Journal of Photochemistry & Photobiology, B: Biology 162 (2016) 641–645

Contents lists available at ScienceDirect

Journal of Photochemistry & Photobiology, B: Biology

journal homepage: www.elsevier.com/locate/jphotobiol

Application of UV–Vis spectrophotometric process for the assessment of indoloacridines as free radical scavenger

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ARTICLE INFO

Article history:
Received 29 June 2016
Accepted 21 July 2016
Available online 26 July 2016

Keywords:
Benzophenone
Carbazolone
Indoloacridine
Antibacterial
Antifungal
Free radical scavenger

ABSTRACT

A conventional approach has been used to synthesis Indole fused acridine, **4a–e**. In this paper to achieve the target molecule, **4** the reaction was performed *via* two steps. In step 1, there was a reaction between Carbazolone, **1** and benzophenone, **2** to get dihydroindoloacridine, **3**. In step 2, compound, **3** was treated with 5% Palladium/Carbon in the presence of diphenyl ether for 5 h to give a dark brown product, **4**. The column chromatography was used to purify final product, **4**. All the synthesized compounds such as **3** and **4** were characterized by melting point, FTIR, ^{1}H NMR, and Mass spectra. Further to check the purity of the compounds it was subjected to CHN analyzer. The target molecules such as **3** and **4** were screened for antimicrobial studies against bacteria such as *Bacillus subtilis* (*B. subtilis*), *Staphylococcus aureus* (*S. aureus*), *Klebsiella pneumonia* (*K. pneumonia*), *Salmonella typhi* (*S. typhi*); and fungi like *Aspergillus niger* (*A. niger*), *Aspergillus fumigatus* (*A. fumigatus*). The obtained results clearly proves that the target molecules shown reasonable activity against *K. pneumonia* and *A. niger*. Further the compounds were screened for free radical scavenging activity using 2,2-diphenyl-1-picrylhydrazyl (DPPH). The free radical scavenging property was performed using UV–Visible spectroscopy. The results were compared with the standard BHT (Butylated Hydroxy Toluene). Compounds, **4a** and **4e** were shown higher percentage of inhibition when compare to the standard. The result confirms that further research on indoloacridine will leads effective drug to the market.

1. Introduction

Mostly due to presence of mismatched electrons free radicals are unstable in nature, which can be manufactured by various steps like stress due to oxidation, and natural metabolic disorder [1]. If suddenly our body temperature were high all free radicals lead to act as toxins which can eradicate through anti-oxidants or else known as free radical scavengers [2]. Recently most of the researchers focused their research progress towards nitrogen containing heterocyclic compounds [3–11]. It is consider as one of the best natural products which score better results against various pharmacological and biological applications. The continuous increase of natural products as well as pharmacological action of these molecules has generated synthetic interest. Nowadays most of the free radical scavengers available in all over the globe which can be attain easily by various green approaches were studied and reported [12], but it contains some side effects due to presence of various phytoconstituents which will not suit for drastic conditions for several human beings. So to overcome these drawbacks we have focused towards synthetic free radical scavenger. In this manuscript authors synthesize Indoloacridine molecule to treat against free radicals which can be monitored by UV–Visible spectroscopy at the wavelength of 515 to 520 nm [13]. Also we have processed anti-microbial activity for various pathogens like bacteria, fungi and yeast.

