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SYNTHESIS OF DIHYDROOXEPINS BY THE CYCLOADDITION OF 2-AMINO-4,5-DIHYDRO-3-FURANCARBONITRILES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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Abstract – A facile and efficient synthesis of dihydrooxepins is described. Treatment of readily available 2-amino-4,5-dihydro-3-furancarbonitriles with dimethyl acetylenedicarboxylate at room temperature caused smoothly a cycloaddition reaction, followed by a ring expansion, giving the corresponding dihydrooxepin derivatives.

Seven-membered oxacycles represent an important area of organic chemistry. A remarkable diversity of natural products contains a seven-membered oxacycle in their molecular architecture.[1] Therefore, interest in the synthesis of seven-membered oxacycles has steadily increased in recent years because of their occurrence in natural products[2] and pharmacological applications.[3] Notably, a majority of the natural products are from marine sources. Examples of their occurrence in nature range from the monocyclic zoapatanol,[4] isolaurepinnacin,[5] crambescidin acid,[6] and lobatrienetriol[7] to the highly complex ciguatoxin[8] (Figure 1). Reported pharmacological investigations on these structures showed that they have antiviral,[6] antifungal,[7] and ion-channel blocking[8a] activities. In view of the interest and challenges these molecules present as potential synthetic targets, Elliot[9] and Hoberg[1b] have treated the synthesis of medium ring oxacycles previously in reviews.

In this context, there have been many attempts to develop alternative methods for the synthesis of oxepin derivatives.[10] For example, Nicolaou and coworkers reported the synthesis of dihydrooxepins from dihydrofurans and dimethyl acetylenedicarboxylate (DMAD) through a cycloaddition/ring expansion.[11] Wamhoff and coworkers[12] also discussed the cycloaddition reaction[13] of heterocyclic enamines with DMAD. In the course of our studies on heterocyclic β-enaminonitriles, we have previously reported the cycloaddition reaction of heterocyclic β-enaminonitriles with DMAD.[14] For these reasons, we have been

interested in the development of the methods for the synthesis of dihydrooxepin derivatives. As part of our current studies on the development of new routes in heterocyclic synthesis,[15] we herein wish to report a facile and efficient method for preparing new dihydrooxepin derivatives by the reaction of 2-amino-4,5-dihydro-3-furancarbonitriles as one of versatile starting materials and DMAD.

