Novel pyrazolo pyrazoly heterocyclic in the synthesis of positive solvatochromic cyanine dyes

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Abstract
Novel cyanine dyes monomethine, bismonomethine and trimethine cyanine dyes were synthesized from 5-hydroxy-2-(5-hydroxy-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-2-ium as a nucleus. Structure confirmed by elemental analysis, IR, 1H-NMR, mass and visible was determined. The electronic visible absorption spectra of all the newly synthesized cyanine dyes were investigated in 95% ethanol solution. Solvatochromism for the newly prepared cyanine dyes were performed in pure solvents having different polarities.

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Capsule Summary: Novel cyanine dyes have been synthesized and their visible and solvatochromism properties were investigated.


INTRODUCTION

Cyanine dyes are cationic molecules in which two terminal nitrogen heterocyclic subunits are linked by a polymethine bridge which have been extensively used in wide range of applications, such as laser, bioanalysis and imaging of DNA and antitumor agent (Parvaathy, et al., 2015, Kazuhide, et al., 2016, Fadda and Rasha, 2013). Different methods and heterocyclic moieties were used for synthesis of various types of cyanine dyes that have extensively used as photosensitizers, optical recording, storage media, solar cell and semiconducting material (Abdel Aal et al., 2012, Fadda and Rasha 2015, Ansari et al., 2014, Owens et al., 2014, Giu, et al. 2016, Sandra et al., 2015).

Herein novel monomethine, bismonomethine and trimethine cyanine dyes were synthesized, characterized, their visible and solvatochromic behavior have been studied which may be used as photosensitizer dyes.

MATERIAL AND METHODS

Chemical, reagents and instruments

Starting materials were synthesized according to (Mann and Saunders, 1960). All of the solvents are commercial products from Sigma Aldrich (USA) and were used without further purification.

Melting points are uncorrected. Elemental analyses were carried out at the micro analytical centre (Cairo-University). The IR spectra were determined with Perkin Elmer Infrared 137B spectrophotometer (Cairo University).
H-NMR spectra were recorded with Burker AMX-300 spectrometer (Cairo University). Mass spectra were recorded on HpMs 6988 spectrometer (Cairo University). The electronic absorption spectra were recorded within the wavelength range (350-700) on Shimadzu 1601A UV-visible spectrophotometer, Faculty of Science, Suez University.

**Synthesis**

2a-c, 4a-c:

a:A= pyridin-2-ium ethiodide ,  
b:A= quinolin-2-ium ethiodide ,  
c:A= isoquinolin-2-ium ethiodide  ,  
a:A=1-ethylpyridin-2-ium methiodide  
b:A=1-ethylquinolin-2-ium methiodide  
c:A=1-ethylpyridin-2-ium methiodide
Table 1: Characterization of compounds 1, 3 and 5

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>m. p. °C</th>
<th>Yield %</th>
<th>Colour</th>
<th>Mol. Formula (M.wt)</th>
<th>Calcd. % (found)</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95-99</td>
<td>57</td>
<td>White-yellow</td>
<td>C_{20}H_{19}N_{2}O_{7}Br (434.5)</td>
<td>55.23 (55.11)</td>
<td>4.37</td>
<td>12.88</td>
<td>(11.55)</td>
</tr>
<tr>
<td>3</td>
<td>178-183</td>
<td>65</td>
<td>Red</td>
<td>C_{25}H_{29}N_{4}O_{4}Br (528.5)</td>
<td>56.76 (55.8)</td>
<td>5.48</td>
<td>10.59</td>
<td>(10.2)</td>
</tr>
<tr>
<td>5</td>
<td>120-123</td>
<td>60</td>
<td>brown</td>
<td>C_{28}H_{23}N_{2}O_{2}Br (581.5)</td>
<td>45.39 (45.11)</td>
<td>4.12</td>
<td>9.63</td>
<td>(10.4)</td>
</tr>
</tbody>
</table>

