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Original article

Synthesis, photochemical *E* (*trans*) → *Z* (*cis*) isomerization and antimicrobial activity of 2-chloro-5-methylpyridine-3-olefin derivatives

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ABSTRACT

2-Chloro-5-methylpyridine-3-olefin derivatives (**3a**–**e**) have been synthesized from 2-chloro-5-methylnicotinaldehyde (**1**) and studied their photochemical *E* (*trans*) → *Z* (*cis*) isomerization upon direct irradiation and triplet sensitized excitation for the first time. The triplet sensitized excitations of the compounds yielded high *Z* (**4a**–**e**) isomer composition, whereas the direct excitation results in less *Z* (**4a**–**e**) isomer composition, indicating triplet pathway is very efficient in converting the *E* (*trans*) → *Z* (*cis*) isomer. Thus synthesized *E* (**3a**–**c** and **3e**) and generated *Z* (**4a**–**c** and **4e**) isomers were tested for antimicrobial activity. Antifungal activity of these pyridine derivatives are closely comparable to the standard used.

1. Introduction

Heterocyclic compounds and their derivatives are important and are present in many biological systems [1]. Among them pyridine derivatives have found several applications in pharmaceutical and in agrochemical fields [2]. Extensive studies have been carried out on the synthesis of pyridine compounds because of their importance as drugs, biologically active natural products, and for other various applications. Chloronicotinaldehydes are very good precursors for annulation of wide variety of heterocyclic ring systems such as synthesis of arachidonic acid metabolites, heterocyclic analogues of 8-HETE [3]. Imidacloprid is the first chloronicotinyl insecticide, used worldwide for controlling pests due to its potency, broad spectrum of insecticidal activity and low mammalian toxicity [4]. Neonicotinoids interacting with nicotinic acetylcholine receptors (nAChR) have a higher affinity for the insect receptor than for the mammalian and are relatively safe towards mammals and aquatic life [5]. Photochemical *E* (*trans*) → *Z* (*cis*) isomerization is a major area of interest in modern molecular photochemistry and photobiology [6]. The isomerization has practical application in vitamin-A and vitamin-D industrial processes [7–9], and it is known to play an important role in many optomechanical and optoelectrical switching and storage devices [10]. Our continuing interest in the synthesis and photochemical *E* (*trans*) → *Z* (*cis*) isomerization of various compounds [11], herein we report the synthesis of 2-chloro-5-methylpyridine-3-olefin derivatives (Fig. 1, **3a**–**e**); *E* (*trans*) → *Z* (*cis*) isomerization (**4a**–**e**) and evaluated their microbial activity (**3a**–**c**, **3e**, **4a**–**c** and **4e**) for the first time.

2. Chemistry

2-Chloro-5-methylnicotinaldehyde was synthesized by Vilsmeier cyclization of enamide substrates according to our earlier reported method [12]. Thus prepared 2-chloro-5-methylnicotinaldehyde is an important synthon utilized for various organic transformations such as synthesis of 2-chloro-5-methylpyridine-3-carbaldehydeimines (Schiff's base) [13a], *Baylis–Hillman* adducts [13b], reactions with cyclic enones [13c], and conversion of *Baylis–Hillman* adducts to biologically important quinolines [13d]. Further we have utilized 2-chloro-5-methylnicotinaldehydes for the

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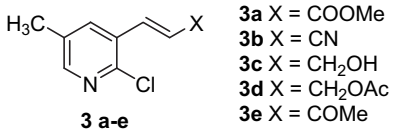
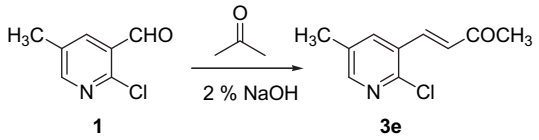


Fig. 1. Compounds **3a**–**e**.



Scheme 2. Synthesis of compound **3e**.

synthesis of imidacloprid derivatives [14a] and 1,8-naphthyridines [14b]. As mentioned in Scheme 1, the 2-chloro-5-methyl-nicotinaldehyde (**1**) was reacted with methyl 2-(dimethoxyphosphoryl)acetate (**2**) by adopting Horner–Wadsworth–Emmons (HWE) [15] reaction to give methyl(*E*)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenoate (**3a**, Scheme 1). Similarly we have synthesized (2*E*)-3-(2-chloro-5-methylpyridin-3-yl) acrylonitrile (**3b**) by using dimethyl cyanomethylphosphonate. Methyl(*E*)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenoate (**3a**) on reduction with DIBAL-H afforded (2*E*)-3-(2-chloro-5-methylpyridin-3-yl)-prop-2-en-1-ol (**3c**). Compound **3c** acetylated with acetic anhydride in presence of base in dry dichloromethane obtained (2*E*)-3-(2-chloro-5-methyl-pyridin-3-yl) prop-2-enyl acetate (**3d**). The compound (*E*)-4-(2-chloro-5-methyl-3-pyridyl)-3-buten-2-one (**3e**) was prepared by the condensation of **1** with acetone in presence of dilute sodium hydroxide (Scheme 2). The synthesized compounds are new and characterized by spectral data. The *Z* (*cis*) isomer of methyl (*Z*)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenoate (**4a**) prepared using a modified phosphonate (HWE reagent, methyl bis-2,2,2-trichloroethyl phosphanoacetate) to compare with the isomerized product (authentic sample, Scheme 1). Remaining *cis* isomers (**4b**–**c**) were isolated from the photo mixtures.

