Synthesis, Absorption Spectra Studies and Antimicrobial Activity of Novel Monomethine, Dimethine, Trimethine and Azastyrylmethine Cyanine Dyes

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Abstract: ***Novel monomethine, dimethine, trimethine and azastyryl cyanine dyes having 2-amino (methyl) benzimidazole were prepared. The electronic visible absorption spectra of all synthesized cyanines were investigated in 95% ethanol to attempt and throw some light on the influence of such new heterocyclic nuclei and to compare spectral behavior. Antimicrobial activity of selected compounds against some bacterial strains was tested. Structural identification was carried out via elemental analysis, IR AND ^{1}HNMR.***

Keywords: Benzimidazole, Synthesis, Cyanine dyes, Visible spectra, Antimicrobial activity.

1. Introduction

Methine cyanine dyes have been widely reasearched and explored as optical recording material (1), fluorescent dyes inDNA detection (2), antimicrobialagents (3-5), antioxidants (6), and fungicides (7).On the other side, benzimidazole and their derivatives have wide biological activities (8, 9) like cyclooxygenase inhibitors (10), antimicrobial (11-14), antihelmintic (15-17), antihypertensive (18), anti-inflammatory (19), analgesic (20), antiprotozoa (21, 22), antihepatitis B virus activity (23), antibiotics (24), therapeutic activities (25, 26), and anticancer (27). This work describes the synthesis and spectral behavior of new monomethine, dimethine, tri and azastyryl cyanine dyes incorporating 2-methyl benzimidazole. Also, this work reports investigates the antibacterial activity of the synthesized derivatives against selected bacterial strains.

2. Experimental

2.1. Instrumentation

All melting points are uncorrected. Elemental analysis was carried out at the Micro Analytical Center (Cairo University). The IR (KBr) spectra were determined with Perkin-Elmer Infrared 127B Spectrophotometer (Cairo University). ^{1}H NMR spectra were recorded with a Bruker AMX-250 spectrometer. The electronic absorption spectra were recorded within the wavelength range (350-700 nm) on 6405 UV-Visible recording spectrophotometer, Faculty of Science, Aswan, Egypt. Mass spectra were recorded on an HPMs 6988 spectrometer (Cairo University).

2.2 Synthesis of 2-amino (methyl) benzimidazole (1, 4)

This compound was prepared according to references described earlier [28-34]

2.3 Synthesis of 2-amino (methyl) benzimidazole 1-ium iodide (2, 5)

A pure sample of compounds (1, 4) was suspended in excess of ethyl (methyl) iodide and heated in a sealed tube at 140C for 3 h. The sealed tube was cooled, opened and the products (2, 5) were collected, washed with ether and crystallized from ethyl alcohol to give crystals.

(2): Color: Dark black.
Yield: 70 %
M.p.: 240-243 °C.
FT-IR (KBr,ν, cm^{-1}): 1489 (C=N), 2917 (quaternary salt), 1360 (C-N), 3400 (spreading NH2).
^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.10 (S, 3H, CH_3 (Methyl iodide)), 5.88 (S, NHcyclic), 7.43-8.52 (m, 6H, 4Ar-H+NH2).
MS (El, *m/z*): 275.
Anal.calcd. forC_8H_{10}N3I: C, 34.90; H, 3.63; N, 15.27 Found: C, 34.92; `H, 3.19; N, 15.49%.

(5): Color: Brownish red.
Yield: 80 %
M.p.: 275-277 °C.
FT-IR (KBr, ν, cm^{-1}): 1489 (C=N), 2917 (quaternary salt), 1360 (C-N), 1183 (C-N-C cyclic).
^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.10 (s, 3H, CH_3 (Methyl iodide)), 3.30 (S, 3H, CH3), 5.72 (S, 1H (NH), 7.63-8.82 (m, 4H, Ar-H).
MS (El, *m/z*): 274.
Anal.calcd. forC_9H_{11}N2I: C, 39.41; H, 4.01; N, 10.21Found: C, 39.53; H, 4.21; N, 10.35%.

2.4 Synthesis of benzimidazole-2[2 (4)] monomethine cyanine dyes (3a-c)

Equimolar amounts of compound 2 and 2-methyl quaternary salts (α (γ) -picoline and\or quinaldine) ethyl iodide (0.01 mol) were dissolved in ethanol (30 mL) then piperidine (3-5 drops) was added. The reaction mixture was refluxed for 8 h, filtered hot, concentrated, cooled and acidified with acetic acid. The precipitated products (3a-c) after dilution with water were collected and crystallized from aqueous ethanol (Scheme1).

