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ORIGINAL ARTICLE

One-Pot Synthesis, Spectroscopic and Physicochemical Studies of Quinoline Based Blue Emitting Donor—Acceptor Chromophores with Their Biological Application

Abdullah M. Asiri[1,2] · **Salman A. Khan**[1] · **Saad H. Al-Thaqafya**[1]

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Abstract Blue emitting cyano substituted isoquinoline dyes were synthesized by one-pot multicomponent reactions (MCRs) of aldehydes, malononitrile, 6-methoxy-1,2,3,4-tetrahydro-naphthalin-1-one and ammonium acetate. Results obtained from spectroscopic (FT-IR, ^{1}H-NMR, ^{13}C-NMR, EI-MS) and elemental analysis of synthesized compounds was in good agreement with their chemical structures. UV–vis and fluorescence spectroscopy measurements proved that all compounds are good absorbent and fluorescent. Fluorescence polarity study demonstrated that these compounds were sensitive to the polarity of the microenvironment provided by different solvents. In addition, spectroscopic and physicochemical parameters, including electronic absorption, excitation coefficient, stokes shift, oscillator strength, transition dipole moment and fluorescence quantum yield were investigated in order to explore the analytical potential of synthesized compounds. The anti-bacterial activity of these compounds were first studied in vitro by the disk diffusion assay against two Gram-positive and two Gram-negative bacteria then the minimum inhibitory concentration (MIC) was determined with the reference of standard drug chloramphenicol. The results displayed that compound **3** was better inhibitors of both types of the bacteria (Gram-positive and Gram-negative) than chloramphenicol.

Keywords Isoquinoline · Oscillator strength · Dipole moment · Fluorescence quantum yield · Anti-bacterial activity

✉ Salman A. Khan
sahmad_phd@yahoo.co.in

[1] Department of Chemistry, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia

[2] Center of Excellence for Advanced Materials Research (CEAMR), King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia

Introduction

Quinoline derivatives have attracted increasing attention due to their medicinal applications such as anticancer, antidepressant, anti-inflammatory, antiamoebic antimicrobial, antinociceptive [1–3]. Due to presence of double bond chain conjugation its have potential application blue emitting fluorescence fluorescent dyes with high florescence quantum yield [4, 5] and photonics materials such as optical switching, electrochemical sensing, langmuir films and photoinitiated polymerization [6–8]. Therefore quinoline derivatives have widely been used as whitening or brightening reagents for synthetic fibers, for recognition of hole-transport materials in the electroluminescence fields [9, 10]. Bifungsional group conation quinoline derivatives dramatically increase the blue emitting fluorescence fluorescent dyes and also increase the optical properties [11, 12]. Quinoline are also use in the field of inorganic chemistry for the coordination with Cu(II), Ni(II), Co(II), Pt (II), Pd(II), Cd(II) and Zn (II) metal [13, 14]. Cyano substituted 2-amino quinoline is used as intermediate for the formation of various fused bi-cyclic heterocyclic compounds such as pyrazolo quinoline, thiazolo quinoline, oxazolo-quinoline [15–17]. Physicochemical characteristics, such as, solvatochromic, piezochromic, oscillator strength, dipole moment, florescent quantum yield and photostability, are also the most important studies for determining the physical behavior

of compounds [18, 19]. Numerous reactions were reported for the synthesis of quinoline derivatives through ring intermolecular, intramolecular cyclization and annulations. All these type reaction are multi steps reaction and low harsh reaction conditions and relatively overall low yields [20]. But quinoline can be directly prepared via one-pot multicomponent reaction (MCR). Such type of reactions has received considerable interest since it is easier to perform, gives higher yields and less time consuming [21]. The present work may show good significance in the field of industrial chemistry due to the high florescent properties of these blue misting dyes [22]. Thus, in continuation of our efforts on the synthesis one-pot multicomponent reaction of various biologically and optically active of heterocyclic compounds [23, 24], we would like to synthesis novel bifungsional quinoline derivatives via one-pot multicomponent reaction with potential bioactivity and physicochemical property such as solvatochromic, piezochromic, oscillator strength, dipole moment and florescent quantum yield are also determine.

Experimental

Chemicals and Reagents

The appropriate aldehyde, 6-methoxy-1,2,3,4-tetrahydronaphthalin-1-one, malononitrile and ammonium acetate were purchased from Acros Organic. Other reagents and solvents (A.R.) were obtained commercially and used without further purification, except dimethylformamide (DMF), ethanol and methanol.

Apparatus

Melting points were recorded on a Thomas Hoover capillary melting apparatus without correction. FT-IR spectra were recorded on a Nicolet Magna 520 FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR experiments were performed in $CDCl_3$ on a Brucker DPX 600 MHz spectrometer using tetramethyl silane (TMS) as internal standard at room temperature. UV–vis electronic absorption spectra were acquired on a Shimadzu UV-1650 PC spectrophotometer. Absorption spectra were collected using a 1 cm quartz cell. Steady state fluorescence spectra were measured using Shimadzu RF 5301 PC spectrofluorphotometer with a rectangular quartz cell. Emission spectra were monitored at right angle. All fluorescence spectra were blank subtracted before proceeding in data analyses.

General Method for the Synthesis of Benzoquinoline Derivatives

A one-pot mixture of the appropriate aldehyde (10 mmol), 6-methoxy-1,2,3,4-tetrahydro-naphthalin-1-one (1.46 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and ammonium acetate (6.2 g, 80 mmol) in absolute ethanol (50 mL) was refluxed for 6 h [25]. The reaction mixture was allowed to cool, and the resulting precipitate was filtered, washed with water, dried and recrystallized from ethanol and chloroform.