2.1. Photochemistry

2.1.1. Direct irradiation of photoisomerization of *3a*–*e* compounds

Thus synthesized pyridine derivative **3a** was subjected to study the *E* (*trans*) → *Z* (*cis*) isomerization process in various solvents such as hexane, DCM, CH_3CN and MeOH upon direct irradiation. The results obtained are tabulated in Table 1, and are based on HPLC analysis. Compound **3a** underwent *E*–*Z* isomerization upon direct excitation (Scheme 3; Table 1) leading to formation of *Z* (*cis*) isomer with poor selectivity. The isomer composition given at the photo stationary state (PSS) under these photochemical conditions. By changing the wavelength of irradiation to >400 nm did not show any isomerization (Scheme 4).

2.1.2. Triplet sensitized photoisomerization of *3a*–*e* compounds

The *Z* (*cis*) isomer formation is found to be less (Table 1) upon direct excitation and to improve the *Z* (*cis*) isomer content, we restored to triplet sensitized isomerization studies. Triplet sensitization studies were conducted with various sensitizers such as 9-fluorenone, benzil, 1-acetonaphthone and 2-acetonaphthone to improve the *Z* (*cis*) isomer content of PSS. Initially we have carried out the reaction of **3a** using above mentioned sensitizers with wavelength >400 nm in CH_3CN solvent (30 min) and the results indicate a higher *Z* (*cis*) contents. Among the 4 sensitizers used, the benzil is the suitable sensitizer to give *Z* (*cis*) isomer **4a** (Scheme 4). All the reactions were monitored by HPLC and the results are tabulated in Table 2. The results were encouraged us to carry out on other pyridine derivatives (**3b**–**e**) under similar conditions to give **4b**–**e** (Scheme 4 and Table 2).

2.1.3. Absorption and fluorescence properties

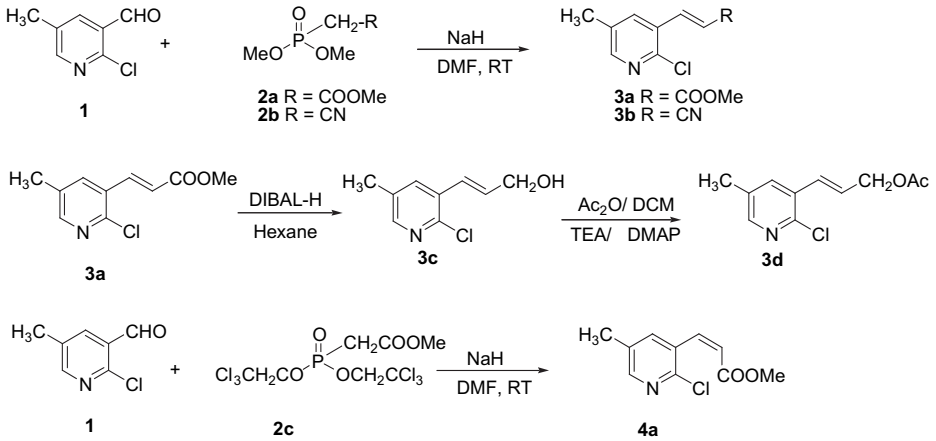
To understand the nature of the excited state we have generated absorption and fluorescence data for compounds **3a**–**e**. Fluorescence spectra of **3a**–**e** are structured in non-polar solvent hexane and become broad or structure less upon changing the solvent to acetonitrile or methanol (Fig. 2, Table 3). The quantum yield of fluorescence is relatively less for all the compounds (Table 3 and Scheme 4). The UV–visible spectra of **3a** and **4a** are given in Fig. 3 and Fig. 4. There is not much change observed for the compounds in the UV–visible absorption and fluorescence emission upon changing the polarity of the solvents (Table 3).

2.1.4. Preparative scale photochemistry

A gram of compound **3a** (0.003 M) was irradiated in methanol to isolate the *Z* (*cis*) isomer. The reaction was monitored by HPLC and *Z* (*cis*) was achieved upon column chromatography in 88% (**4a**).

3. Pharmacology

Thus synthesized compounds **3a**–**c**, **3e** and **4a**–**c**, **4e** were tested for their *in vitro* antibacterial activity against two representative



Scheme 1. Synthesis of compounds **3a**–**d** and **4a**.

Table 1
Isomer distribution upon direct excitation of compound **3a**.

Compound	Solvent	λ_{exc}	*cis* (%)	*trans* (%)
3a	Hexane	>300 nm	29	71
	Dichloromethane	>300 nm	38	62
	Acetonitrile	>300 nm	37	63
	Methanol	>300 nm	35	65
	Hexane	~350 nm	35	65
	Dichloromethane	~350 nm	41	59
	Acetonitrile	~350 nm	41	59
	Methanol	~350 nm	38	62

Nitrogen bubbled 0.003 M solutions were irradiated; Rayonet reactor for ~350 nm and pyrex filter with 450 W Hg arc lamp for >300 nm were used for irradiation.

