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Design, Synthesis, Fluorescence Properties and Antibacterial Activities of New 8-Chloro-3-Alkyl-3*H*-Pyrazolo[4,3-*a*]acridine-11-Carbonitriles

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The treatment of alkylated nitro derivatives of indazole with 2-(4-chlorophenyl)acetonitrile under basic conditions gave the new 8-chloro-3-alkyl-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitriles *via* the nucleophilic substitution of hydrogen which proceeds at room temperature with concomitant cyclisation in fairly good yields. The structures of all newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Fluorescence experimental results of all newly synthesized compounds revealed remarkable photoluminescence properties and strong green fluorescence properties. Also, the new compounds exhibited potent antibacterial activity and their antibacterial activity (MIC) against Gram positive (*Staphylococcuse aureus methicillin resistant S. aureus* and *Bacillus subtilis*) and negative bacterial (*Pseudomonas aeruginosa* and *Escherichia coli*) species were determined.

Key Words : 5-Nitro-1*H*-indazole, Pyrazolo[4,3-*a*]acridine, Fluorescence, Antibacterial agents

Introduction

Nitrogen heterocyclic compounds are of immense interests, because they constitute an important class of natural and non natural products, many of which exhibit useful biological activities and unique electrical and optical properties.[1-5] They can act as functional materials in the emitters of electroluminescence devices and in the molecular probes used for biochemical research, as well as in the traditional textile and polymer fields.[6-8] In particular, fluorescent dye materials whose fluorescence emission occur at a longer wavelength in the red light region play a leading role in full color electroluminescence displays. Heterocyclic fluorophores are useful materials in the search for new biologically active compounds and diagnostic methods.[9] Fluorescent chromophores are generally known to have planar and rigid π-conjugated systems, and many fluorescent chromophores are based on rigid ring systems such as stilbene, coumarin, naphthalimide, perylene, rodamine and *etc*.

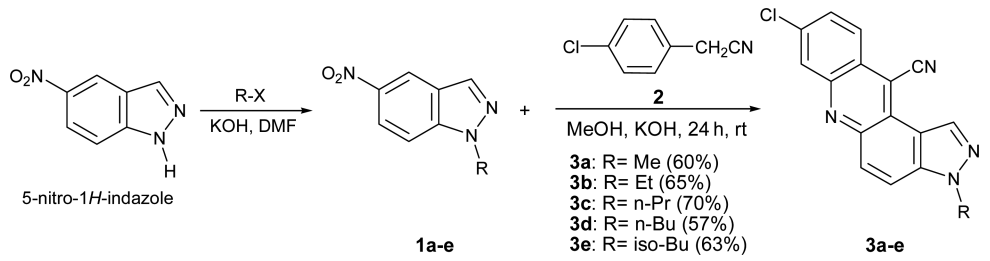
Based on these aspects and in continuation with our research work on the synthesis of new fluorescent nitrogen heterocycles[10-15] and bioactive[16-21] nitrogen heterocyclic compounds, we now decided to examine the transformation of alkylated 5-nitro-1*H*-indazoles and 2-(4-chlorophenyl) acetonitrile to new 8-chloro-3-alkyl-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitriles in basic media and to evaluate their spectroscopic properties and biological activities.

Experimental

Materials and Physical Measurement. Methanol, *N*,*N*-Dimethylformamide (DMF), ethyl bromide, *n*-propyl bromide, *n*-butyl bromide, iso-butyl bromide, 2-(4-chlorophenyl)-acetonitrile, 2-(4-methylphenyl)acetonitrile and 2-(4-methoxyphenyl)acetonitrile were purchased from Merck. Potassium hydroxide was purchased from Sigma–Aldrich. All solvents were dried according to standard procedures. Compounds **1a-e** were synthesized as in literature.[22] The microorganisms *S. aureus* ATCC 1112, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922 were purchased from Pasteur Institute of Iran and *S. aureus* methicillin resistant was isolated from different specimens which were referred to the Microbiological Laboratory of Ghaem Hospital of Medical University of Mashhad, Iran and its methicillin resistance was tested according to the NCCLS guidelines.[23] Absorption and fluorescence spectra were recorded on Varian 50-bio UV-Visible spectrophotometer and Varian Cary Eclipse spectrofluorophotometer. UV–vis and fluorescence scans were recorded from 350 to 700 nm. Melting points were measured on an Electrothermaltype-9100 melting-point apparatus. The IR (as KBr discs) spectra were obtained on a Tensor 27 spectrometer and only noteworthy absorptions are listed. The ^{13}C NMR (100 MHz) and the ^{1}H NMR (400 MHz) were recorded on a Bruker Avance DRX-400 FT spectrometer in $CDCl_3$. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constant *J* is given in Hz. The mass spectra were recorded on a Varian Mat, CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer. All measurements were carried out at room temperature.

