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Construction of heterocycles via 1,4-dipolar cycloaddition of quinoline–DMAD zwitterion with various dipolarophiles

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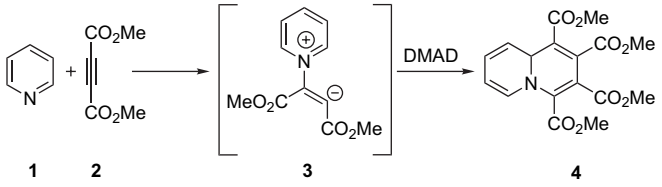
Abstract

Quinoline forms 1,4-zwitterion with dimethyl acetylenedicarboxylate, which is trapped by various dipolarophiles to yield a variety of pyridoquinoline and oxazinoquinoline derivatives.

1. Introduction

1,4-Dipolar cycloaddition provides an efficient and convenient route for the synthesis of six-membered heterocyclic compounds. However, these reactions have received only scant attention when compared to the related 1,3-dipolar cycloaddition reactions. The advent of 1,4-dipolar cycloaddition reactions dates back to 1932, when Diels and Alder showed that pyridine reacts smoothly with dimethyl acetylenedicarboxylate (DMAD) to form an adduct of unknown structure.[1] Three decades later, Acheson et al. established the structure of the adduct as the 4*H*-quinolizine **4** (Scheme 1).[2] It was Huisgen who recognized this reaction as the 1,4-dipolar variant of the classical Diels–Alder reaction involving the intermediate **3**.[3] Reports of the intermolecular trapping of the 1,4-dipole **3** by Winterfeldt,[4] Acheson and Plunkett,[5] and Huisgen et al.[6] are noteworthy.

Extensive work has been done by our group on the reactivities of 1,4-dipoles derived from DMAD and nucleophiles such as phosphines,[7] isocyanides,[8] dimethoxycarbene,[9] nitrogen heterocycles,[10] and nucleophilic heterocyclic carbenes (NHC).[11] These studies have led to a number of interesting carbon–carbon bond forming reactions and heterocyclic constructions.[12] Recent investigations in our laboratory have shown that the zwitterionic intermediate generated by the reaction of quinoline and DMAD undergoes facile addition to aldehydes and diaryl 1,2-diones to afford oxazinoquinoline derivatives in good yields (Scheme 2).[13]



Scheme 1.

In view of the success of this reaction, and in the context of our general interest in the chemistry of zwitterions in general and quinoline–DMAD zwitterion in particular, we have carried out a systematic study of the reaction of the quinoline–DMAD zwitterion with various dipolarophiles. The results of these studies are presented here.

2. Results and discussion

2.1. Reaction with activated olefins

Our detailed studies commenced with the reaction of quinoline and DMAD with the aryl cyanoacrylate **11a**. A mixture of

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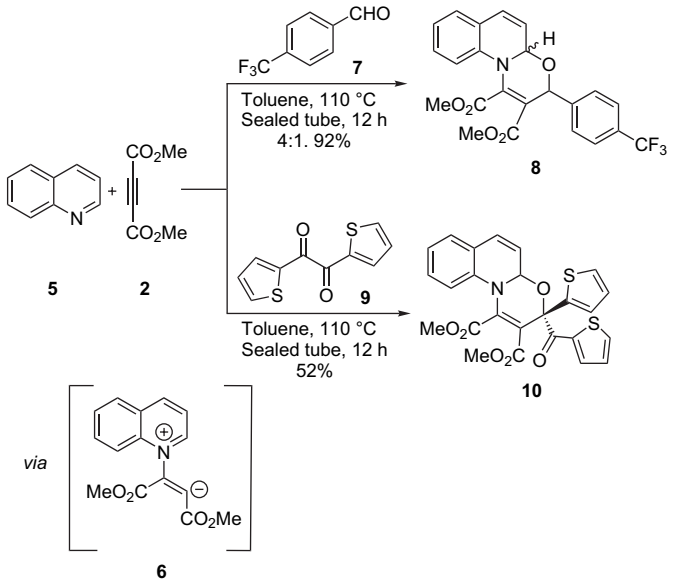
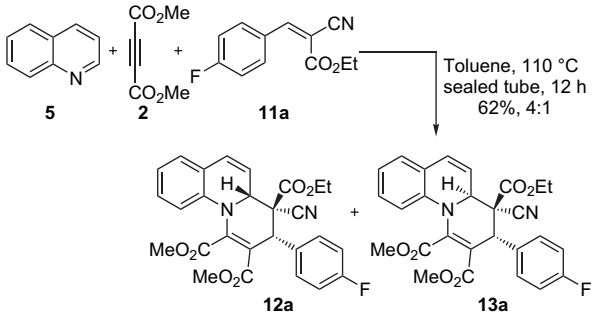


Scheme 2.

the three in dry toluene, when heated under reflux in a sealed tube for 12 h, afforded the pyridoquinoline derivatives **12a** and **13a** in 62% total yield in the ratio 4:1 (Scheme 3).



Scheme 3.

The product **12a** was obtained in the pure form by fractional crystallization and was characterized on the basis of spectroscopic data. In the IR spectrum, the ester carbonyls showed strong absorptions at 1740 and 1744 cm^{-1} and the cyano group displayed its characteristic signal at 2229 cm^{-1}. In the ^1H NMR spectrum, the methoxy carbonyl protons were visible at δ 3.54 and 3.81 as sharp singlets. The ring junction proton signal was observed as a doublet at δ 4.52 (J=4.2 Hz) and the benzylic proton displayed a singlet at δ 4.59. The signals due to the olefinic protons of the dihydroquinoline moiety were visible as a doublet of doublet at δ 6.05 (J_1=4.2 Hz, J_2=9.6 Hz) and as a multiplet in the region δ 6.65–6.71. The ^{13}C NMR spectrum was also in good agreement with the assigned structure. The peaks at δ 163.9, 164.2, and 165.3 were typical of the ester carbonyls. The nitrile carbon was found to resonate at δ 111.2. X-ray crystallographic analysis[15] revealed the relative configuration of the isomer **12a** as depicted in Figure 1.

Similar reactivity was observed with other aryl cyanoacrylates **11b–h**, which underwent facile reaction with quinoline

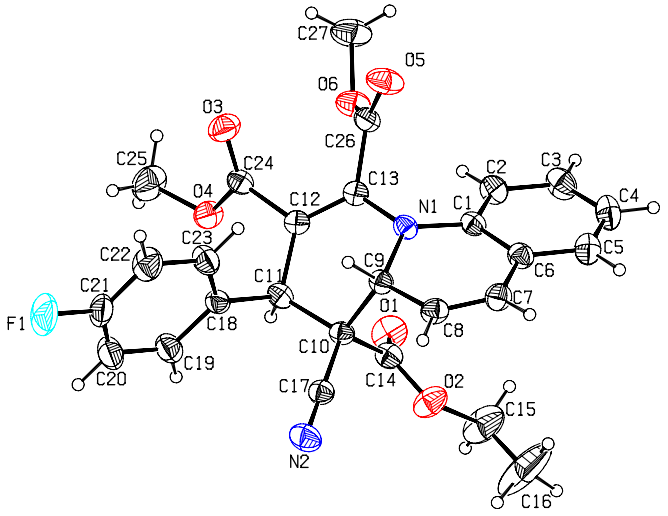
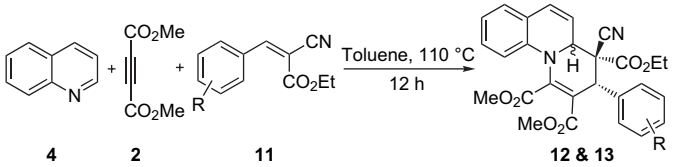


Figure 1. ORTEP diagram of **12a**.

and DMAD yielding the pyridoquinoline derivatives in good yields (Table 1). The diastereomeric ratios of the products were determined on the basis of ^1H NMR spectroscopy of the mixtures.

Table 1
Reaction of quinoline and DMAD with aryl cyanoacrylates

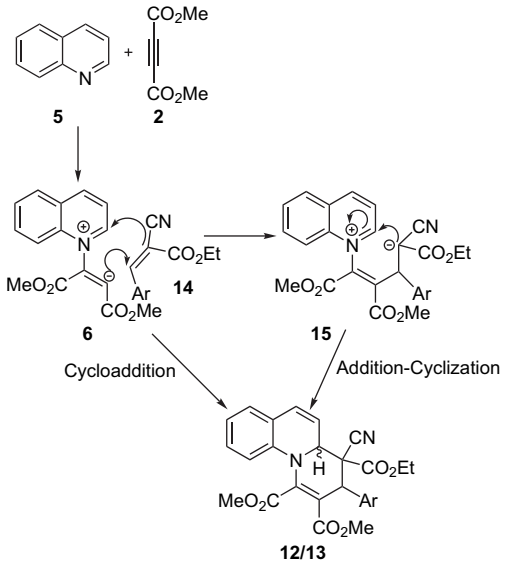


Entry	R	Products	Ratio	Yield (%)
1	**11b**, 4-chloro	**12b/13b**	4:1	56
2	**11c**, 4-trifluoromethyl	**12c/13c**	3.6:1	58
3	**11d**, 4-nitro	**12d/13d**	4:1	54
4	**11e**, 4-bromo	**12e/13e**	4:1	56
5	**11f**, naphthyl	**12f/13f**	4:1	65
6	**11g**, H	**12g/13g**	4:1	49
7	**11h**, 4-methoxy	**12h/13h**	4:1	44

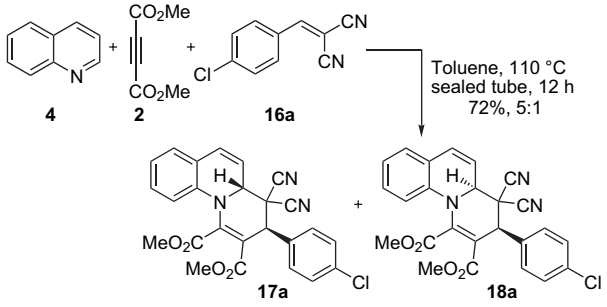
In the absence of any theoretical studies, the mechanistic details of the reaction are not fully understood. The initial event is the formation of the 1,4-dipole **6** from quinoline and DMAD. The trapping of **6** with the electrophilic carbon–carbon double bond of the aryl cyanoacrylate affords pyridoquinolines. Alternatively, the reaction may take place in two steps. The zwitterion may add to the cyanoacrylate to form the intermediate **15**, which then undergoes cyclization to give the products (Scheme 4).