Gram-positive organisms (*Bacillus subtilis* MTCC 441; *Staphylococcus aureus* MTCC 11) and two Gram-negative organisms (*Escherichia coli*, *Pseudomonas aeroginsa* MTCC 741) by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards [16]. Penicillin and Streptomycin were used as standard drugs. *In vitro* antifungal activity of pyridine derivatives tested against two representative microorganism Yeast (*Candida albicans*, *Saccharomyces cerviseae*) and Filamentous fungi (*Rhizopus oryzae*, *Aspergillus niger*) and Amphotericin-B was used as standard drug.

4. Results and discussion

4.1. Antibacterial activity of pyridine derivatives

Compounds **3a**–**c**, **3e**, **4a**–**c** and **4e** were screened for their antibacterial activity (Table 4) against *B. subtilis* and found to be moderate activity except **3b**. Compound **4a** with an olefin ester group at C-3 position displayed very good *in vitro* antibacterial activity against tested bacterial organism *S. aureus* (MIC in the range of 8.25 μg/mL) and other compounds **3e** and **4c** displayed moderate activity. Similarly compounds **3a**, **3c**, **4a**, **4b** and **4c** shown moderate activity against Gram-negative bacteria *E. coli*, and **3c**, **4a** and **4e** showed moderate activity against Gram-negative bacteria *P. aeroginsa*. Though the comparison of compounds among *E* (*trans*) and *Z* (*cis*) isomers, the *Z* (*cis*) isomer of **4a** has shown high degree of antibacterial activity than its corresponding *E* (*trans*) isomer, this may be due to C=C double bond functional group having *Z* (*cis*) configuration. When the nitrile group on pyridyl olefin rings, the *Z* (*cis*) isomer displayed moderate activity when compared with the *E* (*trans*) isomer. Among the isomers **3c** and **4c**, the *Z* (*cis*) isomer (**4c**) having the carbinol group showed good activity against Gram-positive organism compared to its *E* (*trans*) isomer **3c**, whereas in case of Gram-negative organism the *E* (*trans*) isomer **3c** displayed better activity compared to its *Z* (*cis*) isomer. In the case of **3e** and **4e** isomers, the *Z* (*cis*) isomer **4e** having keto functional group showed better overall antibacterial activity when compared to its *trans* isomer.

4.2. Antifungal activity of pyridine derivatives

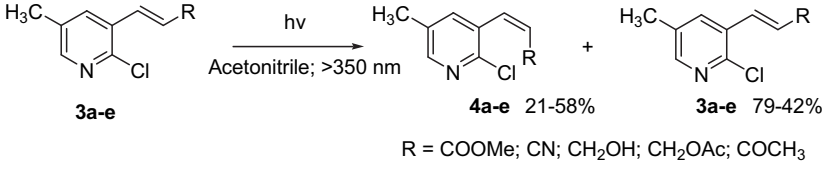
The *in vitro* antibacterial activity results of these heterocyclic compounds encouraged us to screen the *in vitro* antifungal activity of pyridine derivatives against two representative microorganisms *Yeast* and *Filamentous fungi*. Amphotericin-B was used as standard drug whose minimum zone of inhibition values is presented in Table 5. The investigation of antifungal screening data revealed that all the tested compounds **3a**–**c**, **3e**, **4a**–**c** and **4e** were shown moderate activity against *C. albicans*, *R. oryzae*, *A. niger*. Among these tested compounds **3c** and **4c** showed moderate activity against Yeast *S. cerviseae* may be due to the presence of alcohol moiety, whereas **3a**, **4b** and **4e** showed moderate activity against *C. albicans*. Compounds **3c** and **4c** displayed substantial activity against *S. cerviseae*. Compounds **3c** and **4c** showed significant, **3e**, **4e**, **3b**, **3a**, **4a** and **4b** showed substantial activity against *R. oryzae*, whereas **3a**, **4a**, **3c**, **4c**, and **4e** showed significant whereas **4b** and **3e** showed substantial activity against *A. niger* with a zone of inhibition value in the range of 17–12 mm at the concentration of 150 μg/mL.

5. Conclusion

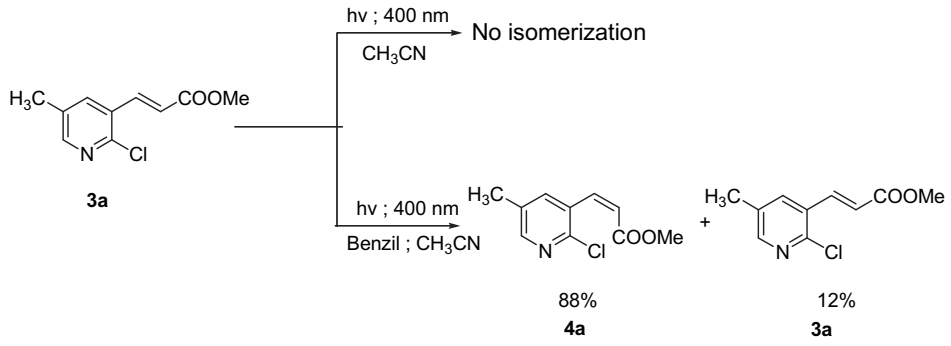
2-Chloro-5-methylpyridine-3-olefin derivatives (**3a**–**e**) are synthesized from 2-chloro-5-methylnicotinaldehyde and studied their *E* (*trans*) → *Z* (*cis*) isomerizations for the first time. The *E* (*trans*) → *Z* (*cis*) isomerization is efficient in triplet excited state when compared to singlet exited state. Fluorescence studies clearly indicate that the charge transfer or polar singlet excited state is involved in these isomerizations. The synthesized 2-chloro-5-methylpyridine-3-olefin derivatives and their isomerized *E* (*trans*)-*Z* (*cis*) compounds are new and well characterized by spectral data. The compounds were screened for their antimicrobial activity and a few compounds were found to be good to moderate activity when compared with the standard compounds.