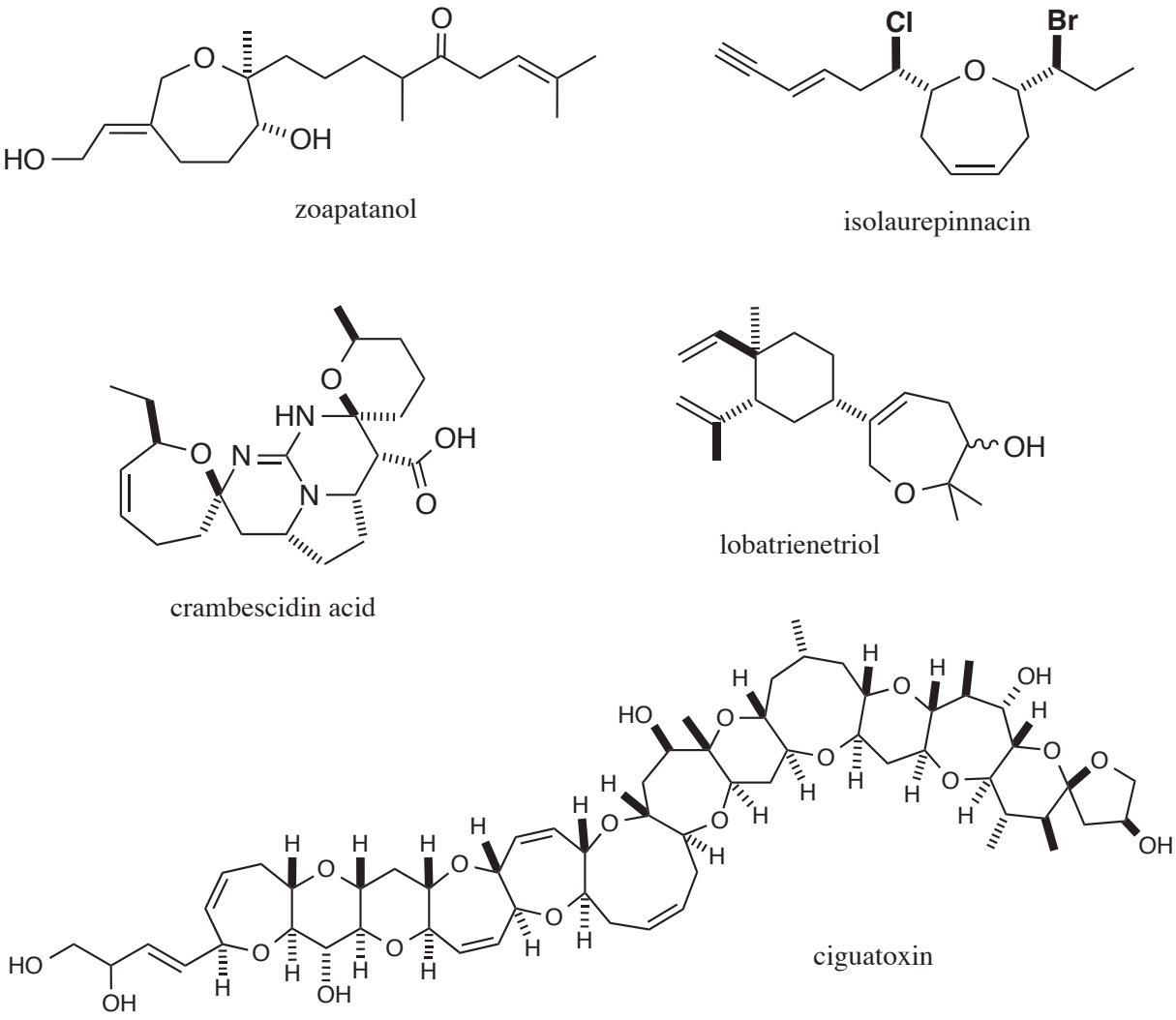
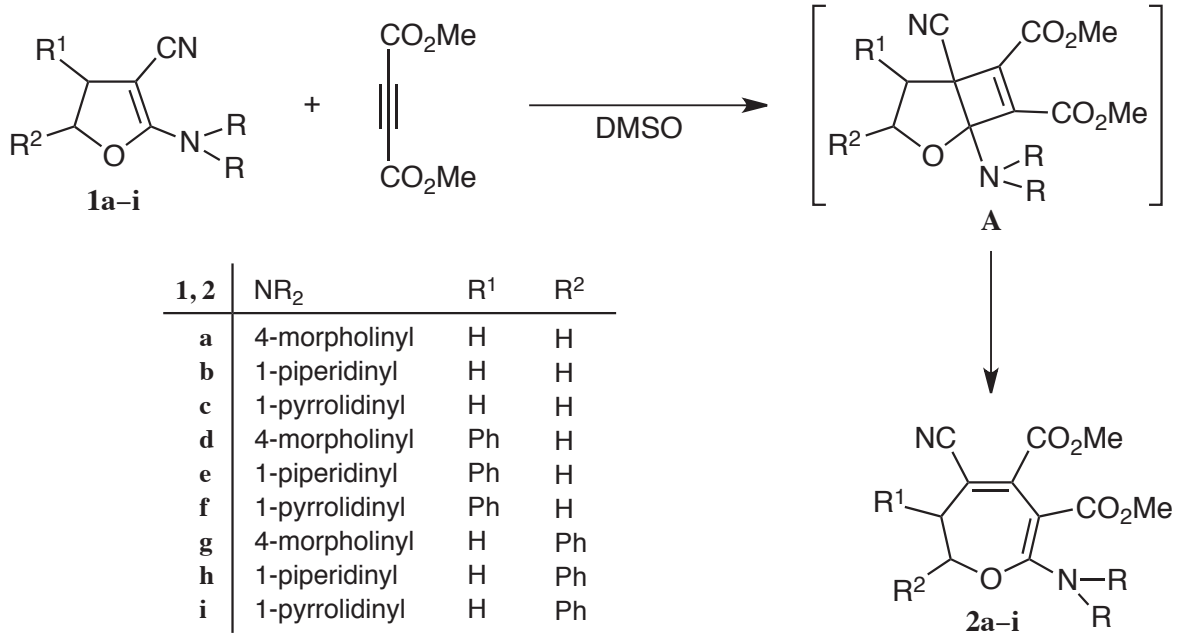


Figure 1. Representative seven-membered oxacycle derivatives

On the basis of the above experimental results together with some literature reports, we focused attention on the extension of our studies to synthesize functionalized dihydrooxepin derivatives, which might have useful biological and therapeutic activities. Thus, we hypothesized that if a cycloaddition reaction of 2-amino-4,5-dihydro-3- furancarbonitriles **1a–i** with DMAD could undergo readily under an appropriate reaction condition, the synthesis of dihydrooxepin derivatives **2a–i** would be possible by a ring expansion of the intermediate cycloadducts **A** (Scheme 1).