Acridine is a molecule which contains nitrogen molecule with system of heterocycles [5] which plays a major role in medicinal chemistry field as scavenger of free radicals [14]. An Indolo molecule is stated to be a glycosidic product which occurs naturally and plays a several biological role as anti-cancer agents. Also it has high binding affinity to any other molecules [15–20]. So with this high affinity of binding indole molecule was binded with acridine and subjected to various pharmaceutical and biological applications. Already some researchers focused on synthetic anti-oxidants which lead to better anti-oxidant activity with BHT (butylated hydroxyl toluene) as standard [21] and also studied for various biological applications [22–24]. Most of the articles stated about larvicidal and anti-oxidant properties; but there are very few reports on synthetic microbial agents. So in this manuscript we process

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http://dx.doi.org/10.1016/j.jphotobiol.2016.07.026
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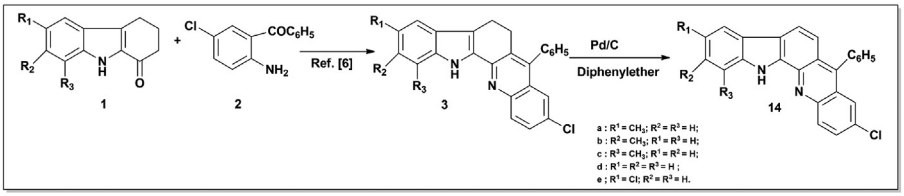


Scheme. 1. Conventional approach for the synthesis of compounds, **4a–e.**

to study the synthetic compound against various pathogenic bacteria such as *B. subtilis, S. aureus*, *K. pneumonia*, *S. typhi*; and fungi like *A. niger, A. fumigatus* were tested by agar well diffusion method and reported.

2. Experimental Parts

2.1. Materials and Methods

Chemicals and solvents which we have used for this experiment has been used without any further purification. Melting point was recorded with standard benzoic acid for the calibration. Bruker Avance 400 MHz spectrometer was used to record ^{1}H and ^{13}C NMR in $CDCl_3$ or DMSO-d_6.

*2.2. General Procedure for the Preparation of Indolo Fused Acridines, **4a–e***

Compounds, **3a–e** were prepared as per the earlier report [6] and the corresponding melting point, ^{1}H and ^{13}C NMR were matched with the literature. Further compounds, **4a–e** were prepared as follows: About 1 mmol of dihydroindoloacridine, **3** and 50 mg of Palladium/Carbon was refluxed in the presence of diphenyl ether (3 mL) for 5 h (Scheme 1). The reaction progress was noted by Thin Layer Chromatography. After the reaction completion, it was filtered through Whatman-41 paper to remove Palladium/Carbon. From the reaction mixture the excess solvent was removed. Then the residue was transferred into crushed ice. The product is the form of crude as separated with ethyl acetate. To get the pure product column chromatography technique was adopted with the help of petroleum ether and ethyl acetate system using 98:2 solvent system. The spectral data and physical constants of the compounds are reported in Tables 1-3.

*2.3. Antimicrobial Activity of the Synthesized Compounds, **4a–e***

2.3.1. Source of Microorganism

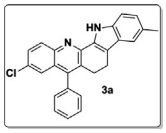
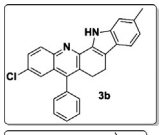
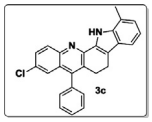
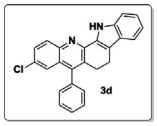
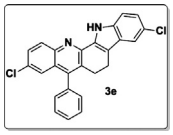
In order to find the antimicrobial activity for the synthesized compounds the following microorganisms were used

- *S. aureus (ATCC 700699)* and *B. subtilis* (ATCC 11778) - Gram positive bacteria.
- *K. pneumonia (ATCC 2719)* and *S. typhi* (ATCC 700931) - Gram negative bacteria.
- *niger* and *A. fumigatus*-Yeast like fungi.

2.3.2. Standardization of Microorganism and Culture Media

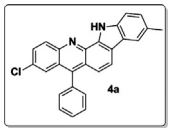
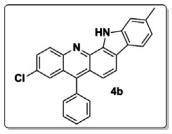
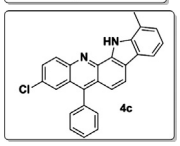
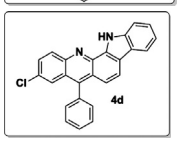
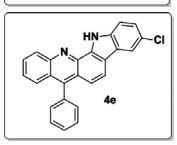
About 0.2 mL cultures (overnight) of all organisms were dispended into 20 mL of sterile nutrient broth and then incubated for about 5 h to standardize the culture to 10^{6} cfu/mL. A loopful of standard culture was used for antimicrobial assay. The solid growth of medium used for bacteria was nutrient agar and for fungi was sabouraud dextrose agar.

