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Synthesis of multisubstituted quinolines from Baylis–Hillman adducts obtained from substituted 2-chloronicotinaldehydes and their antimicrobial activity

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Abstract—Baylis–Hillman acetates were synthesized from substituted 2-chloronicotinaldehydes and were conveniently transformed into multisubstituted quinolines and cyclopenta[*g*]quinolines on reaction with nitroethane or ethyl cyanoacetate via a successive S_N2'–S_NAr elimination strategy. Thus, synthesized quinolines were evaluated for antimicrobial activity and found having substantial antibacterial and antifungal activity.

1. Introduction

The steadily increasing bacterial resistance to existing drugs is a serious problem in antibacterial therapy and necessitates continuing research into new classes of antibacterials.[1] Of particular concern are severe infections caused by multidrug-resistant Gram-positive pathogens, which cause high mortality rates especially in the hospital setting. The individual organisms responsible include methicillin-resistant *Staphylococcus aureus* (MRSA),[2,3] vancomycin-resistant *Enterococcus faecalis* (VRE),[4,5] and penicillin-resistant *Streptococcus pneumoniae*.[6,7] A more controlled usage of these drugs may be a way to partially counterbalance this challenge. In view of the above, the design and synthesis of newer antimicrobials is an area of immense significance and continues to attract the attention of increasing number of medicinal chemists.

Quinolines and their derivatives occur in numerous natural products, many of which possess interesting physiological and biological properties.[8] Quinoline derivatives have been developed for the treatment of many diseases like malaria,[9] HIV,[10] tumor,[11] and antibacterial infections.[12] Substituted quinolines have also been reported to act as antagonists for endothelin,[13] $5HT_3$,[14] NK-3,[15] and leucotriene[16,17] receptors. They also function as inhibitors of gastric (H^+/K^+)-ATPase,[18] dihydroorotate dehydrogenase,[19] and 5-lipoxygenase.[20] In addition to the medicinal importance, multisubstituted quinolines are valuable synthons used for the preparation of nano- and mesostructures with enhanced electronic and photonic properties.[21] Many methods for the synthesis of quinoline derivatives are reported in the literature,[22] but due to their interesting and important biological properties, the development of new, simple, convenient, and environmentally benign synthetic approaches using mild conditions remains an active research area.[23]

The Baylis–Hillman (BH) reaction, a carbon–carbon bond forming reaction between a carbonyl compound and an activated olefin, is atom-economic and the resulting products (BH adducts) are densely functionalized molecules. These BH adducts have applications in many organic stereoselective transformation methodologies.[24] Variety of natural, unnatural compounds, several biologically important natural products have been synthesized using BH adducts as precursors.[25] Some publications have reported the formation of

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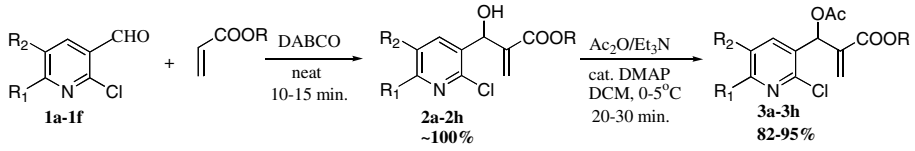
quinolines[26] and dihydroquinolines[27] from the BH adducts originating from aromatic aldehydes. Even though many methodologies appeared on the applications of BH adducts in the literature, there are very few reports for the applications of BH adducts derived from the heterocyclic compounds. In continuation of our work on bio-evaluation of heterocycles,[28] we wish to report herein the synthesis of new title quinolines from the reaction of Baylis–Hillman acetates obtained from substituted 2-chloronicotinaldehydes[29] and nitroethane or cyanoacetates in high yield and under moderate conditions in order to study their antimicrobial activities.

2. Chemistry

BH acetates, resulting from BH adducts, have been used to make γ-lactams, γ-keto-esters, and naphthalenes.[30] We anticipated that, by analogy to the above work, if the aromatic moiety of the Baylis–Hillman acetate were a 2-chloro-3-pyridinyl moiety, it should undergo aromatic nucleophilic substitution reaction (S_NAr) followed by aromatization, which would lead to the formation of substituted quinolines. The BH adducts obtained from the reaction between substituted 2-chloronicotinaldehydes (**1a**–**1f**) and acyclic alkenes (**2a**–**2h**)[31]/cyclic enones (**2i**–**2l**)[32] were efficiently acetylated[33] by treatment with either AcCl/pyridine or Ac_2O/Et_3N, cat. DMAP to give the corresponding BH acetates **3a**–**3h** (Scheme 1) in 80–92% yield and **3i**–**3l** (Scheme 2) in 90–98% yield, respectively.

The reaction between Baylis–Hillman acetates (**3a**–**3l**) and nitroethane was carried out via the successive S_N2'–S_NAr elimination strategy. Reaction of the Baylis–Hillman acetates (**3a**–**3h**) in *N*,*N*-dimethylformamide, in the presence of potassium carbonate and nitroethane at 50–70 °C, afforded the desired substituted 8-methyl quinolines (**4a**–**4h**) in 80–92% yield in a short time (3–4 h). Under the same reaction conditions the acetates (**3i**–**3l**), obtained from the BH adducts with

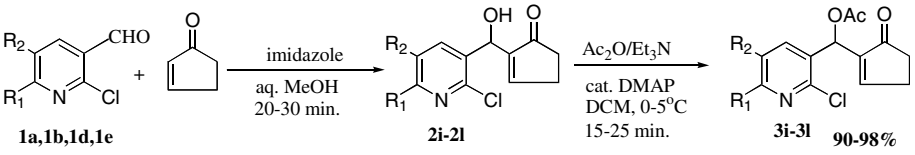


1a: R_1 = H, R_2 = Me
1b: R_1 = H, R_2 = Ph
1c: R_1 = H, R_2 = p-OMe-Ph
1d: R_1 = Ph, R_2 = CH_3
1e: R_1 = COOMe, R_2 = H
1f: R_1 = Ph, R_2 = COOEt

2a & **3a** : R_1 = H, R_2 = Me, R = Me
2b & **3b** : R_1 = H, R_2 = p-OMe-Ph, R = Me
2c & **3c** : R_1 = COOMe, R_2 = H, R = Me
2d & **3d** : R_1 = Ph, R_2 =COOEt, R =Me