Table 2: Characterization of prepared dyes (2a-c), (4a-c) and (6a-c)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>m. p. °C</th>
<th>Yield %</th>
<th>Colour</th>
<th>Mol. Formula (M.wt)</th>
<th>Calcd. % (found)</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Absorption Spectra in EtOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>138-142°C</td>
<td>66</td>
<td>red</td>
<td>C_{27}H_{28}N_{2}O_{7} (578)</td>
<td>56.05 (55.1)</td>
<td>4.5</td>
<td>12.00</td>
<td>(6.5)</td>
<td>λ_max: 486, ε_max: 972</td>
</tr>
<tr>
<td>2b</td>
<td>130-135°C</td>
<td>86</td>
<td>Reddish brown</td>
<td>C_{31}H_{32}N_{2}O_{7} (628)</td>
<td>59.23 (57.1)</td>
<td>4.45</td>
<td>11.14</td>
<td>(10.4)</td>
<td>λ_max: 491, ε_max: 2455</td>
</tr>
<tr>
<td>2c</td>
<td>165-168°C</td>
<td>37</td>
<td>brown</td>
<td>C_{31}H_{32}N_{2}O_{7} (628)</td>
<td>59.23 (57.8)</td>
<td>4.45</td>
<td>11.14</td>
<td>(10.2)</td>
<td>λ_max: 512, ε_max: 2865</td>
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<tr>
<td>4a</td>
<td>150-160°C</td>
<td>67</td>
<td>Faint brown</td>
<td>C_{34}H_{33}N_{2}O_{7} (809)</td>
<td>50.43 (50.1)</td>
<td>4.07</td>
<td>11.58</td>
<td>(11.4)</td>
<td>λ_max: 510, ε_max: 1018</td>
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<tr>
<td>4b</td>
<td>115-120°C</td>
<td>74</td>
<td>Reddish brown</td>
<td>C_{40}H_{37}N_{2}O_{7} (885)</td>
<td>54.23 (52.1)</td>
<td>4.18</td>
<td>9.49</td>
<td>(8.4)</td>
<td>λ_max: 489, ε_max: 3150</td>
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<tr>
<td>4c</td>
<td>110-115°C</td>
<td>70</td>
<td>brown</td>
<td>C_{40}H_{37}N_{2}O_{7} (885)</td>
<td>54.23 (53.4)</td>
<td>4.18</td>
<td>9.49</td>
<td>(8.2)</td>
<td>λ_max: 465, ε_max: 1886</td>
</tr>
<tr>
<td>6a</td>
<td>189-193°C</td>
<td>66</td>
<td>Reddish brown</td>
<td>C_{29}H_{26}N_{2}O_{7} (604)</td>
<td>57.61 (55.1)</td>
<td>4.63</td>
<td>11.58</td>
<td>(11.4)</td>
<td>λ_max: 472, ε_max: 4720</td>
</tr>
<tr>
<td>6b</td>
<td>169-176°C</td>
<td>86</td>
<td>violet</td>
<td>C_{33}H_{30}N_{2}O_{7} (654)</td>
<td>60.55 (58.1)</td>
<td>4.58</td>
<td>10.70</td>
<td>(10.4)</td>
<td>λ_max: 504, ε_max: 1212</td>
</tr>
<tr>
<td>6c</td>
<td>156-164°C</td>
<td>37</td>
<td>brown</td>
<td>C_{29}H_{26}N_{2}O_{7} (604)</td>
<td>57.61 (57.4)</td>
<td>4.63</td>
<td>11.58</td>
<td>(11.2)</td>
<td>λ_max: 492, ε_max: 634</td>
</tr>
</tbody>
</table>

Synthesis of 5-hydroxy-2-(5-hydroxy-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-2-ium (1)

A mixture of 4-bromo-3-methyl-1-phenyl-1H-pyrazol-5-ol (0.01mol) and 3-methyl-1-phenyl-1H-pyrazol-5-ol (0.01mol) in benzene (10mL). The reaction mixture was fused for 15 minutes. The red-mixture was poured into a clean 250 mL beaker to evaporate the excess solvent, filtered, dried and crystallized from benzene. The results are registered in Table (1).

Synthesis of monomethinecyanine dyes 2-((5-hydroxy-2-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-phenyl-1H-pyrazol-3(2H)-ylidene)methyl)-1-methylquinolinium pyridinium/isoquinolinium iodide (2a-c)
A mixture of equimolar amounts of compound 1 (0.001 mol) and 1-ethylpyridin-2-ium ethiodide (0.001 mol) were dissolved in ethanol (20 mL) and catalyzed by piperidine (0.5 mL). The reaction mixture was refluxed for 10 hours, filtered hot, concentrated, cooled and neutralized with acetic acid (0.3 mL). The precipitated compound was collected and recrystallized from methanol to afford 2a. Analogously, reaction of equimolar amounts of heterocyclic quaternary salts 1-ethylquinolin-2-ium ethiodide and 1-ethyl isoquinolin-2-ium ethiodide and compound 2, respectively afforded 2b and 2c, Table (2).

Synthesis of 1H,2H-1',4'-bipyrazole-1,2'-diium bromide iodide (3)

Compound 1 (2g) reacted with excess amount of ethyliodide. The reaction mixture was refluxed gently for 2 hours. The precipitated product was collected, washed with ether and dried, Table (1).

