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Utility of quaternary ammonium salts in synthesis of some novel cyanine dyes as potential antibacterial and antitumor agents

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ABSTRACT

A novel class of quaternary ammonium salts has been synthesized in high yield by a convenient procedure which cleanly afforded a new series of methine cyanine dyes **5**–**11**. Structural spectral studies were carried out *via* measuring the electronic visible absorption spectra of these dyes in DMF. Structural confirmations were determined through elemental analysis, IR, ^{13}C NMR, ^{1}H NMR spectroscopy and mass spectral data. The newly synthesized compounds were screened for their antibacterial and antitumor activity. Among all the tested compounds, it was found that compound **5** revealed better activity against Gram positive rather than Gram negative bacteria. Also, compound **5** showed better activity as antitumor agent.

1. Introduction

Cyanine dyes have long held the interest of the scientific community due to their unique optical properties and continues to be the focus of considerable interest in the chemistry of dyes and pigments. They have a set of original properties and are rather widespread in various areas of science, technology and engineering such as their use in photographic industry as a spectral sensitizer [1,2]. They can also be applied in optoelectronic [3,4] and data storage [5,6] as molecular probes in biological systems [7,8] and in solar cells [9,10]. Besides, cyanine dyes are also useful as textile dyes [11], as analytical reagents over a wide pH range [12]. As inhibitor for cell growth and division [13], as anticancer agents [14] and in DNA detection research [15–18]. Otherwise, compounds containing a pyridinium moiety are important in natural product chemistry [19] and in organic synthesis [20,21]. Pyridinium salts have found use as acylating agents [22], phase transfer catalysts [23], biocides with a wide range of antimicrobial activity [24], dyes [25] and cationic surfactants. The 1-alkylpyridinium salts, which are liquid at r. t., so-called ionic liquids, are potential new solvents for synthesis and catalysis [26]. Several synthetic routes to pyridinium salts are known, but the most commonly used method is the Menschutkin reaction, the SN^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 SN^1 mechanism [27–29].

2. Materials and methods

2.1. General remarks

All melting points are uncorrected 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 300 MHz spectrometer with tetramethylsilane (TMS) as an internal standard and the chemical shifts are in δ ppm using dimethylsulfoxide (DMSO) as a solvent. The mass spectra were recorded at 70 eV with a 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. 4-(2-Benzylpyridinium-1-yl) butane-1-sulfonate (**2**)

A mixture of 2-benzylpyridine (10 g, 62.3 mmol) and 1,4-butane sultone (12.71 g, 93.5 mmol) was heated under reflux for 8 h. The

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reaction mixture was then allowed to cool to room temperature. The resulting white crystals were filtered and washed with acetone (3 × 10 mL). The filtered product was crystallized from a solution of methanol and diethyl ether.

Yield 89%; white needle crystals; m.p. 158 °C; IR (KBr): $\acute{u}$/cm^{-1} = 3089 (Ar–CH), 2925 (CH_2), 1625 (C=N), 1366, 1152 (2 S=O), 619 (S–O); ^{1}H NMR (DMSO-d_6) δ/ppm = 1.36 (m, 2H, CH_2), 1.67 (m, 2H, CH_2), 2.76 (t, 2H, CH_2–SO_3), 3.52 (t, 2H, CH_2–N^+), 3.81 (s, 2H, CH_2 of benzyl protons), 7.06–7.28 (m, 5H, Ar–H), 8.30 (d.d, 1H, CH), 8.60 (d, 1H, CH), 9.00 (d.d, 1H, CH), 9.3 (d, 1H, CH); ^{13}C NMR (DMSO-d_6) δ/ppm = 22.61, 28.95, 39.14, 51.88, 59.63, 125.86, 126.41, 128.76, 129.00, 145.65, 146.32, 151.30; MS: (*m*/*z*, %) 305 (M^+, 16), 304 (40%), 279 (43%), 276 (50%), 258 (57%), 228 (62%), 188 (72%), 173 (55), 134 (70%), 110 (71 5), 78 (82%), 76 (100%). Anal. Calcd for $C_{16}H_{19}NO_3S$ (305.1): C, 62.93; H, 6.27; N, 4.59%. Found: C, 62.73; H, 6.21; N, 4.55%.