Table 1
Physical constants of the synthesized compounds, **3a–e**.

Compounds	Nature	Yield (%)	MP (°C) [literature report]	Reference
	Orange crystals	84	230–232 [231]	[6]
	Yellow solid	81	250–252 [250]	[6]
	Orange solid	82	282–284 [282]	[6]
	Orange solid	75	231–233	NA
	Orange crystals	66	207–209	NA

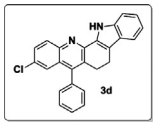
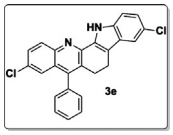
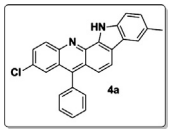
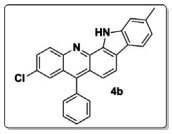
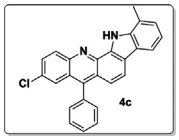
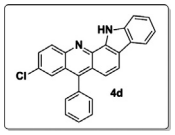
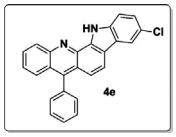
Note: NA – not reported earlier in the literature.

Table 2
Physical constants of the synthesized compounds, **4a–e.**

Compounds	Nature	Yield (%)	MP (°C)	Reference
	Pale yellow prisms	67	251–253	NA
	Yellow prisms	74	282–284	NA
	Yellow prisms	71	248–250	NA
	Yellow solid	64	274–276	NA
	Pale yellow powder	62	269–271	NA

Note: NA – not reported earlier in the literature.

Table 3
Spectral characterizations of compounds, **3d**, **3e**, and **4a–e.**

Compounds	FTIR (Cm^{-1})	^1H NMR	Mass [actual/observed]	CHN analysis (%)
	3414, 2923, 2854, 1643, 1596, 1029	11.75 (b s, 1H, N—H), 8.20–7.04 (m, 12H), 3.08–2.89 (m, 4H)	382/380	C, 78.61; H, 4.40; N, 7.22
	3445, 2925, 2818, 1641, 1592, 1060	11.95 (b s, 1H, N—H), 8.05–7.15 (m, 11H), 2.97–2.88 (m, 4H)	418/416	C, 72.11; H, 3.71; N, 6.59
	3431, 2922, 2855, 1648, 1592, 1044, 820, 768	11.67 (b s, 1H, N_{13}—H), 8.10–7.01 (m, 13H), 2.51 (s, 3H, CH_3)	392/394	C, 79.04; H, 4.17; N, 7.24
	3434, 2921, 2862, 1646, 1592, 1046, 701	11.52 (b s, 1H, N—H), 8.12–6.93 (m, 13H), 2.52 (s, 3H, CH_3)	392/394	C, 79.84; H, 4.52; N, 7.01
	3446, 2881, 2858, 1672, 1591, 1028, 763	11.57 (b s,1H, N—H), 8.02–6.72 (m, 13H), 2.58 (s, 3H, CH_3)	392/394	C, 79.20; H, 4.10; N, 7.07
	3362, 2923, 2871, 1640, 1593, 1028, 735	11.72 (b s, 1H, N—H), 8.04–7.01 (m, 14H)	380/378	C, 79.14; H, 4.06; N, 7.29
	3365, 2927, 2889, 1643, 1593, 1477, 1067, 1054, 767	11.55(b s,1H, N—H), 8.02–7.05 (m, 13H)	414/412	C, 72.44; H, 3.27; N, 6.64