6. Experimental protocols

All the solvents were distilled and dried by standard procedures. Melting points were determined by using capillary melting point apparatus (VMP-AM) and are uncorrected. IR spectra were recorded on Perkin–Elmer Model 283B and Nicolet-740 FT-IR instruments. Absorption spectra were recorded by using Perkin–Elmer Lamda-2 and Jasco UV–visible spectrometers. Mass spectra were recorded on a VG Micro Mass 7070H instrument. ^{1}H NMR spectra were recorded on a Gemini-200 MHz and Avance 300 MHz instruments in $CDCl_3$ solvent and data are reported in δ units with TMS as internal standard. A SPEX fluorolog 0.22 m fluoremeter was used for the fluorescence measurements. A Jasco PU-2080 plus intelligent dual pump system equipped with Jasco UV-2075 plus intelligent UV–visible detector and Jasco MX-2080-31 solvent mixing module connected to Jasco LC-Net/ADC couple with Acer personal computer was used for high performance liquid chromatography (HPLC) analysis. A Rayonet reactor equipped with RUL-3500 (~350 nm) lamps and a 450 W medium pressure Hg arc lamp along with Pyrex filters and TL-04 20 W, 2 ft length lamps were used for irradiation. An applied photolysis QYR-20 quantum yield reactor coupled with a 200 W Hg-lamp was used to determine the relative quantum yields. Elemental analyses were performed using



Scheme 3. Direct photochemical irradiation of compounds **3a**–**e** *E* (*trans*) → *Z* (*cis*) **4a**–**e**.



Scheme 4. Triplet sentitized photoisomerization of **3a** *E* (*trans*) → *Z* (*cis*) **4a**.

a Vario-EL elemental analyzer. Column chromatography was performed by using silica gel (60–120 and 200 meshes).

6.1. Synthesis of methyl(E)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenoate (*3a*)

Methyl 2-(dimethoxyphosphoryl)acetate (**2a**, 2 g, 11 mmol) in dry DMF (10 ml) was added slowly at room temperature to a suspension of NaH (0.26 g, 11 mmol) in DMF (15 ml). After the addition, the reaction mixture was allowed to stir for 10 min at the same temperature. The 2-chloro-5-methylnicotinaldehyde (**1**, 1.55 g 10 mmol) in DMF (10 ml) was added slowly to the reaction mixture and stirred for 2 h. After completion of the reaction, the reaction mixture was pored into ice-cold water and extracted with ether, the ether layer washed with water, organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure, the obtained crude product was subjected for column chromatography by using silica gel gave methyl(*E*)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenoate **3a** as solid in 92% yield; m.p. 112 °C; ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H), 3.85 (s, 3H), 6.38–6.42 (d, 1H, $J = 12.6$ Hz), 7.7 (s, 1H), 7.90–7.95 (d, 1H, $J = 10.8$ Hz), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 166.5, 151.2, 148.8, 139.4, 136.8, 133.1, 128.9, 122.5, 52.2, 17.9; EI-MS (*m*/*z*): 211 (M^+) (5), 180 (12), 176 (100), 148 (21), 116 (38), 89 (38), 63 (21); UV λ_{max} (hexane): 304 nm; $\varepsilon = 8644\ cm^{-1}\ M^{-1}$; Emission maxima (hexane) = 422 nm; quantum yield of fluorescence = 0.012; IR (KBr): 3420, 1724, 1636, 1431, 1320, 1288, 1175, 1066, 982, 766 cm^{-1}; Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.73; H, 4.72; N, 6.61%. Found C, 56.69; H, 4.66; N, 6.72%.

Table 2
Triplet sensitized isomerization studies of compounds (**3a**–**e**).

Compound	Triplet sensitizer	Trip. energy (kcal/mol)	*cis* (%)	*trans* (%)
3a	9-Fluorinone	51	63	37
	Benzil	54	86	14
	1-Acetonaphthone	57	24	76
	2-Acetonaphthone	59	06	94
3b	9-Fluorinone	51	44	56
	Benzil	54	65	35
	1-Acetonaphthone	57	23	77
	2-Acetonaphthone	59	16	84
3c	9-Fluorinone	51	64	36
	Benzil	54	75	25
	1-Acetonaphthone	57	48	52
	2-Acetonaphthone	59	24	76
3d	9-Fluorinone	51	41	59
	Benzil	54	68	32
	1-Acetonaphthone	57	15	85
	2-Acetonaphthone	59	11	89
3e	9-Fluorinone	51	58	42
	Benzil	54	65	35
	1-Acetonaphthone	57	18	82
	2-Acetonaphthone	59	14	86

Nitrogen bubbled 0.003 M, 10 mL solution containing 0.01 M sensitizer were irradiated using Tl-04 20 W lamps (>400 nm) for 30 min and analyzed by HPLC.