2.2.2. (E)-N-(((E)-2-Chloro-3-((phenylamino)methylene)cyclohex-1-enyl)methylene) benzeneaminium chloride (**4**)

At 0 °C, phosphorus oxychloride (1.12 g, 12 mmol) was added dropwise from a pressure-equalizing addition funnel to anhydrous DMF (1.37 mL, 17 mmol). After 30 min, cyclohexanone (**7**) (0.52 mL, 5.3 mmol) was added to the reaction mixture and the reaction mixture was refluxed for 1 h on a water bath. After that, the reaction mixture was cooled at 20 °C, then a mixture of aniline/ethanol [1:1 (v/v), 18 mL] was added dropwise. Heating the reaction mixture was continued for additional 30 min. After aniline addition, the deep purple mixture was poured into ice cold water/concentrated HCl [10:1 (v/v) 11 mL]. The formed crystals were allowed to stand for 2 h in an ice bath then filtered off, washed with cold water and diethyl ether and then dried to yield compound **4**. Yield 89%; purple crystals; m.p 220 °C; IR (KBr): $\acute{u}$/cm^{-1} = 3452 (NH), 3145 (Ar–H), 3096 (=CH), 2934 (CH_2), 1623 (C=N), 760 (C–Cl); ^{1}H NMR (DMSO-d_6) δ/ppm = 2.74 (t, 4H, CH_2), 1.85 (m, 2H, CH_2), 8.5 (s, 2H, CH), 7.6–7.2 (m, 10H, Ar–H); Anal. Calcd for $C_{20}H_{20}N_2Cl_2$ (359): C, 66.86; H, 5.61; N, 7.80%. Found: C, 66.87; H, 5.62; N, 7.81%.

2.2.3. 4-((Z)-2-((E)-2-(2-Chloro-3-((E)-2-phenyl-2-(1-(4-sulfonatobutyl)pyridinium-2-yl)vinyl)cyclohex-2-enylidene)-1-phenylethylidene)pyridin-1-(2H-yl)butane-1-sulfonate (**5**)

2.2.3.1. Pathway 1. A mixture of quaternary salt **2** (0.096 g, 0.3 mmol), anilinium salt **4** (0.052 g, 0.15 mmol) and anhydrous sodium acetate (0.033 g, 0.4 mmol) was stirred under reflux for 3.5 h in absolute ethanol under N_2 atmosphere. The ethanol was removed under reduced pressure. The resulting crystals were collected, washed with ethanol then dried to afford the isolated compound **5**.

2.2.3.2. Pathway 2. A mixture of quaternary salt **2** (0.048 g, 0.15 mmol) and hexamethine cyanine dye **6** (0.04 g, 0.15 mmol) was heated under reflux in 20 mL pyridine under nitrogen gas for 3 h at 150 °C. The solvent was removed under reduced pressure. The resulting crystals were collected, washed with ethanol and diethyl ether then dried to afford compound **5**.

2.2.3.3. Pathway 3. A mixture of quaternary salt **2** (0.048 g, 0.15 mmol), hexamethine cyanine dye **7** (0.08 g, 0.15 mmol) and anhydrous sodium acetate (0.013 g, 0.16 mmol) was stirred under reflux for 3.5 h in absolute ethanol under N_2 atmosphere. The ethanol was removed under reduced pressure. The resulting crystals were collected, washed with acetone then dried to afford compound **5**. Yield 56%; reddish brown crystals; m.p. 119 °C; IR (KBr): $\acute{u}$/cm^{-1} = 3224 (Ar–H), 2854 (CH_2), 1603 (C=N), 1584 (C=C), 746 (C–Cl); ^{1}H NMR (DMSO-d_6) δ/ppm = 1.24 (m, 2H, C5-H_2 of cyclohexenyl ring), 1.38 (m, 4H, 2 CH_2), 1.69 (m, 4H, 2 CH_2), 1.90 (t, 4H, C4-H_2 and C6-H_2 of cyclohexenyl ring), 2.10 (t, 4H, 2 CH_2–SO_3), 2.78 (t, 2H, CH_2–N), 3.09 (t, 2H, CH_2–N^+), 5.50 (d.d, 1H, CH of pyridine ring), 6.15 (s, 1H, =CH), 6.39 (d, 1H, CH of pyridine ring), 6.65 (d, 1H, CH of pyridine ring), 6.85 (d.d, 1H, CH of pyridine ring), 7.0 (s, 1H, =CH), 7.39–7.58 (m, 10H, Ar–H), 8.39 (d.d, 1H, CH of pyridinium ring), 8.61 (d, 1H, CH of pyridinium ring), 8.80 (d.d, 1H, CH of pyridinium ring), 9.38 (d, 1H, CH of pyridinium ring); ^{13}C NMR (DMSO-d_6) δ/ppm = 22.10, 22.63, 25.87, 27.25, 29.00, 30.10, 50.33, 51.87, 60.00, 107.54, 112.40, 121.10, 122.40, 125.20, 126.41, 126.66, 127.21, 128.77, 129.30, 136.90, 138.50, 140.00, 141.31, 144.60, 145.80, 147.11; MS: (*m*/*z*, %) 748 (M^+, 15), 672 (34%), 596 (25%), 561 (29%), 481 (54%), 401 (60%), 345 (39%), 289 (26%), 211 (42%), 186 (53%), 108 (45%), 83 (100%), 59 (62%); UV–Vis spectrum: λ_{max}(nm)/logε 771/4.71. Anal. Calcd for $C_{40}H_{43}N_2O_6S_2Cl$ (745): C, 64.68; H, 5.96; N, 3.68%. Found: C, 64.69; H, 5.94; N, 3.59%.