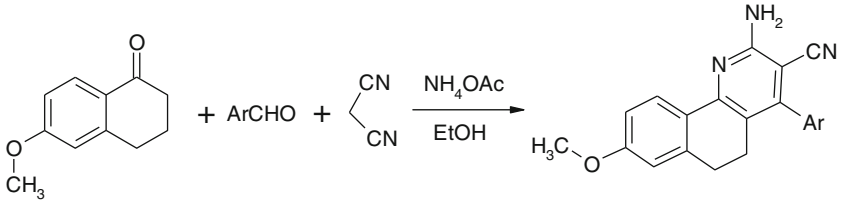
2-amino-4-(2,3, 4-tri methoxyphenyl)-9-methoxy-5,6 dihydrobenzo[f]isoquinoline-1-carbonitrile (1)

EI-MS *m/z* (rel. int. %): 419 (78) $[M+1]^{+\cdot}$; IR (KBr) ν_{max} cm^{-1}: 3458 (NH_2), 2945 (C-H), 2212 (CN),1556(C=C), 1252 (N=C); ^{1}H NMR (600MXz $CDCl_3$) δ: 8.11 (d, 1H, CH_{Ar}, *J=9.6*Hz), 7.85 (s,1H, CH_{Ar}), 6.89 (d, 1H, CH_{Ar}, *J*= 2.4 Hz), 6.87 (d, 1H, CH_{Ar}, *J*=3.0 Hz), 6.63 (s, 1H, CH_{Ar}), 5.05 (s, 2H, NH_2) 3.99 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.75−2.72 (m, 2H, C5), 2.63−2.53 (m, 2H, C6); ^{13}CNMR ($CDCl_3$) δ: 161.30, 158.14, 156.87, 156.52, 154.80, 152.50, 150.78, 150.55, 149.83, 143.62, 143.12, 141.42, 127.92 (Ar-C), 117.53 (CN), 115.77, 114.47, 113.55, 112.80, 109.22, 97.52, 95.51, 90.40, 56.70, 56.40, 56.37, 56.36, 56.11, 28.22 (C6), 26.35 (C5); Anal. calc.for $C_{24}H_{23}N_3O_4$: C, 69.05, H, 5.55, N, 10.07. Found: C, 68.98, H, 5.51 N, 9.97.

2-amino-4-(4-phenyl)-9-methoxy-5,6 dihydrobenzo[f] isoquinoline-1-carbonitrile (2)

EI-MS *m/z* (rel. int. %): 359 (65) $[M+1]^{+\cdot}$; IR (KBr) ν_{max} cm^{-1}: 3468 (NH_2), 2943 (C-H), 2232 (CN), 1547 (C=C), 1245 (C=N); ^{1}H NMR (600MXz $CDCl_3$) δ: 8.21 (d, 1H, CH_{Ar}, *J*=8.4 Hz), 7.02 (d, 1H, CH_{Ar}, *J*=8.4 Hz), 7.01 (d, 1H, $CH_{Ar,}$ *J*=1.8 Hz), 6.93 (s, 1H, CH_{Ar}), 6.89 (d, 1H, CH_{Ar}, *J*=2.4 Hz), 6.88 (d, 1H, CH_{Ar}, *J*=2.4 Hz), 6.77 (d, 1H, CH_{Ar}, *J*=2.4 Hz), 5.11 (s,2H, NH_2), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, N-CH_3), 2.76−2.74 (m, 2H, C5), 2.65

Scheme 1 Synthesis of benzoquinoline derivatives

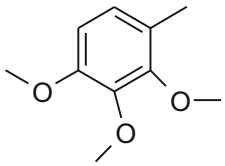
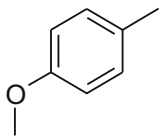
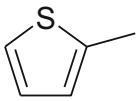
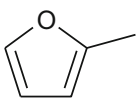
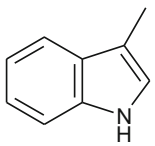


−2.63 (m, 2H, C6): ^{13}CNMR ($CDCl_3$) δ: 161.41, 160.04, 152.64, 141.26, 129.97, 128.18, 128.00, 126.97 119.50 (Ar-C), 117.56 (CN), 114.07, 112.78, 112.75, 89.54, 55.37, 55.35, 28.55 (C6), 24.64 (C5); Anal. calc. for $C_{22}H_{19}N_3O_2$: C, 73.93, H, 5.36, N, 11.76. Found: C, 73.86, H, 5.28, N, 11.72.

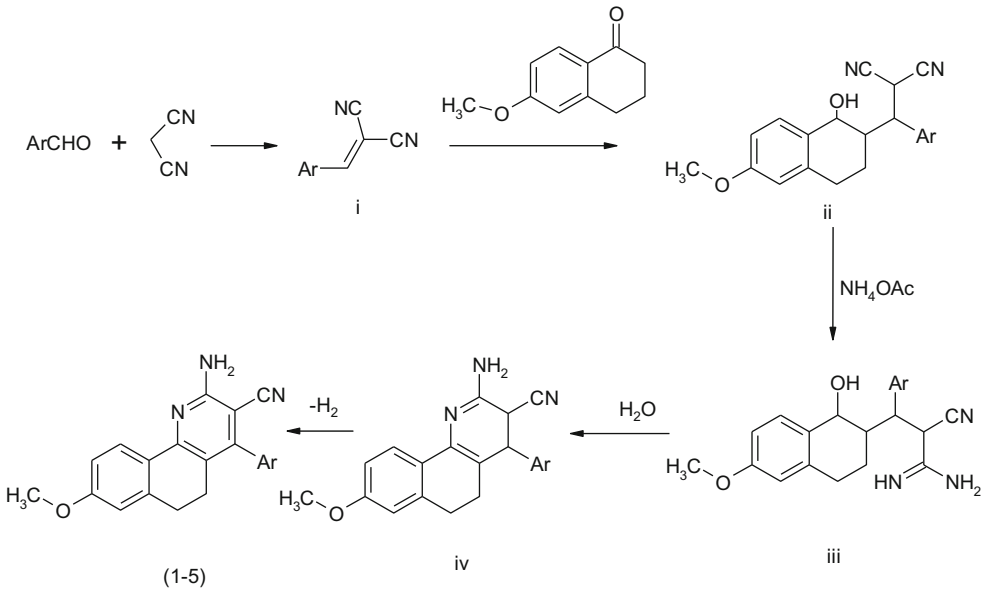
2-amino-9-methoxy-4-(thiophen-2-yl)-5, 6-dihydrobenzo[f]isoquinoline-1-carbonitrile (3)