In the light of these results, attention was directed toward arylidenemalononitriles. In the first instance, the reaction of quinoline and DMAD with **16a** in toluene at 110 °C in a sealed tube for 12 h afforded the corresponding pyridoquinoline derivatives **17a** and **18a** in 72% total yield in the ratio 5:1 (Scheme 5).

The major isomer was isolated by repeated chromatography and characterized by spectroscopic techniques. A strong



Scheme 4.



Scheme 5.

absorption at 1744 cm^{-1} in the IR spectrum of **17a** indicated the presence of ester carbonyl groups, whereas the absorption at 2235 cm^{-1} corresponded to the cyano groups. In the ^1H NMR spectrum, the methoxy carbonyl protons were visible as singlets at δ 3.52 and 3.84. The benzylic proton displayed a singlet at δ 4.62 and the ring junction proton resonated as a doublet at δ 5.93 (J=4.5 Hz). The signals due to the protons of the dihydroquinoline moiety were visible as a doublet of doublet at δ 6.00 (J_1=4.2 Hz, J_2=9.0 Hz) and as a multiplet in the region δ 6.63–6.69. The ^{13}C NMR spectrum displayed the characteristic signals of the ester carbonyls at δ 164.1 and 164.5 and that of the nitrile carbon at δ 110.2. The resonance signals at δ 51.2 and 52.1 were attributed to the carbomethoxy carbons.

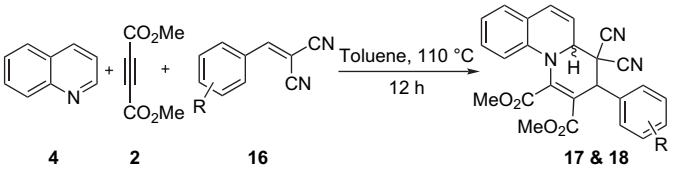
The reaction was found to be general with various arylidenemalononitriles affording diastereomeric mixtures of the corresponding pyridoquinolines in good yields (Table 2). The diastereomeric ratios of the products were determined on the basis of ^1H NMR spectroscopy of the mixtures.

2.2. Reaction with cyclic 1,2-diones

2.2.1. Reaction with isatins

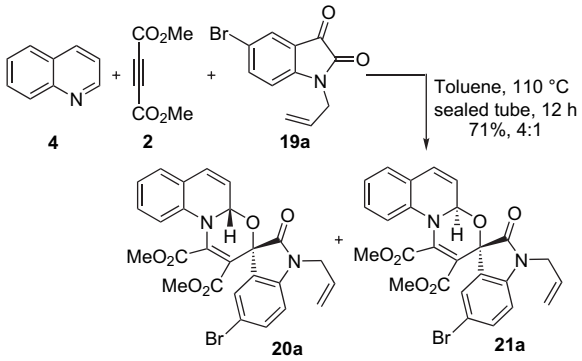
Subsequently we have investigated the reaction of the zwitterionic intermediate with isatins. In an illustrative example,

Table 2
Reaction of quinoline and DMAD with arylidene malononitriles



Entry	R	Products	Ratio	Yield (%)
1	**16b**, 4-fluoro	**17b/18b**	5:1	70
2	**16c**, 4-trifluoromethyl	**17c/18c**	4:1	71
3	**14d**, 4-bromo	**17d/18d**	5:1	78
4	**16e**, 4-nitro	**17e/18e**	6:1	68
5	**16f**, 4-methyl	**17f/18f**	2:1	55

treatment of *N*-allyl, 5-bromoisatin **19a** with quinoline and DMAD in dry toluene in a sealed tube at 110 °C for 12 h resulted in the formation of oxazinoquinoline derivatives **20a** and **21a** in 71% yield as a diastereomeric mixture, in the ratio 4:1 (Scheme 6).



Scheme 6.

The diastereomers were separated by column chromatography and the major isomer **20a** was obtained pure by fractional crystallization. The structure of the product **20a** was assigned on the basis of spectroscopic analysis. In the IR spectrum, the ester carbonyl absorptions were seen at 1732 and 1726 cm^{-1} and that of the amide carbonyl at 1685 cm^{-1}. In the ^1H NMR spectrum, signals due to the methoxy carbonyl protons were observed as sharp singlets at δ 3.92 and 3.61. The ring junction proton was discernible as a doublet at δ 6.63 (J=4.2 Hz). The olefinic protons of the dihydroquinoline moiety were visible as a doublet of doublet at δ 5.60 (J_1=5.7 Hz, J_2=9.9 Hz) and as a multiplet in the region δ 6.65–6.78. The amide carbonyl displayed the ^{13}C resonance signal at δ 172.8 and the methoxycarbonyls at δ 165.2 and 163.6. The signal due to the spirocarbon was observed at δ 79.2. All other signals were also in agreement with the designated structure. Finally, the structure of **20a** was unequivocally established by single crystal X-ray analysis[15] (Fig. 2).

Evidently, the regiospecificity observed in this reaction is attributable to the higher electrophilicity of the keto group vis-a-vis the amide carbonyl. The reaction was found to be general with respect to various *N*-substituted isatins and the

oxazinoquinoline derivatives were obtained in good yields. The results are summarized in Table 3.

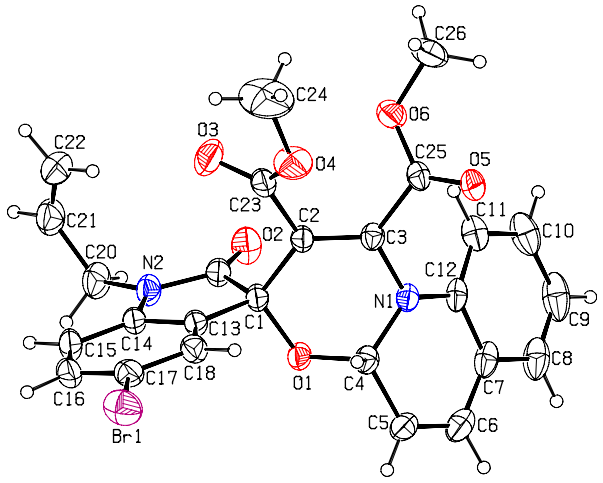
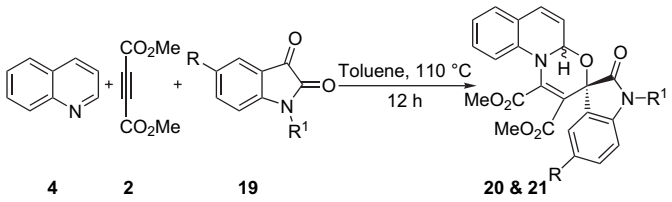


Figure 2. ORTEP diagram of **20a**.

Table 3
Reaction of quinoline and DMAD with isatins

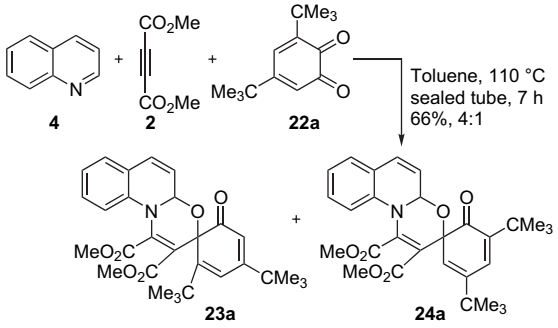


Entry	Isatin	R	R^1	Products	Ratio	Yield (%)
1	**19b**	H	Allyl	**20b/21b**	4:1	70
2	**19c**	Br	Methyl	**20c/21c**	4:1	65
3	**19d**	Br	Propargyl	**20d/21d**	4:1	63
4	**19e**	H	Propargyl	**20e/21e**	5:1	69
5	**19f**	Br	Ethyl	**20f/21f**	5:1	68

2.2.2. *Reaction with 1,2-benzoquinones*

Inspired by the results obtained in the trapping of quinoline–DMAD zwitterion with diaryl 1,2-diones and isatins, we focused our attention on another class of dicarbonyl compounds, i.e., 1,2-benzoquinones. In a pilot experiment, a solution of 3,5-di-*tert*-butyl-1,2-benzoquinone **22a**, quinoline, and DMAD in dry toluene was taken in a sealed tube and was stirred at 110 °C for 7 h. The reaction mixture when subjected to column chromatography afforded the oxazinoquinoline derivatives **23a** and **24a** in 66% yield as a regioisomeric mixture in the ratio 4:1 (Scheme 7).

