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Multicomponent reactions involving zwitterionic intermediates for the construction of heterocyclic systems: one pot synthesis of aminofurans and iminolactones

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This paper is dedicated with best wishes to Professor Dr Ivar Ugi, in recognition of his original contributions to Organic Synthesis

Abstract—The reaction of 1:1 zwitterionic intermediate generated in situ from dimethyl acetylenedicarboxylate (DMAD) and cyclohexyl isocyanide with aldehydes and quinones is described. The reaction of stoichiometric amounts of DMAD, isocyanide and aldehydes afforded 2-aminofurans in good yields, while the reaction with quinones gave iminolactones.

1. Introduction

The rich and fascinating chemistry that stems from the addition of nucleophiles to activated acetylenic compounds has evoked considerable interest. Usually the addition of nucleophiles devoid of acidic hydrogen atoms leads to a 1:1 zwitterionic intermediate that can undergo further transformations culminating in a stabilized product.[1] It has been known from the studies of various groups that triphenyl phosphine,[2] pyridine,[3] amines,[4] dimethyl sulfoxide,[5] phosphoranes,[6] and isocyanides[7] can invoke the zwitterion formation. Investigations in our own laboratory have shown that the zwitterionic intermediate generated by the reaction of triphenylphosphine and dimethyl acetylenedicarboxylate (DMAD) underwent facile addition to 1,2- and 1,4-benzoquinones to afford highly functionalized novel unsaturated γ-spirolactones in good yields.[8] The success of this reaction provided us with a conceptual framework for designing novel multicomponent reactions (MCRs). Of special interest to us has been the addition of nucleophilic carbenes such as isocyanides to DMAD; a reaction that has been investigated in detail.[9] The initially formed 1:1 zwitterionic intermediate can undergo further reaction with DMAD and isocyanide in different molar proportions leading to various adducts. When the reaction was carried out in a protic solvent such as ethanol, the zwitterionic intermediate got protonated and concomitant attack of the resulting nucleophile generated afforded an imino ester and a ketenimine.[9] In all these cases, the observed product formation could be explained through the involvement of an externally stabilized 1,3-dipolar intermediate **1** as shown in the Figure 1.[10]

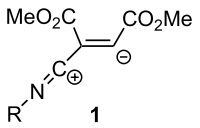

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Figure 1.

Against the literature background given above and in view of our general interest in the synthesis of heterocyclic compounds by the reaction of dipolar species with carbonyl compounds,[11] we were intrigued by the possibility of trapping the zwitterionic intermediate derived from activated acetylenes and isocyanide with a third component, thus constituting novel multicomponent reactions.[12,13] Although previous attempts to trap the zwitterionic intermediate with various olefinic dipolarophiles such as dimethylmaleate, cyclohexene etc. have failed,[9e] with the assumption that a judicious choice of the third component would set off an MCR, we have undertaken a thorough investigation of the addition of the zwitterionic intermediate of isocyanide and DMAD with a number of aldehydes, quinones and other 1,2-diones. The rational design here is supported by the fact that isocyanides have a high affinity towards activated acetylenes rather than to carbonyl

Keywords: isocyanides; multicomponent reactions; dimethyl acetylenedicarboxylate; aldehydes.
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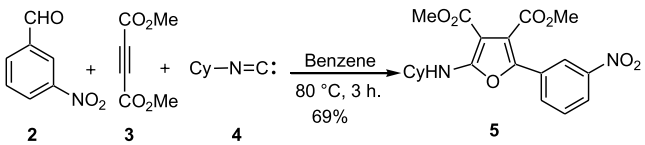
compounds. Although it has been suggested that the reaction of isocyanides and carbonyl compounds produce α-iminooxiranes,[14] to date, no successful attempt at isolating any products from such reactions has been documented. The results of our investigations validating the assumption and the usefulness of the process, leading to novel aminofurans and iminolactones are presented below.

2. Results and discussion

2.1. Reaction with aldehydes

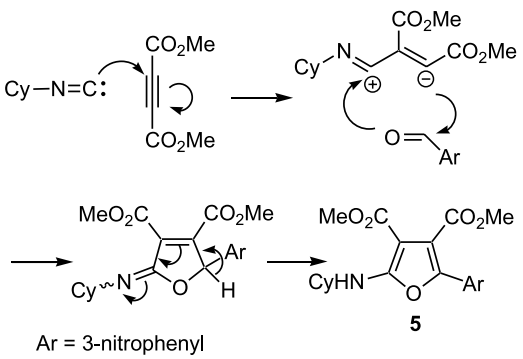
Our investigations were initiated with 3-nitrobenzaldehyde, which on treatment with dimethylacetylenedicarboxylate (DMAD) in presence of stoichiometric amount of cyclohexyl isocyanide in refluxing benzene afforded a product characterized as the aminofuran **5** in 69% yield (Scheme 1).[15]



Scheme 1.

The IR spectrum showed strong absorption at 3367 cm^{-1} indicating the presence of amine functionality. The sharp bands at 1726 and 1663 cm^{-1} were assigned to the two ester carbonyls. In the ^1H NMR spectrum, the signals due to methoxy groups were observed at δ 3.79 and 3.94 as two singlets and the amine hydrogen atom resonated as a doublet at δ 6.70 (exchangeable by D_2O). In the ^{13}C NMR spectrum, the two ester carbonyls were observed at δ 164.6 and 165.2. The $^1H-^{13}C$ connectivity was established unambiguously by 2D-HETCORE analysis.

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1:1 zwitterionic intermediate between cyclohexyl isocyanide and DMAD, which adds to the aldehyde carbonyl leading to a dipolar species. Cyclization of the latter leads to the dihydrofuranone derivative. Subsequently, it undergoes a [1,5] hydrogen shift to yield the aminofuran derivative as the end product. Alternatively, a cycloaddition of the zwitterion to the C=O can also lead to the dihydrofuran derivative (Scheme 2).

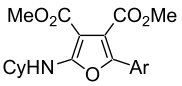


Scheme 2.

Similar reactivity was observed with other aromatic aldehydes, which underwent facile reaction with DMAD and cyclohexyl isocyanide yielding the corresponding aminofuran derivatives in good yields. The results obtained are presented in Table 1.