EI-MS *m/z* (rel. int. %): 335 (68) $[M+1]^{+\cdot}$; IR (KBr) ν_{max} cm^{-1}: 3434 (NH_2), 2937 (C-H), 2201 (CN), 15742 (C=C),

Table 1 Physicochemical data of the synthesized compounds **(1–5)**

Compound no.	R	Molecular formula	Crystallization	% Yield	m.p °C
1		$C_{24}H_{23}N_3O_4$	$CHCl_3$	78.52	159
2		$C_{22}H_{19}N_3O_2$	CH_3OH:$CHCl_3$	75.85	201
3		$C_{19}H_{15}N_3OS$	C_2H_5OH:$CHCl_3$	73.80	182
4		$C_{19}H_{15}N_3O_2$	CH_3OH:$CHCl_3$	75.80	288
5		$C_{23}H_{18}N_4O$	$CHCl_3$	71.50	219

Scheme 2 Mechanism of the formation of benzoquinoline derivatives (1–5)



1247 (C=N); ^{1}H NMR (600MXz $CDCl_3$) δ: 8.20 (d, 1H, CH_{Ar}, J=8.4 Hz), 8.02 (d, 1H, CH_{Ar}, J=8.4 Hz), 7.49 (d, 1H, CH_{Ar}, J=8.4 Hz), 7.40 (d, 1H, CH_{Ar}, J=8.4Hz), 6.90 (d, 1H, CH_{Ar}, J=3.0 Hz), 6.88 (d, 1H, CH_{Ar}, J=2.4 Hz), 6.72 (s, 1H, CH_{Ar}), 5.13 (s, 2H, NH_2), 3.86 (s, 3H, OCH_3), 2.77−2.75 (m, 2H, C5), 2.60−2.58 (m, 2H, C6); ^{13}CNMR ($CDCl_3$) δ: 161.59, 158.21, 155.44, 151.48, 141.23, 134.44, 130.57, 128.10, 126.52, 119.18 (Ar-C), 117.11 (CN), 113.04,

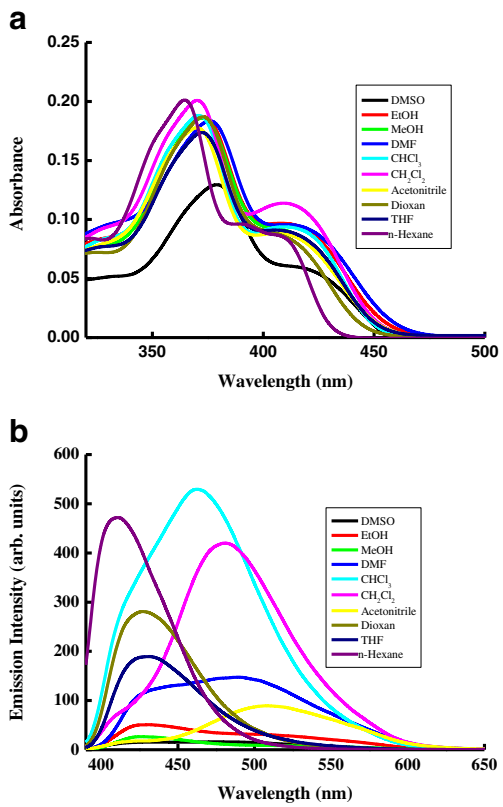


Fig. 1 **a** Electronic absorption spectra of 1×10^{-5} mol dm^{-3} of compound **1** in different solvents. **b** Emission spectra of 1×10^{-5} mol dm^{-3} of compound **1** in different solvents

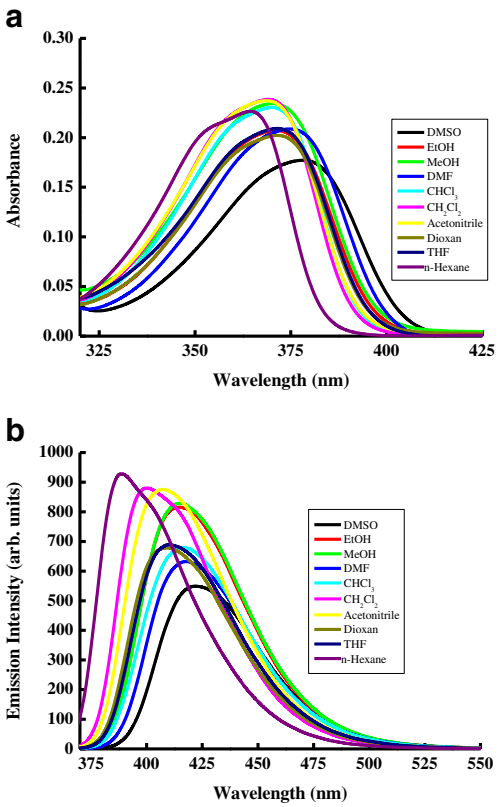


Fig. 2 **a** Electronic absorption spectra of 1×10^{-5} mol dm^{-3} of compound **2** in different solvents. **b** Emission spectra of 1×10^{-5} mol dm^{-3} of compound **2** in different solvents

111.87, 88.98, 55.39, 38.93, 36.07, 30.19, 28.46 (C6), 24.57 (C5); Anal. calc.for $C_{19}H_{15}N_3OS$: C, 68.45, H, 4.53, N, 12.60. Found: C, 67.97, H, 4.33, N, 12.42.

