1,4-Dipolar cycloaddition in organic synthesis: a facile route to isoquinoline fused heterocycles

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Dedicated with best wishes to Professor S. Swaminathan on the occasion of his 80th birthday

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Abstract

The three component condensation reactions involving isoquinoline, dimethyl acetylenedicarboxylate and carbonyl dipolarophiles such as *o*- and *p*-benzoquinones and *N*-substituted isatins constitute a one-pot synthesis of a variety of [1,3]oxazino isoquinoline derivatives *via* 1,4-dipolar cycloaddition.

Keywords: Dimethyl acetylenedicarboxylate, *N*-substituted isatins, isoquinoline, *o*- and *p*-benzoquinones

Introduction

In addition to the well known hetero-Diels-Alder reactions,[1] 1,4-dipolar cycloaddition constitutes a potentially versatile process for the construction of six membered heterocycles. The basic principles of 1,4-dipolar cycloaddition were provided by the pioneering work of Huisgen and co-workers.[2] Noteworthy developments in this area have been the introduction of heteroaromatic betaines as 1,4-dipoles[3] and the utilization of 1,4-dipole equivalents in formal 1,4-dipolar cycloaddition reactions.[4]

Apart from a few isolated reports in the literature,[5] the potential of "Huisgen 1,4-dipoles" for the construction of various six membered heterocycles remains underexploited. An interesting example of this type is the dipole **1** generated from isoquinoline and dimethyl acetylenedicarboxylate (DMAD), whose existence was confirmed by Huisgen[6] (Figure 1).

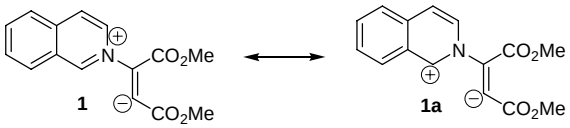


Figure 1

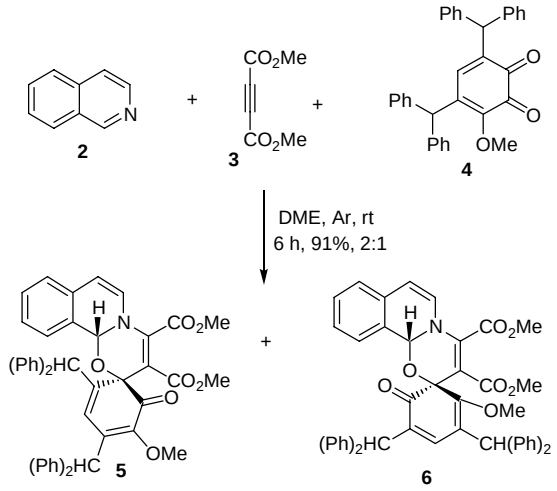
In view of our recent interest in developing novel multicomponent reactions for heterocyclic synthesis *via* dipolar intermediates[7] we were intrigued by the possibility of trapping the dipole **1** with various dipolarophiles. Investigations carried out in this context have demonstrated that the dipole **1** can be effectively trapped by *N*- tosylimines resulting in the diastereoselective synthesis of 2*H*-pyrimido[2,1-a]isoquinolines.[8a] Our preliminary results from studies using quinones as dipolarophiles have shown that the reaction leads to a one-pot synthesis of spiro[1,3]oxazino[2,3-a]isoquinolines.[8b] In this paper we disclose the results of our extended investigations on the reactivity of dipole **1** towards various carbonyl dipolarophiles; the reactions constitute a facile route to isoquinoline fused heterocycles, which are interesting from the standpoint of their potential biological activity.

Results and Discussion

Reaction of isoquinoline and DMAD with 1,2- and 1,4-benzoquinones

Against the background presented above and in the context of our general interest in the dipolarophilic profile of quinonoid compounds,[9] we examined the possibility of trapping the 1,4-dipole **1** with *o*- and *p*-benzoquinones.

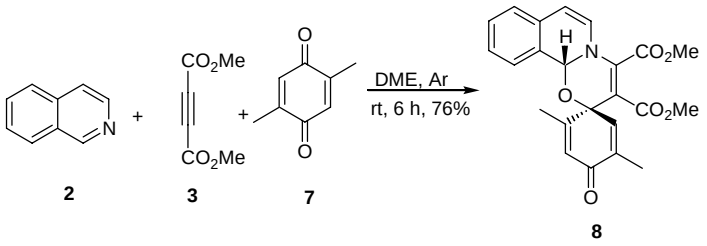
In a pilot experiment, it was observed that a mixture of 3-methoxy-4,6-bis(1,1-diphenylmethyl)-1,2-benzoquinone **4** and DMAD at room temperature in anhydrous DME, when treated with isoquinoline afforded the spiro[1,3]oxazino[2,3-a]isoquinoline derivatives **5** and **6** in 91% yield in the ratio 2:1 (Scheme 1).