Table 1. Reaction of aldehydes with DMAD and isocyanide

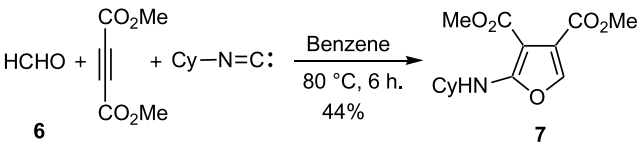
Entry	ArCHO	t (h)	Yield (%)[a]	Product
1	**2a**·2-$NO_2C_6H_4CHO$	3	74	
2	**2b**·3-ClC_6H_4CHO	2	61	
3	**2c**·4-ClC_6H_4CHO	2.5	67	
4	**2d**·4-$CF_3C_6H_4CHO$	7	72	
5	**2e**·C_6H_5CHO	8	61	
6	**2f**·4-$MeOC_6H_4CHO$	9	35	
7	**2g**·4-MeC_6H_4CHO	8	43	
8	**2h**·Furfural	3	68	
9	**2i**·1-Naphthaldehyde	8	54	
10	**2j**·9-Anthraldehyde	8	57	



5a-j

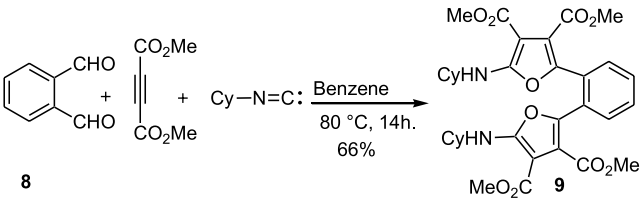
Reaction conditions: benzene, 80°C; Cy=cyclohexyl.
[a] Isolated yield.

Paraformaldehyde **6** on reaction under similar conditions afforded the product **7** in 44% yield (Scheme 3).



Scheme 3.

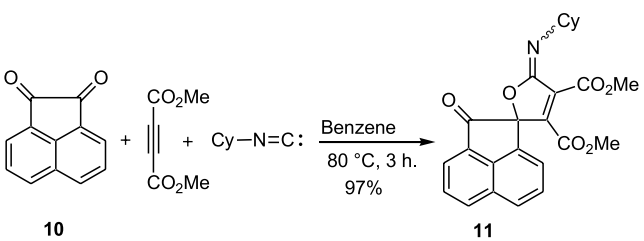
Interestingly, phthalaldehyde **8** when treated with two equivalents of DMAD and isocyanide afforded the bis adduct **9** in 66% yield (Scheme 4).



Scheme 4.

2.2. Reaction with quinones

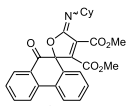
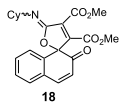
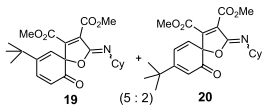
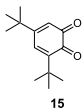
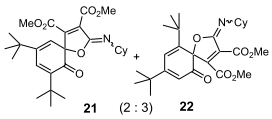
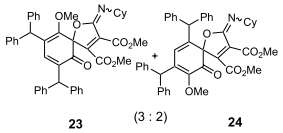
Subsequently we have investigated the reaction of the zwitterionic intermediate with both 1,2 and 1,4-quinones. In a pilot experiment, we observed that a mixture of acenaphthenequinone **10** and DMAD at 80°C in benzene, when treated with cyclohexyl isocyanide afforded the iminolactone **11** in 97% yield (Scheme 5).[16]



Scheme 5.

The structure of the product was established by spectroscopic analysis. Similar reactivity was observed with various 1,2-quinones (**12**–**16**) yielding the iminolactones. The results obtained are summarized in Table 2.

Table 2. Reaction of 1,2-quinones with DMAD and isocyanide

Entry	Quinone	Time (h)	Product(s)	Yield (%)[a]
1	 **12**	6	 **17**	92[b]
2	 **13**	7	 **18**	64[b]
3	 **14**	3	 **19** (5 : 2) **20**	68[c]
4	 **15**	8	 **21** (2 : 3) **22**	58[c]
5	 **16**	5	 **23** (3 : 2) **24**	82[c]

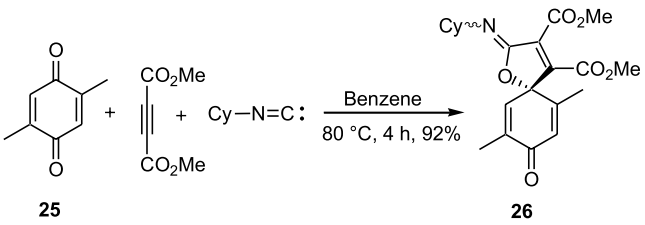
Reaction conditions: benzene, 80°C; Cy=cyclohexyl.
[a] Isolated yield.
[b] Purified by crystallisation.
[c] Purified by column chromatography.

Interestingly, the reaction of 1,2-naphthoquinone **13** afforded a single product **18**, which was purified by crystallization from CH_2Cl_2–hexane mixture. The benzoyl carbonyl being more reactive of the two undergoes addition in preference to the enone carbonyl.

4-*tert*-Butyl-1,2-benzoquinone **14** afforded an inseparable mixture of regioisomers **19** and **20** in 5:2 ratio. Reaction of 3,5-di-*tert*-butyl-1,2-benzoquinone **15** gave a 2:3 regioisomeric mixture of iminolactones **21** and **22**. The isomers were separated by radial chromatography on a Chromatotron® and characterized by spectroscopic analysis. Similar reactivity was observed with 3-methoxy-4,6-bis(1,1-diphenyl methyl)-1,2-benzoquinone **16** which gave an inseparable mixture of regioisomers **23** and **24** in 3:2 ratio.

As in the aminofuran formation, it is reasonable to assume that the reaction involves the initial formation of a zwitterionic intermediate from cyclohexyl isocyanide and DMAD, which adds to the carbonyl moiety of the quinone in a [3+2] fashion or by a two step process involving addition and cyclization to yield the iminolactone

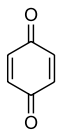
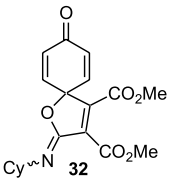
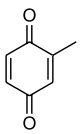
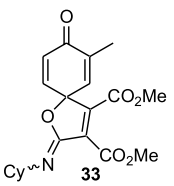
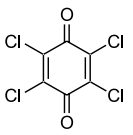
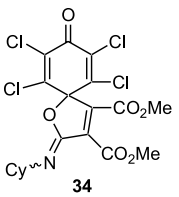
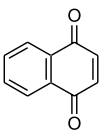
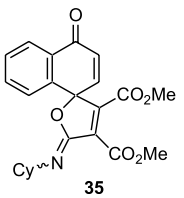
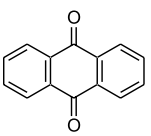
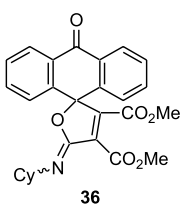
In view of the interesting results obtained by the addition of the zwitterionic intermediate generated from DMAD and cyclohexyl isocyanide to 1,2-benzoquinones, it was logical to explore the reactivity of 1,4-benzoquinones towards the zwitterionic intermediate. 2,5-Dimethyl-1,4-benzoquinone **25** when treated with DMAD and cyclohexyl isocyanide in benzene at 80°C for 4 h afforded the iminolactone **26** in 92% yield (Scheme 6).