(3a): Color: Brownish red.
Yield: 70 %
M.p.: 160-163 °C.
FT-IR (KBr, ν, cm^{-1}): , 1489 (C=N), 1600 (C=C), 1366 (C-N), 2917 (quaternary salt), 3383 (NH cyclic).
^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.9 (S, 3H, CH3N), 1.13 (t, 3H, CH_3 (Ethyl iodide)), 3.10 (q, 2H, CH_2), 5.59 (S, 1H (NH), 7.43-8.52 (m, 9H, 8Ar-H+ =CH).
MS (El, *m/z*): 379.
Anal.calcd. for$C_{16}H_{18}N_3I$: C, 50.65; H, 4.74; N, 11.08.Found: C, 50.87; H, 4.79; N, 11.24%.

(3b): Color: Deep violet.
Yield: 80 %
M.p.: 198-200 °C.
MS (El, *m/z*): 429.
Anal.calcd. for$C_{20}H_{20}N_3I$: C, 55.94; H, 4.66; N, 9.79.Found: C, 55.81; H, 4.89; N, 9.66%.

(3C): Color: Brownish red.
Yield: 75 %
M.p.: 183-185 °C.
MS (El, *m/z*): 379.
Anal.calcd. for$C_{16}H_{18}N_3I$: C, 50.65; H, 4.74; N, 11.08.Found: C, 50.71; H, 4.80; N, 11.30%.

2.5. Synthesis of 2-formyl benzimidazole (6)

Selenium dioxide (0.01mol) and the starting material (4) (0.01) were refluxed in dioxane (50ml) for14-16 h.The product was filtered hot to remove selenium metal, concentrated and cooled.The precipitated products were collected and crystallized from ethanol (Scheme 1).

Color: Red.
Yield: 65 %
M.p.: 160-163 °C.
FT-IR (KBr, ν, cm^{-1}): 1489 (C=N), 1369 (C-N), 1620 (C=C), 3310 (NHcyclic), 1717 (CHO).
^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.67 (S, 1H, NH), 7.43-8.52 (m, 4H, Ar-H) 9.41 (S, 1H, CHO).
MS (El, *m/z*): 146.
Anal.calcd. for$C_8H_6N_2O$: C, 65.75; H, 4.10; N, 19.17.Found: C, 65.90; H, 4.22; N, 19.33%.

2.6 Synthesis of benzimidazole 2[2 (4)]dimethine cyanine dyes (7a-c)

Equimolar amounts of compound 6 and 2-methyl quaternary salts (α (γ) -picoline and\or quinaldine) ethyl iodide (0.01 mol) were dissolved in ethanol (30 mL) then piperidine (3-5 drops) was added. The reaction mixture was refluxed for 8 h, filtered hot, concentrated, cooled and acidified with acetic acid. The precipitated products (7a-c) after dilution with water were collected and crystallized from aqueous ethanol (Scheme 1)

(7a): Color: Red.
Yield: 78 %
M.p.: 220-223°C.
MS (El, *m/z*): 377
Anal.calcd. for$C_{16}H_{16}N_3I$: C, 50.92; H, 4.24; N, 11.14.Found: C, 50.99; H, 4.40; N, 11.33%.
(7b): Color: Violet.
Yield: 80 %
M.p.: 240-243°C.
FT-IR (KBr, ν, cm^{-1}): 1485 (C=N), 2923 (quaternary salt), 1360 (C-N), 3380 (cyclic NH).
^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.17 (t, 3H, CH_3 (Ethyl iodide)), 3.15 (q, 2H, CH_2), 5.90 (S, 1H (NH)), 7.53-9.52 (m, 12H, 10Ar-H+-CH=CH).
MS (El, *m/z*): 427.
Anal.calcd. for$C_{20}H_{18}N_3I$: C, 56.20; H, 4.21; N, 9.83.Found: C, 56.44; H, 4.10N, 9.90%

(7C): Color: Red.
Yield: 84 %
M.p.: 200-203°C.
MS (El, *m/z*): 377
Anal.calcd. for$C_{16}H_{16}N_3I$: C, 50.92; H, 4.24; N, 11.14.Found: C, 50.79; H, 4.20; N, 11.20%

2.7 Synthesis of intermediate compound (8)

A mixture of the quaternary compound 5 (0.01 mol) and (0.01 mol) of triethylorthoformate was dissolved in ethanol (50 mL) containing piperidine (3-5 drops) and refluxed for 4 h, filtered hot to remove unreacted materials, concentrated to one half its initial volume, cooled, acidified with acetic acid, and precipitated by cold water, filtered off and crystallized from ethanol to give the corresponding product 8 (Scheme 1).