General Procedure for the Synthesis of 3a-e and 4a-d. To a solution of KOH (13.3 g, 238 mmol) in methanol (50 mL) the appropriate 1-alkyl-5-nitro-1*H*-indazoles (10 mmol) and arylacetonitrile (12 mmol) were added with stirring. The mixture was stirred at rt for 24 h. After concentration at reduced pressure, the precipitate was collected by filtration, washed with water, following with EtOH, and then air dried to give crude **3a-e** and **4a-d**.

8-Chloro-3-methyl-3*H*-pyrazolo[4,3-*a*]acridine-11 carbonitrile (3a): Compound **3a** was obtained as shiny yellow



Scheme 1. Synthesis of new compounds **3a-e**.

needles (EtOH), yield (60%), mp 317-319 °C; ^{1}H NMR ($CDCl_3$) δ 4.27 (s, 3H), 7.76 (dd, *J* = 9.1 Hz, *J′* = 2.1 Hz, 1H), 7.90 (d, *J* = 9.6 Hz, 1H), 8.06 (d, *J* = 9.6 Hz, 1H), 8.31 (d, *J* = 2.1 Hz, 1H), 8.35 (d, *J* = 9.1 Hz, 1H), 9.10 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 35.18, 110.62, 115.80, 116.22, 117.59, 122.16, 124.22, 125.63, 128.28, 129.75, 130.89, 134.51, 135.76, 137.50, 145.94, 148.21 ppm; IR (KBr disk): ν 2223 cm^{-1} (CN). MS (*m/z*) 294 (M^++2). Anal. Calcd for $C_{16}H_9ClN_4$ (292.7): C, 65.65; H, 3.10; N, 19.14, found: C, 66.02; H, 3.16; N, 18.90.

8-Chloro-3-ethyl-3*H*-pyrazolo[4,3-*a*]acridine-11 carbonitrile (3b): Compound **3b** was obtained as shiny yellow needles (EtOH), yield (65%), mp 295-297 °C; ^{1}H NMR ($CDCl_3$) δ 1.61 (t, *J* = 7.2 Hz, 3H), 4.59 (q, *J* = 7.2 Hz, 2H), 7.76 (dd, *J* = 8.9 Hz, *J′* = 2.1 Hz, 1H), 7.92 (d, *J* = 9.6 Hz, 1H), 8.06 (d, *J* = 9.6 Hz, 1H), 8.34 (d, *J* = 2.1 Hz, 1H), 8.36 (d, *J* = 8.9 Hz, 1H), 9.15 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 15.52, 44.63, 115.62, 115.80, 116.76, 117.75, 122.54, 124.34, 125.87, 128.09, 129.26, 130.51, 132.51, 135.12, 137.20, 145.64, 148.88 ppm; IR (KBr disk): ν 2225 cm^{-1} (CN). MS (*m/z*) 308 (M^++2). Anal. Calcd for $C_{17}H_{11}ClN_4$ (306.7): C, 66.56; H, 3.61; N, 18.26, found: C, 66.23; H, 3.55; N, 18.07.

8-Chloro-3-propyl-3*H*-pyrazolo[4,3-*a*]acridine-11 carbonitrile (3c): Compound **3c** was obtained as shiny yellow needles (EtOH), yield (70%), mp 273-275 °C; ^{1}H NMR ($CDCl_3$) δ 1.01 (t, *J* = 7.2 Hz, 3H), 2.04-2.13 (m, 2H), 4.52 (t, *J* = 7.2 Hz, 2H), 7.76 (dd, *J* = 8.9 Hz, *J′* = 2.1 Hz, 1H), 7.92 (d, *J* = 9.6 Hz, 1H), 8.05 (d, *J* = 9.6 Hz, 1H), 8.32 (d, *J* = 2.1 Hz, 1H), 8.36 (d, *J* = 8.9 Hz, 1H), 9.14 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 13.50, 23.49, 56.55, 113.67, 115.34, 116.89, 117.13, 122.55, 124.20, 125.98, 128.10, 129.25, 130.57, 132.87, 135.19, 137.45, 145.98, 148.50 ppm; IR (KBr disk): ν 2225 cm^{-1} (CN). MS (*m/z*) 322 (M^++2). Anal. Calcd for $C_{18}H_{13}ClN_4$ (320.8): C, 67.40; H, 4.08; N, 17.47, found: C, 67.18; H, 4.01; N, 17.73.

