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Some studies in cyanine dyes incorporating pyridine rings endowed with pharmaceutical potency

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ABSTRACT

We report the synthesis of new series of methine cyanine dyes **1**, **3**–**13**which have been obtained by the one-pot step reaction of quaternized heterocyclic compound **2** with benzenaminium salt **1** under various methodology technique. (*E*)-*N*-(((*E*)-2-Chloro-3-((phenylamino)methylene)cyclopent-1-enyl)methylene) benzenaminium chloride (**1**) was synthesized by the reaction of cyclopentanone with Vilsmeier-Haack reagent, then a mixture of an equimolar ratio of aniline: ethanol (1:1) was added to give the target compound. All the synthesized compounds were subjected to *in vitro* anticancer screening against two cell lines, human cervix carcinoma cell line and human breast carcinoma cell line. Some of these compounds were found to be equipotent or more potentthan commercial anticancer as an evident from the results.

1. Introduction

The last 30 years, and particularly the last decade, has witnessed a phenomenal rise in the growth of dyes for high-technology (hi-tech) applications. The advent and/or consolidation of new imaging technologies, such as electrophotography [1] (photocopying and laser printing), thermal printing [2], and especially ink-jet printing [3]; invisible imaging by using infrared absorbers in optical data storage [4], displays, such as liquid crystal displays and the newer emissive displays such as organic light emitting devices [5]; electronic materials [6], such as organic semiconductors; and biomedical applications, such as fluorescent sensors and probes [7], and anticancer treatments such as photodynamic therapy [8], created the need for novel dyes to meet new and demanding criteria. Dyes, and related ultraviolet (UV) and particularly infrared (IR) active molecules, which have been specifically designed for these hi-tech applications could be related to **cyanine dyes**.

The cyanine dyes have evoked interest primarily because of their unrivaled ability to impart light sensitivity to silver halide emulsions in a region of the spectrum to which the silver halide is normally not sensitive. Polymethine cyanine dyes have dominated the field of photography and other sophisticated arenas of dye application since 1856 [9]. Numerous applications in various areas are published every year on this subject. Near-infrared (NIR) cyanine dyes have been widely used for monitoring the biological function in living system owing to their absorption regions far beyond the absorption of most biological molecules [10]. During the last decades, remarkable efforts have been undertaken in the area of clinical uses of cyanine dyes, in particular famous indocyanine green, such as hepatic function tests and ophthalmic angiography [11,12]. The cyanine dyes have also shown the promising potential in the area of near-infrared (NIR) tissue imaging in small animal and human [13–15]. The absorption and scattering of the tissue in NIR region are much weaker than those of in ultraviolet–visible region, so the light can penetrate deeply into tissues [16]. Thus, cyanine dyes and their derivatives have been intensively investigated for the contrast agent *in vivo* application [17–19]. Cyanine dyes are characterized as possessing two heterocyclic moieties, acting as both electron donors and acceptors, and are joined by a single or odd of number of methine groups in which (n + 1) bi-electrons are distributed over n atoms [20] producing a delocalized cation across the methine chain. This unique characteristic gives cyanine dyes a wider range of absorption than any other known class of dyes. Most of the synthetic cyanines [21,22] are known to absorb in the visible and infrared regions of the electromagnetic spectrum. In addition, cyanines exhibit narrow

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absorption bands and high extinction coefficients. Due to these properties, cyanine dyes have been extensively employed in various applications such as photographic processes, laser printing, nonlinear optical materials, and more recently fluorescent probes for biomolecular labeling [23]. The 1-alkylpyridinium salts, which are liquid at r. t., so-called ionic liquids, are potential new solvents for synthesis and catalysis [24]. Several synthetic routes to pyridinium salts are known, but the most commonly used method is the Menschutkin reaction, the S_N^2 reaction of a pyridine derivative with an organic halide. Chloromethylalkyl ethers or sulphides are also reagents for the quaternization of the pyridine nitrogen. In these cases, the reactions proceed *via* the S_N^1 mechanism [25–29].