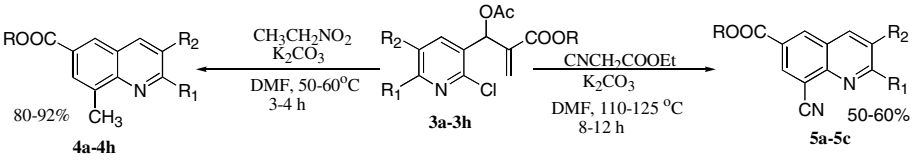
2e & **3e**: R_1 = H, R_2 = CH_3, R = Et
2f & **3f**: R_1 = H, R_2 = Ph, R = Et
2g & **3g**: R_1 = Ph, R_2 = CH_3, R = Et
2h & **3h**: R_1 = COOMe, R_2 = H, R = Et

Scheme 1.



2i & 3i : R_1 = H, R_2 = CH_3
2j & 3j : R_1 = H, R_2 = Ph
2k & 3k: R_1 = Ph, R_2 = CH_3
2l & 3l : R_1 = COOMe, R_2 = H

Scheme 2.

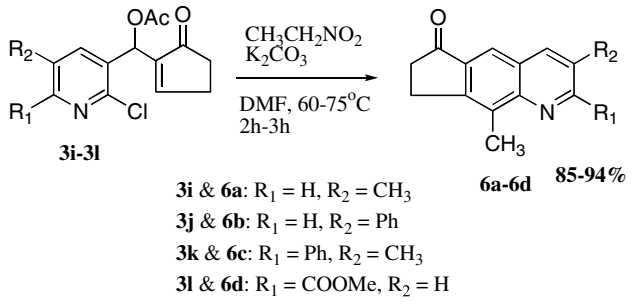


3a & **4a** : R_1 = H, R_2 = CH_3, R = Me
3b & **4b**: R_1 = H, R_2 = p-OMe-Ph, R = Me
3c & **4c** : R_1 = COOMe, R_2 = H, R = Me
3d & **4d**: R_1 = Ph, R_2 = COOEt, R = Me

3e & **4e** : R_1 = H, R_2 = CH_3, R = Et
3f & **4f** : R_1 = H, R_2 = Ph, R = Et
3g & **4g**: R_1 = Ph, R_2 = CH_3, R = Et
3h &**4h**: R_1 = COOMe, R_2 = H, R = Et

5a : R_1 = H, R_2 = CH_3, R = Me
5b: R_1 = H, R_2 = Ph, R = Et
5c: R_1 = Ph, R_2 = CH_3, R = Et

Scheme 3.



Scheme 4.

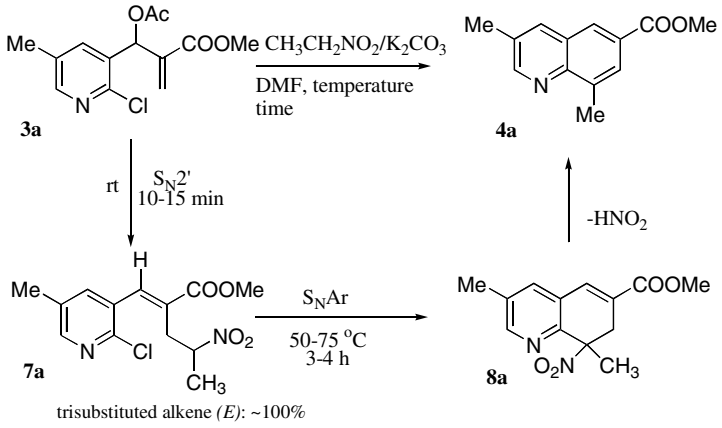
2-cyclopenten-1-ones (**2i**–**2l**), gave substituted 9-methyl cyclopenta[*g*]quinoline-6-ones (**6a**–**6d**) in 85–94% yield (Scheme 4). The same reaction was conducted at room temperature for a longer time to obtain appreciable amounts of 8-methyl quinolines along with (*E*)-3-(2-chloropyridyl)-2-(2-nitropropyl)-2-propenoate (**7a**, trisubstituted alkene, Scheme 5). Similarly, substituted 8-cyano quinolines (**5a**–**5c**) were obtained from the reaction of BH acetates (**3a**–**3h**) and ethylcyano acetate in 50–60% yield (Scheme 3). In the case of ethyl cyanoacetate reaction at relatively higher temperatures (110–125 °C) and longer times (~10 h), it is required to get the substituted 8-cyano quinolines. Synthesized, multisubstituted quinolines are arranged in Table 1 along with reaction conditions. As shown in Table 1, the reaction proceeded irrespective of the electron-withdrawing substituents on the pyridine moiety.

The mechanism of the reaction is depicted in Scheme 5. Conjugate addition of carbananion of nitroalkane (tandem nucleophilic addition–elimination reaction, S_N2')[34] in the presence of potassium carbonate in DMF to the BH acetate **3a** gives trisubstituted alkene **7a** (methyl-(*E*)-3-(2-chloropyridyl)-2-(2-nitropropyl)-2-propenoate) with high stereoselectivity (step 1; Scheme 5). Intra-molecular aromatic nucleophilic substitution reaction (S_NAr) of trisubstituted alkene **7a** gave the 7,8-dihydro quinoline **8a** (Scheme 5; step 2). Finally, 8-methyl-substituted quinolines were formed via elimination of nitrous acid (aromatization process), and the nitrous acid was neutralized in situ by potassium carbonate. Similarly, substituted 8-cyano quinolines were formed via successive S_N2'–S_NAr elimination–decarboxylation and autooxidation reactions, respectively. In this case, decarboxylation takes place at higher temperatures and requires longer reaction times. To assign the stereochemistry of the trisubstituted alkenes formed in this reaction, one of the ester-containing trisubstituted alkenes **7a** was isolated (Scheme 5) with exclusive (*E*)-stereoselectivity (~100%).[35] The assignment of stereochemistry of trisubstituted alkenes (e.g., **7a**) was based on spectroscopic evidence.[36]