Scheme 1

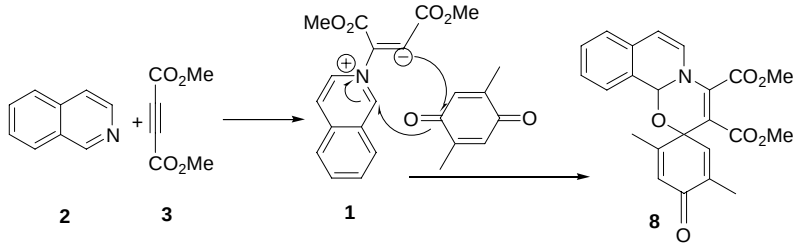
The products **5** and **6** were characterized by spectroscopic techniques. The IR spectrum showed strong absorptions at 1742, 1708 and 1667 cm^{-1} indicating the presence of ester and enone carbonyls. In the ^1H NMR spectrum of **5**, signals due to the three methoxy groups were visible at δ 3.94, 3.54 and 3.40; the corresponding signals for **6** were observed at δ 3.90, 3,64 and 3.47. The ring junction proton of **5** was discernible as a singlet at δ 6.50; the corresponding signal for **6** was seen as singlet at δ 6.68. In ^{13}C NMR spectrum of **5**, the characteristic signal for the spirocarbon was observed at δ 78.2, whereas in the spectrum of **6**, it was discernible at δ 80.9. The signals corresponding to ester and enone carbonyls of **5** were seen at δ 163.4, 163.5 and 194.9 and those for **6** were visible at δ 163.4, 164.2 and 193.1. Finally the structure and stereochemistry of the product **6** was unambiguously established by single crystal X-ray analysis.

Similar reactivity was also observed with 1,4-benzoquinones. Thus 2,5-dimethyl-1,4-benzoquinone **7** when treated with DMAD in presence of isoquinoline gave 76% of the spiro[1,3]oxazino[2,3-*a*]isoquinoline derivative **8** (Scheme 2).



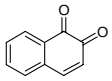
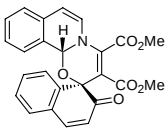
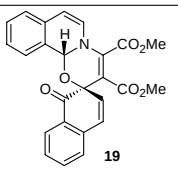
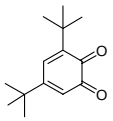
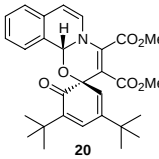
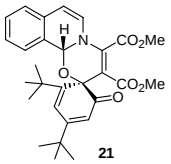
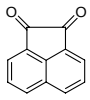
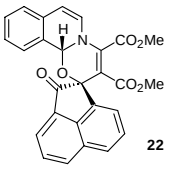
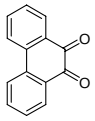
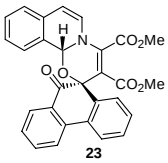
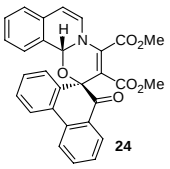
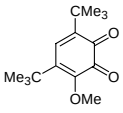
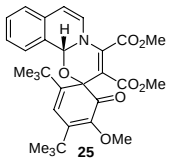
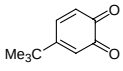
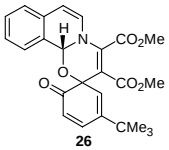
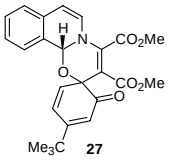
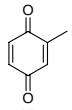
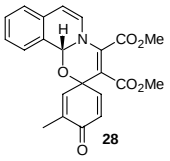
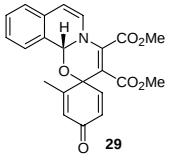
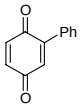
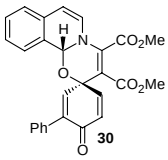
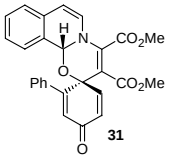
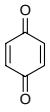
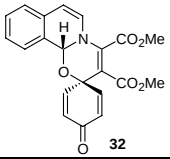
Scheme 2

Analogous results were obtained with a number of other quinones and the results are summarised in Table 1. Mechanistically the reaction can be considered to proceed via the initial formation of the 1,4-dipolar intermediate **1** from isoquinoline and DMAD, followed by its trapping with quinone carbonyl in a cycloaddition mode to give the corresponding spiro[1,3]oxazino isoquinolines (Scheme 3).



Scheme 3

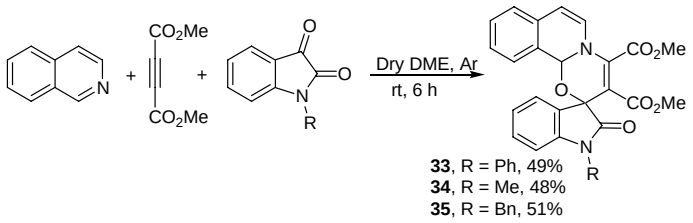
Table 1. Reaction of isoquinoline and DMAD with quinines

Entry	Quinone	Products	Ratio [a]	Yield(%) [b]
1	 **9**	 **18**  **19**	1:1	62
2	 **10**	 **20**  **21**	1:2	85
3	 **11**	 **22**		53
4	 **12**	 **23**  **24**	1:1	75
5	 **13**	 **25**		89
6	 **14**	 **26**  **27**	3.5:1	94
7	 **15**	 **28**  **29**	2.7:1	89
8	 **16**	 **30**  **31**	2:1	90
9	 **17**	 **32**		75

Reaction conditions = DME, Ar,rt, 6 h, [a] ratio of isomers. [b] isolated yield.

