in the subsistence of a catalytic quantity of pipridine below nitrogen gas in 42% yield. Structure **6** was settled on the principle of its correct spectral and analytical analyses. The IR spectrum showed no characteristic absorption band at ύ 1730 cm^{-1} attributable to a formyl group of porphyrin structure and this gave an evidence that the function group was consumed in the reaction forming arylidene as dimethine cyanine dye **6**. The ^{1}H NMR spectrum displayed two doublet signals at δ 2.23 and 2.28 ppm due to 4 $\underline{CH_2}$ of cyclohexyl ring, singlet signals at δ 9.85 ppm owing to two D_2O exchangeable protons of two NH of pyrrole ring of porphyrin. Furthermore, mass spectrometry offered a molecular ion peak at m/z = 742 (M^++2, 67%) related to molecular formula $C_{51}H_{44}N_6Br_2$. ^{13}C NMR spectrum showed additional confirmation of porphyrinodimethine cyanine dye **6**. Noticeably, one mole of pyridinium salt **1** reacted with two moles of 1-formylporphyrin by refluxing in *N,N*-dimethylformamide in the existence of a catalytic quantity of pipridine to yield 2-(*E*-1-phenyl-2-(porphyrin-2-yl)vinyl)-1-(4-(2-(*E*-1-phenyl-2-(porphyrin-2-yl)vinyl) 1λ^4-pyridine-1-yl)cyclohexyl)pyridine-1-ium dibromide (**7**). The IR spectrum showed two interesting strong absorption bands at ύ 3433 and 3387 cm^{-1} according to two NH fuction groups of porphyrin structure. On the other hand, the ^{1}H NMR revealed doublet signals at δ 2.20 ppm corresponds to four CH_2 of cyclohexyl ring, two singlet signals at δ 5.52 and 8.38 ppm related to two vinylic protons (two Ph—C=CH—) and four NH of four pyrrolic rings. The