1, 2	NR_2	R^1	R^2
a	4-morpholinyl	H	H
b	1-piperidinyl	H	H
c	1-pyrrolidinyl	H	H
d	4-morpholinyl	Ph	H
e	1-piperidinyl	Ph	H
f	1-pyrrolidinyl	Ph	H
g	4-morpholinyl	H	Ph
h	1-piperidinyl	H	Ph
i	1-pyrrolidinyl	H	Ph

Scheme 1

The starting materials, 2-(cyclic amino)-substituted 4,5-dihydro-3-furancarbonitriles **1a–i**, were easily prepared according to our previous investigation.[16] Having optimized the cycloaddition/ring expansion reaction parameters, we then carried out several experiments on dihydrofuran **1a**, testing different reaction conditions, for example, time, solvent, and substrate/DMAD molar ratio (Table 1). Best result was obtained when **1a** was treated with DMAD in DMSO as the solvent (entry 4). Indeed, the cycloaddition/ring expansion reaction proceeded smoothly at room temperature for 24 h, giving the desired dihydrooxepins **2a–i** in moderate to good yields (Table 2).

Table 1. Effect of different reaction conditions for synthesis of dihydrooxepin **2a**

Entry	Substrate	DMAD (Equiv.)	Solvent	Conditions	Product	Yield (%)
1	**1a**	1.5	DMF	rt, 24 h	**2a**	71
2	**1a**	1.0	DMF	100 °C, 1 h	**2a**	41
3	**1a**	1.0	DMSO	rt, 24 h	**2a**	49
4	**1a**	1.5	DMSO	rt, 24 h	**2a**	80
5	**1a**	1.5	MeCN	rt, 24 h	**2a**	57
6	**1a**	1.0	MeOH	reflux, 2 h	**2a**	none
7	**1a**	1.5	toluene	rt, 24 h	**2a**	none

Table 2. Synthesis of dihydrooxepins **2a–i** according to Scheme 1

Entry	Substrate	NR_2	R^1	R^2	Product	Yield (%)
1	**1a**	4-morpholinyl	H	H	**2a**	80
2	**1b**	1-piperidinyl	H	H	**2b**	71
3	**1c**	1-pyrrolidinyl	H	H	**2c**	70
4	**1d**	4-morpholinyl	Ph	H	**2d**	77
5	**1e**	1-piperidinyl	Ph	H	**2e**	77
6	**1f**	1-pyrrolidinyl	Ph	H	**2f**	66
7	**1g**	4-morpholinyl	H	Ph	**2g**	62
8	**1h**	1-piperidinyl	H	Ph	**2h**	77
9	**1i**	1-pyrrolidinyl	H	Ph	**2i**	69

Elemental analyses and IR, ^{1}H NMR, ^{13}C NMR, and MS spectra of **2a–i** are consistent with their assigned structures (see experimental section). For example, the IR spectrum of **2a** reveals a band at 2202 cm^{-1} due to a conjugated cyano group and two bands at 1716 and 1663 cm^{-1} attributable to two ester carbonyl groups. The ^{1}H NMR spectrum of **2a** in DMSO-d_6 exhibits two three-proton singlets at δ 3.52 and 3.67 assignable to the two methyl ester protons. The ^{13}C NMR spectrum of **2a** in DMSO-d_6 shows a signal at δ 75.9 because of the C-3 carbon, a signal at δ 99.2 because of the C-5 carbon, a signal at δ 145.5 because of the C-4 carbon, two signals at δ 164.6 and 168.1 because of the two ester carbonyl carbons, and a signal at δ 173.2 because of the C-2 carbon.