2-amino-4-(furan-2-yl)-9-methoxy-5,6-dihydrobenzo[f] isoquinoline-1-carbonitrile (4)

EI-MS *m/z* (rel. int. %): 319 (65) $[M+1]^{+\cdot}$; IR (KBr) v_{max} cm^{-1}: 3454 (NH_2), 2937 (C-H), 2205 (CN), 1548 (C=C), 1243 (C=N); ^{1}H NMR (600MXz $CDCl_3$) δ: 8.19 (d, 1H, CH_{Ar}, *J*=9.0 Hz), 7.63 (dd, CH_{Ar}, *J* =1.2Hz), 7.26 (s, 1H, CH_{Ar}), 6.89−6.85(d, CH_{Ar}, *J*=8.4Hz), 6.74 (d, CH_{Ar}, *J*= 2.4 Hz), 5.15 (s, 1H, NH_2), 3.86 (s, 3H, OCH_3), 2.93−2.90 (m, 2H, C5), 2.82−2.80 (m, 2H, C6); ^{13}CNMR ($CDCl_3$) δ: 161.50, 158.75, 155.73, 148.10, 143.78, 141.20, 140.27, 128.05, 126.64, 119.19 (Ar-C), 117.67 (CN), 113.66, 112.79, 112.69, 111.59, 86.84, 55.38, 28.37 (C6), 24.86 (C5); Anal. calc.for $C_{19}H_{15}N_3O_2$: C, 71.91, H,4.76, N, 13.24. Found: C, 71.85, H,4.71, N, 13.18.

2-amino-4-(1H-indol-3-yl) -9-methoxy-5,6-dihydrobenzo[f] isoquinoline-1-carbonitrile (5)

EI-MS *m/z* (rel. int. %): 368 (65) $[M+1]^{+\cdot}$; IR (KBr) v_{max} cm^{-1}: 3416 (NH_2), 2939 (C-H), 2204 (CN), 1555 (C=C), 1244 (C=N); ^{1}H NMR (600MXz $CDCl_3$) δ: 9.15 (s, 1H, NH), 8.52 (d, CH_{Ar}, *J*=3.0 Hz), 8.50 (s, 1H, CH_{Ar}) 8.24 (d, CH_{Ar}, *J*=9.0 Hz), 8.10 (s, CH_{Ar}), 8.02 (d, 1H, CH_{Ar}, *J*= 9.0 Hz), 7.76 (d, 1H, CH_{Ar}, *J*=7.2), 5.10 (s, 2H, NH_2), 3.86 (s, OCH_3), 2.86−2.69 (m, 2H, C5), 2.62−2.54 (m, 2H, C6); ^{13}CNMR ($CDCl_3$) δ: 150.61, 141.44, 135.88, 131.01, 129.68, 126.61, 124.90, 123.40, 120.68, 119.97(Ar-C), 118.10 (CN), 115.17, 112.80, 111.71, 76.82, 73.91, 55.38, 28.69 (C6), 25.06 (C5); Anal. calc.for $C_{23}H_{18}N_4O$: C, 75.39, H, 4.95, N, 15.29. Found: C, 75.32, H, 4.88, N, 15.21.

In Vitro Screening: Disc –Diffusion and Micro Dilution Assay

Antibacterial activity was done by the disk diffusion method with minor modifications. *S. aureus*, *S. pyogenes*, *S. typhimurium* and *E. coli* were sub-cultured in BHI medium and incubated for 18 h at 37 °C, and then the bacterial cells were suspended, according to the McFarland protocol in saline solution to produce a suspension of about 10^{-5} CFU mL^{-1}: 10 μL of this suspension was mixed with 10 mL of sterile nutrient agar at 40 °C and poured onto an agar plate in a laminar flow cabinet. Five paper disks (6.0 mm diameter) were fixed onto nutrient agar plate. One milligram of each test compound was dissolved in 100 μl DMSO to

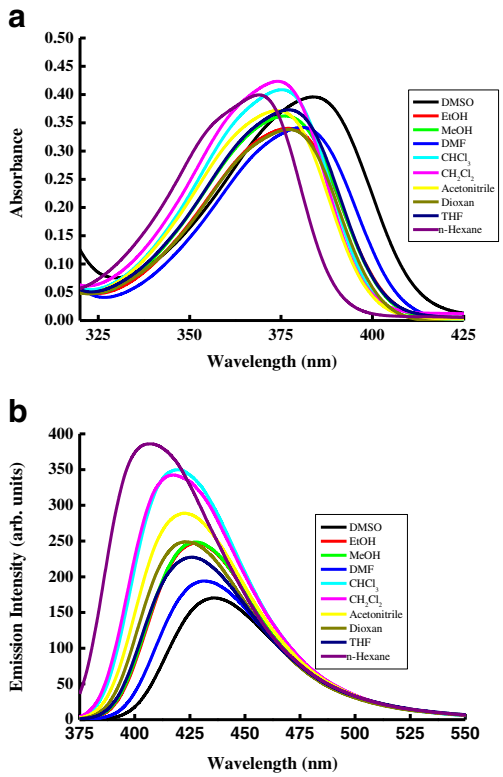


Fig. 3 **a** Electronic absorption spectra of 1×10^{-5} mol dm^{-3} of compound **3** in different solvents. **b** Emission spectra of 1×10^{-5} mol dm^{-3} of compound **3** in different solvents