3-Butyl-8-chloro-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitrile (3d): Compound **3d** was obtained as shiny yellow needles (EtOH), yield (57%), mp 261-264 °C; ^{1}H NMR ($CDCl_3$) δ 1.01 (t, *J* = 7.1 Hz, 3H), 1.38-1.47 (m, 2H), 1.00-2.07 (m, 2H), 4.56 (t, *J* = 7.1 Hz, 2H), 7.76 (dd, *J* = 8.9 Hz, *J′* = 2.1 Hz, 1H), 7.92 (d, *J* = 9.6 Hz, 1H), 8.06 (d, *J* = 9.6 Hz, 1H), 8.32 (d, *J* = 2.1 Hz, 1H), 8.36 (d, *J* = 8.9 Hz, 1H), 9.14 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 13.65, 20.05, 32.34, 49.44, 110.09, 115.34, 116.66, 117.62, 122.26, 124.08, 125.70, 128.80, 129.34, 130.31, 134.94, 135.97, 137.53, 145.79, 148.02 ppm; IR (KBr disk): ν 2225 cm^{-1} (CN). MS (*m/z*) 336 (M^++2). Anal. Calcd for $C_{19}H_{15}ClN_4$ (334.8): C, 68.16; H, 4.52; N, 16.73, found: C, 67.92; H, 4.45; N, 16.49.

8-Chloro-3-isobutyl-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitrile (3e): Compound **3e** was obtained as shiny yellow needles (EtOH), yield (63%), mp 245-247 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, *J* = 6.8 Hz, 6H), 2.41-2.51 (m, 1H), 4.36 (d, *J* = 7.2 Hz, 2H), 7.78 (dd, *J* = 8.8 Hz, *J′* = 2.0 Hz, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 8.04 (d, *J* = 9.6 Hz, 1H), 8.35 (d, *J* = 2.0 Hz, 1H), 8.39 (d, *J* = 8.8 Hz, 1H), 9.19 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.50, 32.01, 55.20, 116.62, 116.80, 117.26, 117.93, 122.45, 124.94, 125.83, 128.26, 129.32, 130.77, 132.92, 135.18, 137.19, 145.32, 148.24 ppm; IR (KBr disk): ν 2223 cm^{-1} (CN). MS (*m/z*) 336 (M^++2). Anal. Calcd for $C_{19}H_{15}ClN_4$ (334.8): C, 68.16; H, 4.52; N, 16.73, found: C, 67.90; H, 4.47; N, 16.48.

8-Methoxy-3-methyl-3*H*-pyrazolo[4,3-*a*]acridin-11-carbonitrile (4a): Compound **4a** was obtained as pale yellow needles (EtOH), yield (69%), mp 327-329 °C, [lit.[13] 325-327 °C].

3-Ethyl-8-methoxy-3*H*-pyrazolo[4,3-*a*]acridin-11-carbonitrile (4b): Compound **4b** was obtained as pale yellow needles (EtOH), yield (65%), mp 310-312 °C, [lit.[13] 310-312 °C].

3,8-Dimethyl-3*H*-pyrazolo[4,3-*a*]acridin-11-carbonitrile (4c): Compound **4c** was obtained as pale yellow needles (EtOH), yield (65%), mp 263-265 °C, [lit.[13] 261-264 °C].

3-Ethyl-8-methyl-3*H*-pyrazolo[4,3-*a*]acridin-11-carbonitrile (4d): Compound **4d** was obtained as pale yellow needles (EtOH), yield (63%), mp 253-255 °C, [lit.[13] 255-256 °C].