3. Antimicrobial activity

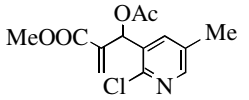
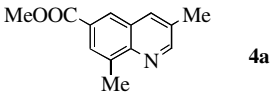
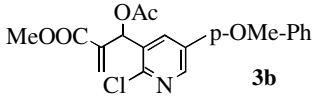
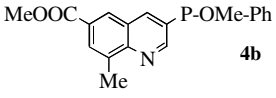
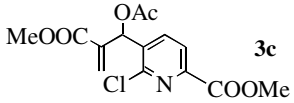
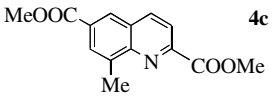
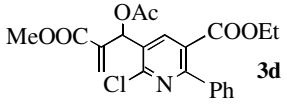
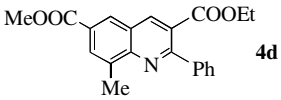
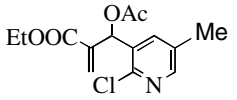
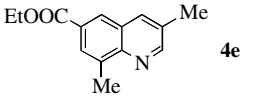
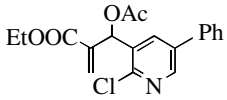
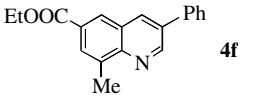
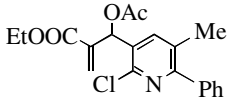
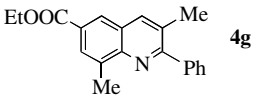
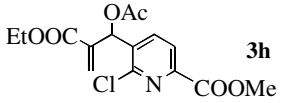
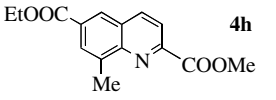
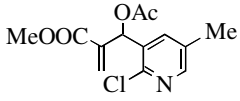
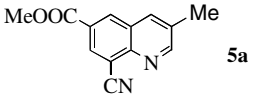
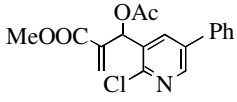
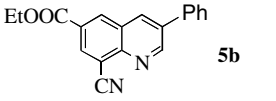
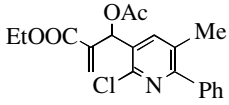
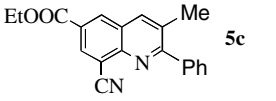
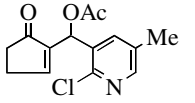
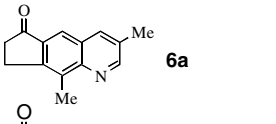
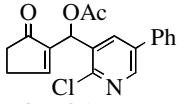
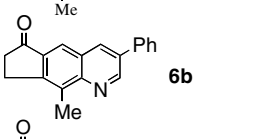
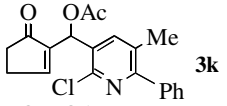
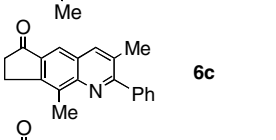
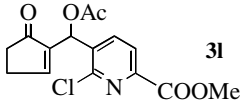
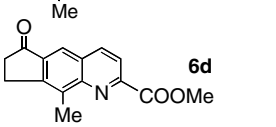
All the three series of newly synthesized novel quinolines **4a**–**4h**, **5a**–**5c**, and **6a**–**6d** were tested for their in vitro antibacterial activity against three representative Gram-positive organisms, viz., *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11), and *S. aureus* (MTCC 96), and three Gram-negative organisms, viz., *Chromobacterium violaceum* (MTCC 2656), *Klebsiella aerogenes* (MTCC 39), and *Pseudomonas aeruginosa* (MTCC 741) by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards.[39] Penicillin and streptomycin were used as standard drugs whose minimum inhibitory concentration (MIC) values are provided in Table 2.

The quinolines **4a**–**4h**, **5a**–**5c**, and **6a**–**6d** exerted a wide range of broad spectrum of antibacterial activity, however, with a degree of variation. Compounds **4a**–**4h** with a methyl group at C-8 position are displaying notable in vitro antibacterial activity against all the tested bacterial organisms (MIC in the range of 6.25–25 μg/mL). In this series of compounds, **4a** and **4e** with alkyl substituent at C-3 position and carboalkoxy substituent at C-6 position are showing substantial activity against Gram-negative bacteria, *P. aeruginosa* and *C. violaceum*. Moderate activity is observed against Gram-positive bacteria and substantial activity against Gram-negative bacteria in the case of compounds **4b** and **4f** where the phenyl group at C-3 replaces the methyl group. By the introduction of an electron-withdrawing group like methyl and ethyl esters at C-2 and C-3 positions in compounds **4c**, **4d**, and



Scheme 5.

Table 1. Conversion of Baylis–Hillman acetates into multisubstituted Quinolines

Serial No.	Baylis–Hillman acetate	Conditions	Quinoline	Mp (°C)	Yield (%)
1	 **3a**	$CH_3CH_2NO_2$ 50 °C, 2 h	 **4a**	88	85
2	 **3b**	$CH_3CH_2NO_2$ 70 °C, 3 h	 **4b**	102	82
3	 **3c**	$CH_3CH_2NO_2$ 50 °C, 2 h	 **4c**	112	92
4	 **3d**	$CH_3CH_2NO_2$ 50 °C, 2 h	 **4d**	79	83
5	 **3e**	$CH_3CH_2NO_2$ 50 °C, 2 h	 **4e**	83	85
6	 **3f**	$CH_3CH_2NO_2$ 50 °C, 3 h	 **4f**	98	86
7	 **3g**	$CH_3CH_2NO_2$ 75 °C, 3 h	 **4g**	98	87
8	 **3h**	$CH_3CH_2NO_2$ 80 °C, 3 h	 **4h**	112	94
9	 **3a**	$NCCH_2COOEt$ 125 °C, 8 h	 **5a**	126	54
10	 **3b**	$NCCH_2COOEt$ 125 °C, 12 h	 **5b**	134	45
11	 **3g**	$NCCH_2COOEt$ 110 °C, 10 h	 **5c**	121	62
12	 **3i**	$CH_3CH_2NO_2$ 80 °C, 5 h	 **6a**	123	88
13	 **3j**	$CH_3CH_2NO_2$ 80 °C, 5 h	 **6b**	132	93
14	 **3k**	$CH_3CH_2NO_2$ 80 °C, 5 h	 **6c**	124	94
15	 **3l**	$CH_3CH_2NO_2$ 80 °C, 5 h	 **6d**	112	85

Isolated yields; uncorrected mp.

