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Dicarbocyanine and tricarbocyanine dyes: Novel synthetic approaches, photosensitization evaluation and antimicrobial screening

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ABSTRACT

Novel dicarbocyanine dyes (pentamethine cyanine dyes), bis dicarbocyanine dyes (bis pentamethine cyanine dyes), tricarbocyanine dyes (heptamethine cyanine dyes) and bis tricarbocyanine dyes (bis heptamethine cyanine dyes) derived from the nucleus of furo[(3,2-d)pyrazole; (3',2'-d)oxazole] were prepared using novel synthetic approaches. The electronic visible absorption spectra were investigated in 95% ethanol to evaluate the photosensitization properties. The cyanine dyes were better photosensitizers in visible light to initiate the electronic transitions at higher wavelength bands (bathochromic shifted and/or red shifted dyes). Consequently, the photosensitization of the cyanine dyes decreases in visible light to initiate the electronic transitions at lower wavelength bands (hypsochromic shifted and/or blue shifted dyes). Antimicrobial activity of ten selected compounds was tested against four bacterial strains (*Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*). The compounds were thought to be better antimicrobial active when they give higher inhibition zone against the tested strains. Consequently, the antimicrobial activity was promising and variable among all synthesized compounds against tested strains. Structural characterization and confirmations were determined by elemental analysis, visible, mass, IR and ¹H NMR spectral data.

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Capsule Summary: Novel dicarbocyanine and tricarbocyanine dyes were prepared and photosensitization of synthesized dyes was evaluated along with antimicrobial activity screening.

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INTRODUCTION

Cyanine dyes (Komljenovic et al., 2016; Zhang et al., 2016; Chen et al., 2016; Arjona et al., 2016; Soriano et al., 2016; Shindy et al., 2016; Shindy et al., 2016a; Shindy 2016; Shindy et al., 2016b; Shindy et al., 2016c) came to the limelight in

1856 for their application to impart light sensitivity to silver halide emulsions in a region of the spectrum to which silver halide is normally not sensitive (Shindy, 2012). Although, this long time of history (more than one century and a half), the interest in their chemistry are still present. Their use in molecular biology, medical as well as clinical analysis has brought them again into limelight (Shindy, 2016a). Cyanine

dyes have been employed as fluorescent probes for several years (Shindy, 2017), and in addition to their application in photography these dyes find wide applications as antitumor, anticancer, inhibitors for cell growth and division, antimicrobial agents and as probes for biological activity (Shindy, 2018; Mishra et al., 1973). Many symmetric near-infrared cyanine dyes with heterocyclic end groups have been described during the last decade (Pisoni et al., 2014). The maximum absorption wavelength of cyanine can be tuned precisely from near UV to near IR (larger than any other class of dye system) by chemical structural modification. On the other side pyrazole compounds possesses a diversified applications in different areas such as technology, medicine and agriculture. In particular, they are described as inhibitors of protein glycation, antibacterial, antifungal, anticancer, antidepressant, antiinflammatory, anti-tuberculosis, antioxidant as well as antiviral agents (Wada et al., 2015; Hyun et al., 2014).

In addition, pyrazole systems, as biomolecules, have attracted more attention due to their interesting pharmacological properties. This heterocycle can be traced in a number of well-established drugs belonging to different categories with diverse therapeutic activities (Hyun et al., 2015; Njiojob et al., 2015; Hyun et al., 2015; El-Shishtawy et al., 2010; Henary and Levitz, 2013; Keter and Darkwa, 2012; Fustero et al., 2010; Ouyang et al., 2008).

Besides, Oxazole compounds is an important scaffold in the area of drug discovery. Oxazole and its derivatives make a prominent structure of number of well-established marketed drugs such as rilmenidine, furazolidone, nifurantoin, oxaprozin, and especially linezolid, which is an active against methicillin-resistant *Staphylococcus aureus*. Indeed, oxazolone based derivatives have shown diverse biological and pharmacological applications such as anticancer (Gokhan-Kelekci et al., 2007; Kaushik et al., 2010), antibacterial (Balbia et al., 2011), antimycobacterial against tuberculosis (Suhasini et al., 2015) and antioxidant (Josh et al., 2017; Turch, 1986) activity.

Based on this point of view, we prepared here new pyrazolo/oxazole cyanine dyes as new synthesis contribution, spectroscopic investigation and antimicrobial activity evaluation in the field, and hoping that a combination of the favourable properties of both pyrazole, oxazole and cyanine dyes may be achieved.

MATERIAL AND METHODS

Instruments and apparatus

All the melting points of the prepared compounds are measured using Electrothermal 15V, 45W 1 A9100 melting point apparatus, Chemistry department, Faculty of Science (Aswan University) and are uncorrected. Elemental analysis were carried out at the Microanalytical Center of Cairo University by an automatic analyzer (Vario EL III Germany). Infrared spectra were measured with a FT/IR (4100 Jasco Japan), Cairo University. ¹H NMR Spectra were accomplished

using Varian Gemini-300 MHz NMR Spectrometer (Cairo University). Mass Spectroscopy was recorded on Mas 1: GC-2010 Shimadzu Spectrometer (Cairo University). Electronic visible absorption spectra were carried out on Visible Spectrophotometer, Spectro 24 RS Labomed, INC, Chemistry department, Faculty of Science (Aswan University). Antimicrobial activity screening was carried out at the Microanalytical center, Microbiology division (Cairo University).

Synthesis of 4, 6-diethyl-7-phenyl-furo[(3,2-d)pyrazolium; (3',2'-d)oxazolium]-3,5-bis(1-acroleinyl)methyl-diiodide quaternary salts (2)

This compound was prepared through heating of 1:2 molar ratios of (1) (0.03 mol, 2.4 g) and acetaldehyde (0.06 mol, 3 ml) in ethanol (50 ml) containing piperidine (3-5 drops) for 4-6 h. The dark brown mixture was filtered off while hot to remove any impurities, concentrated and precipitated using cold water. The separated intermediate compound (2) was filtered off, washed with cold water, air dried and recrystallized from ethanol. The results are summarized in Table (1).

Synthesis of 4,6-diethyl-5(1-acroleinyl)methyl-7-phenyl-furo [(3,2-d)pyrazolium; (3',2'-d)oxazole]-3[2(4)]-pentamethine cyanine dyes (3a-c)

Piperidine (3-5 drops) was added to a mixture of equimolar ratios of (2) (0.01 mol, 0.7 g) and N-ethyl [α -picolinium (0.01 mol, 0.25 g), quinaldinium (0.01 mol, 0.3 g), γ -picolinium (0.01 mol, 0.25 g)] iodide quaternary salts dissolved in ethanol (50 ml). The reaction mixture was heated under reflux for 6-8 h and attained brown colour (for 3a, c) and deep violet colour (for 3b) at the end of the refluxing time. It was filtered off while hot, concentrated and cooled. The precipitated products which appear on dilution with cold water were filtered off, washed with water, dried and crystallized from ethanol. The data are listed in Table (1).