2.2.4. 4-(2-((E)-2-((E)-2-Chloro-3-((N-phenylacetamido)methylene)cyclohex-1-enyl)-1-phenylvinyl)pyridinium-1yl)butane-1-sulfonate (**6**)

A mixture of quaternary salt **2** (0.048 g, 0.15 mmol), anilinium salt **4** (0.052 g, 0.15 mmol) and anhydrous sodium acetate (0.013 g, 0.16 mmol) was stirred under reflux for 3.5 h in absolute ethanol and 1 mL acetic anhydride under N_2 atmosphere. The ethanol was removed under reduced pressure. The resulting solid product was collected, washed with ethanol then dried to afford compound **6**. Yield 53%; reddish brown crystals; m.p. > 300 °C; IR (KBr): $\acute{u}$/cm^{-1} = 3054 (Ar–H), 2921 (CH_2), 1660 (C=O), 1630 (C=N), 1598 (C=C), 743 (C–Cl); ^{1}H NMR (DMSO-d_6) δ/ppm = 1.28 (m, 2H, C5-H_2 of cyclohexenyl ring), 1.40 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 1.90 (t, 4H, C4-H_2 and C6-H_2 of cyclohexenyl ring), 2.10 (t, 2H, CH_2–SO_3), 2.76 (s, 3H, CH_3), 3.64 (t, 2H, CH_2–N^+), 6.15 (s, 1H, =CH), 7.18 (s, 1H, =CH), 7.54–7.64 (m, 10H, Ar–CH), 8.40 (d.d, 1H, CH of pyridinium ring), 8.62 (d, 1H, CH of pyridinium ring), 8.84 (d.d, 1H, CH of pyridinium ring), 9.40 (d, 1H, CH of pyridinium ring); ^{13}C NMR (DMSO-d_6) δ/ppm = 20.80, 22.60, 22.80, 27.72, 29.00, 29.74, 51.80, 60.00, 121.62, 123.99, 124.41, 125.23, 126.43, 126.65, 127.29, 128.00, 128.74, 128.91, 129.00, 138.54, 140.00, 141.32, 145.84, 147.11, 148.45, 168.7; MS: (*m*/*z*, %) 578 (M^+, 30), 535 (17%), 459 (29%), 432 (50%), 352 (35%), 317 (20%), 241 (45%), 185 (9%), 107 (17%), 82 (100%), 58 (53%); UV–Vis spectrum: λ_{max}(nm)/logε 687/4.66. Anal. Calcd for $C_{32}H_{33}N_2O_4SCl$ (576): C, 66.60; H, 5.76, N, 4.85%. Found: C, 66.61; H, 5.76; N, 4.86%.

2.2.5. 4-(2-((E)-2-((E)-2-Chloro-3-((phenylamino)methylene)cyclohex-1-enyl)-1-phenylvinyl)pyridinium-1yl)butane-1-sulfonate (**7**)

A mixture of quaternary salt **2** (0.048 g, 0.15 mmol), anilinium salt **4** (0.052 g, 0.15 mmol) and anhydrous sodium acetate (0.013 g, 0.16 mmol)) was stirred under reflux for 3.5 h in absolute ethanol under N_2 atmosphere. The ethanol was removed under reduced pressure. The collected solid product was washed off by diethyl ether then dried to afford compound **7**. Yield 68%; brown crystals; m.p. 120 °C; IR (KBr): $\acute{u}$/cm^{-1} = 3433 (NH), 3010 (Ar–H), 2976 (CH_2), 1615 (C=N), 1598 (C=C), 755 (C–Cl); ^{1}H NMR (DMSO-d_6) δ/ppm = 1.28 (m, 2H, C5-H_2 of cyclohexenyl ring), 1.40 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 1.90 (t, 4H, C4-H_2 and C6-H_2 of cyclohexenyl ring), 2.10 (t, 2H, CH_2–SO_3), 3.64 (t, 2H, CH_2–N^+), 6.15 (s, 1H, =CH), 7.18 (s, 1H, =CH), 7.42–7.61 (m, 10H, Ar–H), 8.40 (d.d, 1H, CH of pyridinium ring), 8.62 (d, 1H, CH of pyridinium ring), 8.84 (d.d, 1H, CH of pyridinium ring), 9.40 (d, 1H, CH of pyridinium ring), 11.55 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ/ppm = 22.63, 22.80, 27.74, 29.75, 29.00, 51.82, 60.00, 116.30, 118.82, 121.66, 125.22, 125.90, 126.66, 127.20, 129.63, 128.91, 138.54, 140.00, 141.03, 144.30, 145.87, 148.40; MS: (*m*/*z*, %) 536 (M^+, 22), 460 (55%), 380 (19%), 324 (32%), 248 (42%), 170 (25%), 145 (64%), 110 (18%), 83 (100%), 58 (47%); UV–Vis spectrum: λ_{max}(nm)/logε 690/4.65. Anal.