Synthesis of bis-monomethine 2/4-((2-(2-ethyl-5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-2-ium-4-yl)-5-hydroxy-1-phenyl-1H-pyrazol-3(2H)-ylidene)methyl)-1-methylquinolinium/pyridinium iodide cyanine dyes (4a-c)

Compound 3 (0.0003) reacted with bimolar amounts of 1-ethylpyridin-2-ium ethiodide (0.001 mol). The reaction mixture was dissolved in ethanol (20 mL), Piperidine (0.5 mL) was added as basic catalyst, refluxed for 11 hours, filtered hot, concentrated, cooled and neutralized by acetic acid. The solid product was collected and recrystallized from ethanol to give compound 4a. Analogously, compound 3 was reacted with 1-ethylquinolin-2-ium ethiodide and 1-ethyl isoquinolin-2-ium ethiodide to afford 4b and 4c, respectively, Table (2).

Synthesis of 5-(2,2-diethoxyethyl)-2'-ethyl-3,5'-dihydroxy-3',5-dimethyl-1',2'-diphenyl-1'H,2H-1,4'-bipyrazole-1,2'-diium (5)

Compound 5 was prepared by reaction of compound 2 (0.001 mol) with triethylorthoformate (0.001 mol) in ethanol as solvent, purchased by piperidine as basic catalyst. The reaction mixture was refluxed for 7 hours, filtered hot, concentrated, cooled and neutralized by acetic acid. The solid product was collected and recrystallized from ethanol to give compound 5, Table (3).

Synthesis of 2/4-(3-(5-hydroxy-2-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-phenyl-1H-pyrazol-3(2H)-ylidene)prop-1-enyl)-1-methyl quinolinium/ pyridinium trimethine cyanine dyes (6a-c)

A mixture of equimolar amounts of compound 5 (0.002mol) and 1-methyl pyridin-2-ium iodide (0.002mol) dissolved in ethanol and catalyzed by piperidine (0.5 mL). The reaction mixture was refluxed for 11 hours. The product was filtered hot, concentrated, cooled and neutralized by acetic acid (0.3 mL). The precipitated compound was recrystallized from ethanol to give 6a. Analogously, compound 5 reacted with 1-methylquinolin-2-ium methiodide and 1-methylpyridin-4-iummethiodide to afford 6b and 6c, respectively, Table (2).

Visible spectra studies

### Table 3: Spectral data IR, 1H-NMR and mass of compounds 2a, 4a and 6a

<table>
<thead>
<tr>
<th>Comp.</th>
<th>IR Spectrum (KBr, Cm⁻¹)</th>
<th>1H-NMR Spectrum (DMSO, δ) and Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>1218 (C-O)</td>
<td>1.3 (S, 3H, CH₃)</td>
</tr>
<tr>
<td></td>
<td>1360 (C-N)</td>
<td>1.7 (t, 3H, CH₃ of ethiodide)</td>
</tr>
<tr>
<td></td>
<td>1598-1620 (C=C)</td>
<td>2(q, 2H, CH₂ of ethiodide)</td>
</tr>
<tr>
<td></td>
<td>2952 (quaternary salt)</td>
<td>2.5 (S, 2H, 2-OH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.7-8 (m, 15H, Ar+Het. +=CH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M⁺ = 578</td>
</tr>
<tr>
<td>4a</td>
<td>1118 (C-O)</td>
<td>1.6 (t, 6H, 2CH₃ of ethiodide)</td>
</tr>
<tr>
<td></td>
<td>1270 (C-N)</td>
<td>2.2 (q, 4H, 2CH₂ of ethiodide)</td>
</tr>
<tr>
<td></td>
<td>1600-1620 (C=C)</td>
<td>2.4 (S, 2H, twoOH)</td>
</tr>
<tr>
<td></td>
<td>2932-2976 (quaternary salt)</td>
<td>6-8(m, 20H, Ar+Het+=2CH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M⁺=809</td>
</tr>
<tr>
<td>6a</td>
<td>1218 (C-O)</td>
<td>1.3 (S, 3H, CH₃)</td>
</tr>
<tr>
<td></td>
<td>1360 (C-N)</td>
<td>1.65 (t, 3H, CH₃ of ethiodide)</td>
</tr>
<tr>
<td></td>
<td>1598-1620 (C=C)</td>
<td>2 (q, 2H, CH₂ of ethiodide)</td>
</tr>
<tr>
<td></td>
<td>2952 (quaternary salt)</td>
<td>2.5 (d, 1H =CH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.7 (d, 1H, CH=)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 (t, 1H, CH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-7.7 (m, 14H, Ar+Het.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M⁺=604</td>
</tr>
</tbody>
</table>
The electronic visible absorption spectra of the newly synthesized cyanine dyes were examined in 95% ethanol solution. A stock solution of 1x10^{-3}M of the dyes was prepared and used in suitable dilution to obtain the desired lower concentrations.