Color: Brownish red.
Yield: 70 %
M.p.: 162-164°C.
FT-IR (KBr,ν, cm^{-1}): 1360 (C-N) , 1487 (C=N), 2925 (quaternary salt), 3480 (NHcyclic).
^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.10 (S, 3H, CH_3 (Methyl iodide)), 1.29-1.51 (t, 6H, 2CH3 ofEt-O), 2.90-3.17 (d, 2H, CH2 side chain), 4.104.22 (t, 1H, CH side chain), 3.82-3.99 (q, 4H, 2CH2 of Et-O), 6.90 (S, 1H (NH)), 7.43-8.52 (m, 4H, Ar-H).
MS (El, *m/z*): 376.
calcd. for$C_{14}H_{21}N2O_2I$: C, 44.68; H, 5.58; N, 7.44.Found: C, 44.70; H, 5.72; N, 7.50%.

2.8 Synthesis of benzimidazole 2[2 (4)]trimethine cyanine dyes (9a-c)

Equimolar amounts of compound 8 and 2-methyl quaternary salts (α (γ) -picoline and\or quinaldine) ethyl iodide (0.01 mol) were dissolved in ethanol (30 mL) then piperidine (3-5 drops) was added. The reaction mixture was refluxed for 8 h, filtered hot, concentrated, cooled and acidified with acetic acid. The precipitated products (9a-c) after dilution with water were collected and crystallized from aqueous ethanol (Scheme 1)

(9a): Color: Brownish red
Yield: 80 %
M.p.: 238-240°C.
MS (El, *m/z*): =405.
Anal.calcd. for$C_{18}H_{20}N_3I$: C, 53.33; H, 4.93; N, 10.37.Found: C, 53.30; H, 4.79N, 10.50%.

(9b): Color: Deep violet.
Yield: 80 %
M.p.: >300°C.
FT-IR (KBr, ν, cm^{-1}): 1489 (C=N), 3370 (cyclicNH), 2917 (quaternary salt), 1360 (C-N).
^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.37 (S, 3H, CH_3), 5.53 (S, 1H (NH)), 0.88 (t, 3H, CH3), 4.25 (q, 2H, CH2), 7.43-8.52 (m, 13H, 10Ar-H+ =CH-).
MS (El, *m/z*): =455.
Anal.calcd. for$C_{22}H_{22}N_3I$: C, 58.02; H, 4.83; N, 9.23.Found: C, 58.30; H, 4.55 N, 9.30%.

(9C): Color: Brownish red
Yield: 76 %
M.p.: 210-213°C.
MS (El, *m/z*): =405.
Anal.calcd. for$C_{18}H_{20}N_3I$: C, 53.33; H, 4.93; N, 10.37.Found: C, 53.55; H, 4.70N, 10.60%.

2.9 Synthesis of 2-formyl benzimidazole 1-ium iodide (10)

A pure sample of compound (6) was suspended in excess of ethyl (methyl) iodide and heated in a sealed tube at 140C for 3 h. The sealed tube was cooled, opened and the product (10) was collected, washed with ether and crystallized from ethyl alcohol to give crystals (Scheme 1).

Color: Dark black.
Yield: 70 %
M.p.: 140-143 °C.
MS (El, *m/z*): 288.
Anal.calcd. for$C_9H_9N_2OI$: C, 37.50; H, 3.12; N, 9.72.Found: C, 37.40; H, 3.33; N, 9.57%.

2.10 Synthesis of benzimidazole-2-azastyryl cyanine dyes (11a-c)

A mixture of equimolar ratios (0.01 mol) of (10) and aromatic amines (aniline, p-anisidine, and p-amino phenol) (0.01mol) were dissolved in absolute ethanol (30 ml), then piperidine (1ml) was added. The reaction mixture was refluxed for 8-10 h, filtered hot, concentrated, acidified with acetic acid and then cooling. The products were filtered, washed several times with ether and then crystallized from absolute ethanol to give azastyryl cyanine (11a-c) (Scheme 1).