4h, a slightly decreased activity is observed in both tested Gram-positive and Gram-negative strains. On replacement of the methyl group to cyano at C-8 (**5a**–**5c**), increased antibacterial activity against all the tested bacterial organisms is observed (MIC in the range of 6.25–12.5 μg/mL). In this series of compounds, **5b** and **5c** are displaying substantial activity against all the tested strains. Compound **5a** with methyl group at C-3 showing

Table 2. Antibacterial activity of substituted quinolines **4a–4h**, **5a–5c**, and **6a–6d**

Quinoline compounds	Microorganisms (MIC)					
	Gram positive			Gram negative		
	Bacillus subtilis	*Bacillus sphaericus*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Klebsiella aerogenes*	*Chromobacterium violaceum*
4a	25	12.5	12.5	6.25	12.5	6.25
4b	6.25	12.5	25	12.5	12.5	12.5
4c	12.5	12.5	25	25	12.5	12.5
4d	25	12.5	12.5	25	25	12.5
4e	12.5	12.5	25	6.25	12.5	6.25
4f	25	12.5	12.5	6.25	12.5	6.25
4g	12.5	12.5	25	6.25	12.5	6.25
4h	25	12.5	25	12.5	25	12.5
5a	12.5	12.5	6.25	6.25	12.5	12.5
5b	6.25	12.5	6.25	12.5	12.5	6.25
5c	12.5	12.5	6.25	6.25	12.5	12.5
6a	25	25	12.5	12.5	25	12.5
6b	25	25	12.5	25	12.5	12.5
6c	12.5	12.5	12.5	6.25	12.5	12.5
6d	12.5	25	25	25	12.5	25
Penicillin	1.565	3.125	1.565	12.5	6.25	12.5
Streptomycin	6.25	12.5	6.25	3.125	1.562	3.125

Negative control (acetone), no activity.
Values are indicated in μg/mL.

Table 3. Antifungal activity of substituted quinolines **4a–4h**, **5a–5c**, and **6a–6d**

Compound	*Aspergillus niger*		*Chrysosporium tropicum*		*Rhizopus oryzae*	
	30 μg	100 μg	30 μg	100 μg	30 μg	100 μg
4a	8	7	11	11	6	8
4b	9	9	9	12	8	11
4c	8	8	7	9	7	8
4d	9	8	9	9	7	9
4e	8	9	7	9	9	9
4f	9	11	9	12	9	11
4g	9	8	9	11	9	11
4h	8	9	8	9	8	9
5a	9	9	8	11	8	11
5b	8	9	8	11	7	11
5c	9	11	8	9	7	11
6a	9	11	8	9	8	9
6b	8	9	8	11	9	9
6c	9	8	9	9	8	11
6d	7	8	6	9	6	9
Clotrimazole		26		29		23

Negative control (DMSO). No activity.
Well or cup method; zone of inhibition is indicated in mm.

somewhat decreased activity is observed compared to **5b** and **5c**. Compounds **6a–6d** with cyclopentanone group are showing the moderate antibacterial activity (MIC in the range of 12.5–25 μg/mL). Overall, compound **5a** is showing the substantial antibacterial activity against *S. aureus*, *P. aeruginosa*, and *C. violaceum.* Compounds **4a** and **4e** are showing notable antibacterial activity and the remaining compounds exhibit moderate antibacterial activity.

The in vitro antifungal activity of the newly synthesized quinolines **4a–4h**, **5a–5c**, and **6a–6d** was studied against the fungal strains, viz., *Aspergillus niger* (MTCC 282), *Chrysosporium tropicum* (MTCC 2821), *Rhizopus oryzae* (MTCC 262), *Fusarium moniliforme* (MTCC 1848), and *Curvularia lunata* (MTCC 2030) by agar cup diffusion method.[40,41] and the strains were obtained from the Institute of Microbial Technology, Chandigarh. Clotrimazole was used as a standard drug whose minimum zone of inhibition values are presented in Table 3.

The investigation of antifungal screening data revealed that all the tested compounds **4a–4h**, **5a–5c**, and **6a–6d** showed moderate to good antifungal activities against the tested fungal strains. The compounds **4b**, **4f**, and **4g** with the phenyl group displayed good antifungal activity. Compound **4f** was the most active compound with a zone of inhibition value in the range of

11–12 mm at the concentration of 100 μg/mL. Modest activity is shown by compounds **4c** and **4h** with methyl ester at C-2 position. The effect of cyano group at C-8 position (**5a**–**5c**) did not increase the antifungal activity but these are showing moderate activity. Compounds **6a** and **6b** are exhibiting substantial activity against *A. niger* and *C. tropicum*, moderately active against *R. oryzae*. Rest of the compounds (**6c** and **6d**) in this series having a cyclopentanone group are showing moderate activity against all the tested fungal strains. *C. tropicum* is inhibited by most of our newly synthesized multisubstituted quinolines. All the new compounds did not show any activity against *C. lunata* and *F. moniliforme* fungal strains.

4. Conclusions

We have disclosed a facile and simple synthetic method for multisubstituted quinolines and cyclopenta[*g*]quinoline-6-ones from the Baylis–Hillman adducts via successive S_N2'–S_NAr elimination reaction in excellent yields under mild conditions in quicker timings. For the first time, we introduced the Baylis–Hillman application reactions to the heterocyclic compounds successfully. The synthesis of multisubstituted quinolines is very efficient and simple, especially the synthesis of 8-cyano-substituted quinolines and cyclopenta[*g*]quinolines is very easy compared to other methods for their synthesis. The synthesized quinolines were evaluated for antibacterial and antifungal activity and obtained good to moderate values.