**Solvatochromism**

The electronic visible absorption spectra of the synthesized dyes were investigated in pure organic solvents of spectroscopic grade (Abdel Aal et al., 2012). Stock solution with 10^{-3} M was prepared and diluted to the desired lower concentrations.

**RESULT AND DISCUSSION**

**Synthesis**

All the titled cyanine dyes (2a-c), (4a-c) and (6a-c) were started by preparation of compound 5-hydroxy-2-(5-hydroxy-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-2-ium (1) from reaction of 4-bromo-3-methyl-1-phenyl-1H-pyrazol-5-ol (O’Brein and Gates, 1966) and 3-methyl-1-phenyl-1H-pyrazol-5-ol (Mann and Saunders, 1960), Scheme (1).

The structure of compound 1 was established on analytical and spectral data. IR spectra showed characterization absorption bands at 3010 cm^{-1} (Aromatic C-H, str.), 1620 cm^{-1} (C=C ring, str.), 3200 cm^{-1} (-OH), 1340 cm^{-1} (C-N) and 730 cm^{-1} (=C-H bend, benzene ring). ¹H-NMR (DMSO, 300MHz) spectra (Wade, 1999) reveals signals at 2.2 (s,6H, 2CH3), 4.1 (s, 2H, two-OH), 6-8 (m, 13H, Ar-H+Hetero). Mass spectroscopy of compound 1: M=434.5, M+1=435.5.

Reaction of compound 1 with equimolar ratios of HBr was suggested to proceed through oxidative elimination reaction followed by dehydrohalogenation of HBr to give (2a-c) according to Scheme 2.
Scheme 2: 2a-c structure (confirmed by analytical and spectral data)

Scheme 3: 6a-c structure (confirmed by analytical and spectral data)
Fig. 1: Visible spectra of monomethine cyanine dyes (2a-c) in ethanol

Fig. 2: Visible spectra of bis monomethine cyanine dyes (4a-c) in ethanol

Fig. 3: Visible spectra of trimethine cyanine dyes (6a-c) in ethanol

Fig. 4: Absorption spectra of monomethine cyanine dye 2a in different solvents

Fig. 5: Absorption spectra of monomethine cyanine dye 2b in different solvents.

Fig. 6: Absorption spectra of monomethine cyanine dye 2c in different solvents.
**Fig. 7:** Absorption spectra of bismonomethine cyanine dye 4a in different solvents.

**Fig. 8:** Absorption spectra of bismonomethine cyanine dye 4b in different solvents.

**Fig. 9:** Absorption spectra of bismonomethine cyanine dye 4c in different solvents.

**Fig. 10:** Absorption spectra of trimethine cyanine dye 6a in different solvents.

**Fig. 11:** Absorption spectra of trimethine cyanine dye 6b in different solvents.

**Fig. 12:** Absorption spectra of trimethine cyanine dye 6c in different solvents.
The structure of compounds (2a-c) was confirmed by analytical and spectral data, Table (3). Synthesis of bismonomethine cyanine dyes (4a-c) was performed by compound 3, which was prepared by reaction of compound 1 with excess amount of ethanolid. The structure of compound 3 was established on analytical and spectral data. IR spectra showed characterization absorption bands at 2958-2976 cm⁻¹ (C₂H₅), 3025 cm⁻¹ (Aromatic C-H, str.), 1635 cm⁻¹ (C=C ring, str.), 3200 cm⁻¹ (OH), 1340 cm⁻¹ (C-N) and 727 cm⁻¹ (=C-H, benzene ring). ¹H-NMR (DMSO, 300MHz) spectra (Wade, 1999) reveals signals at 1.7 (t, 3H, CH₃), 2.2 (s, 6H, 2CH₃), 4.4 (S, 2H, two-OH), 4.6 (q, 2H, N-CH₂) 6-8 (m, 13H, Ar-H+Hetero). Mass spectroscopy of compound 3: M⁺=443.5.

Compound 3 reacted with bimolar ratios of heterocyclic quaternary salts in the presence of piperidine as basic catalyst afforded the corresponding bismonomethine cyanine dyes (4a-c). The reaction was proceeding through the same mechanism as mechanism of formation of monomethine cyanine dyes (2a-c). The structure of compounds (4a-c) was confirmed by analytical and spectral data, Table (3).