The regioisomers were characterized by spectroscopic techniques. The product **23a** was characterized on the basis of spectroscopic data. In the IR spectrum, the ketone carbonyl absorption was seen at 1738 cm^{-1} and the ester carbonyl absorptions at 1748 and 1755 cm^{-1}. The peaks corresponding to the protons of the *tert*-butyl groups resonated as singlets at δ 1.16 and 1.20 in the ^{1}H NMR spectrum. Signals due to the methoxy carbonyl protons were observed as sharp singlets at δ 3.60 and 3.86. The olefinic protons of the dihydroquinoline



Scheme 7.

moiety were visible as a doublet of doublet at δ 5.91 (J_1=4.2 Hz, J_2=9.8 Hz) and as a multiplet in the region δ 6.95–6.98. The ring junction proton signal was observed as a doublet at δ 5.42 (J=4.2 Hz). The methoxycarbonyls displayed the ^{13}C resonance signals at δ 164.4 and 164.9 and the keto carbonyl at δ 196.6. The spirocarbon signal was observed at δ 78.4. The compound gave satisfactory HRMS data also.

In order to obtain additional support for the structure of **23a**, HMBC experiment was carried out (Fig. 3). The keto carbonyl at δ 196.6 correlates with the proton at δ 6.05. This means that the carbon atom, which is α to the carbonyl carbon bears a proton. The spirocarbon at δ 78.4 does not show any correlation with protons. The carbon atom in the α-position has no attached proton and so there is no correlation to it from the spirocarbon.

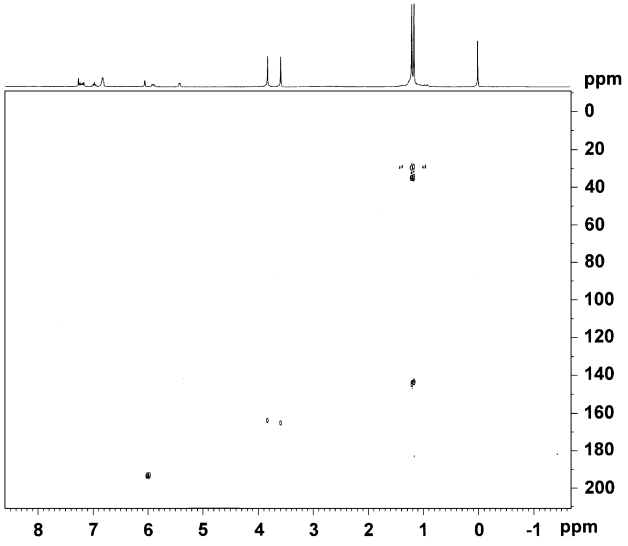
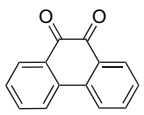
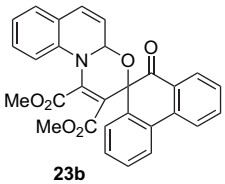
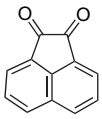
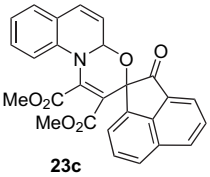
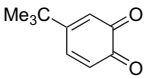
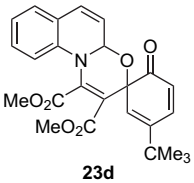
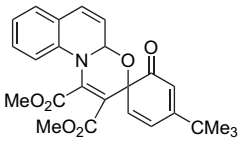
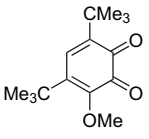
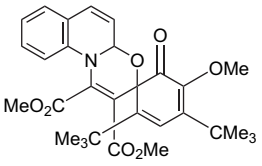
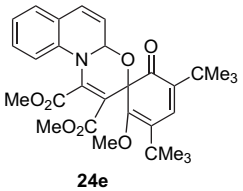
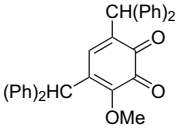
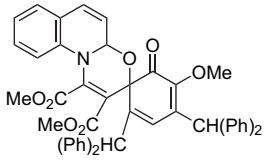
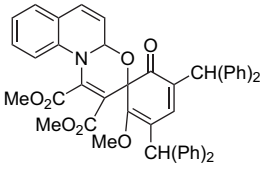


Figure 3. HMBC spectrum of compound **23a**.

In the ^{1}H NMR spectrum of **24a**, the methoxy carbonyl protons exhibited sharp signals at δ 3.63 and 3.88, supporting the absorptions at 1749 and 1757 cm^{-1}. The olefinic protons of the dihydroquinoline moiety were observed as a doublet of doublet at δ 5.93 (J_1=4.2 Hz, J_2=9.8 Hz) and as a multiplet in the region δ 6.91–6.94. The ring junction proton signal was observed as a doublet at δ 5.46 (J=4.3 Hz). The ^{13}C resonance signals for the ester and keto carbonyls were seen at δ 164.6,

Table 4
Reaction of quinoline and DMAD with 1,2-benzoquinones

Entry	Quinone	Products	Yield (%)
1	 **22b**	 **23b**	55
2	 **22c**	 **23c**	58
3	 **22d**	 **23d**  **24d**	70 (2:1)
4	 **22e**	 **23e**  **24e**	65 (2:1)
5	 **22f**	 **23f**  **24f**	60 (2:1)

165.5, and 192.6. The spirocarbon signal was discernible at δ 79.4.

The reaction was found to be applicable to other 1,2-benzoquinones as well and the results are summarized in Table 4.

A mechanistic rationalization as suggested for the reaction of activated olefins may be invoked in the case of isatins and benzoquinones also.

3. Conclusion

In conclusion, we have observed some new and efficient 1,4-dipolar cycloaddition reactions leading to the synthesis of oxazinoquinolines and pyridoquinolines. Operational simplicity and good yields are the salient features of these one pot reactions leading to the synthesis of novel functionalized heterocyclic compounds. It is worthy of mention that a wide range of biologically active molecules contain oxazino and pyridoquinoline moieties as the central core.[14]

4. Experimental

4.1. General

Melting points were recorded on a Büchi melting point apparatus. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Brüker Avance DPX-300 MHz NMR spectrometer. Chemical shifts are reported (δ) relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constants (J) are reported in hertz (Hz). High resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) resolution using JEOL JMS 600H mass spectrometer. IR spectra were recorded on Nicolet Impact 400D FT-IR spectrophotometer. Quinoline and dimethyl acetylenedicarboxylate were purchased from Aldrich Chemical Co. and were used without further purification. Commercial grade solvents were distilled prior to use. Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate as the binder. Gravity column

chromatography was performed using 100–200 mesh silica gel and mixtures of hexane–ethyl acetate were used for elution.

4.2. Experimental procedure for the synthesis of pyridoquinoline derivatives by the reaction of quinoline, DMAD, and aryl cyanoacrylates

Quinoline (0.53 mmol), DMAD (0.53 mmol), and aryl cyanoacrylate (0.44 mmol) were taken in a sealed tube in dry toluene (3 mL) and the mixture was heated at 110 °C for 12 h. After removal of the solvent under vacuum using a rotary evaporator, the residue was subjected to chromatography on a silica gel (100–200 mesh) column using hexane–ethyl acetate (85:15) solvent mixtures to afford a diastereomeric mixture of the pyridoquinolines (the ratio was determined from ^{1}H NMR).

4.2.1. 4-Ethyl 1,2-dimethyl 4-cyano-3-(4-fluorophenyl)-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2,4-tricarboxylate, ***12a***

Yellow crystalline solid (245 mg, 50%). Mp=116–118 °C (recrystallized from CH_2Cl_2–hexane). IR (KBr) ν_{max}: 3012, 2229, 1744, 1740, 1611, 1222, 1116 cm^{-1}. ^{1}H NMR: δ 7.85–7.82 (m, 2H), 7.80–7.74 (m, 2H), 6.71–6.65 (m, 3H), 6.53 (d, J=9.0 Hz, 2H), 6.05 (dd, J_1=4.2 Hz, J_2=9.6 Hz, 1H), 4.59 (s, 1H), 4.52 (d, J=4.2 Hz, 1H), 4.13 (q, J=4.8 Hz, 2H), 3.81 (s, 3H), 3.54 (s, 3H), 0.98 (t, 3H). ^{13}C NMR: δ 165.3, 164.2, 163.9, 146.9, 144.3, 140.3, 136.5, 128.7, 128.5, 122.2, 119.5, 118.6, 114.5, 111.2, 107.7, 99.2, 88.3, 66.5, 61.6, 61.5, 54.7, 54.4, 53.1, 52.2, 51.1, 45.4, 14.7. HRMS (EI) *m/z* calcd for $C_{27}H_{23}FN_2O_6$, 490.1540; found, 490.1544.

Key ^{1}H NMR values for the minor isomer, **13a**: 5.98 (dd, J_1=4.2 Hz, J_2=9.5 Hz, 0.27H), 4.57 (s, 0.24H), 4.48 (d, J=4.2 Hz, 0.25H), 3.80 (s, 0.76H), 3.53 (s, 0.75H).

4.2.2. 4-Ethyl 1,2-dimethyl 3-(4-chlorophenyl)-4-cyano-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2,4-tricarboxylate, ***12b***

Yellow solid (227 mg, 45%). Mp=114–116 °C. IR (KBr) ν_{max}: 3030, 2232, 1748, 1698, 1621, 1307, 1210, 998 cm^{-1}. ^{1}H NMR: δ 7.88–7.84 (m, 2H), 7.83–7.74 (m, 2H), 7.11–7.04 (m, 3H), 6.81 (d, J=9.0 Hz, 2H), 5.97 (dd, J_1=4.2 Hz, J_2=9.6 Hz, 1H), 5.71 (s, 1H), 5.29 (d, J=4.2 Hz, 1H), 4.13 (q, J=4.8 Hz, 2H), 3.86 (s, 3H), 3.53 (s, 3H), 1.12 (t, 3H). ^{13}C NMR: δ 166.5, 165.2, 163.4, 144.9, 144.6, 143.3, 136.1, 129.8, 128.7, 127.5, 120.9, 119.0, 117.9, 114.3, 111.6, 107.1, 96.2, 70.3, 66.8, 54.7, 54.5, 53.1, 52.3, 50.8, 14.3. HRMS (EI) *m/z* calcd for $C_{27}H_{23}ClN_2O_6$, 506.1245; found, 506.1248.