Synthesis of 4,6-diethyl-7-phenyl-furo[(3,2-d)pyrazole;(3',2'-d)oxazole]-3,5[2(4)]-bis pentamethine cyanine dyes (4a-c).

Two different routes are employed to prepare these cyanine dyes: Route (1): was carried out by adding piperidine (3-5 drops) to a mixture of an ethanolic solution (50 ml) of the compound (2) (0.01mol, 0.7 g) and iodoethane quaternary salts (0.02 mol) of [α -picoline (0.5 g), quinaldine (0.6 g), γ -picoline (0.5 g)]. The reaction mixtures were heated under reflux for 6-8 hrs and attained brown colour for (4a, c) and deep violet colour for (4b) at the end of the refluxing time. It was filtered off while hot, concentrated to half its volume and cooled. The precipitated dyes were filtered, washed with water, dried and crystallized from ethanol. The data are given in Table (1).

Table 1: Characterization of the prepared compounds (2), (3a-c) and (4a-c)

Comp No.	Nature of products			Molecular formula (M.Wt)	Analysis%						Absorption spectra in 95%ethanol	
	Colour	Yield %	MP C°		Calculated			Found			λ_{max} (nm)	ϵ_{max} (mol ⁻¹ .cm ²)
					C	H	N	C	H	N		
2	Deep reddish brown	70	120	C ₂₄ H ₂₅ N ₅ O ₄ I ₂ (673)	42.79	3.71	6.24	42.75	3.69	6.21	---	---
3a	Reddish brown	43	177	C ₃₂ H ₃₄ N ₄ O ₃ I ₂ (776)	49.48	4.38	7.22	49.45	4.36	7.19	430, 460, 490, 590, 650	7930, 9600, 8400, 5180, 2140
3b	Violet	52	190	C ₃₆ H ₃₆ N ₄ O ₃ I ₂ (826)	52.3	4.36	6.78	52.28	4.34	6.57	450, 480, 520, 610, 670	10710, 11590, 10880, 6760, 3310
3c	Deep reddish Brown	45	183	C ₃₂ H ₃₄ N ₄ O ₃ I ₂ (776)	49.48	4.38	7.22	49.46	4.35	7.2	440, 450, 500, 600, 660	8230, 8180, 8620, 5340, 2440
4a	Deep reddish brown	47	179	C ₄₀ H ₄₃ N ₅ O ₂ I ₂ (879)	54.61	4.89	7.96	54.59	4.87	7.94	460, 500, 600, 660	10280, 9890, 5690, 2310
4b	Deep violet	60	198	C ₄₈ H ₄₇ N ₅ O ₂ I ₂ (979)	58.84	4.8	7.15	58.81	4.78	7.13	480, 520, 620, 680	11770, 11160, 7000, 3380
4c	Deep reddish brown	46	188	C ₄₀ H ₄₃ N ₅ O ₂ I ₂ (879)	54.61	4.89	7.96	54.58	4.86	7.93	480, 510, 610, 670	11130, 10100, 5740, 2590

Route (2): was proceeded through the reaction between the previously prepared pentamethine cyanine dyes (3a-c) (0.01 mol, 0.77 g for 3a, 0.8 g for 3b, 0.77 g for 3c) and equimolar ratios of iodoethane quaternary salts (0.01 mol) of α -picoline (0.25 g), quinaldine (0.3 g), γ -picoline (0.25 g) in ethanol (50 ml) and presence of piperidine (3-5 drops). The reacting materials were heated under reflux for 6-8 h, whenever it attained brown colour for (4a, c) and deep violet colour for (4b) at the end of the refluxing time. It was filtered off while hot, concentrated, cooled and precipitated by adding cold water. The precipitates were collected and crystallized from ethanol to give the same cyanine dyes obtained by route (1), characterized by melting points, mixed melting points, same visible, IR and ¹H-NMR spectral data, Table (1).

Synthesis of 1-ethyl-2(4)[propenyl(2R-propenyl)]quinaldinium (pyridinium) iodide quaternary salts (5a-g).

These compounds were prepared in accordance methods that described before (Koraiem, et al., 1989).

Synthesis of 4,6-diethyl-5(1-acrolienyl)methyl-7-phenyl-furo [(3,2-d) pyrazolium;(3',2'-d)oxazole]-3[(2(4))-heptamethine cyanine dyes (6a-g).

Piperidine (3-5 drops) was added to a mixture of equimolar ratios of (2) (0.01 mol, 0.7 g) and the compounds (5a-g) (0.01

mol, 0.27 g for 5a, 0.32 g for 5b, 0.27 g for 5c, 0.34 g for 5d, 0.4 g for 5e, 0.43 g for 5f, and 0.45 g for 5g) dissolved in ethanol (50 ml). The reaction mixture was heated under reflux for 6-8 h and attained brown colour (for 6a, c) and deep violet colour (for 6b, 6d, 6e, 6f, 6g) at the end of refluxing. It was filtered off while hot, concentrated and cooled. The precipitated products which appear on dilution with cold water were filtered off, washed with water, air dried and crystallized from ethanol. The data are listed in Table (2).

Synthesis of 4,6-diethyl-7-phenyl-furo [(3,2-d)pyrazole;(3',2'-d)oxazole]-3,5[2(4)]-bis heptamethine cyanine dyes (7a-g)

Two different routes are employed to prepare these cyanine dyes. Route (1): was carried out by adding piperidine (3-5 drops) to a mixture of an ethanolic solution (50 ml) of the compound (2) (0.01 mol, 0.7 g) and the compounds (5a-g) (0.02 mol, 0.55 g for 5a, 0.65 g for 5b, 0.55 gm for 5c, 0.68 g for 5d, 0.8 g for 5e, 0.86 g for 5f and 0.89 g for 5g). The reaction mixtures were heated under reflux for 6-8 h and attained brown colours for (7a, c) and deep violet colour for (7b, 7d, 7e, 7f, 7g) at the end of the refluxing time. It was filtered off while hot, concentrated to half its volume and cooled. The precipitated bis heptamethine dyes were filtered, washed with water, air dried and crystallized from ethanol. The data are given in Table (3).