2.3.3. Test for Antimicrobial Property

Agar well diffusion procedure [25] were utilized to evaluate antimicrobial studies of compounds, **4a–e**. The medium used for the growth for bacteria and fungi were nutrient and sabouraud's agar respectively. Around 24 h broth cultures of all mentioned test organism were used for the assay. Sterilized applicator stick was used to inoculate into the mother bacterial suspension. The bacterial swabs were streaked on all directions firmly inside the test tube above the level of fluid to remove excess of bacterial residue. The petriplates which is already prepared was taken and then swabbed on the surface. Later a sterile well borer was punched on the agar rim to make well of 8 mm size. The agar plates were then dried for few min to which 100 μL of compounds, **4a–e** control and standards where dispersed into well by using micropipette. The test samples were prepared in 1 mg/1 mL of DMSO as solvents. For 24 h the petriplates with the sample were incubated at 37 °C for the growth of microorganism. Later the petriplates were examined for the inhibition zone around the well. It was measured and compared with the standard compounds in mm which was discussed in Table 4. The procedure was repeated twice to confirm the reciprocation of the results.

The standard used for determining bacteria was 1 mg of Penicillin in DMSO (5 mL) and for antifungal activity was 1 mg of Oflaxacin in DMSO (5 mL). The solvent, DMSO was used as a control. The synthesized compounds, **4a–e** were tested for antimicrobial activity. The results obtained are tabulated in Table 4.

Table 4
Antimicrobial activity of target molecules, **4a–e.**

Name of the organisms	Zone inhibition (mm)						
	4a	4b	4c	4d	4e	DMSO	Standard
Gram positive bacteria							
S. aureus	4	4	2	2	3	---	7
B. subtils	4	3	1	2	5	---	8
Gram negative bacteria							
K. pneumonia	5	4	3	2	6		7
S. typhi	---	---	---	---	---	---	7
Yeast like fungi							
A. niger	5	5	2	2	6		8
A. fumigatus	---	2	---	---	---	---	5

Note: "—" represents negative results.

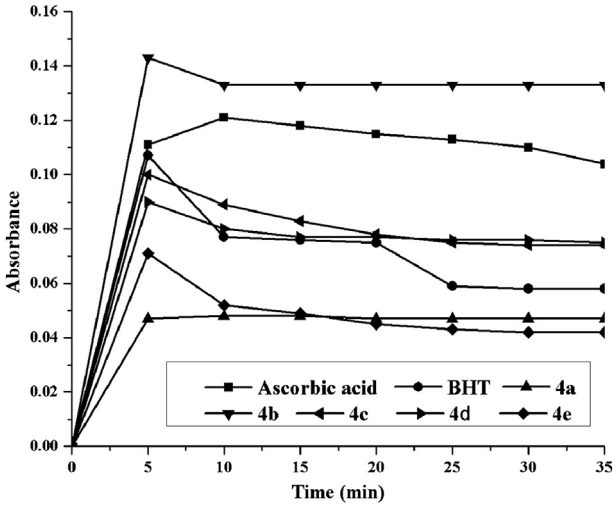


Fig. 1. Free radical activity measured by time vs absorbance.

2.4. Free Radical Scavenging Property of the Synthesized Compounds, *4a–e*

The antiradical scavenging assay of indole fused acridine, **4a–e** was measured by DPPH method [21,26,27]. Stable radical DPPH used as a reagent. The DPPH (0.01 mM) was mixed in absolute ethanol which is named as stock solution. From the stock 1 mL of the DPPH solution was added to 3 mL of compounds, **4a–e** prepared in pure ethanol. BHT, ascorbic acid and compounds, **4a–e** (100 μg/mL) in absolute ethanol was used for this study. The absorbance (Fig. 1) was measured at 517 nm at time interval of 5 min for half an hour (Table 5). The

Table 5
UV–Visible absorbance of target compounds, 4a–e.