Key ^{1}H NMR values for the minor isomer, **13b**: 5.92 (dd, J_1=4.2 Hz, J_2=9.6 Hz, 0.25H), 5.70 (s, 0.24H), 5.31 (d, J=4.2 Hz, 0.24H), 3.85 (s, 0.75H), 3.52 (s, 0.75H).

4.2.3. 4-Ethyl 1,2-dimethyl 4-cyano-3-(4-(trifluoromethyl)-phenyl)-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2,4-tricarboxylate, ***12c***

Yellow solid (243 mg, 45%). Mp=132–134 °C. IR (KBr) ν_{max}: 3022, 2235, 1740, 1700, 1623, 1302, 1216, 1109 cm^{-1}. ^{1}H NMR: δ 7.35–7.22 (m, 2H), 7.19–7.15 (m, 2H), 7.00–6.94 (m, 3H), 6.77 (d, J=9.0 Hz, 2H), 5.79 (dd, J_1=4.2 Hz, J_2=9.6 Hz, 1H), 5.73 (s, 1H), 5.34 (d, J=4.2 Hz, 1H), 4.11 (q, J=4.8 Hz, 2H), 3.83 (s, 3H), 3.65 (s, 3H), 1.01 (t, 3H). ^{13}C NMR: δ 167.5, 165.9, 164.7, 144.7, 144.4, 144.3, 136.1, 129.8, 129.7, 127.4, 122.5, 119.2, 115.3, 114.2, 112.3, 111.6, 104.4, 96.2, 70.5, 61.6, 54.9, 53.4, 53.1, 51.7, 50.6, 14.8. HRMS (EI) *m/z* calcd for $C_{28}H_{23}F_3N_2O_6$, 540.1508; found, 540.1504.

Key ^{1}H NMR values for the minor isomer, **13c**: 5.77 (dd, J_1=4.2 Hz, J_2=9.6 Hz, 0.28H), 5.72 (s, 0.29H), 5.37 (d, J=4.2 Hz, 0.28H), 3.82 (s, 0.83H), 3.66 (s, 0.82H).

4.2.4. 4-Ethyl 1,2-dimethyl 4-cyano-3-(4-nitrophenyl)-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2,4-tricarboxylate, ***12d***

Yellow solid (222 mg, 43%). Mp=144–146 °C. IR (KBr) ν_{max}: 3019, 2238, 1741, 1700, 1638, 1552, 1335, 1325, 1229, 1111, 989 cm^{-1}. ^{1}H NMR: δ 8.01–7.96 (m, 2H), 7.39–7.28 (m, 2H), 7.06–6.92 (m, 3H), 6.69 (d, J=9.1 Hz, 2H), 5.75 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 5.69 (s, 1H), 5.32 (d, J=4.2 Hz, 1H), 4.13 (q, J=4.8 Hz, 2H), 3.83 (s, 3H), 3.66 (s, 3H), 1.06 (t, 3H). ^{13}C NMR: δ 166.7, 165.9, 164.4, 151.0, 144.8, 144.3, 132.3, 129.7, 128.3, 128.0, 118.2, 117.4, 115.7, 99.0, 95.5, 77.5, 77.3, 61.1, 54.3, 53.2, 53.0, 52.7, 50.9, 15.0. HRMS (EI) *m/z* calcd for $C_{27}H_{23}N_3O_8$, 517.1485; found, 517.1489.

Key ^{1}H NMR values for the minor isomer, **13d**: 5.73 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 0.24H), 5.70 (s, 0.24H), 5.33 (d, J=4.2 Hz, 0.25H), 3.84 (s, 0.75H), 3.68 (s, 0.75H).

4.2.5. 4-Ethyl 1,2-dimethyl 3-(4-bromophenyl)-4-cyano-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2,4-tricarboxylate, ***12e***

Yellow solid (247 mg, 45%). Mp=128–130 °C. IR (KBr) ν_{max}: 3012, 2235, 1744, 1710, 1644, 1309, 1233, 1111, 1088 cm^{-1}. ^{1}H NMR: δ 8.03–8.00 (m, 1H), 7.98–7.85 (m, 1H), 7.58–7.53 (m, 2H), 7.34–7.20 (m, 3H), 6.79 (d, J=9.9 Hz, 2H), 6.19 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 5.69 (s, 1H), 5.34 (d, J=4.2 Hz, 1H), 4.12 (q, J=4.8 Hz, 2H), 3.96 (s, 3H), 3.36 (s, 3H), 1.12 (t, 3H). ^{13}C NMR: δ 165.2, 164.3, 164.1, 149.0, 147.6, 141.3, 129.9, 129.7, 125.3, 123.0, 116.2, 115.7, 99.0, 95.5, 78.5, 72.3, 69.1, 69.0, 54.4, 54.2, 53.8, 52.6, 51.4, 15.0. HRMS (EI) *m/z* calcd for $C_{27}H_{23}BrN_2O_6$, 550.0739; found, 550.0734.

Key ^{1}H NMR values for the minor isomer, **13e**: 6.23 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 0.26H), 5.71 (s, 0.25H), 5.30 (d, J=4.2 Hz, 0.24H), 3.94 (s, 0.75H), 3.33 (s, 0.75H).

4.2.6. 4-Ethyl 1,2-dimethyl 4-cyano-3-(naphthalen-2-yl)-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2,4-tricarboxylate, ***12f***

Yellow solid (271 mg, 52%). Mp=136–138 °C. IR (KBr) ν_{max}: 3016, 2236, 1742, 1722, 1643, 1289, 1224, 1108, 1086 cm^{-1}. ^{1}H NMR: δ 8.18–8.16 (m, 1H), 7.87–7.80 (m, 1H), 7.58–7.50 (m, 2H), 7.46–7.41 (m, 3H), 7.02–6.90 (m, 3H), 6.76 (d, J=9.9 Hz, 2H), 6.13 (dd, J_1=4.2 Hz,

J_2=9.7 Hz, 1H), 5.66 (s, 1H), 5.18 (d, J=4.2 Hz, 1H), 4.11 (q, J=4.8 Hz, 2H), 3.98 (s, 3H), 3.37 (s, 3H), 1.11 (t, 3H). ^{13}C NMR: δ 166.8, 166.3, 165.5, 149.0, 147.6, 141.3, 129.9, 127.8, 125.3, 125.2, 125.0, 123.0, 116.2, 113.7, 109.2, 95.5, 77.5, 59.4, 54.8, 54.3, 53.4, 51.2, 45.7, 14.7. HRMS (EI) *m/z* calcd for $C_{31}H_{26}N_2O_6$, 522.1791; found, 522.1796.

Key ^{1}H NMR values for the minor isomer, **13f**: 6.20 (dd, J_1=4.2 Hz, J_2=9.7 Hz, 0.23H), 5.62 (s, 0.25H), 5.22 (d, J=4.2 Hz, 0.24H), 3.97 (s, 0.75H), 3.31 (s, 0.74H).

4.2.7. 4-Ethyl 1,2-dimethyl 4-cyano-3-phenyl-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2,4-tricarboxylate, ***12g***

Pale yellow solid (184 mg, 39%). Mp=112–114 °C. IR (KBr) ν_{max}: 2997, 2237, 1746, 1722, 1640, 1312, 1132 cm^{-1}. ^{1}H NMR: δ 7.34–7.25 (m, 2H), 7.31–7.21 (m, 2H), 7.19–7.16 (m, 1H), 7.12–7.09 (m, 1H), 7.05–6.96 (m, 2H), 6.82 (d, J=9.9 Hz, 2H), 5.97 (dd, J_1=4.2 Hz, J_2=9.0 Hz, 1H), 4.62 (s, 1H), 4.52 (d, J=4.2 Hz, 1H), 4.09 (q, J=4.8 Hz, 2H), 3.82 (s, 3H), 3.58 (s, 3H), 1.12 (t, 3H). ^{13}C NMR: δ 165.5, 165.2, 164.8, 159.0, 141.4, 136.8, 135.1, 130.7, 129.9, 129.5, 125.9, 125.4, 124.2, 118.9, 118.1, 115.9, 113.6, 112.6, 111.2, 96.2, 54.6, 53.0, 51.2, 45.6, 15.2. HRMS (EI) *m/z* calcd for $C_{27}H_{24}N_2O_6$, 472.1634; found, 472.1629.

Key ^{1}H NMR values for the minor isomer, **13g**: 6.02 (dd, J_1=4.2 Hz, J_2=9.0 Hz, 0.25H), 4.60 (s, 0.24H), 4.55 (d, J=4.2 Hz, 0.25H), 3.80 (s, 0.75H), 3.56 (s, 0.75H).