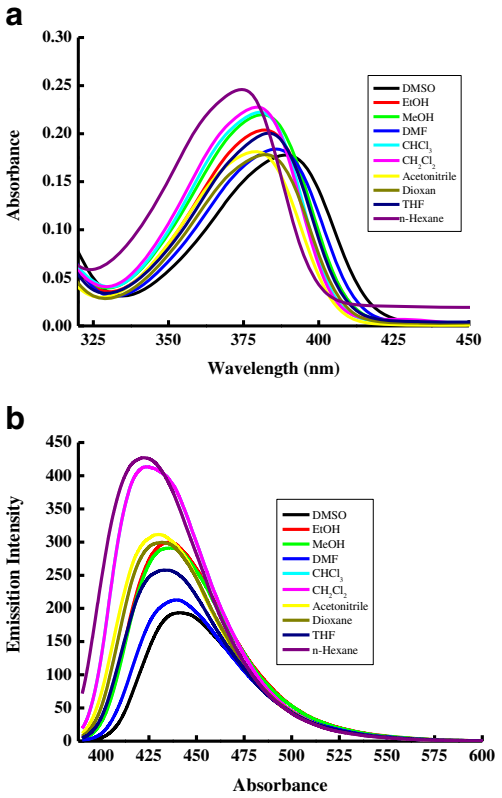


Fig. 4 **a** Electronic absorption spectra of 1×10^{-5} mol dm^{-3} of compound **4** in different solvents. **b** Emission spectra of 1×10^{-5} mol dm^{-3} of compound **4** in different solvents

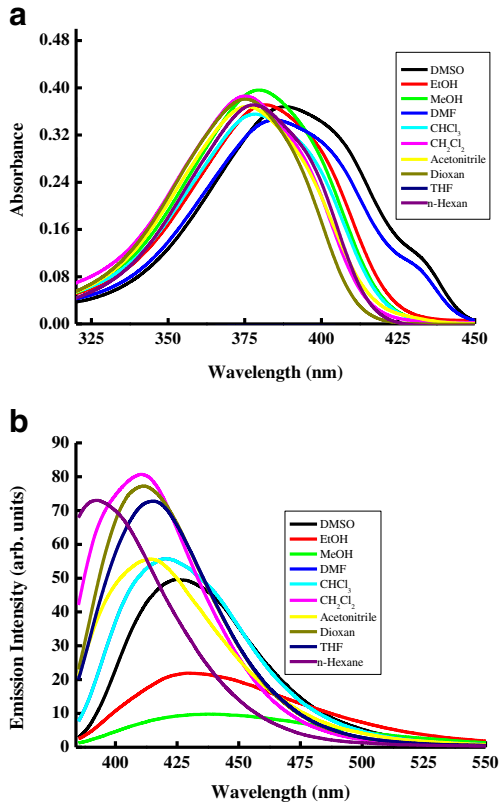


Fig. 5 **a** Electronic absorption spectra of 1×10^{-5} mol dm^{-3} of compound **5** in different solvents. **b** Emission spectra of 1×10^{-5} mol dm^{-3} of compound **5** in different solvents

prepare stock solution from stock solution different concentration 10, 20, 25, 50, and 100 μg/ μl of each test compound were prepared. These compounds of different concentration were poured over disk plate on to it. Chloramphenicol (30 μg/disk) was used as standard drug (positive control). DMSO poured disk was used as negative control. The susceptibility of the bacteria to the test compounds was determined by the formation of an inhibitory zone after 18 h of incubation at 36 °C reports the inhibition zones (mm) of each compound and the controls. The minimum inhibitory concentration (MIC) was evaluated by the macro dilution test using standard inoculums of 10^{-5} CFL mL^{-1}. Serial dilutions of the test compounds, previously dissolved in dimethyl sulfoxide (DMSO) were prepared to final concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1 μg/ mL to each tube was added 100 μL of a 24 h old inoculum. The MIC, defined as the lowest concentration of the test compound, which inhibits the visible growth after 18 h, was determined visually after incubation for 18 h, at 37 °C. Tests using DMSO and chloramphenicol as negative and positive controls.

Result and Discussion

Chemistry

Cyano substituted isoquinoline-1-carbonitrile derivatives were synthesized by one-pot multicomponent reactions (MCRs) of aldehydes, malononitrile, 6-methoxy-1,2,3,4-tetrahydro-naphthalin-1-one and ammonium acetate. However, we found that one-pot MCRs of aldehydes, malononitrile, 6-methoxy-1,2,3,4-tetrahydro-naphthalin-1-one and ammonium acetate yielded the corresponding Cyano substituted isoquinoline-1-carbonitrile derivatives (Scheme 1 and Table 1). The mechanism for the formation of isoquinoline derivatives is shown in Scheme 2. The purified product was characterized by the FT-IR, ^{1}H-NMR, ^{13}C-NMR and EI MS spectra. The formation of the Cyano substituted isoquinoline-1-carbonitrile explained according to the following mechanism (Scheme 2). The reaction seemed to be started by first addition of active hydrogen of 6-methoxy-1,2,3,4-tetrahydro-naphthalin-1-one to the ethylenic double bond of compound **i**. Ammonia was added to the nitrile group in **ii** to give **iii** which looses a molecule of water to give **iv**, which in turn was converted to the final product by auto-oxidation

Table 2 Spectral data and fluorescence quantum yield (φ_f) of compound no. 1 in different solvents

Solvent	Δf	E_T (30) Kcal mol^{-1}	E_T^N	λ_{ab}(nm)	λ_{em}(nm)	ε M^{-1}cm^{-1}	f	μ Debye	$\Delta\overline{\nu}$ (cm^{-1})	Φ_f
DMSO	0.266	75.63	1.38	378	482	12900	0.29	4.85	5709	0.032
EtOH	0.305	77.90	1.45	367	475	17090	0.42	5.73	6195	0.010
MeOH	0.308	79.19	1.49	361	479	15210	0.41	3.63	6824	0.005
DMF	0.263	76.24	1.40	375	465	17900	0.36	5.41	5161	0.028
$CHCl_3$	0.217	77.06	1.43	371	445	18440	0.33	5.09	4483	0.010
CH_2Cl_2	0.255	77.90	1.45	367	461	18770	0.41	5.69	5556	0.075
Acetonitrile	0.274	77.90	1.45	367	472	16810	0.40	5.62	6061	0.017
Dioxan	0.148	76.65	1.41	373	409	18360	0.17	3.69	2360	0.053
THF	0.208	77.06	1.43	371	411	16740	0.17	3.70	2624	0.039
n-Hexane	0.0014	79.19	1.49	361	393	18380	0.16	3.55	2255	0.083