Table 2: Characterization of the prepared compounds (6a-g)

Comp No.	Nature of products			Molecular formula (M.Wt)	Analysis%						Absorption spectra in 95%ethanol	
	Colour	Yield %	MP C°		Calculated			Found			λ_{max} (nm)	ϵ_{max} (mol ⁻¹ .cm ²)
					C	H	N	C	H	N		
6a	Deep reddish brown	43	196	C ₃₄ H ₃₂ N ₄ O ₃ I ₂ (802)	50.87	4.49	6.98	50.85	4.47	6.94	440, 480, 580, 650, 910	9380, 8600, 5280, 2470, 9000
6b	Deep violet	54	220	C ₃₈ H ₃₃ N ₄ O ₃ I ₂ (852)	53.52	4.46	6.57	53.51	4.43	6.55	460, 490, 580, 930	10390, 10040, 5680, 11000
6c	Deep reddish brown	47	215	C ₃₄ H ₃₂ N ₄ O ₃ I ₂ (802)	50.87	4.49	6.98	50.86	4.45	6.94	440, 480, 580, 640, 920	9380, 8600, 5280, 3230, 10000
6d	Deep violet	45	223	C ₃₉ H ₄₀ N ₄ O ₃ I ₂ (866)	54.04	4.62	6.74	54.01	4.59	6.71	450, 490, 570, 640, 940	11450, 10040, 7660, 3240, 11900
6e	Deep violet	47	217	C ₄₄ H ₄₂ N ₄ O ₃ I ₂ (928)	56.9	4.53	6.03	56.88	4.51	6.01	420, 450, 480, 580, 640, 960	10070, 11240, 10540, 8330, 3230, 13700
6f	Deep violet	48	227	C ₄₅ H ₄₄ N ₄ O ₃ I ₂ (958)	56.37	4.59	5.85	56.34	4.56	5.83	420, 450, 470, 580, 970	14670, 15240, 14460, 11870, 14400
6g	Deep violet	49	229	C ₄₄ H ₄₁ N ₅ O ₃ I ₂ (973)	54.27	4.21	7.19	54.25	4.18	7.14	420, 450, 480, 580, 640, 950	10070, 11240, 10540, 8320, 3200, 12800

Route (2): was carried out through the reaction of the previously prepared heptamethine cyanine dyes (6a-g) (0.01 mol, 0.8 g, 0.85 g, 0.8 g, 0.86 g, 0.92 g, 0.95 g, 0.97 g, respectively) and equimolar ratios (0.01 mol) of the compounds (5a-g, 0.27 g for 5a, 0.32 g for 5b, 0.27 g for 5c, 0.34 g for 5d, 0.4 g for 5e, 0.43 g for 5f and 0.45 g for 5g) in ethanol (50 ml) and presence of piperidine (3-5 drops). The reacting materials were refluxed for 6-8 hrs, whenever it attained brown colour for (7a, c) and deep violet colour for (7b, 7d, 7e, 7f, 7g) at the end of the refluxing time. It was filtered off while hot, concentrated, cooled and precipitated by adding cold water. The precipitates were collected and crystallized from ethanol to give the same bis heptamethine dyes obtained by route (1), characterized by melting points, mixed melting points, same visible, IR and ¹H-NMR spectral data, Table (3).

Spectral behavior

The electronic visible absorption spectra of the prepared cyanine dyes were examined in 95% ethanol solution and recorded using 1Cm Qz cell in visible spectrophotometer, spectro 24 RS Labomed, INC. A stock solution (1x10⁻³M) of the dyes was prepared and diluted to a suitable volume in order to obtain the desired lower concentrations. The spectra were recorded immediately to eliminate as much as possible the effect of time.

Antimicrobial activity evaluation

The tested compounds (2, 3b, 4a, 4b, 4c, 7b, 7d, 7e, 7f and 7g) were dissolved in DMSO to give a final concentration (1 mg/ml). Susceptible sterile discs were impregnated by the tested substance (50 µgm/disc) via a means of micropipette. The biological activity for each substance was tested on surface -seeded nutrient agar medium with the prepared susceptible discs. Bacterial strains and the antimicrobial effect are shown in Table (5).

RESULTS AND DISCUSSION

Synthesis

Reaction of the compound (1) (Shindy, et al., 2018) and acetaldehyde in 1 : 2 molar ratios, in ethanol as organic solvent and piperidine as a basic catalyst led to the formation of the intermediate compound 6-diethyl-7-phenyl-furo[(3,2-d) pyrazolium; (3',2'-d) oxazolium]-3,5-bis(1-acroleinyl)methyl-diiodide quaternary salts (2), Scheme (1), Table (1). Further reaction of the intermediate compound (2) with either N-ethyl (2-picolinium, quinaldinium, 4-picolinium) iodide quaternary salts in equimolar ratios and in ethanol containing few drops of piperidine gave the 4,6-diethyl-5(1-acroleinyl)-methyl-7-phenyl-furo[(3,2-d) pyrazolium;(3',2'-d)oxazole]-3[2(4)]-pentamethine cyanine dyes (3a-c), Scheme (1), Table (1).

Table 3: Characterization of the prepared compounds (7a-g)

Comp No.	Nature of products			Molecular formula (M.Wt)	Analysis%						Absorption spectra in 95% ethanol	
	Colour	Yield %	MP C°		Calculated			Found			λ_{max} (nm)	ϵ_{max} (mol ⁻¹ .cm ²)
					C	H	N	C	H	N		
7a	Deep reddish brown	48	220	C ₄₄ H ₄₇ N ₅ O ₂ I ₂ (931)	56.71	5.05	7.52	56.69	5.01	7.5	370, 440, 480, 580, 650, 920	14080, 9020, 8150, 5430, 2960, 9000
7b	Deep violet	57	240	C ₅₂ H ₅₁ N ₅ O ₂ I ₂ (1031)	60.52	4.95	6.79	60.49	4.93	6.75	450, 480, 590, 640, 940	13100, 12670, 9040, 3850, 11000
7c	Deep reddish brown	46	230	C ₄₄ H ₄₇ N ₅ O ₂ I ₂ (931)	56.71	5.05	7.52	56.69	5.02	7.49	450, 480, 570, 650, 930	13000, 12600, 6700, 2960, 10000
7d	Deep violet	48	240	C ₅₄ H ₅₅ N ₅ O ₂ I ₂ (1059)	61.19	5.19	6.61	61.17	5.15	6.59	410, 450, 480, 580, 640, 950	15550, 13100, 12670, 10820, 3860, 12000
7e	Deep violet	50	245	C ₄₄ H ₄₉ N ₅ O ₂ I ₂ (1083)	64.92	4.99	5.92	64.9	4.97	5.89	450, 480, 580, 970	15880, 15640, 12370, 13700
7f	Deep violet	52	250	C ₅₆ H ₅₃ N ₅ O ₂ I ₂ (1243)	63.72	5.07	5.63	63.71	5.05	5.61	450, 480, 580, 980	16000, 16480, 10840, 14600
7g	Deep violet	54	243	C ₄₄ H ₄₇ N ₇ O ₂ I ₂ (1273)	60.33	4.48	7.7	60.29	4.47	7.68	420, 460, 480, 580, 950	11800, 12720, 13640, 12360, 12000