In this paper, the features of pure organic dyes and several ways for the design towards higher efficiency are presented. The recent progress and selection of these pure dyes are formations of biologically active polymethine cyanine dyes.

2. Materials and methods

2.1. General remarks

All melting points are incorrect in degree centigrade and determined on Gallenkamp electric melting point apparatus. The infrared (IR) spectra were recorded (KBr disk) on a Mattson 5000 FTIR spectrometer at the Faculty of Science, Mansoura University, Egypt. The ^{1}H NMR spectra were determined on a Bruker WPSY 200 MHz spectrometer with tetramethylsilane (TMS) as an internal standard and the chemical shifts are in δ ppm using dimethylsulfoxide (DMSO-d_6) as a solvent. The mass spectra were recorded at 70 eV with Varian MAT 311 at the Microanalytical Center, Faculty of Science, Cairo University. Elemental analyses (C, H and N) were carried out at the Faculty of Science, Cairo University. The results were found to be in a good agreement (±0.03) with the calculated values.

2.2. Chemistry

2.2.1. (E)-N-(((E)-2-chloro-3-((phenylamino)methylene)cyclopent-1-enyl)methylene)benzenaminiumchloride (**1**)

At 0 °C phosphorus oxychloride (1.12 gm, 12 mmol) was added dropwise to anhydrous DMF (1.37 ml, 17 mmol). After 30 min, cyclopentanone (0.469 ml, 5.3 mmol) was added and the mixture was refluxed for 1hr on a water bath. The reaction mixture cooled to 20 °C, an aniline/ethanol [1:1 (v/v), 18 ml] mixture was added dropwise. After aniline addition, the deep purple mixture was poured into ice cold water a concentrated HCl [10:1 (v/v) 11 ml]. Crystals allowed to form on cooling in an ice bath, filtered, washed with cold water and diethyl ether, dried and yielded compound **1**.

Violet crystals; Yield 89.5%; m.p 218 °C; IR (KBr): ύ/cm^{-1} = 3423 (NH), 3237 (Ar–CH), 3010 (=CH), 2925 (CH_2), 1617 (C=N), 755 (C–Cl). ^{1}H NMR (DMSO − d_6): δ/ppm = 2.10 (t, 4H, CH_2), 6.12 (s, 1H, CH), 7.10–7.89 (m, 11H, Ar–H), 10.10 (s, 1H, NH). MS: (*m/z*) 310 (M^+ + 1 (−Cl), 23%), 275 (25%), 204 (27%), 182 (21%), 154 (100%), 76 (50%). UV–Vis. spectrum: λ_{max}(nm)/log ε: 499/4.5. Anal. data For $C_{19}H_{18}N_2Cl_2$ (345)Calcd.: C, 66.09; H, 5.25; N, 8.11. Found: C, 66.10; H, 5.25; N, 8.12.

2.2.2. 4-((Z)-2-((E)-2-(2-chloro-3-((E)-2-phenyl-2-(1-(4-sulfonato-butyl)pyridinium-2-yl)vinyl)cyclopent-2-enylidene)-1-phenylethylidene)pyridin-1-(2H-yl)butane-1-sulfonate (**3**)

Pathway 1:

A solution of quaternary salt **2** (0.096 gm, 0.3 mmol), anilinium salt **1** (0.051 gm, 0.15 mmol) and anhydrous sodium acetate (0.033 gm, 0.4 mmol) in absolute ethanol (25 ml) under N_2 atmosphere was heated under reflux with stirring for 3.5 h. The ethanol was removed under reduced pressure. The resulting crystals were collected to afford compound **3**.

Pathway 2:

A solution of quaternary salt **2** (0.096 gm, 0.3 mmol) and anilinium salt **4** (0.06 gm, 0.15 mmol) and anhydrous sodium acetate (0.033 gm, 0.4 mmol) in absolute ethanol (25 ml) under N_2 atmosphere was heated under reflux with stirring for 3.5 h. The ethanol was removed under reduced pressure. The resulting crystals were collected to afford compound **3**.