6.2. Synthesis of (E)-2-(2-chloro-5-methyl-3-pyridyl)-1-ethenyl cyanide (*3b*)

A similar procedure as mentioned for the synthesis of **3a** was adopted using dimethyl cyanomethylphosphonate to synthesize compound **3b**. Yield 68%; solid; m.p. 70 °C; ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 5.88–5.94 (d, 1H, $J = 12.6$ Hz), 7.62 (s, 1H), 7.68–7.72 (d, 1H, $J = 12.6$ Hz), 8.25 (s, 1H); EI-MS (*m*/*z*): 178 (M^+) (100), 166 (8), 143 (100), 116 (56), 104 (10), 89 (40), 77 (30), 63 (43), 39 (58); UV: λ_{max} (hexane): 306 nm; $\varepsilon = 3455\ cm^{-1}\ M^{-1}$; Emission maxima (hexane) = 420 nm; quantum yield of fluorescence = 0.0183; IR (KBr): 3425, 2921, 2218, 1421, 1166, 1073, 965, 755 cm^{-1}; Anal. Calcd for $C_9H_7ClN_2$: C, 60.50; H, 3.92; N, 15.68%. Found C, 60.45; H, 3.89; N, 15.62%.

6.3. Synthesis of (E)-3-(2-chloro-5-methyl-3-pyridyl)-2-propen-1-ol (*3c*)

DIBAL-H (9.4 ml of 1 M hexane solution, 9.4 mmol) was added slowly to a suspension of methyl(*E*)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenoate (**3a**, 1.0 g, 4.7 mmol) in dry hexane (25 ml) at −78 °C under nitrogen atmosphere, after complete addition, the reaction mixture was brought to room temperature and was allowed to stir for 2 h. The reaction mixture was cooled to −78 °C, quenched with NaF/H_2O, and extracted with ether, dried over anhydrous sodium sulfate and solvent removed under reduced

Table 3
Absorption and fluorescence properties of compounds (**3a**–**e**).

Compound	Solvent	$\lambda_{abs/nm}$	$\lambda_{em/nm}$	φ_{flu}
3a	Hexane	304	422	0.012
	Dichloromethane	304	424	0.010
	Acetonitrile	302	422	0.024
	Methanol	302	426	0.031
3b	Hexane	306	420	0.018
	Dichloromethane	306	416	0.345
	Acetonitrile	302	416	0.060
	Methanol	304	432	0.128
3c	Hexane	292	340	0.088
	Dichloromethane	292	340	0.098
	Acetonitrile	292	340	0.082
	Methanol	292	340	0.104
3d	Hexane	288	335	0.054
	Dichloromethane	288	335	0.068
	Acetonitrile	288	335	0.086
	Methanol	288	335	0.076
3e	Hexane	306	424	0.116
	Dichloromethane	308	420	0.144
	Acetonitrile	304	424	0.026
	Methanol	304	424	0.073

0.0005 M solutions were employed for fluorescence studies at room temperature; quantum yield of fluorescence determined using 9,10-diphenyl anthracene as standard; error value ±10%.

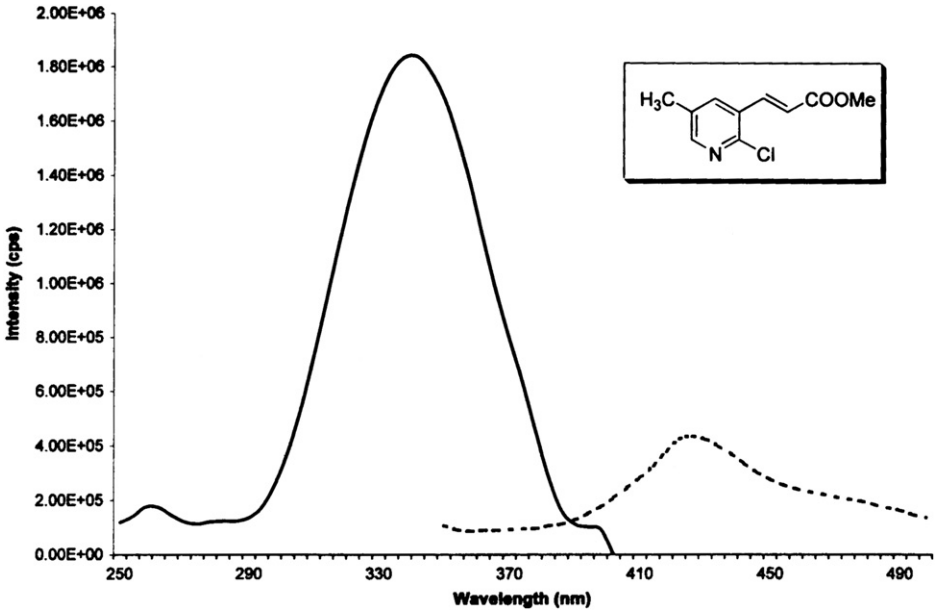


Fig. 2. Fluorescence excitation and emission spectra of compound **3a**.