Scheme 6.

The structure of the product was assigned on the basis of spectroscopic analysis. Finally, the assigned structure was confirmed unambiguously by single crystal X-ray analysis.[16]

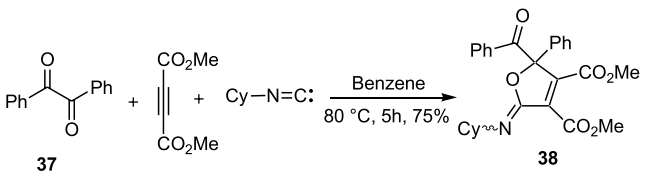
Table 3. Reactions of 1,4-quinones with cyclohexyl isocyanide and DMAD

Entry	Quinone	Time (h)	Product	Yield (%)[a]
1	 **27**	5	 **32**	55
2		3	 **33**	67
3		8	 **34**	63
4		3	 **35**	89
5		4	 **36**	57

Reaction conditions: benzene, 80°C, Cy=cyclohexyl.
[a] Isolated yield.

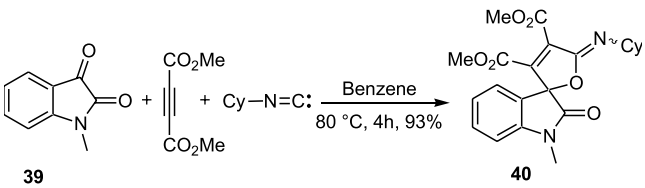
Similar results were obtained with other 1,4-benzoquinones yielding the iminolactones **32**–**36**; the results are summarized in Table 3.

An acyclic 1,2-dione such as benzil **37**, on treatment with DMAD and cyclohexyl isocyanide in benzene afforded the iminolactone **38** in 75% yield (Scheme 7).



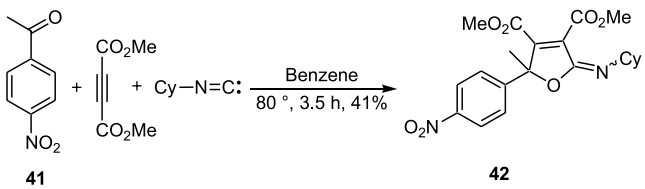
Scheme 7.

N-Methyl isatin **39** when treated with DMAD and cyclohexyl isocyanide afforded the iminolactone **40** in 93% yield (Scheme 8). The product was purified by chromatography on alumina and characterized by spectroscopic analysis.



Scheme 8.

Interestingly, even aromatic ketones such as 4-nitroacetophenone **41** on treatment with DMAD and cyclohexyl isocyanide in benzene afforded the iminolactone **42** in 41% yield (Scheme 9).



Scheme 9.

In conclusion, we have uncovered some novel and efficient multiple component condensation reactions for the synthesis of 2-aminofurans and iminolactones. It may be mentioned that, recently aminofurans have been found to undergo facile Diels–Alder reactions leading to hexahydroindolinones;[17] they also serve as useful intermediates in the synthesis of aromatic as well as aliphatic molecules.[18]

Iminolactones are potentially amenable to a number of synthetic transformations; for example they can be easily hydrolysed to spirolactones, a structural motif, present in a number of biologically active natural products such as kijanolide, tetranolide and chlorothricolide.[19]

3. Experimental

3.1. General

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Bruker 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 constant (J) is reported in hertz (Hz). Mass spectra were recorded under EI/HRMS using Jeol JMS 600H mass spectrometer. IR spectra were recorded on Nicolet Impact 400D FT-IR spectrophotometer. Elemental analyses were performed on a Perkin–Elmer-2400 Elemental Analyzer. Dimethyl acetylenedicarboxylate was purchased from Aldrich Chemical Co. and was used without further purification. Cyclohexyl isocyanide was prepared by a reported procedure.[20] Commercial grade solvents were distilled prior to use. (Hazard Warning: Benzene is a suspected carcinogen and due care must be taken in the handling) Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate as the binder. Gravity column was performed using 100–200 mesh silica gel and mixtures of hexane and ethyl acetate were used for elution.

3.1.1. Typical experimental procedure and spectral data for dimethyl-2-(cyclohexylamino)-5-(3-nitrophenyl)-3,4-furandicarboxylate 5. A mixture of 3-nitrobenzaldehyde (200 mg, 1.32 mmol) and DMAD (207 mg 1.45 mmol) in dry benzene (15 mL) was purged with argon for 5 min. To this mixture, cyclohexyl isocyanide (159 mg, 1.45 mmol) was added by a syringe and the reaction mixture was refluxed for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 85:15 hexane–ethyl acetate mixture gave the aminofuran **5** as an yellow solid (366 mg, 69%). Mp 122–123°C (recrystallized from CH_2Cl_2–hexane). IR (KBr) ν_{max}: 3367 (NH), 2943, 2849, 1726 (C=O), 1663 (C=O), 1620, 1532 cm^{-1}. ^{1}H NMR: δ 1.39–2.07 (10H, m, Cy), 3.79 (4H, s, CO_2CH_3, C*H*NH), 3.94 (3H, s, CO_2CH_3), 6.70 (1H, d, J=7.8 Hz, N*H*), 7.51 (1H, t, J=8.0 Hz, Ar*H*), 7.80 (1H, d, J=7.7 Hz, Ar*H*), 8.06 (1H, d, J=8.1 Hz, Ar*H*), 8.33 (1H, s, Ar*H*). ^{13}C NMR: δ 24.6, 25.5, 33.6, 51.3, 51.7, 52.8, 88.2, 116.3, 119.2, 121.7, 129.7, 129.8, 130.9, 138.3, 148.8, 161.5, 164.6, 165.2. Anal. calcd for $C_{20}H_{22}N_2O_7$: C, 59.68; H, 5.51; N, 6.96. Found: C, 59.62; H, 5.47; N, 6.71.

3.1.2. Dimethyl-2-(cyclohexylamino)-5-(2-nitrophenyl)-3,4-furandicarboxylate 5a. Yellow viscous oil (399 mg, 74%). IR (film) ν_{max}: 3355, 2937, 2856, 1732, 1676, 1613, 1470, 1357, 1226 cm^{-1}. ^{1}H NMR: δ 1.22–1.96 (10H, m, Cy), 3.46 (1H, m, C*H*NH), 3.74 (3H, s, CO_2CH_3), 3.75 (3H, s, CO_2CH_3), 6.60 (1H, d, J=7.8 Hz, N*H*), 7.43–7.58 (3H, m, Ar*H*), 7.81 (1H, d, J=7.8 Hz, C*H*CNO$_2$). ^{13}C NMR: δ 24.5, 25.4, 33.2, 51.0, 51.6, 52.2, 87.2, 116.7, 123.4, 124.3, 129.0, 130.7, 132.1, 137.9, 148.2, 161.9, 164.1, 164.6. HRMS (EI) calcd for $C_{20}H_{22}N_2O_7$: 402.1427. Found: 402.1398.