Results and Discussion

Syntheses and Spectral Characterization. As depicted in Scheme 1, the required starting materials 1-alkyl-5-nitro-1*H*-indazoles **1a-e** were prepared by reaction of 5-nitro-1*H*-indazole with different alkyl halides in DMF and KOH using a literature method.[22] The treatment of 1-alkyl-5-nitro-1*H*-indazoles **1a-e** with 2-(4-chlorophenyl) acetonitrile **2** led to the formation of the new 8-chloro-3-alkyl-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitriles **3a-e** by way of the nucleophilic substitution of hydrogen[24] followed by the ring closure which proceeds *via* an electrocyclic pathway[10-15] in basic MeOH solution in good yields. The simple work-up procedure was performed by filtration of the precipitated product and washing with water and EtOH, respectively. The following mechanism is offered for the formation of compounds **3a-e**.[25,10-15] Attack of the anion of **2** on **1a-e** affords intermediate **A** and thus **B** (Scheme 2). Subsequent prototropy to **C** initiates a

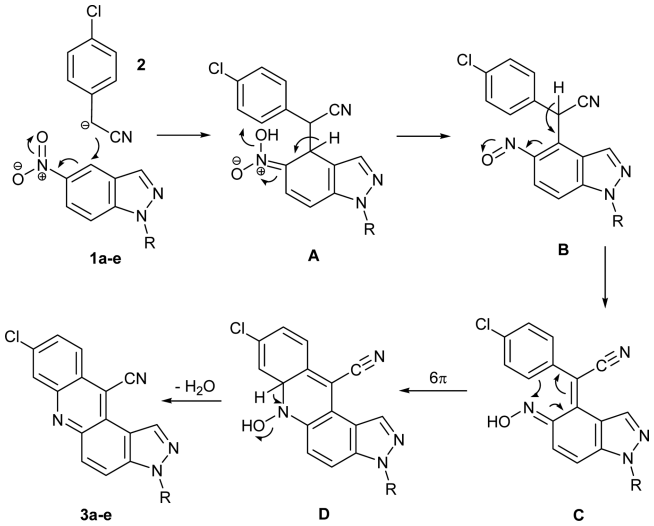
6π-electrocyclisation to **D** and then products **3a-e** result following dehydration (Scheme 2).

The structure of compounds **3a-e** was established by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, ^{1}H NMR of compound **3a** revealed the presence of the doublet of doublet signal at δ 7.76 ppm (J = 9.1 Hz and J' = 2.1 Hz), the doublet signals at δ 7.92 (d, J = 9.6 Hz), δ 8.05 (d, J = 9.6 Hz), δ 8.32 (d, J = 2.1 Hz), and δ 8.36 (d, J = 9.1 Hz) ppm, and singlet signal at δ 9.14 ppm attributed to six protons of aromatic rings. ^{13}C NMR spectrum indicated that there are sixteen different carbons in compound **3a**. Moreover, the FT-IR spectrum of **3a** in KBr showed an absorption band at 2223 cm^{-1} corresponding to the cyanide group. All this evidence plus the molecular ion peak at *m/z* 294 (M+2$^+$) and microanalytical data strongly support the tetracyclic structure of compound **3a**.

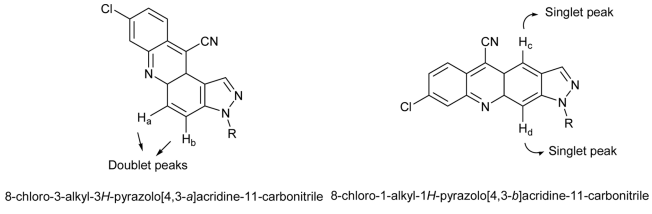
All the newly synthesized compounds have been characterized by elemental analysis and spectroscopic data. The spectral details of all these are given in experimental section.