pressure, the crude product was purified by column chromatography using silica gel (100–200 mesh) with hexane/DCM (4:1) gave (*E*)-3-(2-chloro-5-methyl-3-pyridyl)-2-propen-1-ol **3c** as yellow liquid in 90% yield; ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 4.38 (d, 2H, $J = 8.24$ Hz), 6.30–6.38 (m, 1H, $J = 5.9$ Hz), 6.84–6.88 (d, 1H, $J = 10.7$ Hz), 7.60 (s, 1H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 148.5, 147.9, 135.8, 133.9, 132.4, 131.0, 124.5, 62.6, 17.4; EI-MS (*m*/*z*): 183 (M^+) (16), 156 (40), 146 (100), 127 (7), 118 (46), 93 (25), 91 (35), 77 (31), 63 (35), 39 (53); UV: λ_{max} (hexane): 292 nm; $\varepsilon = 12{,}504$ cm^{-1} M^{-1}; Emission maxima (hexane) = 340 nm; quantum yield of fluorescence = 0.0879; IR (KBr): 3480, 1636, 1431, 1320, 1288, 1180, 1060, 990 cm^{-1}; Anal. Calcd for $C_9H_{10}ClNO$: C, 58.85; H, 5.44; N, 7.62%. Found C, 58.83; H, 5.38; N, 7.67%.

6.4. Synthesis of (E)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenyl acetate (**3d**)

A mixture of (*E*)-3-(2-chloro-5-methyl-3-pyridyl)-2-propen-1-ol (**3c**, 0.988 g, 5.4 mmol), acetic anhydride (0.612 g, 6 mmol), triethylamine (0.6 g, 6 mmol) and DMAP (0.066 g, 0.6 mmol) in dry DCM (20 ml) were stirred for 16 h at room temperature. After completion of the reaction, reaction mixture was diluted with DCM (100 ml), organic layer was washed with water, dried over sodium sulfate, solvent removed under reduced pressure and purified by column chromatography using silica gel (100–200 mesh) with pet-ether as eluent gave (*E*)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenyl acetate **3d** as viscous oil in 94% yield; ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H), 2.35 (s, 3H), 4.78 (d, 2H, $J = 6.6$ Hz), 6.25-6.35 (m, 1H, $J = 5.6$ Hz), 6.90–6.95 (d, 1H, $J = 5.6$ Hz), 7.64 (s, 1H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 170.2, 148.9, 147.3, 135.8, 132.3, 130.4, 128.4, 128.2, 64.2, 20.5, 17.3; EI-MS (*m*/*z*): 225 (M^+) (4), 183 (31), 165 (17), 154 (72), 148 (16), 130 (28), 118 (12), 91 (12), 77 (17), 63 (11), 43 (100); UV: λ_{max} (hexane): 288 nm; $\varepsilon = 3077$ cm^{-1} M^{-1}; Emission maxima (hexane) = 422 nm; quantum yield of fluorescence = 0.012; IR (KBr): 2923, 1720, 1681, 1410, 1390, 1270, 1160, 1060, 970, 890, 788 cm^{-1}; Anal. Calcd for $C_{11}H_{12}ClNO_2$: C, 58.53; H, 5.32; N, 6.20%. Found C, 58.68; H, 5.39; N, 6.15%.

6.5. Synthesis of (E)-4-(2-chloro-5-methyl-3-pyridyl)-3-buten-2-one (**3e**)

Sodium hydroxide solution (5 ml, 1 M) was added dropwise to a stirred mixture of 2-chloro-5-methylnicotinaldehyde (**1**, 1.55 g, 10 mmol) and dry acetone (50 ml) at room temperature and stirring was continued for another 1 h. The reaction was quenched with water, extracted with ether; organic layer was washed brine solution and dried over sodium sulfate. The solvent removed under reduced pressure and crude product purified by column chromatography using silica gel gave (*E*)-4-(2-chloro-5-methyl-3-pyridyl)-3-buten-2-one **3e** as white solid in 70% yield; m.p. 80 °C; ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 2.40 (s, 3H), 6.56–6.62 (d, 1H, $J = 12.3$ Hz), 7.70–7.76 (d, 1H, $J = 12.3$ Hz), 7.72 (s, 1H), 8.18

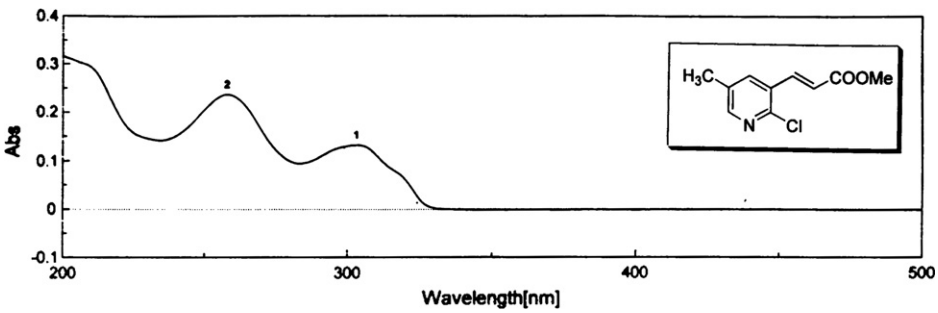


Fig. 3. UV–visible spectra of compound **3a**.