Table 3 Spectral data and fluorescence quantum yield (φ_f) of compound no. 2 in different solvents

Solvent	Δf	E_T^N	E_T (30) Kcal mol^{-1}	λ_{ab}(nm)	λ_{em}(nm)	ε M^{-1}cm^{-1}	f	μ Debye	$\Delta\bar{\nu}$ (cm^{-1})	Φ_f
DMSO	0.266	1.35	74.45	384	427	17530	0.18	3.86	2622	0.26
EtOH	0.305	1.39	75.83	377	419	20500	0.21	4.17	2659	0.33
MeOH	0.308	1.38	75.63	378	418	22630	0.22	4.28	2523	0.29
DMF	0.263	1.37	75.23	380	422	20780	0.21	4.17	2619	0.25
$CHCl_3$	0.217	1.40	76.24	375	420	22990	0.26	4.56	2857	0.31
CH_2Cl_2	0.255	1.40	76.24	375	404	23520	0.18	3.78	1914	0.23
Acetonitrile	0.274	1.39	76.03	376	412	22900	0.21	4.09	2324	0.31
Dioxan	0.148	1.36	75.63	378	413	19800	0.17	3.76	2242	0.28
THF	0.208	1.39	75.83	377	414	20750	0.19	3.95	2371	0.27
n-Hexane	0.0014	1.43	77.27	370	392	22300	0.13	3.25	1517	0.34

(Scheme 2). The IR spectrum of compounds **(1–5)** shows the characteristic band at 3416–3468 cm^{-1} due to presence -NH_2 group and at 2201–2232 cm^{-1} attributed to the CN group. IR spectra shows sharp peek at 1243–1252 cm^{-1} due presence of C=N stretch which is conform to formation of quinoline**.** ^{1}H-NMR spectra, which prove diagnostic tool for the positional elucidation of the proton. Assignments of the signals are based on chemical shift and intensity pattern. The ^{1}H-NMR spectra of all the compounds (**1**–**5**) measured at room temperature shows one singlet at 5.05–5.15 ppm for the NH_2. The appearance of multiplets at δ 8.52−6.63 was due to aromatic protons and two multiplets at δ 2.93−2.69 and 2.82−2.53 ppm corresponding to the benzylic protons (C5-*H* and C6-*H* respectively). Moreover, ^{13}C-NMR spectra showed signals in the range of δ 28.22–28.69 ppm and at δ 26.35−24.57 ppm due to C6 and C5, respectively and the structure of the compounds was further conformed due to present of CN group at δ 117.10–118.10 ppm. Finally characteristic peaks were observed in the mass spectra of compounds (1–5) by the molecular ion peak. The mass spectrum of compound 1 shows a molecular ion peak ($M^{+\cdot}$) m/z 419. All the compounds give similar fragmentation pattern.

Spectral Behaviour of 3-Cyano-2-oxo-4-substituted-1, 2,5,6-tetrahydrobenzo[h]quinolines in Different Media (1–5)

Absorption and emission spectra of 1×10^{-5} mol dm^{-3} compounds (**1**–**5**) in various non-polar, polar aprotic and protic solvents were studied (Figs. 1a, 2, 3, 4, and 5b). Calculated physicochemical parameters obtained from steady state absorption and fluorescence spectra were measured and listed in Tables 2, 3, 4, 5 and 6 [26]. A close examination of Figs. 1a, 2, 3, 4, and 5a displays that the polarity of solvent has a little effect on absorption maxima, indicating the weak polar character of compounds (**1**–**5**) in the ground state. However, the emission spectra of these compounds are broad and red shifted as the solvent polarity increases, as shown in Figs. 1b, 2, 3, 4, and 5b. The red-shift in n-Hexane to DMSO indicates that photoinduced intramolecular charge transfer (ICT) occurring in the singlet excited state from electron donating group to electron acceptor group [27]. As a result, the polarity of compounds (**1**–**5**) increases on excitation.

Table 4 Spectral data and fluorescence quantum yield (φ_f) of compound no. 3 in different solvents

Solvent	Δf	E_T (30) Kcal mol^{-1}	E_T^N	λ_{ab}(nm)	λ_{em}(nm)	ε M^{-1}cm^{-1}	f	μ Debye	$\Delta\bar{\nu}$ (cm^{-1})	Φ_f
DMSO	0.266	74.65	1.35	383	445	39220	0.57	6.80	3638	0.11
EtOH	0.305	76.85	1.42	372	435	31870	0.49	6.25	3893	0.071
MeOH	0.308	75.04	1.36	381	434	36400	0.46	6.13	3205	0.070
DMF	0.263	74.45	1.35	384	429	34400	0.44	6.03	3262	0.056
$CHCl_3$	0.217	75.23	1.37	380	427	41220	0.47	6.19	2896	0.084
CH_2Cl_2	0.255	75.43	1.38	379	426	42680	0.49	6.31	2911	0.079
Acetonitrile	0.274	75.63	1.38	378	435	37440	0.51	6.44	3467	0.075
Dioxan	0.148	74.48	1.35	382	430	34110	0.39	5.64	2923	0.072
THF	0.208	75.23	1.37	380	434	37560	0.49	6.28	3274	0.061
n-Hexane	0.0014	76.44	1.41	374	415	40630	0.42	5.83	2641	0.095

Table 5 Spectral data and fluorescence quantum yield (φ_f) of compound no. 4 in different solvents