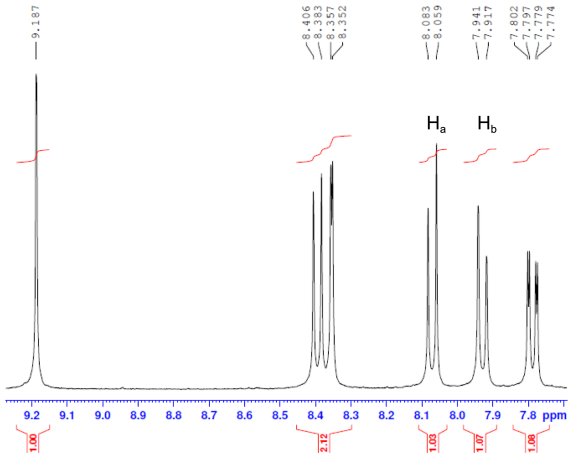
As an explanation for heterocyclization reaction demonstrated by Scheme 3, there is another possible mode of cyclisation in this reaction. According to the expanded view (aromatic region) of ^{1}H NMR spectrum of compound **3e**, two doublet signals at δ 7.93 (J = 9.6 Hz, 1H), δ 8.07 (J = 9.6 Hz, 1H) ppm are assignable to two protons of aromatic rings (H_a, H_b) in **3e** and thus the latter cyclisation has not occurred, since two singlet attributed to protons of aromatic rings (H_c, H_d) aren't observed in the ^{1}H NMR spectrum of compound **3e**.

Fluorescence Spectra and Quantum Yields. The compounds **3a-e** were characterized by using an UV-Vis spectrophotometer and a fluorescence spectrophotometer. The wavelength range of both spectrophotometers is 200 nm-1000 nm. The fluorescence absorption and emission spectra of **3a-e** were recorded at concentrations of 2 × 10^{-5} and 6 × 10^{-6} mol L^{-1} in dichloromethane (DCM), respectively. Figure 1 shows the visible absorption and emission spectra of compounds **3a-e**.

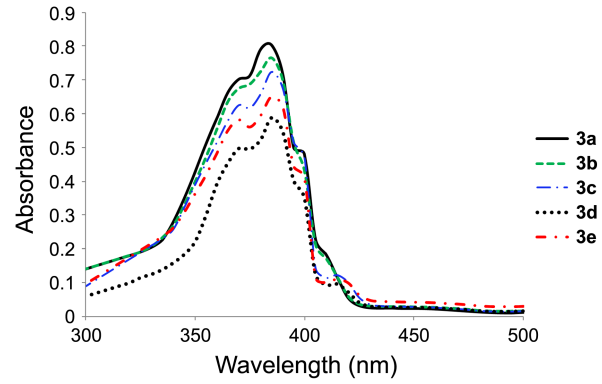


Scheme 2. Proposed reaction mechanism for the formation of compounds **3a-e**.





Scheme 3. Two possible modes of cyclisation in the reaction of **1a-e** with **2** and the expanded view of ^{1}H NMR spectrum of compound **3e** in downfield region.



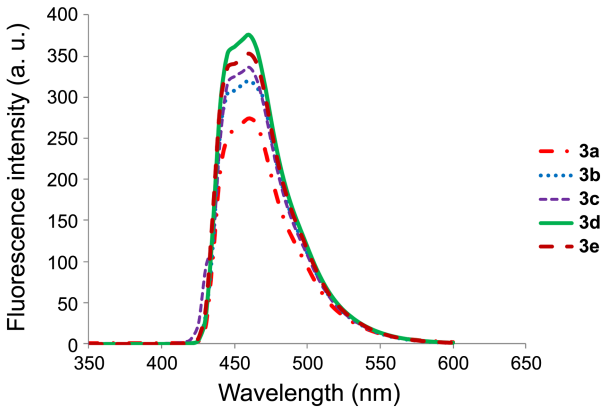
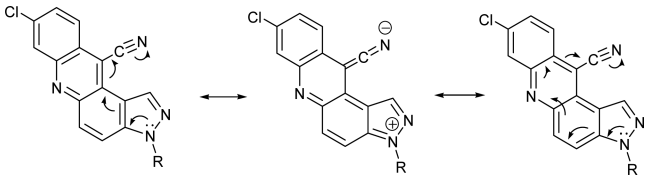


Figure 1. Visible absorption and emission spectra of compounds **3a-e** in DCM solution.



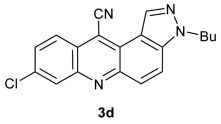
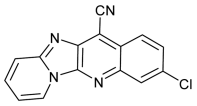
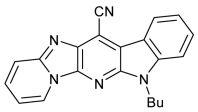
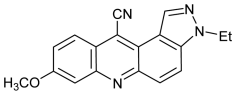
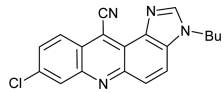
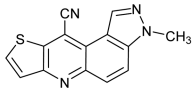
Scheme 4. Neutral and charge-separated mesomeric structures of **3a-e**.