3.1.3. Dimethyl-2-(cyclohexylamino)-5-(3-chlorophenyl)-3,4-furandicarboxylate 5b. Colorless viscous oil (340 mg, 61%). IR (film) ν_{max}: 3355, 2943, 2856, 1745,

1682, 1626, 1482, 1370, 1226 cm^{-1}. ^1H NMR: δ 1.26–2.05 (10H, m, Cy), 3.76 (1H, m, C*H*NH), 3.77 (3H, s, CO_2CH_3), 3.90 (3H, s, CO_2CH_3), 6.62 (1H, d, J=8.0 Hz, N*H*), 7.21–7.46 (4H, m, Ar*H*). ^{13}C NMR: δ 24.6, 25.6, 33.6, 51.2, 51.5, 52.7, 87.9, 114.9, 122.6, 124.6, 127.54 130.0, 131.0, 134.8, 139.4, 161.3, 164.7, 165.5. HRMS (EI) calcd for $C_{20}H_{22}ClNO_5$: 391.1186. Found: 391.1113.

3.1.4. Dimethyl-2-(cyclohexylamino)-5-(4-chlorophenyl)-3,4-furandicarboxylate 5c. Colorless viscous oil (375 mg, 67%). IR (film) ν_{max}: 3355, 2943, 2856, 1745, 1682, 1626, 1482, 1370, 1226 cm^{-1}. ^1H NMR: δ 1.26–2.05 (10H, m, Cy), 3.76 (1H, m, C*H*NH), 3.77 (3H, s, CO_2CH_3), 3.90 (3H, s, CO_2CH_3), 6.62 (1H, d, J=8.0 Hz, N*H*), 7.21–7.46 (4H, m, Ar*H*). ^{13}C NMR: δ 24.4, 25.3, 33.4, 51.0, 51.4, 52.4, 87.6, 114.0, 125.8, 127.6, 128.7, 133.2, 139.9, 161.1, 164.6, 165.4. HRMS (EI) calcd for $C_{20}H_{22}ClNO_5$: 391.1186. Found: 391.1222.

3.1.5. Dimethyl-2-(cyclohexylamino)-5-(4-trifluoromethyl phenyl)-3,4-furandicarboxylate 5d. Pale yellow viscous oil (306 mg, 72%). IR (film) ν_{max}: 3349, 2937, 2857, 1754, 1703, 1619, 1530, 1440, 1326, 1267 cm^{-1}. ^1H NMR: δ 1.31–2.11 (10H, m, Cy), 3.78 (1H, m, C*H*NH), 3.83 (3H, s, CO_2CH_3), 3.96 (3H, s, CO_2CH_3), 6.73 (1H, d, J=7.9 Hz, N*H*), 7.65 (4H, m, Ar*H*). ^{13}C NMR: δ 24.4, 25.3, 33.3, 51.0, 51.5, 52.5, 88.0, 115.7, 124.2, 125.5, 125.6, 132.4, 139.0, 161.3, 164.4, 165.3. HRMS (EI) calcd for $C_{21}H_{22}NO_5F_3$: 425.1450. Found: 425.1458.

3.1.6. Dimethyl-2-(cyclohexylamino)-5-phenyl-3,4-furan dicarboxylate 5e. Viscous pale yellow oil (407 mg, 61%). IR (film) ν_{max}: 3353, 2935, 2854, 1735, 1681, 1613, 1472, 1357, 1222 cm^{-1}. ^1H NMR: δ 1.26–2.07 (10H, m, Cy), 3.73 (1H, m, C*H*NH), 3.78 (3H, s, CO_2CH_3), 3.90 (3H, s, CO_2CH_3), 6.60 (1H, d, J=7.8 Hz, N*H*), 7.23–7.53 (5H, m, Ar*H*). ^{13}C NMR: δ 24.7, 25.6, 33.6, 51.2, 51.6, 52.6, 87.7, 113.6, 124.8, 127.7, 128.7, 129.4, 141.1, 161.4, 165.0, 165.9. HRMS (EI) calcd for $C_{20}H_{23}NO_5$: 357.1576. Found: 357.1523.

3.1.7. Dimethyl-2-(cyclohexylamino)-5-(4-methoxyphenyl)-3,4-furandicarboxylate 5f. Colorless viscous liquid (135 mg, 35%). IR (KBr) ν_{max}: 3361, 2937, 2856, 1751, 1688, 1595, 1513, 1439, 1258, 1170 cm^{-1}. ^1H NMR: δ 1.27–2.04 (10H, m, Cy), 3.68 (1H, m, C*H*NH), 3.76 (3H, s, PhO*Me*), 3.80 (3H, s, CO_2CH_3), 3.86 (3H, s, CO_2CH_3), 6.56 (1H, d, J=7.7 Hz, N*H*), 6.88 (2H, d, J=8.5 Hz, Ar*H*), 7.47 (2H, d, J=8.5 Hz, Ar*H*). ^{13}C NMR: δ 24.5, 25.4, 33.5, 50.9, 51.4, 52.2, 55.1, 87.2, 111.8, 114.0, 122.0, 126.6, 141.8, 159.3, 161.0, 164.9, 165.7. HRMS (EI) calcd for $C_{21}H_{25}NO_6$: 387.1682. Found: 387.1649.

3.1.8. Dimethyl-2-(cyclohexylamino)-5-(4-methylphenyl)-3,4-furandicarboxylate 5g. Colorless viscous liquid (158 mg, 43%). IR (film) ν_{max}: 3335, 2930, 2852, 1736, 1682, 1622, 1468, 1362, 1273 cm^{-1}. ^1H NMR: δ 1.11–2.04 (10H, m, Cy), 2.34 (3H, s, Ph*Me*), 3.69 (1H, m, C*H*NH), 3.74 (3H, s, CO_2CH_3), 3.83 (3H, s, CO_2CH_3), 6.59 (1H, d, J=7.8 Hz, N*H*), 7.11 (2H, d, J=7.8 Hz, Ar*H*), 7.37 (2H, d, J=7.9 Hz, Ar*H*). ^{13}C NMR: δ 21.3, 24.3, 24.5, 25.5, 32.2, 33.4, 50.8, 51.2, 52.0, 87.5, 112.8, 124.8, 126.6, 129.1, 137.1, 141.4, 161.0, 164.6, 165.3. HRMS (EI) calcd for $C_{21}H_{25}NO_5$: 371.1682. Found: 387.1649.