Solvent	Δf	E_T (30) Kcal mol^{-1}	E_T^N	λ_{ab}(nm)	λ_{em}(nm)	ε M^{-1}cm^{-1}	f	μ Debye	$\Delta\overline{\nu}$ (cm^{-1})	Φ_f
DMSO	0.266	72.01	1.27	397	446	17610	0.19	4.03	2767	0.19
EtOH	0.305	73.49	1.32	389	442	20360	0.25	4.53	3082	0.25
MeOH	0.308	73.49	1.32	389	441	21810	0.26	4.66	3031	0.22
DMF	0.263	72.75	1.29	393	445	18330	0.21	4.26	2974	0.20
$CHCl_3$	0.217	73.87	1.33	387	430	22300	0.23	4.34	2584	0.31
CH_2Cl_2	0.255	74.06	1.33	386	428	22850	0.23	4.35	2542	0.32
Acetonitrile	0.274	74.06	1.33	386	435	18730	0.21	4.22	2918	0.29
Dioxan	0.148	73.49	1.32	389	435	17860	0.19	3.22	2718	0.28
THF	0.208	73.49	1.32	389	434	20250	0.21	4.20	2665	0.17
n-Hexane	0.0014	74.84	1.36	382	429	24440	0.28	4.76	2868	0.21

Determination of Oscillator Strength and Transition Dipole Moment

The solvatochromic behaviour in compounds (**1**–**5**) allows one to determine the difference in the dipole moment between the excited singlet and the ground state ($\Delta\mu=\mu_e-\mu_g$). This difference can be obtained using the simplified Lippert-Mataga equation as follows [27, 28]:

$$\Delta\overline{\nu}_{st}=\frac{2\left(\mu_e-\mu_g\right)^2}{hca^3}\Delta f+Const. \quad (1)$$

$$\Delta f=\frac{D-1}{2D+1}-\frac{n^2-1}{2n^2+1} \quad (2)$$

where $\Delta\overline{\nu}_{st}$ is the Stokes–shift [29], which increases with increasing the solvent polarity pointing to stronger stabilization of the excited state in polar solvents, h denotes Planck's constant, c refers to the speed of light in vacuum and a is the Onsager cavity radius. Parameters D and n, in Eq. 2, correspond to the dielectric constant and refractive index of the solvent, respectively. The Onsager cavity radius was chosen to be 4.2 Å because this value is comparable to the radius of a typical aromatic fluorophore [30]. Stokes shifts ($\Delta\overline{\nu}_{ss}$) of compounds (**1**–**5**) in different solvents were calculated, as shown in Tables 2, 3, 4, 5, and 6, using the following the equation [27]:

$$\Delta\overline{\nu}_{ss}=\overline{\nu}_{ab}-\overline{\nu}_{em} \quad (3)$$

where $\overline{\nu}_{ab}$ and $\overline{\nu}_{em}$ denote the wavenumbers of absorbance and emission maxima (cm^{-1}), respectively. The changes in dipole moment ($\Delta\mu$) for compounds (1–5) are positive value which indicates that the singlet exaited is more polar than the ground state. The values of $\Delta\mu$ are listed in Table 7.

The effective number of electrons transition from the ground to excited state is usually described by the oscillator strength, which provides the absorption area in the electronic spectrum. The oscillator strength, f, can be calculated using the following equation [31]:

$$f=4.32\times10^{-9}\int\varepsilon\left(\overline{\nu}\right)d\overline{\nu} \quad (4)$$

where ε is the extinction coefficient (Lmol^{-1} cm^{-1}), and $\overline{\nu}$ represents the numerical value of wavenumber (cm^{-1}). Oscillator

Table 6 Spectral data and fluorescence quantum yield (φ_f) of compound no. 5 in different solvents

Solvent	Δf	E_T (30) Kcal mol^{-1}	E_T^N	λ_{ab}(nm)	λ_{em}(nm)	ε M^{-1}cm^{-1}	f	μ Debye	$\Delta\overline{\nu}$ (cm^{-1})	Φ_f
DMSO	0.266	66.04	1.09	392	436	37010	0.38	5.61	2575	0.023
EtOH	0.305	74.06	1.33	386	439	37400	0.46	6.13	3127	0.010
MeOH	0.308	74.26	1.33	385	441	39880	0.52	6.51	3299	0.027
DMF	0.263	73.49	1.32	389	428	34750	0.32	5.13	2342	0.027
$CHCl_3$	0.217	74.84	1.36	382	430	35890	0.41	5.76	2923	0.026
CH_2Cl_2	0.255	75.23	1.46	380	418	38920	0.37	5.45	2392	0.036
Acetonitrile	0.274	75.23	1.46	380	422	37120	0.38	5.53	2619	0.026
Dioxan	0.148	75.23	1.46	380	417	38370	0.35	5.30	2335	0.035
THF	0.208	74.45	1.35	384	422	37420	0.35	5.33	2345	0.034
n-Hexane	0.0014	76.03	1.39	376	397	23140	0.13	3.21	1407	0.051

Table 7 Change in Δμ of compounds (1–5)

Compound	Δμ (Debye)
1	3.42
2	1.51
3	1.48
4	0.06
5	1.89

strength values of compounds (**1–5**) in different solvents are reported in Tables 2, 3, 4, 5, and 6. In addition, the transition dipole moment (μ) for compounds (**1–5**) from ground to excited state in Debye was estimated in different solvents (Table 7) using the following relation [32]:

$$\mu^2 = \frac{f}{4.72 \times 10^{-7} \times E_{\max}} \quad (5)$$

where E_{max} is the maximum energy of absorption in cm^{-1}

Fluorescence Polarity Study of Compounds (1–5)

The steady state absorption and fluorescence parameters of 1×10^{-5} M were recorded in various polar aportic and polar protic solvents, as summarized in Tables 2, 3, 4, 5, and 6. The emission spectra of compounds **(1–5)** are shown in Figs. 1b, 2, 3, 4, and 5b. It can be clearly noted from Figs. 1b, 2, 3, 4, and 5b that the polarity of solvent has a significant effect on emission spectra, indicating the strong polar character of all compounds in the ground state. The emission spectra, however, are broad and red shifted as the solvent polarity increases from n-hexane to DMSO. The empirical Dimroth polarity parameter, E_T (30) and E^T_N of dye (1–5) were also calculated according to the following equation [33, 34].