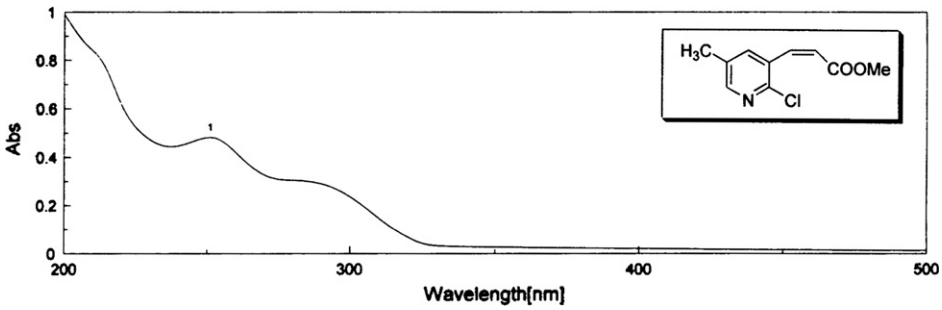


Fig. 4. UV–visible spectra of compound **4a**.

(s, 1H); ^{13}C NMR ($CDCl_3$): δ 198.6, 150.9, 137.6, 136.4, 132.8, 130.9, 128.8, 126.2, 27.2, 17.6; EI-MS (*m*/*z*): 195 (M^+) (6), 180 (17), 160 (100), 116 (38), 89 (22), 43 (23); UV: λ_{max} (hexane): 306 nm; $\varepsilon = 5028\ cm^{-1}\ M^{-1}$; Emission maxima (hexane) = 424 nm; quantum yield of fluorescence = 0.1163; IR (KBr): 3427, 2923, 2856, 1681, 1607, 1417, 1353, 1271, 1161, 1069, 977, 895 cm^{-1}; Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.38; H, 5.11; N, 7.16%. Found C, 61.29; H, 5.19; N, 7.15%.

6.6. Synthesis of methyl (Z)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenoate (*4a*)

Methyl bis-2,2,2-trichloroethyl phosphanoacetate (**2c**, 2.07 g, 5 mmol) in dry DMF (10 ml) was added slowly at room temperature to a suspension of NaH (0.240 g, 5 mmol) in DMF (20 ml) and stirred for 15 min. The reaction mixture was cooled to −78 °C and 2-chloro-5-methylnicotinaldehyde (**1**, 0.744 g, 4.8 mmol) in DMF (10 ml) was added slowly over a period of 10 min, and the reaction mixture stirred for 4 h at room temperature. After completion of the reaction, the mixture was poured into crushed ice, extracted with ether, washed with water, organic layer was dried over sodium sulfate, solvent was removed under reduced pressure and the crude product was purified by column chromatography by using silica gel (100–200 mesh) with pet-ether as eluent gave methyl (*Z*)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenoate **4a** as solid in 90% yield; m.p. 65 °C; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 3.70 (s, 3H), 6.12–6.16 (d, 1H, J = 12.5 Hz), 7.04–7.08 (d, 1H, J = 11.7 Hz), 7.75 (s, 1H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 165.5, 149.6, 147.0, 140.1, 138.9, 131.5, 129.3, 122.4, 51.5, 17.6; EI-MS (*m*/*z*): 211 (M^+) (5), 180 (12), 176 (100), 148 (21), 116 (38), 89 (38), 63 (21); UV: λ_{max} (hexane): 282 nm; $\varepsilon = 6873\ cm^{-1}\ M^{-1}$; Emission maxima (hexane) = 424 nm; quantum yield of fluorescence = 0.0967; IR (KBr): 3420, 1724, 1636, 1431, 1320, 1288, 1175, 1066, 982, 766 cm^{-1}; Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.73; H, 4.72; N, 6.61%. Found C, 56.66; H, 4.69; N, 6.59%.

6.7. Triplet sensitized photoisomerization of *3a–e* compounds

In a typical experiment, triplet sensitized reactions were carried out by using a mixture of sensitizer (benzil, 0.01 M) and substrate (**3a**, 0.01 M) in acetonitrile (200 ml), N_2 bubbled, which was irradiated for 2 h using Philips TL/03-20 W 2 ft lamps. The reaction was monitored by HPLC and the *Z* (*cis*) isomer **4a** was isolated by column chromatography using silica gel (100–200 mesh). Remaining compounds **4b–e** were prepared using the similar procedure.

6.7.1. (Z)-2-(2-Chloro-5-methyl-3-pyridyl)-1-ethenyl cyanide (*4b*)

Compound **4b** was synthesized by using above mentioned photochemical procedure 6.7. Solid; m.p: 62 °C; ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H), 5.62-5.66 (d, 1H, J = 10.0 Hz), 7.42-7.46 (d, 1H, J = 12.0 Hz), 8.22 (s, 1H), 8.24 (s, 1H); UV: λ_{max} (hexane): 300 nm; $\varepsilon = 664\ cm^{-1}\ M^{-1}$; Emission maxima (hexane) = 420 nm; quantum yield of fluorescence = 0.1028; Anal. Calcd for $C_9H_7ClN_2$: C, 60.50; H, 3.92; N, 15.68%. Found C, 60.53; H, 3.87; N, 15.70%.