3.1.9. Dimethyl-2-(cyclohexylamino)-5-(2-furyl)-3,4-furan dicarboxylate 5h. Pale brown crystalline solid (470 mg, 68%). Mp 136–137°C (recrystallized from CH_2Cl_2–hexane). IR (KBr) ν_{max}: 3349, 3130, 2930, 2856, 1732, 1676, 1607, 1483, 1365, 1269, 1237, 1220, 1148 cm^{-1}. ^1H NMR: δ 1.25–2.04 (10H, m, Cy), 3.70 (1H, m, C*H*NH), 3.76 (3H, s, CO_2CH_3), 3.88 (3H, s, CO_2CH_3), 6.42 (s, 1H), 6.58 (1H, d, J=2.9 Hz, N*H*), 6.64 (d, J=7.8 Hz, 1H), 7.41 (s, 1H). ^{13}C NMR: δ 24.5, 25.4, 33.5, 51.0, 51.4, 52.2, 86.7, 107.5, 111.3, 112.8, 134.8, 142.4, 144.1, 161.3, 164.4, 164.9. HRMS calcd for $C_{18}H_{21}NO_6$: 347.1368. Found: 347.1375.

3.1.10. Dimethyl-2-(cyclohexylamino)-5-(1-naphthyl)-3,4-furan dicarboxylate 5i. Pale yellow viscous oil (439 mg, 54%). IR (film) ν_{max}: 3332, 2932, 2862, 1736, 1676, 1568, 1439, 1368, 1230 cm^{-1}. ^1H NMR: δ 1.24–2.01 (10H, m, Cy), 3.61 (3H, s, CO_2CH_3), 3.62 (1H, m, C*H*NH), 3.79 (3H, s, CO_2CH_3), 6.72 (1H, d, J=8.0 Hz, N*H*), 7.42–7.61 (4H, m, Ar*H*), 7.82–7.98 (3H, m, Ar*H*). ^{13}C NMR: δ 24.3, 25.2, 33.4, 50.8, 51.2, 51.8, 86.5, 116.3, 124.9, 125.3, 125.9, 126.3, 128.2, 128.3, 129.5, 131.6, 133.5, 142.5, 161.9, 164.4, 164.9. HRMS (EI) calcd for $C_{24}H_{25}NO_5$: 407.1733. Found: 407.1712.

3.1.11. Dimethyl-2-(9-anthryl)-5-(cyclohexylamino)-3,4-furan dicarboxylate 5j. Yellow amorphous solid (130 mg, 57%). IR (film) ν_{max}: 3338, 3054, 2936, 2848, 1728, 1682, 1568, 1458, 1370, 1310, 1232 cm^{-1}. ^1H NMR: δ 1.18–1.98 (10H, m, Cy), 3.32 (3H, s, CO_2CH_3), 3.55 (1H, m, C*H*NH), 3.84 (3H, s, CO_2CH_3), 6.84 (1H, d, J=8.1 Hz, N*H*), 7.40–7.47 (4H, m, Ar*H*), 7.85–7.98 (4H, m, Ar*H*), 8.48 (1H, s, Ar*H*). ^{13}C NMR: δ 24.4, 25.3, 33.5, 50.9, 51.1, 51.5, 86.1, 118.8, 123.1, 125.3, 125.8, 126.4, 128.4, 129.3, 131.1, 132.1, 162.8, 163.8, 165.3. HRMS (EI) calcd for $C_{28}H_{27}NO_5$: 457.1889. Found 457.1885.

3.1.12. Dimethyl-2-(cyclohexylamino)-3,4-furandicarboxylate 7. Pale brown viscous liquid (123 mg, 44%). IR (film) ν_{max}: 3355, 2937, 2856, 1744, 1676, 1607, 1470, 1357, 1239 cm^{-1}. ^1H NMR: δ 1.18–1.92 (10H, m, Cy), 3.51 (1H, m, C*H*NH), 3.71 (3H, s, CO_2CH_3), 3.73 (3H, s, CO_2CH_3), 6.71 (1H, d, J=7.8 Hz, N*H*), 7.15 (1H, s, OC*H*C). ^{13}C NMR: δ 24.5, 25.3, 33.5, 50.8, 51.1, 51.5, 84.4, 118.0, 136.9, 162.6, 163.5, 165.4. HRMS (EI) calcd for $C_{14}H_{19}NO_5$: 281.1263. Found 281.1301.

3.1.13. Dimethyl-2-(cyclohexylamino)-5-{2-[5-cyclohexyl amino)-3,4-bis(methoxycarbonyl)-2-furyl]phenyl}-3,4-furandicarboxylate 9. Pale yellow crystalline solid (209 mg, 66%). Mp 145–146°C (recrystallized from CH_2Cl_2–hexane). IR (KBr) ν_{max}: 3357, 2934, 2854, 1749, 1678, 1610, 1520, 1470, 1449, 1364, 1255 cm^{-1}. ^1H NMR: δ 1.10–1.79 (20H, m, Cy), 3.29 (2H, m, C*H*NH), 3.76 (6H, s, CO_2CH_3), 3.80 (6H, s, CO_2CH_3), 6.46 (2H, d, J=8.2 Hz, N*H*), 7.34–7.37 (2H, m, Ar*H*), 7.56–7.59 (2H, m, Ar*H*). ^{13}C NMR: δ 24.5, 25.3, 33.8, 50.8, 51.3, 52.0, 86.1, 114.9, 127.8, 128.4, 130.2, 142.0, 161.4, 164.6, 164.8. Anal. calcd for $C_{34}H_{40}N_2O_{10}$: C, 64.14; H, 6.33; N, 4.40. Found: C, 64.43; H, 6.34; N, 4.28.

3.1.14. Typical experimental procedure and spectral data for spiro[acenaphthylene-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-2-one 11. A mixture of acenaphthenequinone (182 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene was purged with argon for 5 min. To this mixture, cyclohexyl isocyanide (120 mg. 1.1 mmol) was added by a syringe and the reaction mixture was refluxed for 3 h. The solvent was removed under vacuum and the product was crystallized from CH_2Cl_2–hexane mixture. It was washed with hexane (4×3 mL) to give **11** as a pale brown amorphous solid (427 mg, 97%). Mp 218–219°C.

IR (KBr) ν_{max}: 2955, 2928, 2854, 1755, 1721, 1688, 1647, 1445, 1303 cm^{-1}. ^1H NMR: δ 1.16–1.76 (10H, m, Cy), 3.46 (3H, s, CO_2CH_3), 3.54 (1H, m, C*H*N), 3.97 (3H, s, CO_2CH_3), 7.34–8.19 (6H, m, Ar*H*). ^{13}C NMR: δ 24.9, 25.8, 33.2, 33.4, 52.7, 53.2, 56.9, 90.7, 121.5, 123.2, 127.1, 128.7, 128.8, 132.2, 133.8, 138.3, 141.2, 143.1, 154.7, 160.3, 161.9, 195.4. Anal. calcd for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N, 3.23. Found: C, 69.41; H, 5.32; N, 3.16.