Reaction of unimolar ratio of the intermediate compound (2) with bimolar ratio of iodoethane quaternary salts of 2-picoline, quinaldine, 4-picoline in ethanol containing piperidine yielded the 4,6-diethyl-7-phenyl-furo[(3,2-d)pyrazole;(3',2'-d)oxazole]-3,5[2(4)]-bis pentamethine cyanine dyes (4a-c), Scheme (1), Route (1), Table (1). Chemical confirmations for the bis pentamethine cyanine dyes compounds (4a-c) took place via reaction of the previously prepared pentamethine cyanine dyes (3a-c) with equimolar ratios of iodoethane quaternary salts of either 2-picoline, quinaldine, 4-picoline in ethanol catalyzed by piperidine through Route (2) to achieve the same bis pentamethine cyanine dyes (4a-c) obtained through route 1, characterized by melting points, mixed melting points, same visible, IR and ¹H-NMR spectral data, Scheme (1), Route (2), Table (1).

Reaction of the intermediate compound (2) with 1-ethyl-2(4)[propenyl(2R-propenyl)] quinaldinium (pyridinium) iodide quaternary salts (5a-g) (Koraiem, et al., 1989) in equimolar ratios and in ethanol containing few drops of piperidine gave the 4,6-diethyl-5(1-acrolienyl)methyl-7-phenyl-furo[(3,2-d)pyrazolium;(3',2'-d)oxazole]-3[2(4)]-heptamethine cyanine dyes (6a-g), Scheme (1), Table (2). Reaction of unimolar ratio of the intermediate compound (2) with bimolar ratios of the compounds (5a-g) in ethanol containing piperidine yielded the 4,6-diethyl-7-phenyl-furo [(3,2-d)pyrazole;(3',2'-d)oxazole]-3,5[2(4)]-bis heptamethine cyanine dyes (7a-g), Scheme (1), Route (1), Table (3). Chemical confirmations for compounds (7a-g) took place via reactions of the previously prepared

heptamethine cyanine dyes (6a-g) with equimolar ratios of the compounds (5a-g) in ethanol catalyzed by piperidine through Route (2) to achieve the same bis heptamethine cyanine dyes (7a-g) obtained through route (1), characterized by melting points, mixed melting points, same visible, IR and ¹H-NMR spectral data, Scheme (1), Route (2), Table (3). The structure of the compounds were characterized and identified by elemental analysis, Tables (1), (2) and (3) visible spectra, Tables (1), (2) and (3), IR (Wade, 1999) and ¹H-NMR (Wade, 1999a) spectroscopic data, Table (4).

Photosensitization evaluation

Photosensitization evaluation for all the synthesized cyanine dyes was carried out through examining their electronic visible absorption spectra in 95% ethanol solution. The cyanine dyes were thought to be better photosensitizers when they absorb the visible light to initiate the electronic transitions at higher wavelength bands (bathochromic shifted and/or red shifted dyes). Consequently, the photosensitization of the cyanine dyes decreases when they absorb the visible light to initiate the electronic transitions at lower wavelength bands (hypsochromic shifted and/or blue shifted dyes). So, we may say that the photosensitization of one cyanine dye is higher than the other one if the wavelength of the maximum absorption spectrum of the former one is longer than that of the latter one.

Table 4: IR and ¹H NMR (Mass) spectral data of the prepared compounds (2), (3b) and (4b)

Comp. No.	IR Spectrum (KBr, Cm ⁻¹)	¹ H NMR Spectrum (DMSO, δ); & (Mass data).
2	689, 755 (monosubstituted phenyl). 1111 (C—O—C cyclic). 1366 (C—N). 1496, 1442 (C=N). 1599 (C=C). 1704 (CHO). 2925 (quaternary salt).	0.8-1.4 (m, 3H, CH ₃ of position 6). 1.5-2.4 (m, 6H, 3CH ₃ of positions 3, 5, 6). 3.2-3.4 (b, 3H, CH ₃ of positions 4). 3.5-4.3 (m, 2H, CH ₂ of positions 4). 4.7-5.3 (m, 4H, 4 —CH=). 7.0-8.2 (m, 5H, aromatic). 9.4-10 (m, 2H, 2CHO). M ⁺ : 673 M ⁺¹ : 674 M ⁺² : 675
3b	691 (monosubstituted phenyl). 755 (o.disubstituted phenyl). 1119 (C—O—C cyclic). 1365 (C—N). 1496, 1447 (C=N). 1600 (C=C). 1704 (CHO). 2923 (quaternary salt).	0.8-1.3 (m, 6H, 2CH ₃ of positions 4, 6). 1.4-2.4 (m, 6H, 3CH ₂ of positions 4, 5, 6). 2.6-3.1 (m, 3H, CH ₃ of N-quinolinium). 3.2-4 (m, 2H, CH ₂ of N-quinolinium). 4.7-5.4 (b, 7H, 7 —CH=). 6.6-8.7 (m, 11H, aromatic + heterocyclic). 9.2-9.7 (b, 1H, CHO).
4b	691 (monosubstituted phenyl). 755 (o.disubstituted phenyl). 1125 (C—O—C cyclic). 1369 (C—N). 1495 (C=N). 1598 (C=C). 2925 (quaternary salt).	0.8-1.3 (m, 6H, 2CH ₃ of positions 4, 6). 1.4-2.4 (m, 4H, 2CH ₂ of positions 4, 6). 2.6-3 (m, 3H, CH ₃ of N-quinolinium). 3.1-4 (m, 2H, CH ₂ of N-quinolinium). 4.9-5.4 (b, 10H, 10 —CH=). 6.6-8.8 (m, 17H, aromatic + heterocyclic).
6b	606, 690 (monosubstituted phenyl). 754 (o.disubstituted phenyl). 1119 (C—O—C cyclic). 1368 (C—N). 1496, 1450 (C=N). 1606 (C=C). 1704 (CHO). 2925 (quaternary salt).	0.8-1.3 (m, 6H, 2CH ₃ of positions 4, 6). 1.4-2.4 (m, 6H, 3CH ₂ of positions 4, 5, 6). 2.6-3.1 (m, 3H, CH ₃ of N-quinolinium). 3.2-4 (m, 2H, CH ₂ of N-quinolinium). 4.8-5.3 (b, 9H, 9 —CH=). 6.6-8.4 (m, 11H, aromatic + heterocyclic). 9.5-10.0 (b, 1H, CHO).
7b	613, 691 (monosubstituted phenyl). 754 (o.disubstituted phenyl). 1121 (C—O—C cyclic). 1366 (C—N). 1496, 1449 (C=N). 1599 (C=C). 2925 (quaternary salt).	0.9-1.4 (m, 6H, 2CH ₃ of positions 4, 6). 1.5-2.4 (m, 4H, 2CH ₂ of positions 4, 6). 2.6-3.1 (m, 6H, 2CH ₃ of N-quinolinium). 3.2-4 (m, 4H, 2CH ₂ of N-quinolinium). 5-5.4 (b, 14H, 14 —CH=). 6.6-8.8 (m, 17H, aromatic + heterocyclic).