Reaction of Isoquinoline and DMAD with *N*-substituted Isatins

Impressed by the reactivity of the dipole **1** towards quinones, it was interesting to explore its reactivity towards 1,2-diones such as *N*-substituted isatins. Thus the reaction of *N*-substituted isatins with DMAD and isoquinoline afforded the spiro[1,3]oxazino[2,3-a]isoquinoline derivatives **33**-**35** in moderate yields (Scheme 4).



Scheme 4

he products were purified by chromatography and characterized by spectroscopic analysis. The IR spectrum of **33** showed the characteristic ester carbonyl absorptions at 1741 and 1711 cm^{-1}. The amide carbonyl absorption was seen at 1620 cm^{-1}. In the ^{1}H NMR spectrum, signals due to the methoxy groups were observed as singlets at δ 3.98 and 3.53 whereas the olefinic protons were visible as doublets at δ 6.42 (J = 7.73 Hz) and 5.83 (J = 7.74 Hz). In the ^{13}C NMR spectrum, the three resonance signals corresponding to the ester and amide carbonyls were seen at δ 162.9, 163.1 and 173.3. The signal due to the spirocarbon was discernible at δ 79.1. All the other signals were also in agreement with the assigned structure.

Conclusions

In conclusion, we have developed some novel and interesting three component condensation reactions *via* 1,4-dipolar cycloaddition, affording a facile entry into a variety of isoquinoline fused heterocycles. In this context, it is noteworthy that these isoquinoline derivatives are known to possess interesting biological activities.[10]

Experimental Section

General Procedures. Melting points were recorded on a Buchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Bruker DPX-300 MHz NMR spectrometer. The spectra were run in $CDCl_3$ - CCl_4, v/v 3:1 and chemical shifts are reported (δ) relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Mass spectra were recorded under EI/HRMS (at 5000) resolution using an Auto Spec. M mass spectrometer. IR spectra were recorded on a Nicolet Impact 400D FT-IR spectrophotometer. Elemental analyses

were obtained on a Perkin-Elmer-2400 elemental analyzer. Dimethyl acetylenedicarboxylate was purchased from Aldrich Chemical Co. and was used without further purification.

Experimental procedure for the preparation of [1,3]oxazino[2,3-a]isoquinoline derivatives. To a stirred solution of dimethyl acetylenedicarboxylate (1 equiv) and quinone (1 equiv) in dry DME (10 mL) under an argon atmosphere, was added isoquinoline (1 equiv) and the reaction mixture was stirred for 6 h at room temperature. The solvent was then removed under vacuum and the residue on chromatographic separation on silica gel using hexane- ethyl acetate (80:20) gave spiro[1,3]oxazino[2,3-a]isoquinoline derivatives.

Dimethyl-2-methoxy-3,5-(dibenzhydryl)-6-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (5). Yellow crystalline solid; mp 208-210 °C.IR(KBr) ν_{max}: 2948, 1742, 1708, 1667, 1600, 1499, 1431, 1276, 1236, 1148 cm^{-1}. ^1H NMR: δ 7.28-6.88 (m, 21H), 6.72 (d, J = 7.66 Hz, 2H), 6.50 (s, 1H), 6.39 (s, 1H), 6.34 (d, J = 7.67 Hz, 1H), 5.84-5.72 (m, 2H), 5.55 (s, 1H), 5.49 (s, 1H), 3.94 (s, 3H), 3.54 (s, 3H), 3.40 (s, 3H). ^{13}C NMR: δ 194.9, 163.6, 163.5, 155.9, 148.0, 143.2, 141.0, 134.6, 129.9, 129.5, 129.3, 129.1, 129.0, 128.9, 128.5, 128.5, 128.3, 128.2, 128.1, 126.5, 126.4, 126.3, 123.3, 105.1, 104.6, 78.2, 61.6, 53.3, 51.6, 48.9, 47.9.Anal. Calcd. for $C_{48}H_{39}NO_7$; C, 77.72; H, 5.30; N, 1.89; Found C, 77.52; H, 5.19; N, 1.78.