In conclusion, we have demonstrated a facile synthesis of new dihydrooxepin derivatives. A key step is the generation of an intermediate 2-oxabicyclo[3.2.0]hept-6-enes under the mild reaction condition through a cycloaddition reaction of 2-(cyclic amino)-substituted 4,5-dihydro-3-furancarbonitriles and DMAD. This methodology offers significant advantages with regard to the simplicity of operation. Functionalized dihydrooxepin derivatives are important building blocks in organic synthesis and for the preparation of biologically active compounds with interest in medicinal chemistry.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-A500 spectrometer at 500.00 and 125.65 MHz, respectively. The ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to TMS as internal standard. Positive FAB MS spectra were obtained on a JEOL JMS-700T spectrometer. Elemental analyses were performed on YANACO MT-6 CHN analyzer. The substrate **1a–i** were prepared in this laboratory according to procedure reported in literature.[16]

General procedure for the preparation of dihydrooxepins 2a–i from 1a–i and DMAD. A solution of **1a–i** (5 mmol) and DMAD (1.07 g, 7.5 mmol) in DMSO (5 mL) was stirred at rt for 24 h. After removal of the solvent *in vacuo*, cold water was added to the residue. The precipitate was collected by filtration, dried, and recrystallized from an appropriate solvent to give **2a–i**.

Dimethyl 5-cyano-6,7-dihydro-2-(4-morpholinyl)-3,4-oxepindicarboxylate (2a): Colorless prisms (1.61 g, 80%), mp 231–232 °C (MeOH/$CHCl_3$); IR (KBr): ν 2202 (CN), 1716, 1663 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 2.49–2.50 (m, 2H, 6-H), 3.40–3.43 (m, 4H, $2NCH_2$), 3.52 (s, 3H, OCH_3), 3.66–3.68 (m, 4H, $2OCH_2$), 3.67 (s, 3H, OCH_3), 4.57–4.60 (m, 2H, 7-H); ^{13}C NMR (DMSO-d_6): δ 33.1 (C-6), 49.0 ($2NCH_2$), 50.4, 52.1 (OCH_3), 65.6 (OCH_2), 69.9 (C-7), 75.9 (C-3), 99.2 (C-5), 119.2 (CN), 145.5 (C-4), 164.6, 168.1 (CO), 173.2 (C-2); MS: *m/z* 323 $[M+H]^+$. Anal. Calcd for $C_{15}H_{18}N_2O_6$: C, 55.90; H, 5.63; N, 8.69. Found: C, 55.77; H, 5.60; N, 8.71.

Dimethyl 5-cyano-6,7-dihydro-2-(1-piperidinyl)-3,4-oxepindicarboxylate (2b): Colorless prisms (1.14 g, 71%) (dec.) 161–162 °C (Et_2O); IR (KBr): ν 2211 (CN), 1732, 1656 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 1.55–1.64 (m, 6H, $3CH_2$), 2.77 (t, *J* = 5.2 Hz, 2H, 6-H), 3.35–3.38 (m, 4H, $2NCH_2$), 3.50 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 4.57 (t, *J* = 5.2 Hz, 2H, 7-H); ^{13}C NMR (DMSO-d_6): δ 23.3 (piperidine C-4), 25.3 (piperidine C-3 and -5), 33.1 (C-6), 49.7 ($2NCH_2$), 50.3, 52.0 (OCH_3), 69.3 (C-7), 75.3 (C-3), 98.1 (C-5), 119.3 (CN), 145.9 (C-4), 164.8, 168.2 (CO), 173.1 (C-2); MS: *m/z* 321 $[M+H]^+$. Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 59.82; H, 6.28; N, 8.71.

Dimethyl 5-cyano-6,7-dihydro-2-(1-pyrrolidinyl)-3,4-oxepindicarboxylate (2c): Colorless prisms (1.08 g, 70%) (dec.) 181–182 °C (CH_2Cl_2/petroleum ether); IR (KBr): ν 2198 (CN), 1720, 1665 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 1.86–1.90 (m, 4H, $2CH_2$), 2.73 (t, *J* = 4.9 Hz, 2H, 6-H), 3.43 (br s, 4H, $2NCH_2$), 3.50 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 4.61 (t, *J* = 4.9 Hz, 2H, 7-H); ^{13}C NMR (DMSO-d_6): δ 24.4 ($2CH_2$), 32.9 (C-6), 49.8 ($2NCH_2$), 50.1, 52.0 (OCH_3), 70.3 (C-7), 76.1 (C-3), 95.9 (C-5), 119.6 (CN), 146.2 (C-4), 164.1, 168.2 (CO), 171.4 (C-2); MS: *m/z* 307 $[M+H]^+$. Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.55; H, 5.93; N, 9.05.