Time (min)	Absorbance of the compounds[a] (nm)						
	Ascorbic acid	BHT	14a	14b	14c	14d	14e
0	0.111	0.107	0.047	0.143	0.100	0.090	0.071
5	0.121	0.077	0.048	0.133	0.089	0.080	0.052
10	0.118	0.076	0.048	0.133	0.083	0.077	0.049
15	0.115	0.075	0.047	0.133	0.078	0.077	0.045
20	0.113	0.059	0.047	0.133	0.075	0.076	0.043
25	0.110	0.058	0.047	0.133	0.074	0.076	0.042
30	0.104	0.058	0.047	0.133	0.074	0.075	0.042

[a] BHT, ascorbic acid, DPPH, **14**(**b–e**), (each one is 1.5×10^{-4} mM in ethanol solution) at 517 nm.

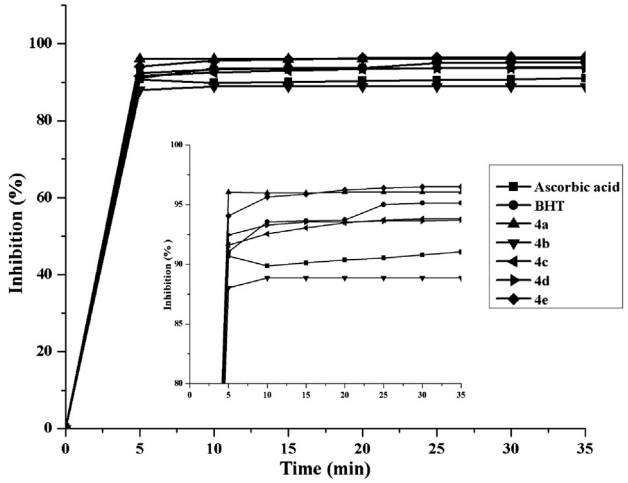


Fig. 2. Percentage inhibition of free radical scavenger.

Table 6
Percentage inhibition of target compounds, 4a-e.

Time (min)	% inhibition						
	Ascorbic acid	BHT	14a	14b	14c	14d	14e
0	90.70	91.04	96.06	88.02	91.62	92.46	94.05
5	89.87	93.55	95.98	88.86	92.55	93.29	95.64
10	90.12	93.63	95.98	88.86	93.05	93.55	95.89
15	90.37	93.72	96.06	88.86	93.47	93.55	96.23
20	90.54	95.01	96.06	88.86	93.72	93.63	96.39
25	90.79	95.14	96.06	88.86	93.80	93.63	96.48
30	91.04	95.14	96.06	88.86	93.80	93.70	96.48

percentage of radical scavenging (Fig. 2, Table 6) was calculated with the following equation

$$\%DPPHradicalscavenging = [A_D - A_s]/A_D \times 100$$

where, A_D - absorbance taken only for DPPH in absolute ethanol.

A_s - absorbance taken for compound, **4** with DPPH in absolute ethanol.

3. Results and Discussion

3.1. Chemistry of Compounds, *3* and *4*

1-Carbazolone, 1a on treatment with benzophenone, 2 in glacial acetic acid yielded an orange solid. Its IR spectrum showed a strong ν_{NH} band at 3279 cm^{-1} and $\nu_{C=N}$ at 1643 cm^{-1}. Its ^1H NMR spectrum of carbazole -NH proton at δ 11.58 as singlet, eleven aromatic protons as a cluster from δ 8.02–7.10, a four proton multiplet in the region δ 2.92–2.66, and a three-proton singlet at δ 2.48 for the CH_3 group. In mass analysis 392 corresponds to the molecular ion peak of compound, 4a. These spectral details and also the CHN report were matched with the molecular formula $C_{26}H_{19}N_2Cl$, corresponding to the structure dihydroindoloacridine, 3a.