In contrary, we may say that the photosensitization of one cyanine dye is lower than the other one if the wavelength of the maximum absorption spectrum of the former one is shorter than that of the latter one (Shindy, 2018a).

Studying the electronic visible spectra of cyanine dyes in 95 % ethanol solution is very important in the case of cyanine dyes because the extensive uses of these dyes as photographic sensitizers for silver halide emulsion in photosensitive material industry for colored and non colored (black and white) films. The visible electronic transitions absorption spectra of the pentamethine cyanine dyes (3a-c) and the bis pentamethine cyanine dyes (4a-c) in 95% ethanol solution discloses bands in the visible region

430-670 nm and 460-680 nm, respectively. The positions of these bands and their molar extinction coefficient are largely influenced by the nature of the heterocyclic quaternary residue (A), their linkage positions, number of methine units and by the number of the electronic charge transfer pathways inside the dyes molecules. So, substituting A = 1-ethyl pyridinium-2-yl salts in the pentamethine cyanine dye 3a and in the bis pentamethine cyanine dye 4a by A=1-ethyl quinolinium-2-yl salts to get the pentamethine cyanine dye 3b and the bis pentamethine cyanine dye 4b causes strong bathochromic shifts by 20 nm, accompanied by increasing the intensity of the absorption bands, Scheme (1), Table (1).

Table 5: Antimicrobial activity of some prepared compounds (antimicrobial screening)

Sample	Inhibition zone diameter (mm / mg sample)				
	<i>Bacillus Subtilis</i> (G ⁺)	<i>Escherichia Coli</i> (G ⁻)	<i>Pseudomonas Aeruginosa</i> (G ⁻)	<i>Staphylococcus Aureus</i> (G ⁺)	
Control: DMSO	0.0	0.0	0.0	0.0	
Standard: Tetracycline	30	32	31	28	
Antibacterial Agent Ampicillin	20	22	17	18	
2	10	11	9	11	
3b	11	9	9	11	
4a	0.0	9	9	0.0	
4b	13	13	13	13	
4c	10	11	10	11	
7b	15	15	15	14	
7d	18	18	17	16	
7e	18	17	19	16	
7f	18	17	16	16	
7g	13	12	15	13	

The increase in the wavelength and intensity of the absorption bands can be attributed to increasing π -delocalization conjugation in the latter dyes due to the presence of quinoline ring system in correspondence to the pyridine ring system in the former dyes. Changing the linkage positions from 2-yl salts to 4-yl salts passing from the pentamethine cyanine dye 3a and the bis pentamethine cyanine dye 4a to the pentamethine cyanine dye 3c and the bis pentamethine cyanine dye 4c resulted in a remarkable red shifts by 10 nm accompanied by increasing the intensity of the absorption bands, Scheme (1), Table (1). This can be explained in the light of increasing the length of the π -delocalization conjugation in the latter 4-yl salts dyes 3c and 4c due to the presence of the γ -picolinium structure system compared to the former 2-yl salts dyes 3a and 4a which contain the α -picolinium structure system.

Comparing the visible electronic transitions absorption spectra of pentamethine cyanine dyes (3a-c) with those of the bis pentamethine cyanine dyes (4a-c) declared that the latter dyes have bathochromically shifted bands related to the former ones. This can be attributed to the presence of two factors. The first factor is increasing conjugation due to increasing the number of methine units in the latter dyes by five methine units than those of the former dyes, Scheme (1) Table (1). The second factor is the presence of two electronic charge transfer pathways inside the latter dyes molecules in correspondence to one electronic charge transfer pathways inside the former dyes molecules, Scheme (2), Table (1).

In addition, the visible electronic transitions absorption spectra of the heptamethine and bis

heptamethine cyanine dyes (6a-g) & (7a-g) displays bands in the visible region (420 nm- 970 nm) and (370 nm-980 nm), respectively. The positions of these bands and their molar absorptivity are remarkably effected by the nature of the heterocyclic quaternary salt residue (A), their linkage positions, number of methine units, types of the tetra ene side chain (R) and by the number of the electronic charge transfer pathways inside the dyes molecules. So, substituting A = 1-ethyl pyridinium-2-yl salt by A = 1-ethyl quinolinium-2-yl salt, transferring from dyes (6a) and (7a) to dyes (6b) and (7b) causes strong bathochromic shifts by 20 nm accompanied by increasing the intensity of the bands. This can be illustrated according to increasing π -delocalization conjugation in the quinaldinium nucleus dyes (6b) and (7b) compared to α -picolinium nucleus dyes (6a) and (7a), Tables (2) and (3).