5. Experimental

5.1. General methods

The chemicals, nitroethane, ethyl cyanoacetate, triethyl amine, acetic anhydride, DMAP, and all the solvents were obtained commercially. All the melting points were determined on a Mel-Temp apparatus and are uncorrected. IR were recorded with a Perkin-Elmer Model 1600 series FTIR spectrometer. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Gemini 200 MHz and 300 MHz. EIMS was detected on VG Micromass 7070 H (70 eV).

5.1.1. Typical experimental procedure for acetylation of the Baylis–Hillman adducts. To a solution of the Baylis–Hillman adduct (allylic alcohol derivative) (1 mmol) in dry dichloromethane (CH_2Cl_2; 30 mL) was added triethyl amine (Et_3N) (1.2 mmol) followed by catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP). This solution was stirred at 0 °C and was added a solution of acetic anhydride (Ac_2O) (1 mmol in 5 mL of CH_2Cl_2) dropwise and stirred at 0–5 °C for about 20–25 min. After completion of the reaction (as evidenced by TLC), the solvent and triethyl amine were removed under reduced pressure to afford the residue. Purification of the residue by column chromatography on silica gel and 20% ethyl acetate in hexane as eluent solvent furnished 80–98% of acetyl derivative.

5.1.2. Typical experimental procedure for the preparation of substituted quinolines from the Baylis–Hillman acetates. To a stirred solution of pre-heated potassium carbonate (3 mmol) in *N*,*N*-dimethylformamide (3 mL) was added nitroethane (3 mmol) at room temperature and stirred for about 10 min. A solution of Baylis–Hillman acetate (1 mmol) in 2 mL of *N*,*N*-dimethylformamide was stirred at room temperature for about 10–15 min to obtain (*E*)-trisubstituted alkene (pyridinyl-4-cyano (or) nitro alkanoates). Further stirring of the reaction mixture was done for about ~3–4 h at 50–70 °C to obtain methyl-substituted quinoline and for about ~10–12 h at 110–120 °C to obtain cyano-substituted quinoline. After completion of the reaction (as judged by TLC), the reaction mixture was poured into dilute hydrochloric acid solution and extracted with chloroform thrice. The combined organic layer was washed with brine solution thrice and concentrated to afford a residue. The residue was purified by column chromatography using 10% ethyl acetate in hexane as the eluent solvent to isolate 50–60% of cyano-substituted quinoline and 75–92% of methyl-substituted quinoline.

5.1.3. Typical experimental procedure for the preparation of methyl (*E*)-3-(2-chloro-5-methyl-3-pyridyl)-2-(2-nitropropyl)-2-propenoate (7a). A solution of Baylis–Hillman acetate (1 mmol) in 2 mL DMF was added to the pre-stirred solution of potassium carbonate (1.5 mmol) and nitroethane (3 mmol) in DMF solution and stirred at room temperature for about 15 min. After completion of the reaction (as evidenced by TLC), the reaction mixture was poured into dilute hydrochloric acid solution and extracted with ethyl acetate twice. The organic layer was washed with brine solution and concentrated to afford a residue. The residue was purified by column chromatography using 5% ethyl acetate in hexane as eluent solvent. The trisubstituted alkene (**7a**) was obtained as ~100% of *E*-isomer.

5.2. Characterization data

5.2.1. Methyl 2-[(2-chloro-5-methylpyridine-3-yl)(hydroxy)-methyl]acrylate (2a). Yield: 99.5%; white solid; mp: 98 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 8.11 (s, 1H), 7.71 (s, 1H), 6.32 (s, 1H), 5.8 (s, 1H), 5.56 (s, 1H), 3.8 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.1, 148.2, 146.5, 140.2, 137.8, 134.8, 132.4, 126.7, 67.9, 51.7, 17.3; MS (EI), *m*/*z*: 241 [M^+], 206, 156, 120, 92, 65; IR (KBr): 3350, 2953, 1727, 1433, 1053, 972, 753 cm^{-1}; Anal. Calcd for $C_{11}H_{12}ClNO_3$: C, 54.68; H, 4.99; N, 5.80. Found: C, 54.86; H, 5.10; N, 5.98.

5.2.2. Methyl 2-{[2-chloro-5-(4-methoxyphenyl)-pyridine-3-yl](hydroxy)methyl}acrylate (2b). Yield: 98%; light yellow solid; mp: 102 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.1 (s, 1H), 7.5 (m, 2H), 6.98 (m, 2H), 6.38 (s, 1H), 5.9 (s, 1H), 5.65 (s, 1H), 3.85 (s, 3H), 3.8 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.6, 160.0, 147.6, 146.2, 139.9, 135.7, 135.2, 135.0, 128.1, 127.5, 114.8, 114.6, 69.0, 60.3, 55.3, 52.1, 24.6; MS (EI), *m*/*z*: 333 [M^+] (33), 298(33), 274(15), 248(22), 212(18),

99(33), 43(100); IR (KBr): 3295, 2927, 2835, 1727, 1664, 1434, 1258, 1152, 766; Anal. Calcd for $C_{17}H_{16}ClNO_4$: C, 61.18; H, 4.83; N, 4.20. Found: C, 61.45; H, 4.99; N, 4.67.

5.2.3. Methyl 6-chloro-5[1-hydroxy-2-(methoxycarbonyl)prop-2-en-1-yl]pyridine-2-carboxylate (2c). Yield: 99%; viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.12 (m, 2H), 6.32 (s, 1H), 5.82 (s, 1H), 5.52 (s, 1H), 3.98 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.4, 164.3, 149.6, 147.0, 139.4, 138.3, 127.8, 124.0, 69.1, 53.0, 52.2; MS (EI), *m/z*: 285 [M^+] (2), 249(100), 217(70), 197(50), 164(20), 140(22), 115(18), 83(45), 59(60); IR (KBr): 3272, 2999, 1721, 14333, 1265, 1155, 1045, 764 cm^{-1}; Anal. Calcd for $C_{12}H_{12}ClNO_5$: C, 50.45; H, 4.23; N, 4.41. Found: C, 50.89; H, 4.44; N, 4.67.