(11a): Color: Rose crystal.
Yield: 70 %
M.p.: 120-123 °C.
MS (El, *m/z*): 363.
Anal.calcd. for$C_{15}H_{14}N_3I$: C, 49.58; H, 3.85; N, 11.57.Found: C, 49.40; H, 3.72; N, 11.44%.

(11b): Color: Pale red crystal.
Yield: 75 %
M.p.: 160-163 °C.
MS (El, m/z): 393.
Anal.calcd. for$C_{16}H_{16}N_3IO$: C, 48.85; H, 4.07; N, 10.68.Found: C, 48.70; H, 4.15; N, 10.60%.

(11C): Color: Brownish red.
Yield: 79 %
M.p.: 178-180 °C.
FT-IR (KBr, ν, cm^{-1}): , 1489 (C=N) , 2910 (quaternary salt), 1369 (C-N).
^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.10 (S, 3H, CH_3 (Methyl iodide)), 5.88 (S, 1H (NH)), 6.43-8.40 (m, 10H, 8Ar-H, OH, -CH=).
MS (El, *m/z*): 379
Anal.calcd. for$C_{15}H_{14}N_3IO$: C, 47.49; H, 3.69; N, 10.08.Found: C, 47.70; H, 3.45; N, 10.10.

2.11 Antimicrobial Studies

The tested compounds (2, 3a-c, 4, 6, 7a-c, 9a-c&11a-c) were dissolved in DMSO to give a final concentration (1 mg/mL). Susceptible sterile discs were impregnated by the tested substance (50 µg/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 biological effect are shown in Table 2.

3. Results and Discussion

3.1Synthesis

Quaternization of 2-amino benzimidazole (1) using iodomethane resulted in the corresponding quaternized compound (2) (Scheme1).Further reaction of the compound (2) with equimolar ratios of active methyl heterocyclic quaternary salts [α (γ)picoline and/or quinaldine] ethyl iodide gave the corresponding benzimidazole 2[2 (4)] monomethine cyanine dyes

(3a-c), Scheme1.
Treating on the latter compound (3a-c) by conc. H2SO4 resulted in liberating iodine vapor on warming.This is due to that the above reaction between the compound (2) and heterocyclic quaternary salts of [α (γ) -picoline and/or quinaldine]. ethyl iodide was suggested to proceed through liberation of ammonia gas followed by hydrogen iodide molecule. Selenium dioxide oxidation of the starting comound (4) in dioxane resulted in the 2-formyl benzimidazole (6).Further reaction of (6) and active methyl heterocyclic quaternary salts [α (γ) picoline and/or quinaldine) ethyl iodide gave the corresponding benzimidazole 2[2 (4)] dimethine cyanine dyes (7a-c), Scheme1.

Treating on the latter compound (7a-c) by conc.H2SO4 resulted in liberating iodine vapor on warming.This is due to that the above reaction was suggested to proceed through condensation reaction.

Equimolar interaction of the quaternized compound (5) and triethylorthoformate in ethanol and piperidine gave the intermediate compound (8).Subsequent reaction of the intermediate (8) with active methyl heterocyclic quaternary salts[α (γ) -picoline and/or quinaldine) ethyl iodide resulted in the benzimidazole 2[2 (4)] trimethine cyanine dyes (9a-c), Scheme1.Treatment on the latter compound (9a-c) by conc.H_2SO_4 resulted in liberating iodine vapor on warming.This is due to that the above reaction between the compound (8) and heterocyclic quaternary salts of[α (γ) -picoline and/or quinaldine) ethyl iodide was suggested to proceed through elimination two molecules of ethanol and liberation of hydrogen iodide molecule.

Condensation reaction of equimolar ratio of compound (10) and aniline, anisidine and/or p-amino phenol in the presence of piperidine as basic catalyst and ethyl alcohol as solvent gave the corresponding benzimidazole 2 - azastyryl cyanine dyes (11a-c), Scheme1.

3.2 Characterization

The newly prepared cyanine dyes are highly coloured compounds, partially soluble in nonpolar organic solvents and readily soluble in polar organic solvents giving colored solution, accompanied by pale to intense fluorescence.The intensity and color of the fluorescence depend upon the type of dye and solvent used.The dyes are soluble in concentrated H_2SO_4 liberating iodine vapor on warming.