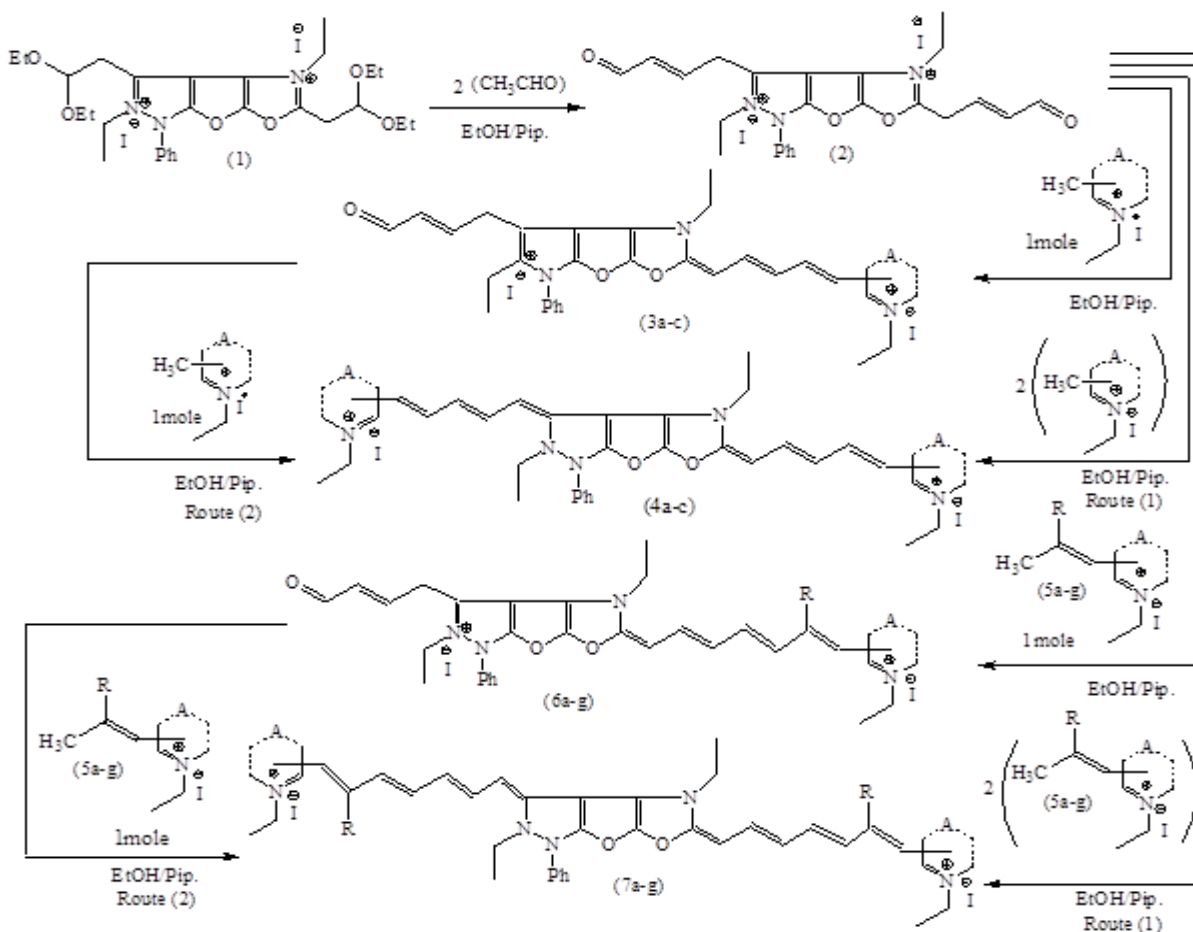
Changing the linkage position from 2-yl salt in dyes (6a) and (7a) to 4-yl salt to give dyes (6c) and (7c) produced red shifted absorption bands by 10 nm. This can be explained in the light of increasing the length of π -delocalization conjugation to the quaternary nitrogen in the γ -picolinium dyes (6c) and (7c) compared to the α -picolinium dyes (6a) and (7a), Scheme (1), Tables (2) and (3). Substituting R=H in the tetra ene side chain by, R= CH₃ and/or ph, transferring from dyes 6b (7b) to dyes 6d (7d) and/or (6e) (7e) resulted in a bathochromic shifted by 10 nm (20 nm) and / or 30 nm for the bands in addition to increasing the number and intensity of the bands in the case of the dyes 6e and 7d, respectively. This can be related to the electron donating character of CH₃ in the dyes (6d)

and (7d) and/or increasing conjugation of phenyl ring in dyes (6e) and (7e), Scheme (1), Tables (2) and (3).

Substituting $R=C_6H_5$ - in the tetra ene side chain in dyes 6e (7e) by $R=C_6H_4-p.OCH_3$ and/or $R=C_6H_4-p.NO_2$ to obtain dyes 6f (7f) and/or 6g (7g) makes red shifted and intensified bands in the case of dyes 6f (7f) and/or blue shifted bands accompanied with decreasing the intensity of the bands in the case of dyes 6g (7g). This is because the electron donating character of OCH_3 in dyes 6f (7f) and / or electron attracting character of NO_2 group in dyes 6g (7g), Scheme (1), Tables (2) and (3). Electron donating and/or pushing groups like CH_3 , OCH_3 makes increasing for the intensity of the electronic charge transfer pathways to the heterocyclic quaternary nitrogen (acidic center of the dyes), and consequently, red shift occur. Inversely, electron attracting and/or pulling groups like NO_2 makes decreasing for the intensity of the electronic charge transfer pathways to the heterocyclic quaternary nitrogen (acidic center of the dyes) and accordingly, blue shift occurs.

Comparison of the electronic visible absorption spectra of the heptamethine cyanine dyes (6a-g) with those of the bis heptamethine cyanine (7a-g) dyes revealed that the latter dyes have bathochromically shifted bands related to the former dyes. This can be attributed to two factors. The first factor is increasing conjugation due to increasing the number of methine units in the bis heptamethine cyanine (7a-g) in correspondence to the heptamethine cyanine dyes (6a-g) by seven methine units, Scheme (1). The second factor is the presence of two electronic charge transfer pathways in the latter dyes in correspondence to one electronic charge transfer pathways inside the former dyes molecules, Scheme (2).

Comparison the electronic visible absorption spectra of the heptamethine cyanine dyes (6a-g) and bis heptamethine cyanine (7a-g) dyes with those of the pentamethine cyanine dyes (3a-c) and bis pentamethine cyanine dyes (4a-c) showed that the former heptamethine cyanine dyes (6a-g) and bis heptamethine cyanine dyes (7a-



Scheme 1: Synthesis strategy of the prepared compounds (2), (3a-c), (4a-c), (6a-g) and (7a-g)

[Substituents in scheme (1): (3a-c), (4a-c): A = 1-ethyl pyridinium-2-yl salt (a), 1-ethyl quinolinium-2-yl salt (b), 1-ethyl pyridinium-4-yl salt (c). (5a-g), (6a-g), (7a-g): R = H, A = 1-ethyl pyridinium-2-yl salt (a), R = H, A = 1-ethyl quinolinium-2-yl salt (b), R = H, A = 1-ethyl pyridinium-4-yl salt (c), R = CH_3 , A = 1-ethyl quinolinium-2-yl salt (d), R = ph, A = 1-ethyl quinolinium-2-yl salt (e), R = $C_6H_4-p.OCH_3$, A = 1-ethyl quinolinium-2-yl salt (f), R = $C_6H_4-p.NO_2$, A = 1-ethyl quinolinium-2-yl salt (g)].

g) have red shifted and intensified absorption bands in comparison to the latter pentamethine (3a-c) and bis pentamethine (4a-c) cyanine dyes, Tables (1), (2) and (3). This can be attributed to increasing conjugation due to increasing the number of methine units in the former heptamethine cyanine dyes (6a-c) and bis heptamethine cyanine dyes (7a-c) in comparison to the later pentamethine cyanine dyes (3a-c) and bis pentamethine cyanine dyes (4a-c) by two methine units and four methine units, respectively, Scheme (1), Tables (1), (2) and (3).