4.2.8. 4-Ethyl 1,2-dimethyl 4-cyano-3-(4-methoxyphenyl)-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2,4-tricarboxylate, ***12h***

Yellow solid (176 mg, 35%). Mp=132–134 °C. IR (KBr) ν_{max}: 3011, 2235, 1749, 1736, 1644, 1316, 1128 cm^{-1}. ^{1}H NMR: δ 7.52–7.45 (m, 2H), 7.04–6.91 (m, 3H), 6.60–6.56 (m, 2H), 6.42 (d, J=9.9 Hz, 2H), 5.97 (dd, J_1=4.2 Hz, J_2=9.0 Hz, 1H), 4.66 (s, 1H), 4.55 (d, J=4.2 Hz, 1H), 4.12 (q, J=4.8 Hz, 2H), 3.84 (s, 3H), 3.65 (s, 3H), 3.60 (s, 3H), 1.11 (t, 3H). ^{13}C NMR: δ 165.2, 164.9, 163.7, 141.4, 136.8, 135.1, 130.7, 129.9, 129.5, 128.2, 124.4, 124.2, 118.9, 117.1, 113.6, 112.6, 111.2, 96.2, 77.4, 77.0, 76.5, 56.0, 53.2, 52.4. HRMS (EI) *m/z* calcd for $C_{28}H_{26}N_2O_7$, 502.1740; found, 502.1746.

Key ^{1}H NMR values for the minor isomer, **13h**: 6.11 (dd, J_1=4.2 Hz, J_2=9.0 Hz, 0.26H), 4.59 (s, 0.25H), 4.50 (d, J=4.2 Hz, 0.23H), 3.81 (s, 0.75H), 3.62 (s, 0.76H).

4.3. Experimental procedure for the synthesis of pyridoquinoline derivatives by the reaction of quinoline, DMAD, and arylidenemalononitriles

A solution of quinoline (0.53 mmol), DMAD (0.53 mmol), and arylidenemalononitrile (0.44 mmol) in dry toluene (3 mL) was stirred at 110 °C in a sealed tube for 12 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel (100–200 mesh) column using hexane–ethyl acetate (85:15) solvent mixtures to afford a diastereomeric mixture of the pyridoquinolines (the ratio was determined from ^{1}H NMR).

4.3.1. Dimethyl 3-(4-chlorophenyl)-4,4-dicyano-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2-dicarboxylate, ***17a***

Yellow solid (275 mg, 60%). Mp=128–130 °C. IR (KBr) ν_{max}: 3031, 2933, 2235, 1744, 1712, 1667, 1646, 1528, 1435, 1357 cm^{-1}. ^{1}H NMR: δ 7.53 (d, J=7.5 Hz, 2H), 7.44–7.32 (m, 3H), 7.30–7.21 (m, 2H), 6.69–6.63 (m, 1H), 6.00 (dd, J_1=4.2 Hz, J_2=9.0 Hz, 1H), 5.93 (d, J=4.5 Hz, 1H), 4.62 (s, 1H), 4.55 (d, J=4.2 Hz, 1H), 3.84 (s, 3H), 3.52 (s, 3H). ^{13}C NMR: δ 164.5, 164.1, 145.3, 134.6, 129.0, 125.6, 125.4, 125.2, 114.7, 112.9, 111.7, 110.2, 109.3, 104.7, 66.7, 53.4, 52.1, 51.2. HRMS (EI) *m/z* calcd for $C_{25}H_{18}ClN_3O_4$, 459.0986; found, 459.0982.

Key ^{1}H NMR values for the minor isomer, **18a**: 6.14 (dd, J_1=4.2 Hz, J_2=9.0 Hz, 0.21H), 5.88 (d, J=4.5 Hz, 0.20H), 4.61 (s, 0.22H), 3.83 (s, 0.60H), 3.51 (s, 0.61H).

4.3.2. Dimethyl 4,4-dicyano-3-(4-fluorophenyl)-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2-dicarboxylate, ***17b***

Yellow solid (257 mg, 58%). Mp=138–140 °C. IR (KBr) ν_{max}: 3110, 2965, 2232, 1747, 1716, 1667, 1640, 1532, 1444, 1361 cm^{-1}. ^{1}H NMR: δ 7.56 (d, J=7.4 Hz, 3H), 7.39–7.31 (m, 2H), 7.28–6.65 (m, 2H), 6.69–6.59 (m, 1H), 6.07 (dd, J_1=4.4 Hz, J_2=9.0 Hz, 1H), 5.98 (d, J=4.5 Hz, 1H), 4.60 (s, 1H), 4.52 (d, J=4.2 Hz, 1H), 3.83 (s, 3H), 3.53 (s, 3H). ^{13}C NMR: δ 165.7, 165.3, 147.7, 134.4, 128.4, 125.6, 125.4, 123.2, 116.7, 112.6, 111.2, 110.0, 88.7, 63.7, 53.5, 53.1, 52.4. HRMS (EI) *m/z* calcd for $C_{25}H_{18}FN_3O_4$; 443.1281; found, 443.1286.

Key ^{1}H NMR values for the minor isomer, **18b**: 6.0 (dd, J_1=4.4 Hz, J_2=9.0 Hz, 0.20H), 5.95 (d, J=4.5 Hz, 0.22H), 4.64 (s, 0.20H), 3.82 (s, 0.60H), 3.52 (s, 0.60H).

4.3.3. Dimethyl 4,4-dicyano-3-(4-(trifluoromethyl)phenyl)-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2-dicarboxylate, ***17c***

Yellow solid (281 mg, 57%). Mp=140–142 °C. IR (KBr) ν_{max}: 3032, 2975, 2229, 1734, 1658, 1603, 1579, 1428, 1334 cm^{-1}. ^{1}H NMR: δ 8.06–8.01 (m, 2H), 7.72–7.69 (m, 3H), 7.58–7.52 (m, 2H), 6.65–6.60 (m, 1H), 6.21 (dd, J_1=4.2 Hz, J_2=9.2 Hz, 1H), 5.92 (d, J=4.2 Hz, 1H), 4.63 (s, 1H), 4.50 (d, J=4.2 Hz, 1H), 3.82 (s, 3H), 3.59 (s, 3H). ^{13}C NMR: δ 165.6, 164.6, 144.2, 142.3, 132.5, 131.3, 130.5, 130.2, 128.8, 127.3, 125.3, 122.6, 116.7, 112.0, 111.7, 109.7, 105.5, 57.7, 53.3, 51.6, 47.4. HRMS (EI) *m/z* calcd for $C_{26}H_{18}F_3N_3O_4$, 493.1249; found, 493.1244.

Key ^{1}H NMR values for the minor isomer, **18c**: 6.30 (dd, J_1=4.2 Hz, J_2=92 Hz, 0.25H), 5.96 (d, J=4.5 Hz, 0.24H), 4.68 (s, 0.24H), 3.83 (s, 0.75H), 3.60 (s, 0.75H).

4.3.4. Dimethyl 3-(4-bromophenyl)-4,4-dicyano-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2-dicarboxylate, ***17d***

Yellow solid (287 mg, 57%). Mp=154–156 °C. IR (KBr) ν_{max}: 2955, 2239, 1742, 1715, 1607, 1546, 1435, 1236 cm^{-1}. ^{1}H NMR: δ 7.48 (d, J=7.2 Hz, 2H), 7.41–7.38 (m, 3H),7.30–7.18 (m, 2H), 6.67–6.55 (m, 1H), 6.12 (dd, J_1=4.5 Hz, J_2=9.1 Hz, 1H), 5.87 (d, J=4.5 Hz, 1H), 4.62 (s, 1H), 4.52 (d, J=4.2 Hz, 1H), 3.83 (s, 3H), 3.54 (s, 3H). ^{13}C NMR: δ 164.5, 164.2, 133.8, 130.6, 129.3, 128.8, 128.5, 126.1, 125.3, 125.0,

122.7, 113.3, 112.8, 111.1, 109.8, 65.6, 62.8, 52.1, 51.6. HRMS (EI) *m/z* calcd for $C_{25}H_{18}BrN_3O_4$, 503.0481; found, 503.0485.

Key ^{1}H NMR values for the minor isomer, **18d**: 6.09 (dd, J_1=4.5 Hz, J_2=9.1 Hz, 0.21H), 5.92 (d, J=4.5 Hz, 0.20H), 4.66 (s, 0.22H), 3.80 (s, 0.60H), 3.50 (s, 0.60H).

4.3.5. Dimethyl 4,4-dicyano-3-(4-nitrophenyl)-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2-dicarboxylate, ***17e***

Yellow solid (268 mg, 57%). Mp=148–150 °C. IR (KBr) ν_{max}: 3054, 2235, 1724, 1612, 1603, 1596, 1426, 1329, 1265 cm^{-1}. ^{1}H NMR: δ 7.59–7.53 (m, 2H), 7.49–7.42 (m, 3H), 7.36–7.29 (m, 2H), 6.66–6.59 (m, 1H), 6.32 (dd, J_1=4.2 Hz, J_2=9.0 Hz, 1H), 5.88 (d, J=4.2 Hz, 1H), 4.71 (s, 1H), 4.54 (d, J=4.2 Hz, 1H), 3.85 (s, 3H), 3.63 (s, 3H). ^{13}C NMR: δ 166.4, 165.6, 149.8, 131.6, 131.4, 129.7, 127.4, 127.2, 125.5, 125.2, 123.5, 122.7, 112.9, 112.6, 110.1, 109.5, 69.4, 53.5, 52.1, 51.4, 47.7, 38.5. HRMS (EI) *m/z* calcd for $C_{25}H_{18}N_4O_6$, 470.1226; found, 470.1222.

Key ^{1}H NMR values for the minor isomer, **18e**: 6.39 (dd, J_1=4.2 Hz, J_2=9.0 Hz, 0.16H), 5.93 (d, J=4.2 Hz, 0.17H), 4.69 (s, 0.14H), 3.86 (s, 0.5H), 3.64 (s, 0.5H).