3.1.15. Spiro[phenanthrene-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-2-one 17. Pale yellow crystalline solid (424 mg, 92%). Mp 221–222°C. IR (KBr) ν_{max}: 2924, 2850, 1751, 1719, 1682, 1601, 1451, 1364, 1295, 1270 cm^{-1}. ^1H NMR: δ 1.19–1.86 (10H, m, Cy), 3.46 (3H, s, CO_2CH_3), 3.55 (1H, m, C*H*N), 3.94 (3H, s, CO_2CH_3), 7.25–7.49 (4H, m, Ar*H*), 7.71–7.73 (1H, m, Ar*H*), 8.04–8.13 (3H, m, Ar*H*). ^{13}C NMR: δ 24.7, 25.7, 32.9, 33.2, 52.5, 53.0, 56.8, 86.7, 123.1, 123.8, 128.2, 128.6, 129.4, 130.0, 131.2, 133.4, 135.4, 144.1, 154.9, 160.0, 161.6, 190.5. HRMS (EI) calcd for $C_{27}H_{25}NO_6$: 459.1681. Found: 459.1709.

3.1.16. Spiro[naphthylene-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-2-one 18. Pale brown crystals (263 mg, 64%). Mp 190–191°C. IR (KBr) ν_{max}: 2927, 2853, 1757, 1726, 1676, 1434 cm^{-1}. ^1H NMR: δ 1.18–1.72 (10H, m, Cy), 3.54 (1H, m, C*H*N), 3.61 (3H, s, CO_2CH_3), 3.94 (3H, s, CO_2CH_3), 6.28 (1H, d, J=9.9 Hz, Ar*H*), 7.26–7.50 (4H, m, Ar*H*), 7.51 (1H, d, J=10.0 Hz, Ar*H*). ^{13}C NMR: δ 24.7, 24.8, 25.7, 33.0, 33.2, 52.7, 53.0, 56.7, 85.6, 124.3, 128.0, 130.0, 130.4, 130.6, 136.1, 137.3, 143.7, 145.5, 154.9, 160.0, 161.7, 191.6. HRMS (EI) calcd for $C_{23}H_{23}NO_6$: 409.1525. Found: 409.1473.

3.1.17. Dimethyl-7-(*tert*-butyl)-2-(cyclohexylimino)-10-oxo-1-oxaspiro[4.5]deca-3,6,8-triene-3,4-dicarboxylate 19 and dimethyl-8-(*tert*-butyl)-2-(cyclohexylimino)-10-oxo-1-oxaspiro[4.5]deca-3,6,8-triene-3,4-dicarboxylate 20. Pale yellow solid (274 mg, 68%). IR (KBr) ν_{max}: 2932, 2859, 1748, 1739, 1669, 1646, 1573, 1440, 1348, 1275 cm^{-1}. ^1H NMR: δ 1.12–1.71 (38H, m, Cy,C(CH_3)$_3$), 3.42 (1H, m, C*H*N), 3.55 (1H, m, C*H*N), 3.69 (3H, s, CO_2CH_3), 3.76 (3H, s, CO_2CH_3), 3.84 (3H, s, CO_2CH_3), 3.91 (3H, s, CO_2CH_3), 5.77 (1H, d, J=1.8 Hz, COC*H*), 6.07 (1H, s, COC*H*), 6.10 (1H, s, C*HC*^{t}Bu), 6.19 (1H, d, J=10.3 Hz, C=C*H*), 6.55–6.59 (1H, dd, J=8.4, 1.5 Hz, C*HC*^{t}Bu), 7.18–7.23 (1H, dd, J=7.9, 2.3 Hz, C*HC*^{t}Bu). ^{13}C NMR: δ 24.7, 24.8, 24.9, 25.1, 25.8, 28.0, 28.1, 28.4, 32.8, 32.9, 33.0, 33.3, 33.4, 34.4, 34.7, 35.7, 52.4, 52.5, 52.7, 53.0, 56.6, 56.7, 57.1, 57.2, 77.4, 83.8, 117.0, 119.1, 125.2, 125.5, 125.6, 127.2, 127.3, 133.0, 138.3, 142.0, 142.2, 146.5, 153.1, 154.6, 159.9, 161.5, 161.7, 161.8, 163.6, 193.4. HRMS (EI) calcd for $C_{23}H_{29}NO_6$: 415.1995. Found: 415.1973.

3.1.18. Dimethyl-7,9-di(*tert*-butyl)-2-(cyclohexylimino)-10-oxo-1-oxaspiro-[4.5]deca-3,6,8-triene-3,4-dicarboxylate 21. Pale yellow puffy solid (96 mg, 22%). IR (KBr) ν_{max}: 2937, 2862, 1755, 1738, 1689, 1445, 1376, 1226 cm^{-1}. ^1H NMR: δ 1.17 (9H, s, ^{t}Bu), 1.24 (9H, s, ^{t}Bu), 1.28–1.91 (10H, m, Cy), 3.59 (1H, m, C*H*N), 3.67 (3H, s, CO_2CH_3), 3.89 (3H, s, CO_2CH_3), 5.69 (1H, d, J=1.9 Hz, ^{t}BuCC*H*C), 6.95 (1H, s, ^{t}BuCC*HC*^{t}Bu). ^{13}C NMR: δ 24.8, 24.9, 28.4, 29.0, 29.2, 33.0, 33.4, 35.0, 52.4, 53.0, 56.0, 86.8, 123.1, 135.8, 137.1, 143.7, 144.5, 146.8, 153.0, 160.3, 161.9, 193.1. HRMS (EI) calcd for $C_{27}H_{37}NO_6$: 471.2621. Found: 471.2643.

3.1.19. Dimethyl-6,8-di(*tert*-butyl)-2-(cyclohexylimino)-10-oxo-1-oxaspiro-[4.5]deca-3,6,8-triene-3,4-dicarboxylate 22. Pale yellow solid (153 mg, 36%). IR (KBr) ν_{max}: 2930, 2850, 1751, 1732, 1676, 1576, 1432, 1351, 1283 cm^{-1}. ^1H NMR: δ 1.15 (9H, s, ^{t}Bu), 1.18 (9H, s, ^{t}Bu), 1.21–1.82 (10H, m, Cy), 3.60 (1H, m, C*H*N), 3.65 (3H, s, CO_2CH_3), 3.83 (3H, s, CO_2CH_3), 5.92 (1H, d, J=1.2 Hz, ^{t}BuCC*H*C), 6.52 (1H, d, J=1.1 Hz, ^{t}BuCC*HC*^{t}Bu). ^{13}C NMR: δ 24.7, 25.7, 28.1, 31.0, 32.8, 33.7, 35.9, 38.1, 52.4, 52.7, 56.9, 86.0, 116.4, 123.4, 135.7, 146.3, 153.1, 154.9, 160.5, 161.4, 165.0, 194.4. HRMS (EI) calcd for $C_{27}H_{37}NO_6$: 471.2621. Found: 471.2599.