Antimicrobial activity

Antimicrobial activity evaluation of cyanine dyes can be made through measuring their inhibition zone diameter against a number of bacterial and/or fungi strains. The cyanine dyes were thought to be better antimicrobial active when they give higher inhibition zone diameter against the tested bacterial and/or the fungi strains. Consequently, the antimicrobial activity of the cyanine dyes decrease when they give lower inhibition zone diameter against the tested bacterial and/or the fungi strains. So, we may say that the antimicrobial activity of one cyanine dye is stronger than the other one if the inhibition zone diameter against the tested bacterial and/or the fungi strains of the former one is higher than that of the latter one. In contrary, we may say that the antimicrobial activity of one cyanine dye is weaker than the other one if the inhibition zone diameter against the tested bacterial and/or the fungi strains of the former one is lower than that of the latter one (Shindy et al., 2018).

Studying the antimicrobial activity evaluation against a number of bacterial and/or fungi strains bears to have a great practical value in the case of cyanine dyes because the extensive uses and applications of these dyes as bactericidal (anti-bacterial strains) and/or as fungicidal (anti-fungi strains) in pharmaceutical (pharmacological) industry and/or in pharmacology. So, in this study, the antimicrobial activity evaluation for a number of 10 (ten) selected newly synthesized compounds (2, 3b, 4a, 4b, 4c, 7b, 7d, 7e, 7f and 7g) were studied and determined against a number of 4 (four) various bacterial strains (*Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*), Table (5). According to this study, it was observed that: Comparing the antimicrobial activity of the bis pentamethine cyanine dye (4a) by their analogous (4b) resulted in that the latter dye (4b) have higher inhibition zone diameter against all the bacterial strains, Table (5). This may be related to increasing π -delocalization conjugation in the latter dyes (4b) due to the presence of quinoline ring system in correspondance to pyridine ring system in the former dye (4a), Scheme (1).

The antimicrobial activity of the bis pentamethine cyanine dye (4c) possesses higher inhibition zone diameter against all the bacterial strains compared with their analogous bis pentamethine cyanine dye (4a), Table (5). This may be attributed to increasing the length of π -delocalization conjugation in the former dye (4c) due to

presence of γ -picoline ring system in correspondance to presence of α -picoline ring system in the latter dye (4a), Scheme (1). Comparison the antimicrobial activity of the pentamethine cyanine dye (3b) with the bis pentamethine cyanine dye (4b) showed that the latter one have higher potency effect toward all the tested bacterial strains, Table (5). This may be attributed to two factors. The first factor is increasing the number of methine groups in the latter bis pentamethine cyanine dye (4b) by 5 methine units compared with those of the pentamethine cyanine dye (3b), Scheme (1). The second factor is presence of two electronic charge transfer pathways inside the dye (4b) molecule compared with one electronic charge transfer pathways inside the dye (3b) molecule, Scheme (2).

Comparison the antimicrobial activity of the intermediate compound (2) with its derived quinaldinium bis pentamethine cyanine dye (4b) declared that, the latter compound (4b) have higher inhibition zone diameter for all the bacterial strains Table (5). This could be illustrated in the light of cyanine dye structure effects in compound (4b), Scheme (1). Substituting the tetra ene side chain (R) from (H) in the bis heptamethine cyanine dye (7b) by CH_3 or ph to get the bis heptamethine cyanine dyes (7d) or (7e) causes increasing for the antimicrobial activity towards all the bacterial strains Table (5). This could be correlated to the electron pushing character of CH_3 group in dye (7d) and increasing π -delocalization conjugation in dye (7e) due to the phenyl ring system, Scheme (1).

Replacing the H atom in the p. position of the tetra ene side chain of the bis heptamethine cyanine dye (7e) by OCH_3 group to obtain dye (7f) resulted in decreasing for the inhibition zone diameter only for *Pseudomonas* bacterial strain, Table (5). This may be related to the presence of the oxygenated methyl group (OCH_3) in the latter dye (7f), Scheme (1). Replacing the H-atom in the p. position of the tetra ene side chain of the bis heptamethine cyanine dye (7e) by NO_2 group to get the bis heptamethine cyanine dye (7g) makes decreasing for the bacterial inhibition effect for all the bacterial strains Table (5). This could be attributed to the electron accepting character of the dioxygenated nitrogen atom (NO_2) in the latter dye (7g), Scheme (1). Comparison between the antimicrobial activity of the bis heptamethine cyanine dye (7e) and the standard antibacterial agent Ampicillin against *Pseudomonas aeruginosa* showed that the former one have higher potency inhibition zone than the latter one Table (5). This indicates the strong effective of the bis heptamethine cyanine dye (7e) against this bacterial strain.

General comparison of the antibacterial activity for all the tested compounds disclosed that, the bis heptamethine cyanine dye (7e) give the highest inhibition zone diameter against all the bacterial strains and particularly against the *Pseudomonas aeruginosa* (Table 5). This reflects its increasing effect to may be used and / or applied as antimicrobial active against these bacterial strains. General comparison the antimicrobial effects of the tested compounds showed that the pentamethine cyanine

dye (4a) gives the lowest inhibition zone diameter against all the bacterial strains and particularly against *Bacillus subtilis* and *Staphylococcus aureus* bacterial strains, Table (5). This indicates its weaker and/or decreased effects to may be used and/or applied as antimicrobial active against these bacterial strains compared with the other tested compounds. General comparison of the antimicrobial activity of the acroleinyl methyl intermediate compound (2), pentamethine cyanine dye (3b), bis pentamethine cyanine dyes (4a-c) and bis heptamethine cyanine dyes (7b-g) showed that the later bis heptamethine cyanine dyes (7b-g) gives the highest inhibition zone diameter against all the tested bacterial strains, Table (5). This reflects the powerful and/or the strength of these bis heptamethine dyes (7b-g) to may be used and/or applied as antimicrobial