$$E_T^N = \frac{E_T(solvent) - 30.7}{32.4} \quad (6)$$

Table 9 Minimum inhibition concentration (MIC) of isoquinoline derivatives (**1–5**)

Bacterial Strain	MIC (μg mL^{-1}) compound					Positive
	1	2	3	4	5	Control
S. aureus	128	256	16	64	64	32
S. Pyogenes	128	128	16	64	64	32
S. typhimurium	256	128	32	128	32	32
E. coli	256	256	32	64	64	32

Positive control: chloramphenicol (Chlora.) Negative control: (DMSO)

$$E_T(solvent) = \frac{28591}{\lambda_{max}} \quad (7)$$

where λ_{max} corresponds to the peak wavelength (nm) in the red region of the intramolecular charge transfer absorption of all compounds. The red (bathochromic) shift from n-hexane to DMSO indicates that photoinduced intramolecular charge transfer (ICT) occurs in the singlet excited state, and the polarity of compounds, therefore, increases on excitation.

The fluorescence quantum yield (φ_f) was measured using the optically diluted solution to avoid reabsorption effect absorbance at excition wave relative method with solution of 9, 10-diphenylanthralene (DPA) in DMSO as reference standard. The following relation has applied to calculate the fluorescence quantum yield [35]:

$$\phi_f(s) = \varphi_f(r) \frac{F_{(s)} \left\{1 - \exp\left(-A_{ref} \ \ln \ 10\right)\right\} \times n^2 s}{F_{(ref)} \ \{1 - \exp(-A_s \ \ln \ 10)\} \times n^2 r} \quad (8)$$

where F denotes the integral of the corrected fluorescence spectrum, A is the absorbance at the excitation wavelength, and n is the refractive index of the medium. The subscripts "s" and "r" refer to sample and reference, respectively. Flurescence quantum yield of comopunds (1–5) in different solvent are also listed Tables 2, 3, 4, 5, and 6.

Table 8 Antibacterial activity and cytotoxicity profile of compounds **1–5**

Compounds	Zone of inhibition ZOI (mm)				Cytotoxicity IC_{50} (mM/mL)
	S. aureus	S. Pyogenes	S. typhimurium	E. coli	
1	13.2±0.4	11.5±0.4	12.5±0.5	13.8±0.5	>200
2	11.8±0.3	12.2±0.3	12.5±0.2	11.8±0.5	>100
3	15.2±0.5	14.6±0.4	13.8±0.4	16.2±0.5	50
4	21.3±0.3	20.5±0.5	21.5±0.4	22.4±0.5	>100
5	16.0±0.4	16.8±0.3	16.8±0.4	20.2±0.5	
Chlora.	17.0±0.5	18.2±0.4	17.2±0.8	20.0±0.2	
DMSO	–	–	–	–	

Positive control: chloramphenicol (Chlora.); Negative control: (DMSO) measured by the Halo Zone Test (Unit, mm)

Antimicrobial Activity: Disc –Diffusion and Micro Dilution Assay

The compounds **(1–5)** were tested for their antibacterial activities by disc-diffusion method using nutrient broth medium [contained (g/L): beef extract 3 g; peptone 5 g; pH 7.0] [36, 37]. The Gram-positive bacteria and Gram-negative bacteria utilized in this study consisted of *S. aureus*, *S. pyogenes*, *S. typhimurium* and *E. coli*. The results showed that the Cyano substituted isoquinoline-1-carbonitrile increased the antibacterial activity. Among the entire five compounds, sulfur substituted isoqunioline −1- carbonitrile derivative **(3)** showed better antibacterial activity than the reference drug chloramphenicol. The results are presented in Tables 8 and 9 for disc-diffusion method and MIC method.

Cytotoxicity Against L123 (Human Lung Cells)

Cytotoxicity was performed by MTT assay method [38]. A 96 well flat bottom tissue culture plate was seeded with 2×10^3 cells in 0.1 mL of MEM medium supplemented with 10 % FBS and allowed to attach for 24 h. After 24 h of incubation, cells were treated with test compounds to get a concentration of 5, 10, 20, 50 and 100 mM/mL incubated for 48 h. The cells in the control group received only the medium containing the 0.2 % DMSO. Each treatment was performed in duplication. After the treatment, drug containing media was removed and washed with 200 mL of PBS. To each well of the 96 well plate, 100 mL of MTT reagent (stock: 1 mg/mL in serum free medium) was added and incubated for 4 h at 37 °C. After 4 h of incubation the plate was inverted on tissue paper to remove the MTT reagent. To solubilize formazan crystals in the wells, 100 mL of 100 % DMSO was added to each well. The optical density was measured by microtiter plate reader at 590 nm. Compound concentration (mM) required to reduce the viability of mockinfected cells by 50 % as determined by MTT method which summarized in Table 8. Results of MTT assay mentioned on the cell viability based on ability to metabolize the compounds. The results show that compound **1** is comparatively more cytotoxic than **2** and **4**, compound no **3** is the less cytotoxic as these derivatives showed IC50 values more than 100 mM/mL.

Conclusion

Cyano substituted isoquinoline-1-carbonitrile derivative were synthesized by one-pot multicomponent reactions (MCRs) of aldehydes, malononitrile, 6-methoxy-1,2,3,4-tetrahydronaphthalin-1-one and ammonium acetate. In addition, studying spectroscopic and physicochemical properties of Cyano substituted isoquinoline-1-carbonitrile derivatives may show considerable promise towards their potential applications. The antibacterial activity of these compounds was investigated using culture of bacteria. Results demonstrated that the Cyano substituted isoquinoline-1-carbonitrile derivative increased the antibacterial activity. Among the entire five compounds, thiophene substituted isoqunioline −1- carbonitrile derivative **(3)** showed better antibacterial activity than the reference drug chloramphenicol. Physicochemical studies of the compounds including singlet absorption, extinction coefficient, Stokes shift, oscillator strength, dipole moment, fluorescence quantum yield were investigated on the basis of the polarity of solvent.

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