4.3.6. Dimethyl 4,4-dicyano-3-p-tolyl-4,4a-dihydro-3H-pyrido[1,2-a]quinoline-1,2-dicarboxylate, ***17f***

Yellow solid (162 mg, 37%). Mp=116–118 °C. IR (KBr) ν_{max}: 3041, 2219, 1739, 1703, 1609, 1582, 1533, 1461, 1335, 1277, 1184 cm^{-1}. ^{1}H NMR: δ 7.51 (d, J=4.4 Hz, 2H), 7.46–7.40 (m, 3H), 7.32–7.27 (m, 2H), 6.58–6.47 (m, 1H), 6.59 (dd, J_1=4.1 Hz, J_2=9.2 Hz, 1H), 5.85 (d, J=4.2 Hz, 1H), 4.88 (s, 1H), 4.60 (d, J=4.2 Hz, 1H), 3.99 (s, 3H), 3.72 (s, 3H), 2.34 (s, 3H). ^{13}C NMR: δ 165.0, 164.7, 140.9, 139.5, 139.2, 128.7, 128.5, 125.0, 124.7, 119.8, 115.6, 112.5, 111.8, 109.8, 109.6, 69.6, 53.4, 51.3, 47.2, 37.6, 22.4. HRMS (EI) *m/z* calcd for $C_{26}H_{21}N_3O_4$, 439.1532; found, 439.1538.

Key ^{1}H NMR values for the minor isomer, **18f**: 6.61 (dd, J_1=4.1 Hz, J_2=9.2 Hz, 0.46H), 5.88 (d, J=4.2 Hz, 0.48H), 4.91 (s, 0.5H), 3.97 (s, 1.5H), 3.71 (s, 1.5H).

4.4. Experimental procedure for the synthesis of oxazinoquinoline derivatives by the reaction of quinoline, DMAD, and N-alkylated isatins

N-Substituted isatin (0.44 mmol), quinoline (0.53 mmol), and DMAD (0.53 mmol) were taken in a sealed tube in dry toluene (3 mL), and the mixture was heated at 110 °C for 12 h. The solvent was distilled off under reduced pressure on a rotary evaporator and the residue was subjected to column chromatography on silica gel (100–200 mesh) column using 90:10 hexane–ethyl acetate as eluent to afford a diastereomeric mixture of oxazinoquinoline derivatives. The data of the major isomer is given in each case.

4.4.1. Dimethyl 1′-allyl-5′-bromo-2′-oxo-4aH-spiro[[1,3]-oxazino[3,2-a]quinoline, 3-3′-indoline]-1,2-dicarboxylate, ***20a***

Orange crystalline solid (306 mg, 57%). Mp=164–166 °C (recrystallized from CH_2Cl_2–hexane). IR (KBr) ν_{max}: 3680, 3018, 3012, 2432, 2399, 1732, 1726, 1521, 1496, 1477, 1423, 1232 cm^{-1}. ^{1}H NMR: δ 7.37–7.22 (m, 3H), 7.08–7.02 (m, 3H), 6.84–6.81 (m, 1H), 6.78–6.65 (m, 1H), 6.63 (d, J=4.2 Hz, 1H), 5.60 (dd, J_1=5.7 Hz, J_2=9.9 Hz, 1H), 5.49–5.44 (m, 1H), 5.38–5.22 (m, 2H), 4.44–4.37 (m, 1H), 4.25–4.18 (m, 1H), 3.92 (s, 3H), 3.61 (s, 3H). ^{13}C NMR: δ 172.8, 165.2, 163.6, 144.7, 138.0, 137.4, 131.6, 128.9, 128.6, 127.4, 127.0, 126.3, 125.5, 121.9, 121.8, 120.4, 119.9, 118.2, 113.5, 104.6, 102.7, 79.2, 53.5, 53.3, 51.7. HRMS (EI) *m/z* calcd for $C_{26}H_{21}BrN_2O_6$, 536.0583; found, 536.0580.

Key ^{1}H NMR values for the minor isomer, **21a**: 6.61 (d, J=4.2 Hz, 0.25H), 5.68 (dd, J_1=5.6 Hz, J_2=9.9 Hz, 0.23H), 3.91 (s, 0.75H), 3.60 (s, 0.75H).

4.4.2. Dimethyl 1′-allyl-2′-oxo-4aH-spiro[[1,3]oxazino-[3,2-a]quinoline, 3-3′-indoline]-1,2-dicarboxylate, ***20b***

Orange crystalline solid (256 mg, 56%). Mp=154–156 °C. IR (KBr) ν_{max}: 3685, 3010, 2989, 2369, 1739, 1686, 1532, 1455, 1221 cm^{-1}. ^{1}H NMR: δ 7.36–7.22 (m, 4H), 7.08–7.0 (m, 3H), 6.85–6.83 (m, 1H), 6.68–6.66 (m, 1H), 6.20 (d, J=4.2 Hz, 1H), 5.99 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 5.89–5.82 (m, 1H), 5.40–5.24 (m, 2H), 4.41–4.32 (m, 1H), 4.23–4.19 (m, 1H), 3.90 (s, 3H), 3.63 (s, 3H). ^{13}C NMR: δ 164.7, 164.2, 163.9, 144.7, 138.0, 131.6, 128.9, 128.6, 127.4, 127.0, 126.3, 125.5, 121.9, 120.4, 119.9, 118.2, 116.6, 113.5, 102.7, 80.1, 53.5, 53.0, 52.9. HRMS (EI) *m/z* calcd for $C_{26}H_{22}N_2O_6$, 458.1478; found, 458.1473.

Key ^{1}H NMR values for the minor isomer, **21b**: 6.16 (d, J=4.2 Hz, 0.26H), 6.02 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 0.24H), 3.88 (s, 0.75H), 3.61 (s, 0.75H).

4.4.3. Dimethyl 5′-bromo-1′-methyl-2′-oxo-4aH-spiro-[[1,3]oxazino[3,2-a]quinoline, 3-3′-indoline]-1,2-dicarboxylate, ***20c***

Orange solid (265 mg, 52%). Mp=136–138 °C. IR (KBr) ν_{max}: 3016, 2544, 2367, 1740, 1678, 1556, 1511, 1375 cm^{-1}. ^{1}H NMR: δ 7.27–7.19 (m, 3H), 7.05–7.6.99 (m, 2H), 6.94–6.91 (m, 1H), 6.81–6.77 (m, 2H), 6.13 (d, J=4.3 Hz, 1H), 5.95 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.42 (s, 3H). ^{13}C NMR: δ 165.0, 164.5, 163.3, 144.8, 138.2, 131.6, 128.9, 128.7, 127.0, 126.3, 126.0, 121.9, 120.8, 120.4, 119.9, 117.3, 114.7, 104.5, 95.7, 80.2, 53.3, 51.9, 31.4. HRMS (EI) *m/z* calcd for $C_{24}H_{19}BrN_2O_6$, 510.0426; found, 510.0422.

Key ^{1}H NMR values for the minor isomer, **21c**: 6.21 (d, J=4.3 Hz, 0.25H), 5.98 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 0.24H), 3.80 (s, 0.76H), 3.74 (s, 0.75H).

4.4.4. Dimethyl 5′-bromo-2′-oxo-1′-(prop-2-ynyl)-4aH-spiro[[1,3]oxazino[3,2-a]quinoline, 3-3′-indoline]-1,2-dicarboxylate, ***20d***

Orange solid (267 mg, 50%). Mp=152–154 °C. IR (KBr) ν_{max}: 3012, 2536, 1744, 1680, 1548, 1501, 1299 cm^{-1}. ^{1}H NMR: δ 7.29–7.20 (m, 3H), 7.07–6.98 (m, 2H), 6.25 (d, J=4.2 Hz, 2H), 5.95 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 4.64–4.62 (m, 1H), 4.35 (dd, J_1=3.4 Hz, J_2=7.6 Hz, 1H), 4.89 (s,

2H), 3.90 (s, 3H), 3.58 (s, 3H), 2.30 (s, 1H). ^{13}C NMR: δ 165.8, 164.2, 163.3, 145.0, 143.4, 138.4, 130.1, 129.8, 128.7, 127.9, 122.7, 121.7, 118.9, 118.5, 114.3, 102.8, 96.2, 80.6, 78.3, 77.4, 73.4, 53.2, 52.2, 29.2. HRMS (EI) *m/z* calcd for $C_{26}H_{19}BrN_2O_6$, 534.0426; found, 534.0420.

Key ^{1}H NMR values for the minor isomer, **21d**: 6.23 (d, J=4.2 Hz, 0.22H), 5.97 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 0.24H), 3.89 (s, 0.75H), 3.56 (s, 0.75H).

4.4.5. Dimethyl 2′-oxo-1′-(prop-2-ynyl)-4aH-spiro-[[1,3]oxazino[3,2-a]quinoline, 3-3′-indoline]-1,2-dicarboxylate, ***20e***

Orange solid (476 mg, 58%). Mp=158–160 °C. IR (KBr) ν_{max}: 3292, 3102, 2113, 1748, 1740, 1649, 1566, 1242 cm^{-1}. ^{1}H NMR: δ 7.69–7.65 (m, 2H), 7.38–7.32 (m, 4H), 6.69 (d, J=9.9 Hz, 1H), 6.22 (d, J=4.2 Hz, 1H), 5.88 (dd, J_1=4.2 Hz, J_2=9.6 Hz, 1H), 4.56–4.55 (m, 1H), 4.35 (dd, J_1=3.6 Hz, J_2=7.4 Hz, 1H), 4.54 (s, 2H), 3.88 (s, 3H), 3.60 (s, 3H), 2.32 (s, 1H). ^{13}C NMR: δ 164.8, 163.3, 161.5, 144.8, 144.3, 138.2, 132.5, 129.6, 128.1, 127.8, 127.2, 120.7, 119.7, 118.9, 118.3, 112.0, 102.3, 80.8, 73.4, 72.5, 53.4, 52.5, 30.8. HRMS (EI) *m/z* calcd for $C_{26}H_{20}N_2O_6$, 456.1321; found, 456.1326.