6.7.2. (Z)-3-(2-Chloro-5-methyl-3-pyridyl)-2-propen-1-ol (*4c*)

Compound **4c** was synthesized by using photochemical method mentioned in Section 6.7. Yield 75%, viscous oil; ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 4.38 (d, 2H, J = 7.3 Hz), 6.02–6.06 (m, 1H, J = 5.7 Hz), 6.52–6.56 (d, 1H, J = 10.7 Hz), 7.38 (s, 1H), 8.06 (s, 1H); UV: λ_{max} (hexane): 282 nm; $\varepsilon = 7736\ cm^{-1}\ M^{-1}$; Emission maxima (hexane) = 345 nm; quantum yield of fluorescence = 0.2655; Anal. Calcd for $C_9H_{10}ClNO$: C, 58.85; H, 5.44; N, 7.62%. Found C, 58.78; H, 5.46; N, 7.59%.

6.7.3. (Z)-3-(2-Chloro-5-methyl-3-pyridyl)-2-propenyl acetate (*4d*)

Compound **4d** was synthesized by using photochemical method mentioned in Section 6.7. Liquid; ^{1}H NMR ($CDCl_3$): δ 2.08 (s, 3H), 2.36 (s, 3H), 4.65 (d, 2H, J = 8.0 Hz), 5.94–6.00 (m, 1H, J = 10.7 Hz),

Table 4
Antibacterial activity of synthetic compounds **3a–e** and **4a–e**.

Compound	MIC, μg/ml			
	Gram-positive organisms		Gram-negative organisms	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeroginsa*
3a	37.5	75	37.5	75
4a	37.5	8.125	37.5	37.5
3b	75	75	75	75
4b	37.5	75	37.5	75
3c	37.5	75	37.5	37.5
4c	37.5	37.5	75	75
3e	37.5	37.5	75	75
4e	37.5	75	37.5	37.5
Penicillin	1.562	1.562	12.5	12.5
Streptomycin	6.25	6.25	1.562	3.125

Negative control (DMSO).

Table 5
Antifungal activity of compounds **3a–c** and **3e** and **4a–c** and **4e**.

Microorganism	Yeast				Filamentous fungi			
	Candida albicans		*Saccharomyces cerviseae*		*Rhizopus oryzae*		*Aspergillus niger*	
Compound	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg
3a	8 mm	11 mm	–	–	10 mm	11 mm	16 mm	17 mm
4a	11 mm	13 mm	–	–	10 mm	11 mm	14 mm	17 mm
3b	10 mm	12 mm	–	–	10 mm	12 mm	13 mm	15 mm
4b	–	10 mm	–	–	9 mm	10 mm	9 mm	12 mm
3c	13 mm	15 mm	12 mm	14 mm	16 mm	18 mm	14 mm	17 mm
4c	11 mm	14 mm	11 mm	13 mm	14 mm	17 mm	12 mm	16 mm
3e	13 mm	17 mm	–	–	12 mm	13 mm	13 mm	14 mm
4e	9 mm	11 mm	–	–	11 mm	13 mm	14 mm	16 mm
Amphotericin-B (50 μg)	23.5 mm		22 mm		23 mm		26 mm	

Inhibitory zone diameters are in mm; concentration μg/ml.
Negative control (DMSO).

6.64–6.68 (d, 1H, $J = 10.2$ Hz), 7.38 (s, 1H), 8.15 (s, 1H); UV: λ_{max} (hexane): 282 nm; $\varepsilon = 2095\ cm^{-1}\,M^{-1}$; Emission maxima (hexane) = 388 nm; quantum yield of fluorescence = 0.3198; Anal. Calcd for $C_{11}H_{12}ClNO_2$: C, 58.53; H, 5.32; N, 6.20%. Found C, 58.49; H, 5.29; N, 6.27%.

*6.7.4. (Z)-4-(2-Chloro-5-methyl-3-pyridyl)-3-buten-2-one (**4e**)*

Compound **4e** was synthesized by using photochemical method mentioned in Section 6.7. Solid; m.p: 80 °C; ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H), 2.25 (s, 3H), 6.28–6.32 (d, 1H, $J = 10.8$ Hz), 6.76-6.80 (d, 1H, $J = 12.6$ Hz), 7.65 (s, 1H), 8.05 (s, 1H); UV: λ_{max} (hexane): 306 nm; $\varepsilon = 11{,}385\ cm^{-1}\,M^{-1}$; Emission maxima (hexane) = 424 nm; quantum yield of fluorescence = 0.1293; Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.38; H, 5.11; N, 7.16%. Found C, 61.41; H, 5.08; N, 7.23%.

6.8. Fluorescence

A Fluorolog 2 fluorimeter equipped with a 450 W Xe lamp was used for fluorescence studies. Dry solvents were used, and identical conditions were maintained for all the fluorescence measurements. The slit widths were 2/2/2/2 mm. The quantum yield of fluorescence was determined using 9,10-diphenyl anthracene as standard and all operations were conducted at room temperature.

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