Compound, **4a** FTIR spectrum showed a strong ν_{NH} band at 3431 cm^{-1}, and a $\nu_{C=N}$ band at 1648 cm^{-1}. Its ^1H NMR spectrum showed carbazole NH proton at δ 11.67 as a singlet, thirteen aromatic protons as a cluster from δ 8.10–6.98, and a three-proton singlet at δ 2.51 for the CH_3 group. The molecular ion peak appeared at *m/z* 392 in the MS. The spectral and analytical details attest the compound as indole fused acridine, **4a**.

3.2. Antimicrobial Proerty of Target Compounds, ***4a–e***

The microbial activity of the synthesized compounds, **4a–e** as follows from the Table 5.

- Compound, **4a** and **4b** exhibited vital antibacterial property against *S. aureus*.
- Compound, **4a** and **4e** showed significant antibacterial activity against *B. subtilis* and *K. pneumonia*.
- Neither of the compounds showed activity against *S. typhi*.
- Compounds, **4a**, **b,** and **4e** showed significant antifungal activity against *A. niger*.
- A weak activity against *A. fumigatus* was shown only by compound, **14b**.

3.3. Free Radical Scavenging Proerty of Target Compounds, ***4a–e***

The result suggests that out of five compounds, **4a–e** examined, compound, **4a** showed a decrease in the absorbance (Fig. 1) and increase in percentage inhibition (Fig. 2) whereas compound, **4e** showed a moderate absorbance and moderate percentage inhibition. But

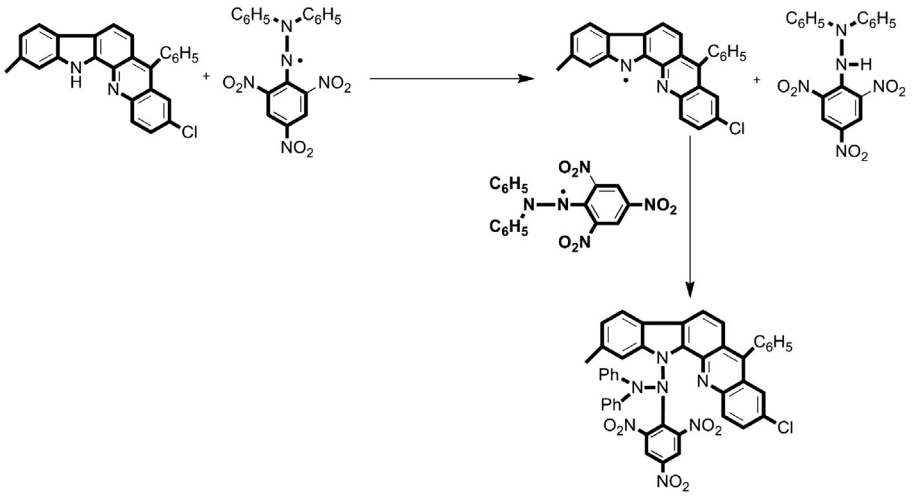


Fig. 3. Free radical scavenging mechanism for the compound, **4.**

molecule, **4b** showed a good absorbance but less percentage inhibition. To conclude from the all the synthesized compounds, compound, **4a** showed good antioxidant property compared to the standards and its other derivatives. The possible mechanism was described in Fig. 3.

4. Conclusion

In this present work, the synthesized compound **4** has been proved as good antimicrobial agent. Further it was acting as a good free radical scavenger, when compared to the standard antioxidant. These results will turn the young researcher to find further view on indoloacridines.

Acknowledgments

Author Dr. M. Sridharan thank to the management of R.V. College of Engineering for their support and encouragement. Naif Abdullah Al-Dhabi and Valan Arasu extend their sincere thankfulness to the Deanship of Scientific Research, King Saud University for its funding to Prolific Research Group (PRG-1437-28). Dr. K J Rajendra Prasad thanks UGC for Emeritus Professorship.

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