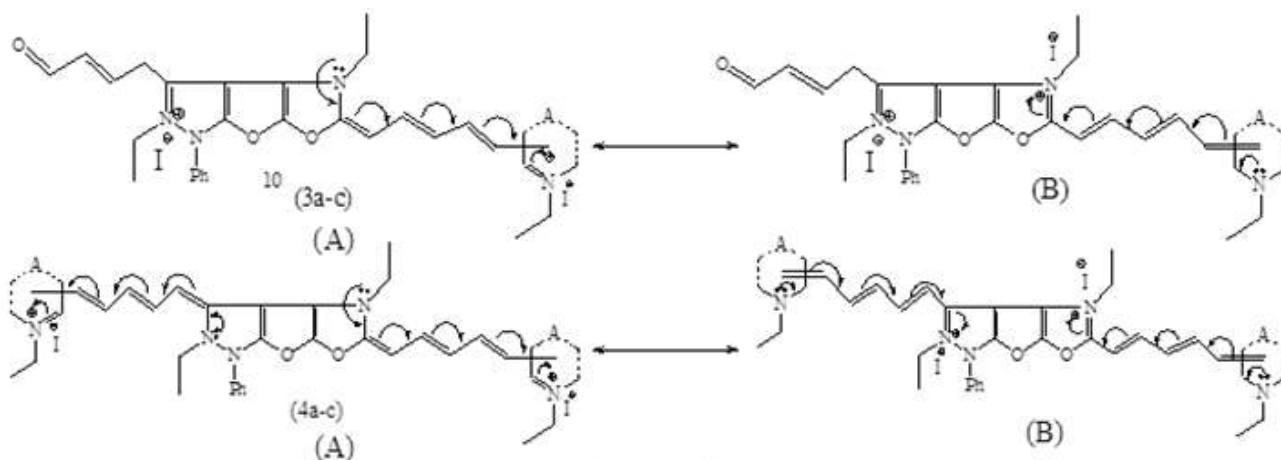
the bis heptamethine cyanine dyes (7b-g) structures, Scheme (1).

CONCLUSION

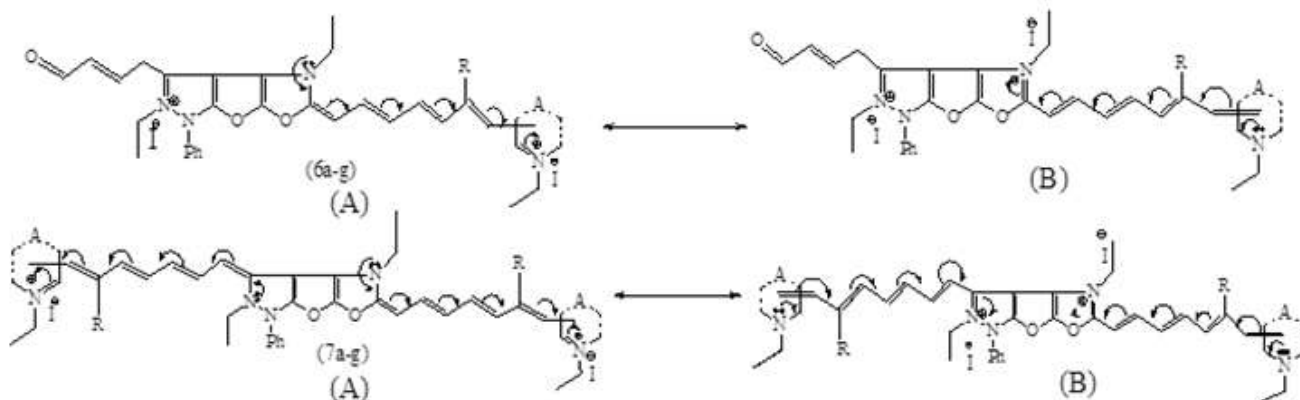
Following major conclusions were extracted from the results discussed in this study:

(1) The electronic visible absorption spectra of the pentamethine cyanine dyes (3a-c), bis pentamethine cyanine dyes (4a-c), heptamethine cyanine dyes (6a-g) and bis heptamethine cyanine dyes (7a-g) underwent displacements to give bathochromic and/or hypsochromic shifts depending upon the following factors:

a) The nature of the heterocyclic quaternary salt residue in the order of: Quinaldinium dyes > α -picolinium dyes (in the



Scheme 2: Colour intensity and the electronic charge transfer pathways illustration of the synthesized pentamethine cyanine dyes (3a-c) and bis pentamethine cyanine dyes (4a-c)



Scheme 2: Continue... colour intensity and the electronic charge transfer pathways illustration of the synthesized heptamethine cyanine dyes (6a-g) and bis heptamethine cyanine dyes (7a-g)

active compounds against all these bacterial strains (Ayare et al., 2019; Liu et al., 2019; Negm et al., 2016; Rajasekaran et al., 2019; Şener et al., 2018). This effect may be correlated to increasing conjugation due to the presence of so many number of methine groups (14 methine units) in

pentamethine, bis pentamethine, heptamethine and bis heptamethine cyanine dyes), b) Linkage position of the heterocyclic quaternary salt residue in the order of: γ -picolinium dyes > α -picolinium dyes (in the pentamethine, bis pentamethine, heptamethine and bis heptamethine

cyanine dyes) and c) Types of the tetra ene side chain (R) in the order of: i) H-dyes < CH₃-dyes < Ph-dyes (in the heptamethine and bis heptamethine cyanine dyes), ii) C₆H₄.p.OCH₃ dyes > C₆H₅-dyes > C₆H₄.p.NO₂ dyes (in the heptamethine and bis heptamethine cyanine dyes).

d) The number of the methine units and/or groups between the two heterocyclic ring system of the cyanine dyes molecules in the order of: i) bis heptamethine cyanine dyes > heptamethine cyanine dyes; ii) bis pentamethine cyanine dyes > pentamethine cyanine dyes; iii) heptamethine cyanine dyes > pentamethine cyanine dyes; iv) bis heptamethine cyanine dyes > bis pentamethine cyanine dyes and e) The number of the electronic charge transfer pathways inside the dyes molecules in the order of: two electronic charge transfer pathways dyes > one electronic charge transfer pathways dyes (bis pentamethine cyanine dyes > pentamethine cyanine dyes; bis heptamethine cyanine dyes > heptamethine cyanine dyes).

(2) The intensity of the colour of the pentamethine cyanine dyes, bis pentamethine cyanine dyes, heptamethine cyanine dyes and bis heptamethine cyanine dyes is illustrated according to the following suggested two mesomeric electronic transitions structures (A) and (B) producing a delocalized positive charges over the conjugated chromophoric group system of the dyes, Scheme (2).

(3) The antimicrobial inhibition action activity of the tested compounds (2, 3b, 4a, 4b, 4c, 7b, 7d, 7e, 7f and 7g) increase and/or decrease to give higher and/or lower bacterial inhibition zone diameter depending upon the following factors: a) Types of cyanine dyes molecules (pentamethine, bis pentamethine and/or bis heptamethine cyanine dyes), b) Electron accepting groups (acroleinyl group), c) Types of the tetra ene side chain (R) in the heptamethine and bis heptamethine cyanine dyes molecules (H, CH₃, ph, C₆H₄.p.OCH₃ and/or C₆H₄.p.NO₂) and d) Kind of the bacterial strains: higher in the case of *Escherichia coli* and *Pseudomonas aeruginosa* bacterial strains compared to *Bacillus subtilis* and *Staphylococcus aureus* bacterial strains (in the case of the bis pentamethine cyanine dye 4a).

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