3.1.20. Dimethyl-7,9-dibenzhydryl-2-(cyclohexylimino)-6-methoxy-10-oxo-1-oxaspiro[4.5]deca-3,6,8-triene-3,4-dicarboxylate 23 and dimethyl 6,8-dibenzhydryl-2-(cyclohexylimino)-9-methoxy-10-oxo-1-oxaspiro[4.5]-deca-3,6,8-triene-3,4-dicarboxylate 24. Yellow solid (255 mg, 82%). IR (KBr) ν_{max}: 2924, 2856, 1751, 1726, 1682, 1495, 1445 cm^{-1}. ^1H NMR: δ 1.05–1.07 (20H, m, Cy), 3.33 (3H, s, OCH_3), 3.40 (1H, m, C*H*N), 3.51 (3H, s, OCH_3), 3.61 (4H, s, CO_2CH_3), *CHN* 3.71 (3H, s, CO_2CH_3), 3.82 (3H, s, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 4.67 (1H, s, PhC*H*Ph), 5.36 (1H, s, PhC*H*Ph), 5.58 (1H, s, PhC*H*Ph), 5.79 (1H, s, PhC*H*Ph), 5.84 (1H, s, C*H*=C), 6.52 (1H, s, C*H*=C), 6.86–7.31 (40H, m, ArH). ^{13}C NMR: δ 24.5, 24.6, 25.7, 32.8, 33.0, 33.4, 47.9, 48.5, 48.9, 51.5, 52.1, 52.5, 52.7, 52.8, 56.4, 56.6, 59.7, 62.5, 88.6, 87.5, 126.4, 126.8, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.6, 135.9, 137.3, 139.0, 139.5, 140.1, 140.7, 140.8, 141.0, 141.3, 141.5, 143.3, 143.4, 144.1, 146.6, 152.1, 154.3, 154.8, 159.7, 159.7, 161.1, 161.4, 189.7, 190.7. HRMS (EI) calcd for $C_{46}H_{43}NO_7$: 721.3040. Found: 721.3072.

3.1.21. Dimethyl-2-(cyclohexylimino)-6,9-dimethyl-8-oxo-1-spiro[4.5]deca-3,6,9-triene-3,4-dicarboxylate 26. White crystalline solid (212 mg, 92%). Mp 167–168°C. IR (KBr) ν_{max}: 2930, 2856, 1757, 1726, 1682, 1646, 1439, 1357, 1283 cm^{-1}. ^1H NMR: δ 1.25–1.84 (10H, m, Cy), 1.85 (3H, d, J=1.1 Hz, CCH_3), 1.93 (3H, d, J=1.2 Hz, CCH_3), 3.59 (1H, m, C*H*N), 3.71 (3H, s, CO_2CH_3), 3.92 (3H, s, CO_2CH_3), 6.22 (1H, d, J=1.22 Hz, CC*H*CO), 6.32 (1H, d, J=1.40 Hz, CC*H*C). ^{13}C NMR: δ 15.5, 17.2, 24.6, 24.8, 25.7, 33.3, 33.5, 52.9, 53.2, 56.8, 85.1, 129.2, 136.8, 138.1,

138.7, 142.6, 151.3, 153.9, 159.9, 161.6, 185.3. HRMS(EI) calcd for $C_{21}H_{25}NO_6$: 387.1681. Found: 387.1690.

Crystal data for **26**: $C_{21}H_{25}NO_6$. M=387.42. The crystal used for X-ray study has the dimensions of 0.36×0.30×0.22 mm. M=387.42, monoclinic, space group $P2_1$, unit cell dimensions: a=13.5925(2) Å, b=9.4664(2) Å, c=16.2656(2) Å, a=90°, b=91.052(1)°, y=90°, V=2092.576(6) Å^3, D_c=1.230 mg/m^3. CCDC number 220681.

3.1.22. Dimethyl-2-(cyclohexylimino)-8-oxo-1-spiro[4.5]-deca-3,6,9-triene-3,4-dicarboxylate 32. Colorless solid (198 mg, 55%). Mp 145–146°C. IR (KBr) ν_{max}: 2939, 2859, 1739, 1682, 1646, 1507, 1407, 1341 cm^{-1}. ^{1}H NMR: δ 1.28–1.88 (10H, m, Cy), 3.58 (1H, m, C*H*N), 3.73 (3H, s, CO_2CH_3), 3.94 (3H, s, CO_2CH_3), 6.38 (s, 2H), 6.59 (s, 2H). ^{13}C NMR: δ 24.6, 24.8, 25.6, 33.3, 52.8, 53.2, 56.7, 82.3, 129.4, 131.0, 139.1, 141.0, 141.8, 153.1, 159.6, 161.5, 183.8. HRMS (EI) calcd for $C_{19}H_{21}NO_6$: 359.1369. Found: 359.1330.

3.1.23. Dimethyl-2-(cyclohexylimino)-7-methyl-8-oxo-1-spiro[4.5]deca-3,6,9-triene-3,4-dicarboxylate 33. White crystalline solid (250 mg, 67%). Mp 156–157°C. IR (KBr) ν_{max}: 2932, 2853, 1732, 1669, 1642, 1507, 1454, 1394 cm^{-1}. ^{1}H NMR: δ 1.27–1.97 (10H, m, Cy), 1.90 (3H, s, CC*H*$_3$), 3.62 (1H, m, C*H*N), 3.75 (3H, s, CO_2CH_3), 3.96 (3H, s, CO_2CH_3), 6.26 (1H, s, CC*H*C), 6.36 (1H, dd, J=9.89, 1.41 Hz, CHC*H*C), 6.59 (1H, d, J=9.9 Hz, COC*H*CH). ^{13}C NMR: δ 17.1, 24.4, 24.5, 25.4, 33.0, 33.1, 52.6, 52.5, 56.6, 84.1, 129.0, 130.5, 138.8, 141.5, 141.8, 151.3, 153.3, 159.4, 161.2, 184.3. HRMS (EI) calcd for $C_{20}H_{23}NO_6$: 373.1525. Found: 373.1520.