5.2.4. Ethyl 6-chloro-5-(1-hydroxy-2-(methoxycarbonyl)allyl)-2-phenyl-nicotinate (2d). Yield: 98%; white solid; mp: 85 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.8 (s, 1H), 7.62 (m, 2H), 7.4 (m, 3H), 6.41 (s, 1H), 5.98 (s, 1H), 5.78 (s, 1H), 4.2 (q, 2H), 3.68 (s, 3H), 1.25 (t, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.3, 165.6, 156.4, 149.4, 140.6, 139.6, 137.9, 133.1, 129.3, 129.0, 128.4, 128.3, 127.6, 67.9, 62.2, 52.1, 29.6, 13.5; MS (EI), *m/z*: 375 [M^+] (15), 346(30), 330(33), 308(100), 262(23), 216(18); Anal. Calcd for $C_{19}H_{18}ClNO_5$: C, 60.73; H, 4.83; N, 3.72. Found: C, 60.89; H, 4.99; N, 3.87.

5.2.5. Ethyl 2-[(2-chloro-5-methylpyridine-3-yl)(hydroxy)-methyl]acrylate (2e). Yield: 99.5%; white solid; mp: 78 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.66 (s, 1H), 6.28 (s, 1H), 5.76 (s, 1H), 5.55 (s, 1H), 4.16 (q, J = 6.69 Hz, 2H), 2.30 (s, 3H), 1.25 (t, J = 6.69 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.3, 148.8, 146.9, 140.1, 138.0, 134.5, 132.7, 127.4, 69.1, 61.2, 17.7, 14.1; MS EI, (*m/z*): 255 [M^+] (10), 220(100), 192(60), 154(85), 146(45), 120(40), 92(10), 65(65); IR (KBr): 3429, 2926, 1721, 1627, 1465, 1168, 771 cm^{-1}; Anal. Calcd for $C_{12}H_{14}ClNO_3$: C, 56.35; H, 5.55; N, 5.48. Found: C, 56.66; H, 5.74; N, 5.62.

5.2.6. Ethyl 2-[(2-chloro-5-phenylpyridine-3-yl)(hydroxy) methyl]acrylate (2f). Yield: 99.5%; viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.5 (d, 1H), 8.12 (s, 1H), 7.35–7.6 (m, 5H), 6.34 (s, 1H), 5.88 (s, 1H), 5.62 (s, 1H), 4.3 (q, J = 7.06 Hz, 2H), 3.88 (br, 1H), 1.3 (t, J = 7.06 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.6, 148.9, 147.1, 140.6, 136.7, 136.5, 136.2, 135.6, 129.5, 128.9, 127.6, 127.5, 69.6, 61.7, 14.4; MS (EI), *m/z*: 317 [M^+] (12), 302(15), 282(70), 268(100), 254(50), 216(65), 182(12), 153(23), 127(40), 115(33); Anal. Calcd for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.07; N, 4.40. Found: C, 64.53; H, 5.25; N, 4.62.

5.2.7. Ethyl 2-[(2-chloro-5-methyl-6-phenylpyridine-3-yl)(hydroxy) methyl]acrylate (2g). Yield: 99%; white solid; mp: 104–106 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.35–7.55 (m, 5H), 6.38 (s, 1H), 5.82 (s, 1H), 5.62 (s, 1H), 4.25 (q, J = 7.43 Hz, 2H), 2.4 (s, 3H), 1.33 (t, J = 7.43 Hz, 3H); MS (EI), *m/z*: 331 [M^+], 302, 231, 165, 77; IR (KBr): 3274, 2981, 1710, 1575, 1436, 1396, 1299, 1077, 634 cm^{-1}; Anal. Calcd for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; Cl, 10.69; N, 4.22; O, 14.46. Found: C, 65.45; H, 4.56; N, 4.44.

5.2.8. Methyl 3,8-dimethyl-6-quinolinecarboxylate (4a)[31]. Light yellow solid; yield: 82%; mp: 88 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.30 (s, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 3.98 (s, 3H), 2.81 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.9, 153.3, 147.5, 137.4, 136.1, 131.0, 128.4, 127.8, 127.6, 127.2, 52.2, 18.55, 18.0; MS (EI), *m/z*: 215 [M^+] (100), 184(68), 156(54), 141(10), 128(10); IR (KBr): 2922, 1715, 1619, 1446, 1270, 1226, 1106, 768 cm^{-1}; Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.63; H, 6. 36; N, 6.27.

5.2.9. Methyl 3-(4-methoxyphenyl)-8-methyl-6-quinolinecarboxylate (4b). Light yellow solid; yield: 78%; mp: 102 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.40 (s, 1H), 8.24 (s, 1H), 8.07 (s, 1H), 7.6 (m, 2H), 7.0 (m, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.7, 160.1, 150.3, 147.2, 137.1, 134.3, 134.0, 129.3, 129.0, 128.9, 128.4, 128.3, 128,2, 114.9, 55.4, 52.3, 18.0; MS (EI), *m/z*: 307 [M^+] (100), 292(15), 276(18), 248(10), 205(10); IR (KBr): 2958, 1720, 1445, 1252, 1029, 783 cm^{-1}; Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.57; N, 4.56. Found: C, 74.53; H, 5.68; N, 4.78.

5.2.10. Dimethyl-8-methyl-2,6-quinolinedicarboxylate (4c). Yellow solid; yield: 88%; mp: 112 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.35 (d, 1H), 8.18 (d, 1H), 8.17 (s, 1H), 4.08 (s, 3H), 3.98 (s, 3H), 2.91 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.5, 165.8, 148.8, 148.5, 139.4, 138.7, 131.6, 129.4, 128.4, 127.5, 121.3, 53.0, 52.4, 17.8; MS (EI), *m/z*: 259 [M+] (58), 227(22), 199(100), 168(25), 140(35), 113(10); IR (KBr): 2958, 1720, 1441, 1341, 1228, 1141, 1099, 775 cm^{-1}; Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.12; H, 5.32; N, 5.55.

5.2.11. 3-Ethyl-6-methyl-2-phenyl-8-methyl-3,6-quinolinedicarboxylate (4d). Light yellow solid; yield: 78%; mp: 79 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.12 (s, 1H), 8.6 (s, 1H), 8.12 (s, 1H), 7.4 (m, 5H), 4.1 (q, J = 6.79 Hz, 2H), 4.0 (s, 3H), 2.68 (s, 3H), 1.02 (t, J = 6.79 Hz, 3H); MS (EI), *m/z*: 349 [M^+] (70), 320(100), 304(65), 277(33), 216(25), 189(8); IR (KBr): 2928, 1706, 1552, 1295, 1132, 904, 770 cm^{-1}; Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.44; H, 5.72; N, 4.23.