3.3 Visible absorption spectra of the new cyanine dyes in ethanol.

The electronic visible absorption spectra of (3a-c) in 95% ethanol showed absorption bands position and molar extinction coefficients were influenced by the nature of the heterocyclic quaternary residue (A) and their linkage position.

Thus, the absoption spectra of dye (3a, A=1-methyl pyridinium-2-yl salt) showed λ_{max} = 490nm.Substituting A=1-methyl pyridinium-2-yl salt in dye (3a) by A=1-methyl quinolinium-2-yl salt in dye (3b) resulted in bathochromic shift of 10nm accompanied by increasing number of absorption bands, Table 1.

(3b, λ_{max} =370, 440, 500&550 nm).This is due to the greater conjugation in the quinoline ring than in the analogous pyridine ring. Changing the linkage position from 2-yl salt in dye (3a) to 4-yl salt in dye (3c) resulted in bathochromic shift of λ_{max}= 5nm.This is due to the increasing of the extension conjugation of 4-linkage moiety better than 2-linkage analogous[35-38], (3c, λ_{max} = 495 nm) (Table1).

In addition, the electronic visible absorption spectra of the dimethine (trimethine) cyanine dyes 7a-c (9a-c) in 95% ethanol reveal absorption bands in the visible region of 440 - 610 (475 - 620), the positions of which and their molar extinction coefficients are affected by the type of the heterocyclic quaternary residue (A) and their linkage positions. So, substituting 1-methyl pyridinium-2-yl salt in dyes 7a (9a) by 1-methyl quinolinium-2-yl salt to give dyes 7b (9b) resulted in bathochromic shifts of the absorption bands accompanied by increases in the intensity and number of the absorption bands, Table 1.This is due to greater conjugation in the quinoline ring than in the analogous pyridine ring. Changing the linkage position from 2-yl salts in dye 7a (9a) to 4-yl salts in dyes 7c (9c) resulted in red shifted and intensified absorption bands, Table1.

Generally, it is noticed that, the electronic visible absorption spectra of the trimethine cyanine dyes (9a-c) changed to give bathochromically shifted bands compared with those of the dimethine cyanine dyes (7a-c) and/or the monomethine cyanine dyes (3a-c), Table 1.Also, the dimethine cyanine dyes (7a-c) displayed red shifted bands compared with those of the monomethine cyanine dyes (3a-c), Table 1.This can be attributed to the increasing number of methine groups in these dyes in the order of trimethine>dimethine>monomethine, Scheme 1.

On the other side, the azastyryl cyanine dyes (11a-c) showed visible absorption spectral bands in the region 450 - 485nm, the positions of which and their molar extinction coefficients are influenced by aryl electron donating substituent's. Thus, the absorption spectra of compound (11a, R=H) showed λ_{max} = 450nm.Substituting R=H in dye (11a) by R=P.OCH_3in dye (11b) resulted in bathochromic shift of λ_{max} = 25 nm (11b, λ_{max} = 475nm).

Finally substituting R=H in dye (11a) by R=P.OH in dye (11c) resulted in bathochromic shift of λ_{max} = 35 nm (11c, λ_{max} = 485nm), Table 1.

3.4 Antimicrobial activity

Structure-antimicrobial (biological) activity relation-ship for some selected newly synthesized benzimidazole compounds were studied and determined against some bacterial and fungi strains (Table 2). The data obtained are expressed as size (mm) of inhibition zone. Diameter of the inhibition zones were high (22-18 mm), moderate (17-12 mm), slight (11-1 mm), no response (-). The final conclusion from this work is that these novel compounds showed significant antibacterial activity according to the following factors:

1) Increasing and/or decreasing conjugation in the dye molecule.
2) Increasing and/or decreasing the number of the methine group.
3) The presence of either electron donating and/or accepting group.

4. Conclusion

New unsymmetrical cyanine dyes have been prepared incorporating 2-methyl (amino) benzimidazole and were identified by chemical and spectroscopic evidences (Elemental analysis, UV-Vis, IR, ^1H NMR and MS spectra). Also, antimicrobial activity of some selected compounds against some bacterial strains was tested.

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Table 1: The electronic absorption spectra of new synthesized cyanine dyes (3a-c), (7a-c), (9a-c) and (11a-c) in 95% EtOH.