Dimethyl-3-methoxy-4,6-(dibenzhydryl)-2-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (6). Yellow crystalline solid; mp 198-200 °C. IR(KBr) ν_{max}: 2955, 1742, 1708, 1667, 1600, 1499, 1431, 1229, 1148 cm^{-1}.^1H NMR: δ 7.30-6.95 (m, 22H), 6.80-6.78 (m, 2H), 6.68 (s, 1H), 6.34 (d, J = 7.48 Hz, 2H), 5.74 (d, J = 7.76 Hz, 1H), 5.62 (s, 1H), 5.33 (s, 1H), 3.90 (s, 3H), 3.64 (s, 3H), 3.47 (s, 3H). ^{13}C NMR: δ 193.1, 164.2, 163.4, 158.9, 142.4, 142.3, 135.1, 129.4, 129.0, 128.9, 128.8, 128.6, 128.5, 128.1, 128.0, 127.8, 126.7, 126.6, 126.2, 126.1, 126.0, 124.1, 108.1, 104.7, 80.9, 62.1, 53.2, 48.9, 48.1.Anal. Calcd. for $C_{48}H_{39}NO_7$; C, 77.72; H, 5.30; N, 1.89; Found C, 77.59; H, 5.16; N, 1.82.

Dimethyl-2,5-dimethyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (8). Yellow crystalline solid; mp 168-170 °C. IR(KBr) ν_{max}: 2955, 1742, 1721, 1681, 1647, 1593, 1566, 1438, 1283, 1236, 1148 cm^{-1}. ^1H NMR: δ 7.33-7.24 (m, 3H), 7.13 (t, J = 8.10 Hz, 1H), 6.89 (s, 1H), 6.39 (dd, J = 7.68, 14.15 Hz, 1H), 6.25-6.19 (m, 1H), 6.06 (s, 1H), 5.83 (q, J = 7.74 Hz, 1H), 3.94 (s, 3H), 3.61 (s, 3H), 1.96 (s, 3H), 1.83 (s, 3H). ^{13}C NMR: δ 186.1, 163.9, 163.2, 156.3, 153.7, 143.6, 138.6, 134.6, 129.7, 129.0, 127.5, 127.2, 125.0, 125.3, 123.6, 109.9, 104.9, 104.6, 79.3, 53.3, 52.0, 17.4, 15.6. Anal. Calcd. for $C_{23}H_{21}NO_6$; C, 67.80; H, 5.20; N, 3.44; Found C, 67.52; H, 5.19; N, 3.82.

Dimethyl-2-oxo-spiro[naphthylene-1,2'-[2*H*,11b*H*][1,3]oxazino[2,3a]isoquinoline] -3',4'-dicarboxylate (18). Yellow crystalline solid; mp 165-167 °C. IR(KBr) ν_{max}: 2955, 1739, 1708, 1679, 1594, 1565, 1431, 1277, 1236, 1148 cm^{-1}. ^1H NMR: δ 8.12 (d, J = 7.60 Hz, 1H), 7.56 (t, J = 7.48 Hz, 1H), 7.39 (t, J = 7.52 Hz, 1H), 7.25-7.06 (m, 5H), 6.92 (s, 1H), 6.71 (d, J = 9.77 Hz, 1H), 6.36 (d, J = 7.73 Hz, 1H), 5.81-5.76 (m, 2H), 3.97 (s, 3H), 3.44 (s, 3H). ^{13}C NMR: δ 196.2, 163.9, 163.5, 144.3, 136.9, 134.6, 132.9, 130.4, 129.7, 129.4, 129.3, 128.9, 128.3, 128.1, 127.7,

127.6, 127.3, 127.1, 126.2, 125.1, 123.1, 108.3, 104.9, 79.3, 53.3, 51.5. HRMS (EI) for $C_{25}H_{19}NO_6$; Calcd. 429.1212; Found 429.1139.

Dimethyl-6-oxo-spiro[naphthylene-1,2'-[2*H*,11b*H*][1,3]oxazino[2,3a]isoquinoline] -3',4'-dicarboxylate (19). Yellow crystalline solid; mp 170-172 °C. IR(KBr) ν_{max}: 2955, 1742, 1708, 1667, 1598, 1570, 1430, 1320, 1277, 1149 cm^{-1}. ^1H NMR: δ 7.44-7.03 (m, 9H), 6.84 (s, 1H), 6.41 (d, J = 7.72 Hz, 1H), 6.24 (d, J = 9.93 Hz, 1H), 5.79 (d, J = 7.74 Hz, 1H), 3.99 (s, 3H), 3.46 (s, 3H). ^{13}C NMR: δ 196.7, 163.5, 163.3, 144.9, 144.7, 140.3, 130.6, 130.3, 129.6, 129.5, 129.2, 128.7, 127.6, 127.0, 126.8, 125.7, 124.9, 123.4, 123.1, 109.3, 104.8, 78.3, 53.1, 51.4. HRMS (EI) for $C_{25}H_{19}NO_6$; Calcd. 429.1212; Found 429.1255