Pathway 3:

A solution of quaternary salt **2** (0.048 gm, 0.15 mmol) and hexamethine cyanine dye **5** (0.08 gm, 0.15 mmol) was heated under reflux in 20 ml pyridine under nitrogen gas for 3 h sat 150 °C.The solvent was removed under reduced pressure. The resulting crystals were collected to afford compound **3**.

Pathway 4:

A solution of quaternary salt **2** (0.048 gm, 0.15 mmol), hexamethine cyanine dye **6** (0.07 gm, 0.15 mmol) and anhydrous sodium acetate (0.013 gm, 0.16 mmol) in absolute ethanol (25 ml) under N_2 atmosphere was heated under reflux with stirring for 3.5 h. The ethanol was removed under reduced pressure. The resulting crystals were collected to afford compound **3**.

Deep red crystals; Yield 53.6%; m.p 146 °C; IR (KBr): ύ/cm^{-1} = 3232(Ar-CH), 3058 (pyridine-CH), 2923 (CH_2), 2854 (CH_2), 1623 (C=N), 1573 (C=C), 1332, 1056 (2 S=O), 712 (S–O), 749 (C–Cl). ^{1}H NMR (DMSO − d_6): δ/ppm = 1.66 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 2.11 (t, 2H, CH_2), 2.78 (t, 2H, CH_2–SO_3), 3.10 (t, 2H, CH_2–N^+), 5.55 (d.d, 1H, CH), 6.15 (s, 1H, CH), 6.39 (d, 1H, CH), 6.63 (d, 1H, CH), 6.90 (d.d, 1H, CH), 7.48 (s, 1H, CH), 7.50–7.58 (m, 1H, Ar–H), 5.82 (d.d, 1H, CH), 8.07 (d, 1H, CH), 8.28 (d.d, 1H, CH), 8.79 (d, 1H, CH). UV–Vis. spectrum: λ_{max}(nm)/log ε: 769/4.7. Anal. data For $C_{39}H_{48}N_2O_6S_2Cl$ (731). Calcd.: C, 63.96; H, 5.51; N, 3.83. Found: C 63.97H 5.52 N 3.83.

2.2.3. (E)-N-(((E)-2-chloro-3-((N-phenylacetamido)methylene) cyclopent-1-enyl)methylene) benzenaminium chloride (**4**)

A mixture of anilinium salt **1** (0.345 gm, 1 mmol) and an excess amount of acetic anhydride (15 ml) in the presence of acetic acid (5 ml) was heated for 4 h at 90 °C. The reaction mixture was allowed to cool at room temperature then poured into ice water giving an oily product. After 30 min, in ice bath, it solidified, and was filtered, dried and recrystallized from ethanol to give compound **4**.

Bright brown crystals; Yield 75%; m.p280 °C; IR (KBr): ύ/cm^{-1} = 3444 (NH), 3054 (Ar–CH), 2923 (CH_2), 1693 (C=O), 1619 (C=N), 752 (C–Cl). MS: (*m/z*) 351 (M^+ + 1 (−Cl), 23%), 322 (27%), 279 (30%), 244 (40%), 229 (47%), 179 (60%), 168 (70%), 151 (100%), 74 (55%). UV–Vis. spectrum: λ_{max}(nm)/log ε: 502/4.5. Anal. data For $C_{21}H_{20}N_2OCl_2$ (386). Calcd.: C 65.12; H, 5.20; N, 7.23. Found: C, 65.10; H, 5.21; N, 7.23.

2.2.4. 4-(2-((E)-2-((E)-2-chloro-3-((N-phenylacetamido) methylene)cyclopent-1-enyl)-1-phenylvinyl)pyridinium-1-yl) butane-1-sulfonate (**5**)

Pathway 1:

A solution of quaternary salt **2** (0.048 gm, 0.15 mmol), anilinium salt **1**(0.051 gm, 0.15 mmol) and anhydrous sodium acetate