Table 1. Photophysical data for absorption (abs) and fluorescence (flu) of **3a-e**

Dye	**3a**	**3b**	**3c**	**3d**	**3e**
λ_{abs} (nm)[a]	384	384	384	384	384
$\varepsilon \times 10^{-4}$ [(mol L^{-1})$^{-1}$ cm^{-1}][b]	4.0	3.65	3.55	2.85	3.15
λ_{ex} (nm)[c]	390	390	390	390	390
λ_{flu} (nm)[d]	460	460	460	460	460
Φ_F[e]	0.45	0.47	0.51	0.55	0.50

[a]Wavelengths of maximum absorbance. [b]Extinction coefficient. [c]Wavelengths of fluorescence excitation. [d]Wavelengths of fluorescence emission. [e]Fluorescence quantum yield

Table 2. Comparing the fluorescence quantum yield of **3d** and some recently synthesized fluorescent heterocyclic compounds

Comp.	Φ_F	Comp.	Φ_F
 **3d**	0.55		0.90[10]
	0.66[11]		0.59[13]
	0.92[14]		0.65[15]

lengths of fluorescence excitation (λ_{ex}/nm), wavelengths of fluorescence emission (λ_{flu}/nm), values of extinction coefficient (ε) and fluorescence quantum yield (Φ_F) data are presented in Table 1. Values of extinction coefficient (ε) were calculated as the slope of the plot of absorbance *vs.* concentration. The fluorescence excitation (λ_{ex}) wavelength at 390 nm (λ_{ex}/nm) was used for all compounds **3a-e**. The fluorescence quantum yields (Φ_F) of compounds **3a-e** were determined *via* comparison methods, using fluorescein as a standard sample in 0.1 M NaOH and MeOH solution.[26] The fluorescence spectral properties (Table 1) of compounds **3a-e** are similar to each other and fluorescence intensity in compound **3d**, with a butyl group, was the highest. It can be concluded from the data in Table 1 that these compounds are highly fluorescent. Intensity of fluorescence emission of compounds **3a-e** can be explained by an efficient intramolecular charge transfer (ICT) states from the donor site (endocyclic N) to the acceptor moiety (CN group). Typical photo-induced charge transfer system consists of a donor (D) and

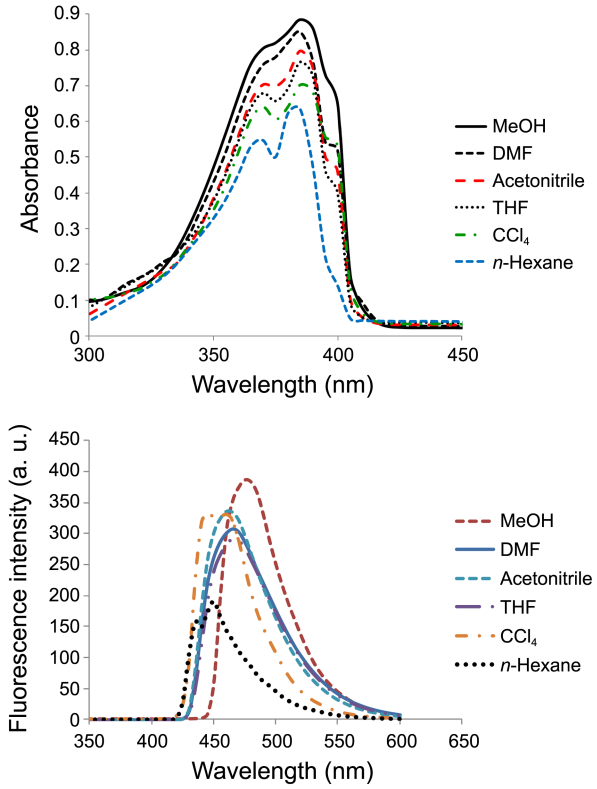


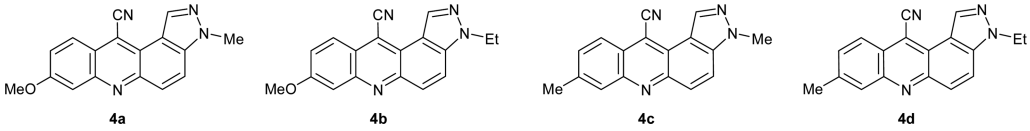
Figure 2. Visible absorption and emission spectra of compound **3e** in different solvents.