Dimethyl-3,5-(t-butyl)-6-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (20). Yellow semi-solid. IR(film) ν_{max}: 2955, 1742, 1708, 1667, 1593, 1566, 1430, 1276, 1229, 1148 cm^{-1}. ^1H NMR: δ 7.25-7.20 (m, 3H), 7.06 (d, J = 7.37 Hz, 1H), 6.89-6.84 (m, 2H), 6.35 (d, J = 7.71 Hz, 1H), 5.76 (d, J = 7.72 Hz, 1H), 5.52 (d, J = 2.22 Hz, 1H), 3.96 (s, 3H), 3.55 (s, 3H), 1.31 (s, 9H), 1.11 (s, 9H). ^{13}C NMR: δ 198.1, 164.0, 163.7, 145.1, 143.9, 142.7, 135.1, 130.0, 129.2, 128.3, 127.9, 126.9, 126.3, 125.1, 123.4, 109.3, 104.3, 78.1, 53.2, 51.1, 34.6, 31.2, 29.4, 28.5. HRMS (EI) for $C_{29}H_{33}NO_6$; Calcd. 491.2308; Found 491.2310.

Dimethyl-4,6-(t-butyl)-2-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (21). Yellow semi-solid. IR(film) ν_{max}: 2955, 1742, 1708, 1667, 1592, 1566, 1430, 1276, 1230, 1150 cm^{-1}. ^1H NMR: δ 7.25-7.13 (m, 3H), 7.04 (d, J = 7.49 Hz, 1H), 6.92 (s, 1H), 6.54 (d, J = 1.29 Hz, 1H), 6.31 (d, J = 7.75 Hz, 1H), 5.95 (d, J = 1.31 Hz, 1H), 5.73 (d, J = 7.74 Hz, 1H), 3.97 (s, 3H), 3.55 (s, 3H), 1.22 (s, 9H), 1.14 (s, 9H). ^{13}C NMR: δ 200.0, 164.1, 163.7, 144.3, 142.5, 136.2, 130.4, 129.9, 129.1, 127.8, 126.9, 126.3, 124.9, 123.7, 123.1, 115.8, 104.6, 78.6, 53.2, 51.3, 37.9, 35.7, 31.4, 28.3.HRMS (EI) for $C_{29}H_{33}NO_6$; Calcd. 491.2308; Found 491.2314.

Dimethyl-2-oxospiro[acenaphthylene-1,2'[2*H*,11b*H*][1,3]oxazino[2,3a] isoquinoline] -3',4'-dicarboxylate (2). Yellow crystalline solid; mp 155-157 °C. IR(KBr) ν_{max}: 2955, 1748, 1728, 1700, 1593, 1573, 1431, 1290, 1222, 1148 cm^{-1}. ^1H NMR: δ 8.05 (q, J = 7.53 Hz, 2H), 7.82 (d, J = 8.16 Hz, 1H), 7.74 (t, J = 7.59 Hz, 1H), 7.57-7.48 (m, 2H), 7.26-7.03 (m, 5H), 6.46 (d, J = 7.75 Hz, 1H), 5.81 (d, J = 7.76 Hz, 1H), 3.99 (s, 3H), 3.17 (s, 3H). ^{13}C NMR: δ 200.8, 163.6, 163.5, 145.1, 143.0, 138.4, 131.4, 130.9, 130.5, 129.7, 129.4, 128.5, 128.1, 127.9, 127.0, 126.2, 125.6, 125.1, 123.2, 122.0, 119.8, 106.1, 105.0, 80.0, 53.3, 51.3. Anal. Calcd. for $C_{27}H_{19}NO_6$; C, 71.52; H, 4.22; N, 3.09; Found C, 76.27; H, 4.44; N, 3.17.

Dimethyl-2-oxospiro[phenanthrene-1,2'-[2H,11b*H*][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (23). Yellow crystalline solid; mp 202-204 °C. IR(KBr) ν_{max}: 2955, 1748, 1708, 1595, 1573, 1431, 1283, 1222, 1162 cm^{-1}. ^1H NMR: δ 8.07 (q, J = 4.56 Hz, 2H), 7.96 (d, J = 7.69 Hz, 1H), 7.70 (t, J = 7.67 Hz, 1H), 7.52 (q, J = 7.05 Hz, 2H), 7.44-7.35 (m, 2H), 7.16 (t, J =7.42 Hz, 1H), 6.98 (d, J = 7.46 Hz, 2H), 6.63 (d, J = 7.57 Hz, 1H), 6.36 (d, J = 7.76 HZ, 1H), 6.23 (s, 1H), 5.72 (d, J = 7.79 Hz, 1H), 4.03 (s, 3H), 3.45 (s, 3H). ^{13}C NMR: δ 193.5, 163.7, 162.9, 145.2, 137.3, 135.9, 134.2, 130.5, 129.2, 129.0, 128.7, 127.9, 127.8, 127.7, 127.4, 126.5,

126.2, 124.9, 124.4, 124.2, 123.1, 122.6, 104.6, 103.8, 79.9, 52.7, 51.0. HRMS (EI) for $C_{29}H_{21}NO_6$; Calcd. 479.1369; Found 479.1380.