5.2.12. Ethyl 3,8-dimethyl-6-quinolinecarboxylate (4e). White solid; yield: 84%; mp: 83 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.30 (s, 1H), 8.06 (s, 1H), 7.94 (s, 1H), 4.44 (q, J = 6.79 Hz, 2H), 2.82 (s, 3H), 2.55 (s, 3H), 1.46 (t, J = 6.79 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.2, 153.0, 147.1, 137.0, 136.0, 130.8, 128.1, 127.8, 127.7, 127.0, 61.0, 18.4, 17.9, 14.2.; MS (EI), *m/z*: 229 [M+] (100), 201 (65), 184 (63), 156 (60), 141 (10), 128 (10); IR (KBr): 2922, 1715, 1619, 1446,

1270, 1226, 1106, 768 cm^{-1}; Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.51; H, 6.35; N, 6.66.

5.2.13. Ethyl 3-phenyl-8-methyl-6-quinolinecarboxylate (4f). Light yellow solid; yield: 88%; mp: 98 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 9.22 (s, 1H), 8.43 (s, 1H), 8.35 (s, 1H), 8.01 (s, 1H), 7.35–7.67 (m, 5H), 4.38 (q, J = 6.65 Hz, 2H), 2.82 (s, 3H), 1.36 (t, J = 6.65 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.2, 150.6, 148.0, 137.4, 137.3, 134.5, 134.1, 129.2, 129.0, 128.7, 128.4, 128.2, 127.3, 127.1, 61.2, 17.9, 14.3; MS (EI) *m/z*: 291 [M+] (100), 276(10), 263(48), 256(33), 218(40), 189(10); IR (KBr): 3061, 2986, 1712, 1379, 1256, 1193, 1106, 1026, 768 cm^{-1}; Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.54; H, 6.14; N, 5.05.

5.2.14. Ethyl 2-phenyl-3,8-dimethyl-6-quinolinecarboxylate (4g). White solid; yield: 84%; mp: 98 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.06 (s, 1H), 8.06 (s, 1H), 7.67 (m, 2H), 7.48 (m, 3H), 4.45 (q, J = 6.41 Hz, 2H), 2.82 (s, 3H), 2.55 (s, 3H), 1.48 (t, J = 6.41 Hz, 3H); MS (EI), *m/z*: 305 [M^+] (100), 276(70), 260(15), 231(25), 217(20), 129(10); IR (KBr): 3061, 2986, 1712, 1379, 1256, 1198, 1105, 1026, 764 cm^{-1}; Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.86; H, 6.27; N, 4.59. Found: C, 78.99; H, 6.66; N, 4.64.

5.2.15. 6-Ethyl-2-methyl-8-methyl-2,6-quinolinedicarboxylate (4h). White solid; yield: 85%; mp: 112 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.3 (d, 1H), 8.18 (d, 1H), 8.17 (s, 1H), 4.4 (q, J = 7.55 Hz, 2H), 4.0 (s, 3H), 2.85 (s, 3H), 1.41 (t, J = 7.55 Hz. 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.4, 166.3, 149.1, 148.9, 139.7, 139.0, 130.2, 129.8, 128.8, 128.6, 121.7, 61.8, 53.4, 18.2, 14.7; MS (EI), *m/z*: 273 [M^+] (85), 241(33), 228(30), 213(100), 185(25), 165(25), 140(30); IR (KBr): 2962, 1726, 1440, 1339, 1267, 1228, 1196, 768 cm^{-1}; Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 66.19; H, 5.64; N, 5.46.

5.2.16. Methyl 3-methyl-8-cyano-6-quinolinecarboxylate (5a). Light yellow solid; yield: 64%; mp: 126 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.66 (s, 1H), 8.60 (s, 1H), 8.06 (s, 1H), 4.01 (s, 3H), 2.62 (s, 3H); MS (EI), *m/z*: 226 [M^+] (100), 211(48), 183(65), 137(10), 128(10); IR (KBr): 2922, 1715, 2226, 1619, 1446, 1270, 1226, 1106, 768 cm^{-1}; Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.18; H, 4.84; N, 12.57.

5.2.17. Ethyl 3-phenyl-8-cyano-6-quinolinecarboxylate (5b). Light yellow solid; yield: 48%; mp: 134 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 9.39 (s, 1H), 8.81 (s, 1H), 8.66 (s, 1H), 8.43 (s, 1H), 7.68–7.74 (m, 5H), 4.47 (q, 2H), 1.48 (t, 3H); MS (EI), *m/z*: 302 [M^+] (100), 273(64), 145(54), 141(10), 128(10); IR (KBr): 3015, 2965, 2246, 1709, 1656, 1496, 1270, 1226, 1078, 770 cm^{-1}; Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: 75.76; H, 4.94; N, 9.58.

5.2.18. Ethyl 2-phenyl-3-methyl-8-cyano-6-quinolinecarboxylate (5c). Light yellow solid; yield: 44%; mp: 121 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 9.6 (s, 1H), 8.8 (s, 1H), 8.13 (s, 1H), 7.68–7.74 (m, 2H), 7.4–7.5 (m, 3H), 4.51 (q, J = 7.2 Hz, 2H), 2.6 (s, 3H), 1.5 (t, J = 7.2 Hz, 3H); MS (EI), *m/z*: 316 [M^+] (100), 273(64), 145(54), 141(10), 128(10); IR (KBr): 3015, 2965, 2246, 1709, 1656, 1496, 1270, 1226, 1078, 770 cm^{-1}; Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.87; H, 4.96; N, 9.14.

5.2.19. 3,9-Dimethyl-7,8-dihydro-6*H*-cyclopenta[*g*]quinolin-6-one (6a)[32]. Yellow solid; yield: 74%; mp: 123 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.02 (s, 1H), 8.01 (s, 1H), 3.28 (t, J = 6.79 Hz, 2H), 2.80(t, J = 6.79 Hz, 2H), 2.78 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.6, 154.0, 153.7, 137.5, 134.5, 133.7, 133.3, 130.5, 127.2, 121.0, 36.7, 24.8, 18.5, 13.0; MS (EI) *m/z*: 211 [M^+] (100), 182(95), 168(12); IR (KBr): 2924, 1710, 1616, 1549, 1389, 1067 cm^{-1}; Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.2; N, 6.63. Found: C, 79.89; H, 6.37; N, 6.78.