Table 3. Spectroscopic data for **3e** at 298K in dependence of the solvent

Solvent	λ_{abs} (nm)	λ_{flu} (nm
Acetonitrile	387	465
MeOH	390	475
n-Hexane	375	450
CCl_4	380	445, 457
THF	385	463
DMF	385	465

acceptor (A) couple, which can be separate chromophores within a large molecule, leading to intramolecular charge transfer (ICT). In Scheme 4, neutral and charge-separated mesomeric structures of **3a-e** are presented. The fluorescence quantum yields (Φ_F) of the new compounds **3a-e** are comparable with some fluorescent heterocyclic compounds which we have reported previously. A comparison of Φ_F between **3d** and some of them has been shown in Table 2. Solvatochromic properties of compound **3e** were studied in some solvents (Fig. 2). As can be seen in these figures, the fluorescence absorption and emission spectra of **3e** in polar solvents undergoes a bathochromic shift. Increasing solvent polarity stabilizes the ICT excited-state molecule relative to the ground-state molecule with the observed red shift of the absorption and the emission maximum (Table 3). For example, λ_{flu} shifts from 450 to 475 nm is observed as the solvent is changed from n-hexane to methanol.

Antibacterial Studies. The antibacterial activity of our



Scheme 5. 8-Substituted-3-alkyl-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitriles **4a-d**.

Table 4. Antibacterial activity (MIC, μg mL^{-1}) of references and compounds **3a-e** and **4a-d**

Compds.	*S.a.* (MRSA)	*B.s.* (ATCC 6633)	*P.a.* (ATCC 27853)	*E.c.* (ATCC 25922)
3a	12	15	20	10
3b	9	9	10	5
3c	6	6	10	5
3d	2	2	5	5
3e	10	10	20	5
4a	20	20	30	10
4b	15	10	20	5
4c	15	10	10	5
4d	10	5	10	5
Ampicillin	62	0.50	125	8
Penicillin G	0.06	8	-	-
Sulfameth-oxazole	16	16	62	16

new products **3a-e** as well as **4a-d** which we have synthesized previously[13] (Scheme 5), was tested against a panel of strains of Gram positive (*Staphylococcuse aureus methicillin resistant S. aureus* (MRSA) clinical isolated and *Bacillus subtilis* (ATCC 6633)) and negative bacterial (*Pseudomonas aeruginosa* (ATCC 27853) and *Escherichia coli*, (ATCC 25922)) species (Table 4) using broth microdilution method as described previously.[27] Ampicillin, Penicillin G and Sulfamethoxazole were used as references. The lowest concentration of the antibacterial agent that prevents growth of the test organism, as detected by lack of visual turbidity (matching the negative growth control), is designated the minimum inhibitory concentration (MIC). Experimental details of the tests can be found in our earlier studies.[17-21]

The antimicrobial tests performed on compounds **3a-e** and **4a-d** confirmed that they are effective against both Gram-positive and Gram-negative bacteria and some showed greater inhibitory activity against a number of Gram-positive and Gram-negative bacteria than the well known antibacterial agents Ampicillin and Sulfamethoxazole.

Also, the results revealed that new compounds **3a-e** which have chlorine substituents, displayed greater antibacterial activity against mentioned organism than **4a-d** in most cases (Table 4). Gratifyingly, compound **3d** with a butyl group was the most potent of the tested compounds against Gram-positive and Gram-negative bacteria in this work and all biological research work that we have reported previously.[16-21] We propose that the chain lengths and chlorine substituent might change the binding characteristics of ligands to their respective receptors and, thereby, improve the biological activities.[18]

Conclusion

The synthesis of five new 8-chloro-3-alkyl-3*H*-pyrazolo-[4,3-*a*]acridine-11-carbonitriles has been described through one pot reaction of 1-alkyl-5-nitro-1*H*-indazoles with 2-(4-chlorophenyl) acetonitrile. All these compounds are hitherto unknown in literature and are observed to exhibit excellent fluorescence properties. This property, together with high antibacterial activity, can offer an excellent opportunity for the study of physiological functions of bacteria such as at single-cell level.[28]

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