Dimethyl 5-cyano-6,7-dihydro-2-(4-morpholinyl)-6-phenyl-3,4-oxepindicarboxylate (2d): Colorless prisms (1.56 g, 77%), mp 202–203 °C (CH_2Cl_2/petroleum ether); IR (KBr): ν 2193 (CN), 1725, 1665 cm^{-1} (CO); ^{1}H NMR: (DMSO-d_6): δ 3.33–3.56 (m, 4H, $2NCH_2$), 3.57 (s, 3H, OCH_3), 3.58–3.70 (m, 4H, $2OCH_2$), 3.70 (s, 3H, OCH_3), 4.26 (q, *J* = 3.8 Hz, 1H, 6-H), 4.50 (dd, *J* = 7.8, 11.6 Hz, 1H, 7-H), 4.61 (dd, *J* = 3.8, 11.6 Hz, 1H, 7-H), 7.25–7.27 (m, 2H, aryl H), 7.32–7.36 (m, 1H, aryl H), 7.40–7.43 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 48.0 (C-6), 49.4 ($2NCH_2$), 50.7, 52.3 (OCH_3), 65.8 ($2OCH_2$), 73.2 (C-7), 75.6 (C-3), 101.0 (C-5), 119.0 (CN), 127.9, 128.4, 128.8, 138.3 (C aryl), 146.4 (C-4), 164.7, 168.4 (CO), 172.9 (C-2); MS: *m/z* 399 $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_6$ $0.4H_2O$: C, 62.18; H, 5.47; N, 6.91. Found: C, 62.16: H, 5.46; N, 6.67.

Dimethyl 5-cyano-6,7-dihydro-6-phenyl-2-(1-piperidinyl)-3,4-oxepindicarboxylate (2e): Colorless prisms (1.53 g, 77%), mp 155–158 °C (CH_2Cl_2/petroleum ether); IR (KBr): ν 2202 (CN), 1723, 1661 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 1.52–1.63 (m, 6H, $3CH_2$), 3.34–3.40 (m, 4H, $2NCH_2$), 3.55 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.24 (dd, *J* = 3.4, 7.3 Hz, 1H, 6-H), 4.49 (dd, *J* = 7.3, 11.5 Hz, 1H, 7-H), 4.62 (dd, *J* = 3.4, 11.5 Hz, 1H, 7-H), 7.22–7.25 (m, 2H, aryl H), 7.31–7.35 (m, 1H, aryl H), 7.39–7.43 (m, 2H, aryl-H); ^{13}C NMR (DMSO-d_6): δ 23.3 (piperidine C-4), 25.7 (piperidine C-3 and -5), 48.0 (C-6), 50.1 ($2NCH_2$), 50.6, 52.3 (OCH_3), 72.7 (C-7), 75.0 (C-3), 99.5 (C-5), 119.2 (CN), 127.8, 128.4, 128.8, 138.6 (C aryl), 146.9 (C-4), 164.9, 168.5 (CO), 172.7 (C-2); MS: *m/z* 397 $[M+H]^+$. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.52: H, 6.09; N, 7.00.

Dimethyl 5-cyano-6,7-dihydro-6-phenyl-2-(1-pyrrolidinyl)-3,4-oxepindicarboxylate (2f): Colorless prisms (1.27 g, 66%), mp 207–210 °C (dec.) (CH_2Cl_2/petroleum ether); IR (KBr): ν 2107 (CN), 1731, 1677 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 1.86–1.89 (m, 4H, $2CH_2$), 3.42–3.60 (m, 4H, $2NCH_2$), 3.55 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.21 (dd, *J* = 3.8, 7.8 Hz, 1H, 6-H), 4.54 (dd, *J* = 7.8, 11.9 Hz, 1H, 7-H), 4.62 (dd, *J* = 3.8, 11.9 Hz, 1H, 7-H), 7.25–7.27 (m, 2H, aryl H), 7.31–7.35 (m, 1H, aryl H), 7.39–7.42 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 24.4 ($2CH_2$), 32.9 (C-6), 47.9 (NCH_2), 50.4 (OCH_3), 51.4 ($2NCH_2$), 52.3 (OCH_3) 73.4 (C-7), 75.6 (C-3), 98.0 (C-5), 119.4 (CN), 127.8, 128.4, 128.8, 138.4 (C aryl), 146.9 (C-4), 164.3, 168.5 (CO), 171.5 (C-2); MS: *m/z* 383 $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 65.89: H, 5.85; N, 7.30.