Also, reaction of compound 1 with triethylorthoformate in presence of piperidine gave compound 5. The formation of compound 5 was suggested to proceed through elimination of two molecules of ethanol to give the corresponding intermediate compound 5, the structure of compound 5 was confirmed by elemental analysis, IR, ¹H-NMR and mass spectroscopy. Thus IR showed in addition to general absorption bands cited before in compound 1, the appearance of well define band 1089-1167 (C-O-C). ¹H-NMR (DMSO, 300MHz) spectra (Wade, 1999) reveals signals at 1.5 (d, 2H, CH₂), 1.7 (t, 6H, 2CH₃ethoxy group), 2.2 (q, 4H, 2CH₂), 2.5 (S, 3H, CH₃), 3.2 (t, 1H, CH), 4.4 (S, 2H, two-OH), 6-8 (m, 11H, Ar+Hetero). Mass spectroscopy of compound 5: M⁺=581.5.

Reaction of compound 5 with equimolar ratios of 2(4)-heterocyclic quaternary salts, reaction mixture was purchased by piperidine to afford the corresponding trimethine cyanine dyes (6a-c). The reaction suggested proceeding through elimination of two molecules of ethanol followed by dehydrohalogenation to give the corresponding cyanine dyes (6a-c), (Scheme 3).

Relation between structure and electronic absorption spectra of novel cyanine dyes

Electronic absorption spectra feature (λmax. and εmax. Values) of newly synthesized cyanine dyes (2a-c), (4a-c) and (6a-c) in ethanol solution are shown in Table (3). The visible absorption of the novel synthesized cyanine dyes undergo bathochromic shift or hypsochromic shift depending on the nature of heterocyclic quaternary residue A and number of methane groups. Thus, substitution of A=pyridine-2-ium in compound 2a by A=quolin-2-ium in compound 2b resulted in a bathochromic shift of 13 nm, which is due to increasing π-conjugation in quinolone-2-ium moiety. Similarly, increasing the number of methane groups in trimethine compound 6b with respect to monomethine compound 2b resulted in a bathochromic shift of 69 nm and appearance of shoulder at 642nm, Figure (2). This could be attributed to extensive π-conjugation in trimethine than monomethine. Also, increasing the heterocyclic residue in bismonomethine compound 4b with respect to monomethine cyanine 2b resulted in a bathochromic shift of 15 nm and appearing of a shoulder at 610 nm. A comparison of the visible absorption between compounds 2b, 4b and 6b gave a result that trimethine cyanine dyes reveals a bathochromic shift than both monomethine 2b and bismonomethine cyanine dyes 4b, Figure (3).

Solvatochromic behavior

The UV-visible spectra of newly synthesized cyanine dyes in different organic solvents were determined, Figures (4-12). All the data were measured at room temperature with concentration of approximately 10⁻⁴ mol/L. The λmax and εmax of the dyes in different solvents are presented in Table (4). It is clear that; table (4) shows λmax ranges from 476-590 nm for dyes (2a-c), 477-630 nm for dyes (4a-c) and from 492-640 nm for dyes (6a-c) in different solvents. At the same time the εmax values were in range from 952-2865 L mol⁻¹ cm⁻¹, 1018-3150 L mol⁻¹ cm⁻¹ and 4710-6430 L mol⁻¹ cm⁻¹ for dyes (2a-c), (4a-c) and (6a-c), respectively. The electronic absorption spectra of novel synthesized dyes showed positive solvatochromism with increasing solvent polarity this is attributed to the structure and type of the dye. Stabilization of ground state with respect to excited state is related to solvation by solvents of higher polarity. It is clear that the absorption bands of these dyes undergo bathochromic shift according to conjugation in the dye molecule.

CONCLUSIONS

Novel cyanine dyes were prepared from the nucleus 5-hydroxy-2-(5-hydroxy-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-2-ium. Physico-Chemical properties of the newly synthesized cyanine dyes were performed. Electronic absorption of the novel synthesized cyanine dyes (2a-c), (4a-c) and (6a-c) undergo bathochromic shift or hypsochromic shift depending on the nature of heterocyclic quaternary residue A and number of methine groups. Also, the spectral characterization of the investigated cyanine dyes in pure organic solvent with different polarities showed positive solvatochromism with increasing solvent polarity depending on increasing or decreasing the polarity and/or the dielectric constant of the solvent, beside type of hydrogen bond formed between the solute and the solvent used.

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REFERENCES


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