Dimethyl-6-oxospiro[phenanthrene-1,2'-[2*H*,11b*H*][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (24). Yellow crystalline solid; mp 192-194 °C. IR(KBr) ν_{max}: 2955, 1748, 1708, 1685, 1600, 1569, 1431, 1276, 1220, 1155 cm^{-1}. ^1H NMR: δ 8.22 (d, J = 7.72 Hz, 1H), 7.96 (dd, J = 8.00, 11.78 Hz, 2H), 7.66 (t, J = 7.65 Hz, 1H), 7.48-7.42 (m, 2H), 7.36-7.23 (m, 2H), 7.16 (t, J = 7.39 Hz, 1H), 7.05-6.98 (m, 3H), 6.77 (s, 1H), 6.41 (d, J = 7.74 Hz, 1H), 5.75 (d, J = 7.74 Hz, 1H), 4.00 (s, 3H), 3.35 (s, 3H). ^{13}C NMR: δ 194.7, 163.8, 163.6, 145.1, 137.3, 136.9, 134.8, 131.2, 129.8, 129.3, 129.3, 129.2, 128.5, 128.2, 127.7, 127.6, 126.9, 125.8, 125.0, 123.6, 123.4, 123.2, 109.5, 104.8, 79.2, 53.3, 51.6. HRMS (EI) for $C_{29}H_{21}NO_6$; Calcd. 479.1369; Found 479.1302.

Dimethyl-2-methoxy-3,5-di(*t*-butyl)-2-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (25). Yellow viscous liquid. IR(film) ν_{max}: 2955, 1748, 1708, 1667, 1600, 1566, 1431, 1270, 1148 cm^{-1}. ^1H NMR: δ 7.28-7.12 (m, 3H), 7.04 (d, J = 8.70 Hz, 2H), 6.62 (s, 1H), 6.33 (d, J = 7.71 Hz, 1H), 5.72 (d, J = 7.72 Hz, 1H), 4.03 (s, 3H), 3.58 (s, 3H), 3.54 (s, 3H), 1.29 (s, 9H), 1.21 (s, 9H). ^{13}C NMR: δ 195.9, 163.8, 163.6, 154.6, 144.9, 141.3, 138.7, 138.4, 130.2, 129.3, 128.6, 127.7, 126.9, 126.1, 124.9, 123.6, 109.5, 104.2, 78.6, 59.5, 53.1, 51.2, 34.6, 34.5, 30.0, 29.8. HRMS (EI) for $C_{30}H_{35}NO_7$; Calcd. 521.2413; Found 521.2452.

Dimethyl-3-(*t*-butyl)-6-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (26). Yellow solid; mp 96-98 °C. IR(KBr) ν_{max}: 2962, 1741, 1708, 1667, 1593, 1566, 1430, 1276, 1236, 1148 cm^{-1}. ^1H NMR: δ 7.31-7.17 (m, 3H), 7.08 (d, J = 7.38 Hz, 1H), 6.87 (s, 1H), 6.46 (d, J = 9.89 Hz, 1H), 6.35 (d, J = 7.71 Hz, 1H), 6.01 (s, 1H), 5.89 (d, J = 9.87 Hz, 1H), 5.79 (d, J = 7.73 Hz, 1H), 3.97 (s, 3H), 3.58 (s, 3H), 1.18 (s, 9H). ^{13}C NMR: δ 198.9, 163.4, 163.0, 144.4, 141.5, 138.7, 130.6, 129.9, 129.3, 128.2, 127.1, 126.3, 125.7, 124.8, 123.2, 118.4, 108.3, 104.9, 78.8, 53.1, 51.3, 35.4, 28.2. HRMS (EI) for $C_{25}H_{25}NO_6$; Calcd. 435.1682; Found 435.1688.

Dimethyl-4-(*t*-butyl)-6-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate(27). Yellow viscous liquid. IR (film) ν_{max}: 2955, 1743, 1712, 1672, 1597, 1565, 1434, 1287 cm^{-1}. ^1H NMR: δ 7.29-7.16 (m, 3H), 7.06 (d, J = 7.50 Hz, 1H), 6.65 (d, J = 10.08 Hz, 1H), 6.43 (d, J = 10.04 Hz, 1H), 6.34 (d, J = 7.73 Hz, 1H), 6.25 (d, J = 9.56 Hz, 1H), 5.98 (s, 1H), 5.75 (d, J = 7.75 Hz, 1H), 3.94 (s, 3H), 3.56 (s, 3H), 1.21 (s, 9H). ^{13}C NMR: δ 195.8, 164.0, 163.4, 144.9, 138.6, 135.3, 130.1, 129.5, 128.2, 127.1, 126.8, 125.9, 125.4, 124.1, 123.8, 119.2, 118.4, 104.6, 79.7, 53.2, 51.5, 35.3, 28.2. HRMS (EI) for $C_{25}H_{25}NO_6$; Calcd. 435.1682; Found 435.1673.