3.1.24. Dimethyl-6,7,9,10-tetrachloro-2-(cyclohexylimino)-8-oxo-1-spiro[4.5]deca-3,6,9-triene-3,4-dicarboxylate 34. Colorless solid (315 mg, 63%). Mp 151–152°C. IR (KBr) ν_{max}: 2934, 2859, 1751, 1732, 1695, 1589, 1434, 1346, 1278 cm^{-1}. ^{1}H NMR: δ 1.25–1.77 (10H, m, Cy), 3.62 (1H, m, C*H*N), 3.79 (3H, s, CO_2CH_3), 3.96 (3H, s, CO_2CH_3). ^{13}C NMR: δ 24.5, 25.5, 33.0, 53.3, 57.3, 86.6, 133.0, 138.2, 141.3, 144.2, 151.7, 158.6, 160.4, 169.0. Anal. calcd for $C_{19}H_{17}NO_6Cl_4$: C, 45.90; H, 3.44; N, 2.81. Found: C, 46.10; H, 3.35; N, 2.82.

3.1.25. Spiro[naphthylene-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-8-one 35. White crystalline solid (364 mg, 89%). Mp 155–156°C. IR (KBr) ν_{max}: 2934, 2859, 1751, 1732, 1676, 1599, 1435, 1348 cm^{-1}. ^{1}H NMR: δ 1.24–1.74 (10H, m, Cy), 3.56 (3H, s, CO_2CH_3), 3.60 (1H, m, C*H*N), 3.95 (3H, s, CO_2CH_3), 6.56 (1H, d, J=10.1 Hz, COC*H*CH), 6.72 (1H, d, J=10.1 Hz, CHC*H*C), 7.27 (1H, d, J=7.3 Hz, Ar*H*), 7.52–7.61 (2H, m, Ar*H*), 8.15 (1H, d, J=7.0 Hz, Ar*H*). ^{13}C NMR: δ 24.6, 25.6, 33.1, 33.3, 52.6, 53.1, 56.8, 83.4, 125.6, 126.9, 129.5, 130.8, 131.2, 133.2, 137.4, 141.8, 143.1, 154.0, 159.5, 161.7, 183.1. HRMS (EI) calcd for $C_{23}H_{23}NO_6$: 409.1525. Found 416.1508.

3.1.26. Spiro[anthracene-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-8-one 36. White crystalline solid (254 mg, 57%). Mp 224–225°C (recrystallized from CH_2Cl_2–hexane). IR (KBr) ν_{max}: 2927, 2853, 1745, 1732, 1676, 1600, 1448, 1430, 1322, 1286 cm^{-1}. ^{1}H NMR: δ 1.21–1.82 (10H, m, Cy), 3.41 (3H, s, CO_2CH_3), 3.67 (1H, m, C*H*N), 3.96 (3H, s, CO_2CH_3), 7.44 (2H, d, J=7.5 Hz, Ar*H*) 7.55–7.70 (4H, m, Ar*H*), 8.34 (2H, d, J=7.3 Hz, Ar*H*). ^{13}C NMR: δ 24.7, 25.7, 33.3, 52.6, 53.3, 57.0, 84.8, 125.8, 127.6, 129.7, 131.3, 133.7, 135.8, 138.3, 146.2, 155.1, 159.7, 162.1, 182.6. HRMS (EI) calcd for $C_{27}H_{25}NO_6$: 459.1682. Found: 459.1681.

3.1.27. Dimethyl-2-benzoyl-5-(cyclohexylimino)-2-phenyl-2,5-dihydro-3,4-furandicarboxylate 38. Colorless solid (349 mg, 75%). Mp 102–103°C. IR (KBr) ν_{max}: 2930, 2850, 1740, 1690, 1677, 1448, 1432 cm^{-1}. ^{1}H NMR: δ 1.13–1.87 (10H, m, Cy), 3.57 (1H, m, C*H*N), 3.74 (3H, s, CO_2CH_3), 3.89 (3H, s, CO_2CH_3), 7.35 (7H, m, Ar*H*), 7.48 (1H, m, Ar*H*), 7.87 (2H, m, Ar*H*). ^{13}C NMR: δ 24.8, 25.0, 25.8, 33.2, 33.4, 52.6, 53.0, 57.4, 95.6, 126.4, 128.3, 128.7, 129.3, 131.0, 133.6, 133.7, 134.2, 136.1, 146.3, 153.9, 161.3, 161.9, 192.8. HRMS (EI) calcd for $C_{27}H_{27}NO_6$: 461.1838. Found: 461.1808.

3.1.28. Spiro[1′-methylindole-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-2-one 40. Colorless solid (381 mg, 93%). Mp 162–163°C. IR (KBr) ν_{max}: 2925, 2854, 1732, 1672, 1639, 1606, 1493, 1434, 1367, 1302, 1238 cm^{-1}. ^{1}H NMR: δ 1.19–1.72 (10H, m, Cy), 3.28 (3H, s, NCH_3), 3.57 (1H, m, C*H*N), 3.64 (3H, s, CO_2CH_3), 3.94 (3H, s, CO_2CH_3), 6.89 (1H, d, J=7.8 Hz, Ar*H*), 7.05–7.43 (3H, m, Ar*H*). ^{13}C NMR: δ 24.7, 24.8, 25.8, 26.8, 33.1, 33.2, 52.8, 53.1, 56.8, 77.2, 108.9, 123.4, 124.2, 124.4, 131.5, 138.4, 144.7, 154.2, 159.9, 161.6, 170.1. HRMS (EI) calcd for $C_{22}H_{24}N_2O_6$: 412.1634. Found 412.1655.

3.1.29. Dimethyl-5-(cyclohexylimino)-2-methyl-2-(4-nitrophenyl)-2,5-dihydro-3,4-furandicarboxylate 42. White solid (170 mg, 41%). Mp 118–119°C (recrystallized from CH_2Cl_2–hexane). IR (KBr) ν_{max}: 2932, 2853, 1759, 1732, 1679, 1646, 1606, 1520, 1440, 1354, 1295 cm^{-1}. ^{1}H NMR: δ 1.20–1.74 (10H, m, Cy), 2.08 (3H, s, COCH_3), 3.63 (1H, m, C*H*N), 3.72 (3H, s, CO_2CH_3), 3.92 (3H, s, CO_2CH_3), 7.59 (2H, d, J=8.8 Hz, Ar*H*), 8.22 (2H, d, J=8.8 Hz, Ar*H*). ^{13}C NMR: δ 24.2, 24.8, 25.7, 33.3, 52.9, 53.1, 56.8, 89.0, 123.7, 127.0, 135.9, 145.6, 146.4, 147.9, 154.3, 160.8, 162.3. HRMS (EI) calcd for $C_{21}H_{24}N_2O_7$: 416.1584. Found 416.1696.

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