Key ^{1}H NMR values for the minor isomer, **21e**: 6.17 (d, J=4.2 Hz, 0.21H), 5.85 (dd, J_1=4.2 Hz, J_2=9.6 Hz, 0.21H), 3.89 (s, 0.6H), 3.61 (s, 0.6H).

4.4.6. Dimethyl 5′-bromo-1′-ethyl-2′-oxo-4aH-spiro-[[1,3]oxazino[3,2-a]quinoline, 3-3′-indoline]-1,2-dicarboxylate, ***20f***

Orange solid (254 mg, 57%). Mp=148–150 °C. IR (KBr) ν_{max}: 2988, 1744, 1740, 1677, 1593, 1566, 1155 cm^{-1}. ^{1}H NMR: δ 7.27–7.19 (m, 3H), 7.05–7.00 (m, 3H), 6.99–6.92 (m, 3H), 6.80–6.77 (m, 1H), 6.13 (d, J=4.3 Hz, 1H), 5.97 (dd, J_1=4.3 Hz, J_2=9.8 Hz, 1H), 3.86–3.79 (m, 1H), 3.68 (s, 3H), 3.57 (s, 3H), 1.29 (t, J=7.2 Hz, 3H). ^{13}C NMR: δ 165.4, 164.4, 163.7, 144.3, 137.8, 128.6, 127.4, 126.5, 125.5, 122.9, 121.8, 118.9, 118.2, 113.7, 112.4, 96.9, 80.6, 52.9, 51.6, 40.8, 14.0. HRMS (EI) *m/z* calcd for $C_{25}H_{22}N_2O_6$, 446.1478; found, 446.1482.

Key ^{1}H NMR values for the minor isomer, **21f**: 6.19 (d, J=4.3 Hz, 0.23H), 5.99 (dd, J_1=4.3 Hz, J_2=9.8 Hz, 0.20H), 3.66 (s, 0.6H), 3.53 (s, 0.6H).

4.5. Experimental procedure for the synthesis of oxazinoquinoline derivatives by the reaction of quinoline, DMAD, and 1,2-benzoquinones

1,2-Benzoquinone (0.44 mmol), quinoline (0.53 mmol), and DMAD (0.53 mmol) were taken in a sealed tube in dry toluene (3 mL) and the mixture was heated at 110 °C for 10–12 h. The solvent was removed under reduced pressure on a rotary evaporator. The residue on chromatographic separation on a silica gel (100–200 mesh) column using 90:10 hexane–ethyl acetate as eluent afforded a regioisomeric mixture of oxazinoquinoline derivatives.

4.5.1. Dimethyl 3′,5′-di-tert-butyl-6′-oxo-4aH-spiro-[[1,3]oxazino[3,2-a]quinoline-3,1′-cyclohexa[2,4]diene]-1,2-dicarboxylate, ***23a***

Yellow solid (260 mg, 53%). Mp=166–168 °C. IR (KBr) ν_{max}: 2949, 1755, 1748, 1738, 1535, 1441, 1254 cm^{-1}. ^{1}H NMR: δ 7.66–7.60 (m, 2H), 6.98–6.95 (m, 1H), 6.88–6.80 (m, 2H), 6.05 (s, 1H), 5.91 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 5.42 (d, J=4.2 Hz, 1H), 5.32 (s, 1H), 3.86 (s, 3H), 3.60 (s, 3H), 1.20 (s, 9H), 1.16 (s, 9H). ^{13}C NMR: δ 196.6, 164.9, 164.4, 148.7, 142.2, 136.8, 132.6, 125.5, 125.3, 122.3, 119.4, 115.1, 110.8, 78.4, 53.4, 51.2, 35.5, 28.7, 28.6. HRMS (EI) *m/z* calcd for $C_{29}H_{33}NO_6$, 491.2308; found, 491.2311.

4.5.2. Dimethyl 2′,4′-di-tert-butyl-6′-oxo-4aH-spiro-[[1,3]oxazino[3,2-a]quinoline-3,1′-cyclohexa[2,4]diene]-1,2-dicarboxylate, ***24a***

Yellow viscous liquid (64 mg, 13%). IR (KBr) ν_{max}: 2952, 1757, 1749, 1742, 1533, 1443, 1256, 998 cm^{-1}. ^{1}H NMR: δ 7.52–7.49 (m, 2H), 7.25 (s, 1H), 7.0–6.98 (m, 1H), 6.94–6.91 (m, 2H), 5.93 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 5.46 (d, J=4.2 Hz, 1H), 5.37 (s, 1H), 3.88 (s, 3H), 3.63 (s, 3H), 1.22 (s, 9H), 1.19 (s, 9H). ^{13}C NMR: δ 192.6, 165.5, 164.6, 148.4, 140.8, 138.4, 137.3, 128.6, 128.3, 126.1, 121.7, 119.6, 114.3, 111.8, 86.3, 79.4, 53.6, 51.3, 35.8, 35.5, 29.0, 28.8. HRMS (EI) *m/z* calcd for $C_{29}H_{33}NO_6$, 491.2308; found, 491.2312.

4.5.3. Dimethyl 10′-oxo-4aH,10′H-spiro[[1,3]oxazino-[3,2-a]quinoline-3,9′-phenanthrene]-1,2-dicarboxylate, ***23b***

Yellow solid (263 mg, 55%). Mp=188–190 °C. IR (KBr) ν_{max}: 2955, 1748, 1712, 1688, 1578, 1443, 1220 cm^{-1}. ^{1}H NMR: δ 8.25–8.23 (m, 2H), 7.98–7.96 (m, 2H), 7.79–7.77 (m, 1H), 7.55–7.52 (m, 2H), 7.39–7.28 (m, 3H), 7.02–6.98 (m, 2H), 6.93–6.86 (m, 1H), 6.75 (d, J=5.2 Hz, 1H), 6.50 (dd, J_1=4.4 Hz, J_2=10.2 Hz, 1H), 3.86 (s, 3H), 3.65 (s, 3H). ^{13}C NMR: δ 191.8, 165.8, 165.2, 148.7, 142.3, 137.6, 136.2, 132.3, 130.9, 128.5, 128.1, 125.6, 124.4, 124.2, 124.0, 121.2, 118.7, 116.6, 114.5, 113.7, 111.2, 90.8, 81.1, 53.3, 51.8. HRMS (EI) *m/z* calcd for $C_{29}H_{21}NO_6$, 479.1369; found, 479.1366.

4.5.4. Dimethyl 2′-oxo-2′H,4aH-spiro[[1,3]oxazino[3,2-a]-quinoline-3,1′-acenaphthylene]-1,2-dicarboxylate, ***23c***

Yellow solid (262 mg, 58%). Mp=162–164 °C. IR (KBr) ν_{max}: 2962, 1744, 1709, 1700, 1588, 1433, 1230 cm^{-1}. ^{1}H NMR: δ 8.07–8.04 (m, 2H), 7.98–7.96 (m, 2H), 7.77–7.73 (m, 2H), 7.64–7.55 (m, 2H), 7.02–6.98 (m, 2H), 6.75–6.73 (d, J=7.8 Hz, 1H), 6.50–6.48 (m, 1H), 6.26 (dd, J_1=4.8 Hz, J_2=9.8 Hz, 1H), 3.86 (s, 3H), 3.65 (s, 3H). ^{13}C NMR: δ 194.4, 165.0, 164.6, 145.1, 142.6, 137.7, 136.2, 132.1, 128.2, 128.0, 125.6, 125.3, 124.2, 124.1, 121.2, 118.7, 116.3, 114.7, 113.7, 111.2, 101.1, 81.6, 53.0, 51.5. HRMS (EI) *m/z* calcd for $C_{27}H_{19}NO_6$, 453.1212; found, 453.1217.

4.5.5. Dimethyl 3′-tert-butyl-6′-oxo-4aH-spiro-[[1,3]oxazino[3,2-a]quinoline-3,1′-cyclohexa[2,4]diene]-1,2-dicarboxylate, ***23d***

Yellow solid (213 mg, 47%). Mp=112–114 °C. IR (KBr) ν_{max}: 2953, 1741, 1705, 1688, 1590, 1522, 1154 cm^{-1}.

^{1}H NMR: δ 7.56–7.51 (m, 2H), 7.41–7.38 (m, 1H), 7.33 (d, J=9 Hz, 1H), 7.04–6.98 (m, 1H), 6.92–6.88 (m, 1H), 6.28 (d, J=9.1 Hz, 1H), 5.84 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 5.66 (s, 1H), 5.48 (d, J=4.4 Hz, 1H), 3.86 (s, 3H), 3.65 (s, 3H), 1.06 (s, 9H). ^{13}C NMR: δ 191.2, 165.1, 164.1, 150.1, 138.6, 137.6, 137.2, 134.4, 128.6, 128.3, 127.8, 122.7, 122.2, 121.2, 114.5, 112.9, 112.7, 111.2, 87.1, 79.4, 53.0, 51.5, 31.9, 27.0. HRMS (EI) *m/z* calcd for $C_{25}H_{25}NO_6$, 435.1682; found, 435.1687.