Dimethyl-3-methyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (28). Yellow crystalline solid; mp 195-197 °C. IR (KBr) ν_{max}: 2955, 1742, 1708, 1670, 1647, 1593, 1566, 1431, 1276, 1236, 1155 cm^{-1}. ^1H NMR: δ 7.32-7.21 (m, 3H), 7.16-7.09 (m, 2H), 6.36 (d, J = 7.71 Hz, 1H), 6.29-6.20 (m, 3H), 5.82 (d, J = 7.74 Hz, 1H), 3.95 (s, 3H), 3.58 (s, 3H), 1.85 (s, 3H). ^{13}C NMR: δ 185.4, 163.7, 163.1, 156.6,

148.4, 145.5, 143.3, 129.7, 129.6, 129.1, 128.5, 127.8, 127.7, 127.5, 127.4, 127.2, 125.8, 125.5, 125.3, 123.6,123.4, 109.0, 105.0, 79.4, 53.3, 51.7, 17.7. Anal. Calcd. for $C_{22}H_{19}NO_6$; C, 67.17; H, 4.87; N, 3.56; Found C, 67.27; H, 4.64; N, 3.42.

Dimethyl-2-methyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (29). Yellow crystalline solid; mp 184-186 °C. IR(KBr) ν_{max}: 2955, 1742, 1715, 1670, 1647, 1593, 1566, 1431, 1236 cm^{-1}. ^1H NMR: δ 7.38-7.22 (m, 3H), 7.11 (d, J = 7.56 Hz, 1H), 6.87 (s, 1H), 6.47 (dd, J = 3.03, 9.82 Hz, 1H), 6.34 (d, J = 7.96 Hz, 1H), 6.28 (d, J = 6.26 Hz, 1H), 6.23 (d, J = 4.38 Hz, 1H), 5.80 (d, J = 7.75 Hz, 1H), 3.95 (s, 3H), 3.58 (s, 3H), 1.93 (s, 3H). ^{13}C NMR: δ 186.1, 163.8, 163.4, 147.3, 144.8, 142.7, 138.5, 137.1, 135.1, 130.1, 129.7, 129.6, 128.3, 127.7, 127.3, 127.2, 125.9, 125.4, 123.3, 107.4, 104.9, 79.3, 53.3, 51.75, 15.9. Anal. Calcd. for $C_{22}H_{19}NO_6$; C, 67.17; H, 4.87; N, 3.56; Found C, 67.11; H, 4.749; N, 3.48.

Dimethyl-3-phenyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (30). Yellow crystalline solid; mp 175-177 °C. IR (KBr) ν_{max}: 2955, 1742, 1708, 1670, 1600, 1566, 1431, 1270, 1235, 1148 cm^{-1}. ^1H NMR: δ 7.45-7.20 (m, 5H), 7.13 (t, J = 8.10 Hz, 2H), 7.01 (d, J = 7.47 Hz, 1H), 6.94 (d, J = 7.58 Hz, 1H), 6.40-6.28 (m, 3H), 6.17 (d, J = 1.64 Hz, 1H), 5.73 (d, J = 7.73 Hz, 1H), 5.48 (s, 1H), 3.96 (s, 3H), 3.71 (s, 3H). ^{13}C NMR: δ 186.0, 163.2, 163.1, 156.4, 149.1, 144.9, 142.0, 138.0, 129.5, 129.1, 128.9, 128.6, 128.5, 128.1, 127.9, 127.7, 127.3, 127.1, 125.4, 123.1, 105.0, 79.6, 53.4, 52.0. HRMS (EI) for $C_{27}H_{21}NO_6$; Calcd. 455.1369; Found 455.1349.

Dimethyl-2-phenyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (31). Yellow crystalline solid; mp 162-164 °C. IR(KBr) ν_{max}: 2955, 1742, 1708, 1667, 1593, 1566, 1431, 1276, 1236, 1148 cm^{-1}. ^1H NMR: δ 7.40-7.14 (m, 10H), 6.37 (d, J = 1.77 Hz, 1H), 6.31 (dd, J = 1.75, 10.02 Hz, 1H), 6.19 (s, 1H), 6.05 (d, J = 7.71 Hz, 1H), 5.80 (d, J = 7.73 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 3H). ^{13}C NMR: δ 185.9, 163.7, 162.7, 157.8, 145.0, 143.3, 136.9, 130.0, 129.8, 129.7, 128.7, 128.2, 128.1, 127.7, 127.3, 127.2, 125.6, 125.4, 123.7, 110.3, 104.7, 79.6, 53.1, 51.7. HRMS (EI) for $C_{27}H_{21}NO_6$; Calcd. 455.1369; Found 455.1315.

Dimethyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2*H*,11b*H*][1,3]oxazino[2,3-a] isoquinoline]-3',4'-dicarboxylate (32). Yellow crystalline solid; mp 167-169 °C. IR(KBr) ν_{max}: 2956, 1742, 1702, 1672, 1587, 1562, 1427, 1273, 1233 cm^{-1}. ^1H NMR: δ 7.37-7.25 (m, 3H), 7.14-7.06 (m, 2H), 6.51 (dd, J = 2.94, 9.92 Hz, 1H), 6.36-6.25 (m, 4H), 5.82 (d, J = 7.74 Hz, 1H), 3.96 (s, 3H), 3.59 (s, 3H). ^{13}C NMR: δ 185.4, 163.7, 163.1, 147.6, 145.3, 143.1, 130.3, 129.9, 129.6, 128.4, 127.7, 127.4, 125.8, 125.5, 123.2, 113.7, 111.8, 105.2, 85.9, 53.4, 51.8. HRMS (EI) for $C_{21}H_{17}NO_6$; Calcd. 379.1056; Found 379.1102.

Dimethyl-1,2-dihydro-2-oxo-1-phenylspiro[3H-indole-3,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a] isoquinoline]-3',4'-dicarboxylate (33). Yellow crystalline solid; mp 240-242 °C. IR(KBr) ν_{max}: 2955, 1741, 1711, 1620, 1580, 1501, 1426, 1276, 1145 cm^{-1}. ^1H NMR: δ 7.57-7.48 (m, 4H), 7.44-7.38 (m, 2H), 7.26-7.14 (m, 5H), 7.08 (d, J = 7.54 Hz, 1H), 6.99 (t, J = 7.18 Hz, 1H), 6.79 (d, J = 7.80 Hz, 1H), 6.42 (d, J = 7.73 Hz, 1H), 5.83 (d, J = 7.74 Hz, 1H), 3.98 (s, 3H), 3.53 (s,

3H). ^{13}C NMR: δ 173.3, 163.1, 162.9, 144.8, 144.7, 133.8, 129.5, 129.2, 129.1, 128.9, 127.7, 127.6, 127.5, 126.6, 125.9, 125.5, 124.6, 123.2, 122.8, 122.5, 109.0, 105.1, 104.7, 79.1, 52.8, 51.2. Anal. Calcd. for $C_{29}H_{22}N_2O_6$: C, 70.44; H, 4.48; N, 5.67; Found C, 70.80; H, 4.62; N, 5.51.

Dimethyl-1,2-dihydro-2-oxo-1-methylspiro[3H-indole-3,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a] isoquinoline]-3',4'-dicarboxylate (34). Yellow crystalline solid; mp 210-212 °C. IR(KBr) ν_{max}: 2955, 1742, 1721, 1647, 1593, 1566, 1431, 1276, 1155 cm^{-1}. ^{1}H NMR: δ 7.36 (d, J = 7.48 Hz, 1H), 7.29-7.16 (m, 4H), 7.08 (t, J = 7.57 Hz, 2H), 6.96 (t, J = 7.47 Hz, 1H), 6.80 (d, J = 7.74 Hz, 1H), 6.39 (d, J = 7.73 Hz, 1H), 5.81 (d, J = 7.74 Hz, 1H), 3.97 (s, 3H), 3.46 (s, 3H), 3.28 (s, 3H). ^{13}C NMR: δ 174.5, 163.4, 163.4, 145.3, 145.2, 130.1, 129.8, 129.4, 128.3, 127.1, 126.2, 125.1, 123.4, 123.2, 122.9, 120.4, 108.2, 105.7, 105.2, 79.6, 53.3, 51.7, 26.3. HRMS (EI) for $C_{24}H_{20}N_2O_6$; Calcd. 432.1321; Found 432.1322.

Dimethyl-1,2-dihydro-2-oxo-1-benzylspiro[3H-indole-3,2'-[2*H*,11b*H*] [1,3]oxazino[2,3-a]iso-quinoline]-3',4'-dicarboxylate (35). Yellow crystalline solid; mp 235-237 °C. IR(KBr) ν_{max}: 2955, 1742, 1715, 1600, 1565, 1431, 1351, 1222, 1148, 1000 cm^{-1}. ^{1}H NMR: δ 7.43-7.06 (m, 9H), 6.92 (t, J = 7.47 Hz, 1H), 6.71 (d, J = 7.74 Hz, 1H), 6.40 (d, J = 7.72 Hz, 1H), 5.81 (d, J = 7.74 Hz, 1H), 5.28 (s, 1H), 5.09 (d, J = 15.58 Hz, 1H), 4. 83 (d, J = 15.59 Hz, 1H), 3.98 (s, 3H), 3.30 (s, 3H), 2.81 (s, 2H). ^{13}C NMR: δ 174.6, 164.8, 163.5, 145.5, 144.3, 135.8, 130.0, 129.8, 129.5, 128.8, 128.6, 128.2, 127.7, 127.6, 127.1, 126.3, 125.2, 123.5, 123.2, 123.0, 109.2, 105.2, 104.9, 79.5, 53.3, 51.5, 43.9. HRMS (EI) for $C_{30}H_{24}N_2O_6$; Calcd. 508.1638; Found 508.1673.

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