Monomethine cyanine dyes (3a-c)	3a	3b	3c
λmax^{nm}	490	370, 440, 500, 550	495
(εmax, $mol^{-1}.cm^{-1}$)	2168	1715, 2154, 2030, 1136	2250
Dimethine cyanine dyes (7a-c)	7a	7b	7c
λmax^{nm}	440, 560	610, 560, 450	470
(εmax, $mol^{-1}.cm^{-1}$)	1798, 553	2013, 2234, 2062	1440
Trimethine cyanine dyes (9a-c)	9a	9b	9c
λmax^{nm}	475, 570	620, 570, 470	580
(εmax, $mol^{-1}.cm^{-1}$)	1553, 1971	875, 1971, 1553	1440
Azastyryl cyanine dyes (11a-c)	11a	11b	11c
λmax^{nm}	450	475	485
(εmax, $mol^{-1}.cm^{-1}$)	2501	2226	2294

Table 2: Biological activity of some newly synthesized compounds

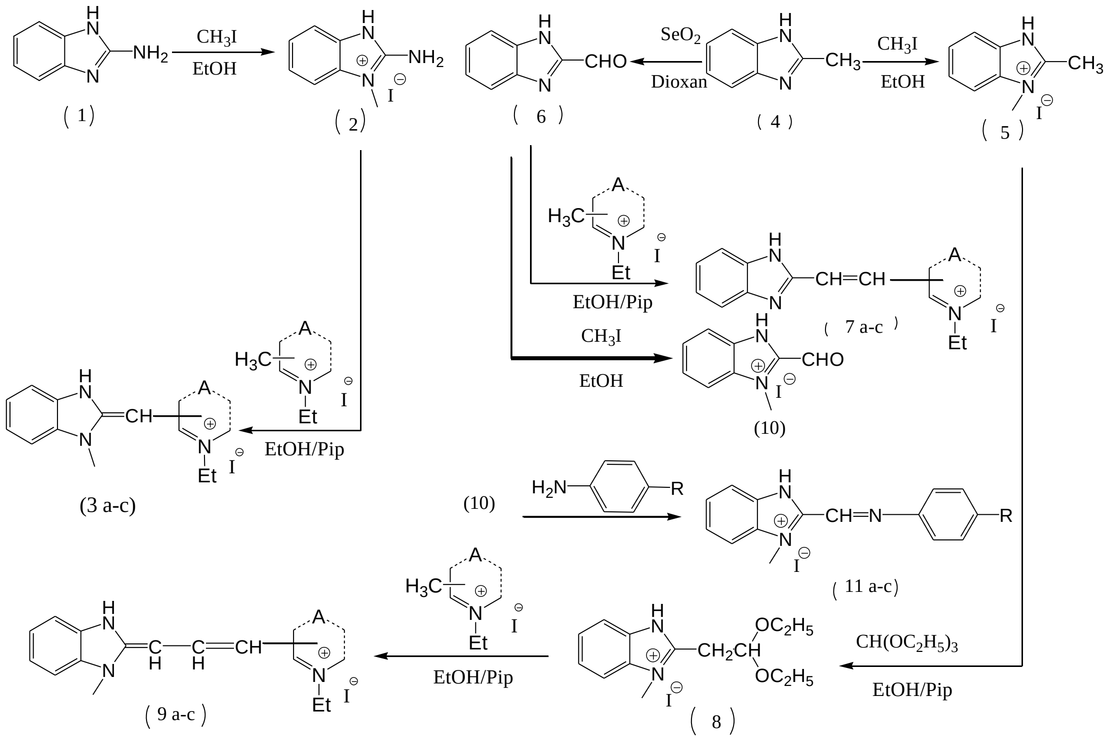
Samp le	Inhibition zone diameter (mm/mg sample)					
	Escherichia Coli (G)		*Staphylococcus Aureus* (G)		*Candida albicans*	*Aspergillus flavus*

Control:
DMSO 0 0 0 0
Ampicillin
Atibacterial 22 18 - - - -
Agent

Amphotericin
B Antifungal
Agent - - - - 19 17

2 14 13 0.0 0.0
3a 10 10 0.0 0.0
3b 19 21 11 0.0
3C 10 10 0.0 0.0
4 16 12 0.0 0.0
6 15 13 14 9

7a 11 11 0.0 0.0
7b 19 21 14 0.0
7c 13 11 10 0.0
9a 18 24 10 0.0
9b 26 30 12 0.0
9c 15 15 0.0 0.0
11a 17 22 9 0.0
11b 24 27 24 7
11c 17 23 9 0.0



Scheme (1)