5.2.20. 3-Phenyl-9-methyl-7,8-dihydro-6*H*-cyclopenta[*g*]quinolin-6-one (6b)[32]. Light yellow solid; yield: 80%; mp: 132 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.38 (s, 1H), 8.18 (s, 1H), 7.67–7.42 (m, 5H), 3.24 (t, J = 6.74 Hz, 2H), 2.8 (t, J = 6.72 Hz, 2H), 2.78 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.0, 150.8, 149.5, 148.1, 136.9, 135.4, 134.6, 133.7, 133.3, 129.2, 129.1, 129.0, 128.2, 127.1, 126.8, 121.2, 36.6, 24.8, 12.9.; MS (EI) *m/z*: 273 [M^+] (100), 245(78), 231(18), 164(15), 77(12); IR (KBr): 2919, 1708, 1611, 1481, 1261, 799 cm^{-1}; Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.64; H, 5.78; N, 5.36.

5.2.21. 2-Phenyl-3-methyl-9-methyl-7,8-dihydro-6*H*-cyclopenta[*g*]quinolin-6-one (6c)[32]. White solid; yield: 85%; mp: 124 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 8.09 (s, 1H), 8.07 (s, 1H), 7.45–7.70 (m, 5H), 3.26 (t, J = 6.76 Hz, 2H), 2.8 (t, J = 6.72 Hz, 2H), 2.78 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.6, 161.2, 149.1, 147.8, 140.5, 139.6, 134.3, 134.0, 129.4, 129.3, 129.2, 128.6, 128.1, 128.0, 126.4, 120.5, 36.8, 24.9, 20.6, 13.0.; MS (EI) *m/z*: 287 [M^+] (100), 245(78), 231(18), 164(15), 77(12); IR (KBr): 2923, 2362, 1718, 1616, 1478, 1057 cm^{-1}; Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.63; H, 5.78; N, 5.21.

5.2.22. Methyl 9-methyl-6-oxo-7,8-dihydro-6*H*-cyclopenta[*g*]quinoline-2-carboxylate (6d)[32]. Yellow solid; yield: 86%; mp: 112 °C; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.4 (d, 1H), 8.18 (s, 1H), 8.16 (d, 1H), 4.08 (s, 1H), 3.32 (t, J = 6.72 Hz, 2H), 2.9 (s, 3H), 2.84 (t, J = 6.72 Hz, 2H). MS (EI) *m/z*: 255 [M^+] (70), 223(26), 196(100), 168(30), 139(25); Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.72; H, 5.59; N, 5.64.

5.2.23. Methyl (*E*)-3-(2-Chloro-5-methyl-3-pyridyl)-2-(2-nitropropyl)-2-propenoate (7a). White solid; yield: 96%; mp: 154–158 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 8.2 (s, 1H), 7.72 (s, 1H), 7.3 (s, 1H), 4.93 (m, 1H), 3.86 (s,

3H), 2.91 (dd, 1H), 2.75 (dd, $J = 8.21$ Hz, 1H), 2.34 (s, 3H), 1.46 (d, $J = 7.21$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.5, 148.8, 147.0, 139.0, 138.6, 132.4, 130.4, 129.2, 81.4, 52.6, 33.4, 18.9, 17.7; MS (EI), *m/z*: 298 [M^+]; IR (KBr): 3021, 2959, 2362, 1709, 1549, 1438, 1416, 1265, 1215, 1133, 1070, 763 cm^{-1}; Anal. Calcd for $C_{13}H_{15}ClN_2O_4$: C, 52.27; H, 5.06; N, 9.38. Found: C, 52.46; H, 5.22; N, 9.48.

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35. In ^{1}H NMR spectrum of the crude 3-aryl-(2-substituted)-prop-2-enoates, the β-vinylic proton cis to the ester group [(*E*)-isomer] appears at abnormal downfield $\delta = 7.5–7.9$ ppm, while the β-vinylic proton trans to the ester group [(*Z*)-isomer] appears at $\delta = 6.7–6.9$ ppm.[37] In ^{13}C NMR spectra of the same trisubstituted olefins, allylic carbon *cis* to aryl group appears upfield, while the same carbon *trans* to aryl group appears downfield.[38].
36. In ^{1}H NMR spectrum of the crude methyl 3-(2-chloro-5-methyl-3-pyridyl)-2-(2-nitropropyl)-2-propenoate, **7a**, the abnormal downfield shift of the vinylic proton at around $\delta = 7.79$ with high intensity indicates the (*E*)-isomer, in addition no peak at around $\delta = 6.7–6.9$ appeared even with very low intensity which indicates the no (*Z*)-isomer. In ^{13}C NMR spectra of the same crude trisubstituted alkene **7a**, a peak at around $\delta = 33.3$ with high intensity indicates the (*E*)-isomer, in addition no peak at around $\delta = 35–40$ which indicates the no (*Z*)-isomer.
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41. The ready-made Potato Dextrose Agar (PDA) medium (Himedia, 39 g) was suspended in distilled water (1000 mL) and heated to boiling until it dissolved completely, the medium and Petri dishes were autoclaved at pressure of 15 lb/inc^2 for 20 min. Agar cup bioassay was employed for testing antifungal activity. The medium was poured into sterile Petri dishes under aseptic conditions in a laminar flow chamber. When the medium in the plates solidified, 0.5 mL of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in DMSO and different concentrations were made (30 and 100 μg/mL). After inoculation, cups were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. To each cup different concentrations of test solutions (30,100 μg/mL) were added. Controls were maintained with acetone and Clotrimazole (100 μg/mL). The treated and the controls were kept at room temperature for 48 h. Inhibition zones were measured and the diameter was calculated in millimeter. Three to four replicates were maintained for each treatment. Media. Potato Dextrose broth and Potato Dextrose agar were procured from M/S Himedia Laboratories, Mumbai.