4.5.6. Dimethyl 4′-tert-butyl-6′-oxo-4aH-spiro[[1,3]oxazino[3,2-a]quinoline-3,1′-cyclohexa[2,4]diene]-1,2-dicarboxylate, ***24d***

Yellow viscous liquid (100 mg, 23%). IR (film) ν_{max}: 2955, 1743, 1712, 1672, 1599, 1565, 1287 cm^{-1}. ^{1}H NMR: δ 7.50–7.47 (m, 2H), 7.41–7.38 (m, 1H), 7.04–6.98 (m, 1H), 6.76 (d, J=5 Hz, 1H), 6.68 (d, J=7.9 Hz, 1H), 6.21 (d, J=8 Hz, 1H), 6.05 (s, 1H), 5.96 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 5.09 (d, J=4.4 Hz, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 1.04 (s, 9H). ^{13}C NMR: δ 190.6, 165.3, 164.4, 145.3, 138.8, 136.5, 136.0, 128.7, 122.6, 121.8, 120.0, 113.3, 112.9, 86.5, 79.6, 54.2, 51.2, 35.3, 27.4. HRMS (EI) *m/z* calcd for $C_{25}H_{25}NO_6$, 435.1682; found, 435.1686.

4.5.7. Dimethyl 2′,4′-di-tert-butyl-5′-methoxy-6′-oxo-4aH-spiro[[1,3]oxazino[3,2-a]quinoline-3,1′-cyclohexa[2,4]diene]-1,2-dicarboxylate, ***23e***

Yellow viscous liquid (224 mg, 43%). IR (film) ν_{max}: 2954, 1748, 1708, 1666, 1600, 1567, 1432 cm^{-1}. ^{1}H NMR: δ 7.52–7.49 (m, 2H), 7.25 (s, 1H), 6.98–6.86 (m, 2H), 6.94–6.91 (m, 2H), 5.93 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 5.83 (m, 1H), 5.46 (d, J=4.2 Hz, 1H), 5.37 (s, 1H), 3.88 (s, 3H), 3.63 (s, 3H), 1.22 (s, 9H), 1.19 (s, 9H). ^{13}C NMR: δ 192.1, 165.2, 164.1, 154.3, 150.4, 138.7, 137.3, 128.9, 128.6, 127.2, 123.3, 121.6, 119.5, 114.6, 113.2, 87.0, 79.5, 60.7, 53.6, 51.6, 35.3, 31.4, 31.2, 30.7. HRMS (EI) *m/z* calcd for $C_{30}H_{35}NO_7$, 521.2414; found, 521.2420.

4.5.8. Dimethyl 3′,5′-di-tert-butyl-2′-methoxy-6′-oxo-4aH-spiro[[1,3]oxazino[3,2-a]quinoline-3,1′-cyclohexa[2,4]diene]-1,2-dicarboxylate, ***24e***

Yellow viscous liquid (115 mg, 22%). IR (film) ν_{max}: 2955, 1746, 1711, 1664, 1602, 1566, 1428 cm^{-1}. ^{1}H NMR: δ 7.52–7.47 (m, 2H), 7.44 (s, 1H), 7.02–6.98 (m, 2H), 6.92–6.88 (m, 2H), 6.74 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 6.01–5.94 (m, 2H), 4.17 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 1.13 (s, 9H), 0.99 (s, 9H). ^{13}C NMR: δ 191.3, 165.5, 163.8, 138.0, 137.3, 137.2, 134.3, 133.1, 128.5, 128.3, 128.1, 126.3, 121.5, 119.2, 114.7, 109.7, 92.8, 78.8, 59.7, 53.3, 51.5, 31.4, 31.3, 29.2, 29.1. HRMS (EI) *m/z* calcd for $C_{30}H_{35}NO_7$, 521.2414; found, 521.2419.

4.5.9. Dimethyl 2′,4′-dibenzhydryl-5′-methoxy-6′-oxo-4aH-spiro[[1,3]oxazino[3,2-a]quinoline-3,1′-cyclohexa[2,4]diene]-1,2-dicarboxylate, ***23f***

Yellow solid (296 mg, 40%). Mp=176–178 °C. IR (KBr) ν_{max}: 2948, 1742, 1708, 1668, 1499, 1434, 1254 cm^{-1}. ^{1}H NMR: δ 7.54–7.52 (m, 2H), 7.30–7.12 (m, 21H), 6.88–6.79 (m, 2H), 6.76–6.73 (m, 1H), 5.93 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 5.46 (d, J=4.2 Hz, 1H), 5.26 (s, 1H), 4.82 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.64 (s, 3H). ^{13}C NMR: δ 193.0, 164.8, 163.3, 156.3, 142.3, 141.4, 138.3, 137.1, 131.3, 128.7, 128.5, 128.2, 128.1, 126.5, 126.2, 126.0, 124.5, 124.4, 124.1, 121.5, 118.8, 114.4, 112.0, 92.4, 80.6, 59.3, 54.3, 53.5, 53.2, 51.3. HRMS (EI) *m/z* calcd for $C_{48}H_{39}NO_7$, 741.2727; found, 741.2722.

4.5.10. Dimethyl 3′,5′-dibenzhydryl-2′-methoxy-6′-oxo-4aH-spiro[[1,3]oxazino[3,2-a]quinoline-3,1′-cyclohexa[2,4]diene]-1,2-dicarboxylate, ***24f***

Yellow solid (148 mg, 20%). Mp=182–184 °C. IR (KBr) ν_{max}: 2952, 1744, 1710, 1672, 1504, 1436, 1255, 1148 cm^{-1}. ^{1}H NMR: δ 7.26–7.18 (m, 23H), 6.92–6.84 (m, 2H), 6.72–6.70 (m, 1H), 5.88 (dd, J_1=4.2 Hz, J_2=9.8 Hz, 1H), 5.42 (d, J=4.2 Hz, 1H), 5.23 (s, 1H), 4.88 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H). ^{13}C NMR: δ 193.4, 164.6, 163.2, 155.7, 142.5, 142.1, 137.3, 128.6, 128.4, 128.0, 126.2, 126.1, 125.5, 124.7, 124.2, 122.2, 116.8, 93.3, 80.3, 58.9, 54.4, 53.6, 52.9, 50.7. HRMS (EI) *m/z* calcd for $C_{48}H_{39}NO_7$, 741.2727; found, 741.2723.

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References and notes

1. Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1932**, *498*, 16–49.
2. (a) Acheson, R. M.; Woollard, J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 438–445; (b) Acheson, R. M.; Taylor, G. A. *Proc. Chem. Soc.* **1959**, 186–187; (c) Acheson, R. M.; Taylor, G. A. *J. Chem. Soc.* **1960**, 1691–1701; (d) Acheson, R. M.; Gagan, J. M. F.; Taylor, G. A. *J. Chem. Soc.* **1963**, 1903–1906.
3. Huisgen, R. *Topics in Heterocyclic Chemistry*; Castle, R., Ed.; John Wiley and Sons: New York, NY, 1969; Chapter 8, p 223; (b) Huisgen, R. *Z. Chem.* **1968**, *8*, 290–298.
4. (a) Winterfeldt, E.; Naumann, A. *Chem. Ber.* **1965**, *98*, 3537–3545; (b) Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 423–434.
5. Acheson, R. M.; Plunkett, A. O. *J. Chem. Soc.* **1964**, 2676–2683.
6. Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber.* **1967**, *100*, 1094–1106.
7. (a) Nair, V.; Nair, J. S.; Vinod, A. U. *Synthesis* **2000**, 1713–1718; (b) Nair, V.; Deepthi, A.; Beneesh, P. B.; Eringathodi, S. *Synthesis* **2006**, 1443–1446.
8. Nair, V.; Menon, R. S.; Beneesh, P. B.; Sreekumar, V.; Bindu, S. *Org. Lett.* **2004**, *6*, 767–769.
9. Nair, V.; Deepthi, A.; Manoj, P.; Bindu, S.; Sreekumar, V.; Beneesh, P. B.; Mohan, R.; Suresh, E. *J. Org. Chem.* **2006**, *71*, 2313–2319.
10. (a) Nair, V.; Sreekanth, A. R.; Vinod, A. U. *Org. Lett.* **2001**, *3*, 3495–3497; (b) Nair, V.; Sreekanth, A. R.; Vinod, A. U. *Org. Lett.* **2002**, *4*, 2807; (c) Nair, V.; Sreekanth, A. R.; Abhilash, N.; Bhadbhade, M. M.; Gonnade, R. C. *Org. Lett.* **2002**, *4*, 3575–3577; (d) Nair, V.; Sreekanth, A. R.; Biju, A. T.; Rath, N. P. *Tetrahedron Lett.* **2003**, *44*, 729–732; (e) Nair, V.; Devi, B. R.; Varma, R. L. *Tetrahedron Lett.* **2005**, *46*, 5333–5335.

11. Nair, V.; Bindu, S.; Sreekumar, V. *Org. Lett.* **2003**, *5*, 665–667.
12. (a) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899–907; (b) Nair, V.; Menon, R. S.; Sreekanth, A.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520–530.
13. Nair, V.; Devipriya, S.; Suresh, E. *Tetrahedron Lett.* **2007**, *48*, 3667–3670.
14. (a) Benameur, L.; Bouaziz, Z.; Nebois, P.; Bartoli, M. H.; Boitard, M.; Fillion, H. *Chem. Pharm. Bull.* **1996**, *44*, 605; (b) Chevalier, J.; Atifi, S.; Eyraud, A.; Mahamoud, A.; Barbe, J.; Pages, J.-M. *J. Med. Chem.* **2001**, *44*, 4023.
15. The crystal structures of compounds **12a** and **20a** have been deposited at the Cambridge Crystallographic Data Centre and allocated the reference numbers CCDC 662517 and 662518, respectively.