Dimethyl 5-cyano-6,7-dihydro-2-(4-morpholinyl)-7-phenyl-3,4-oxepindicarboxylate (2g): Pale yellow prisms (1.23 g, 62%), mp 173–174 °C (CH_2Cl_2/petroleum ether); IR (KBr): ν 2202 (CN), 1734, 1671 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 2.91 (dd, *J* = 2.3, 17.7 Hz, 1H, 6-H), 3.16 (dd, *J* =10.4, 17.7 Hz, 1H, 6-H), 3.21–3.26 (m, 2H, NCH_2), 3.42–3.47 (m, 2H, NCH_2), 3.55 (s, 3H, OCH_3), 3.59–3.70 (m, 4H, $2OCH_2$), 3.71 (s, 3H, OCH_3), 5.97 (dd, *J* = 2.3, 10.4 Hz, 1H, 7-H), 7.37–7.45 (m, 3H, aryl H), 7.49–7.51 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 39.9 (C-6), 49.3 ($2NCH_2$), 50.6, 52.3 (OCH_3), 65.5 (OCH_2), 77.4 (C-3), 83.1 (C-7), 99.4 (C-5), 119.1 (CN), 126.3, 128.7, 137.9 (C aryl), 145.7 (C-4), 164.6, 168.0 (CO), 171.3 (C-2); MS: *m/z* 399 $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.18; H, 5.57; N, 6.90.

Dimethyl 5-cyano-6,7-dihydro-7-phenyl-2-(1-piperidinyl)-3,4-oxepindicarboxylate (2h): Pale yellow prisms (1.52 g, 77%), mp 181–185 °C (dec.) (CH_2Cl_2/petroleum ether); IR (KBr): ν 2197 (CN), 1726, 1682 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 1.53–1.60 (m, 6H, $3CH_2$), 2.50 (dd, *J* = 2.1, 3.6 Hz, 1H, 6-H), 3.12–3.21 (m, 3H, NCH_2, 6-H), 3.38–3.42 (m, 2H, NCH_2), 3.54 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 5.94 (dd, *J* = 2.1, 10.7 Hz, 1H, 7-H), 7.36–7.45 (m, 3H, aryl H), 7.48–7.51 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 23.3 (piperidine C-4), 25.3 (piperidine C-3 and -5), 40.0 (C-6), 50.0 ($2NCH_2$), 50.5, 52.3 (OCH_3), 76.7 (C-3), 82.2 (C-7), 98.4 (C-5), 119.2 (CN), 126.2, 128.65, 128.71, 138.1 (C aryl), 146.0

(C-4), 164.7, 168.2 (CO), 171.3 (C-2); MS: *m/z* 397 $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.44: H, 6.15; N, 6.99.

Dimethyl 5-cyano-6,7-dihydro-7-phenyl-2-(1-pyrrolidinyl)-3,4-oxepindicarboxylate (2i): Pale yellow columns (1.32 g, 69%), mp 158–159 °C (CH_2Cl_2/petroleum ether); IR (KBr): ν 2205 (CN), 1733, 1676 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 1.78–1.80 (m, 2H, $2CH_2$), 1.93–1.94 (m, 2H, $2CH_2$), 2.87 (dd, *J* = 2.4, 17.4 Hz, 1H, 6-H), 3.05 (dd, *J* = 9.9, 17.4 Hz, 1H, 6-H), 3.25 (br s, 2H, NCH_2), 3.53 (s, 3H, OCH_3), 3.56 (br s, 2H, NCH_2), 3.71 (s, 3H, OCH_3), 6.00 (dd, *J* = 2.4, 9.9 Hz, 1H, 7-H), 7.35–7.44 (m, 3H, aryl H), 7.49–7.51 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 24.4 ($2CH_2$), 39.9 (C-6), 50.0 ($2NCH_2$), 50.3, 52.2 (OCH_3), 77.5 (C-3), 83.0 (C-7), 96.3 (C-5), 119.5 (CN), 126.0, 128.5, 128.6, 138.4 (C aryl), 146.4 (C-4), 164.1, 168.1 (CO), 169.4 (C-2); MS: *m/z* 383 $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 66.15: H, 5.88; N, 7.35.

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