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DIELS-ALDER REACTION OF 2-(CYCLIC AMINO)-SUBSTITUTED 3-FURANCARBONITRILES WITH MALEIMIDES TO PHTHALIMIDES

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Abstract – An efficient Diels-Alder reaction is described in the furan series, leading to phthalimides in high yields. Thermal treatment of 2-(4-morpholinyl, 1-piperidinyl, and 1-pyrrolidinyl)-3-furancarbonitriles with maleimide derivatives, e.g. maleimide, *N*-methylmaleimide, *N*-benzylmaleimide, *N*-phenylmaleimide and *N*-(4-nitrophenyl)maleimide, in boiling acetic acid caused a [4 + 2] cycloaddition reaction to give the corresponding phthalimide derivatives.

INTRODUCTION

Synthetic cyclic imides, such as succinimides, maleimides, glutarimides, phthalimides and related compounds, possess structural features, which confer potential biological activity and pharmaceutical use. Their molecules contain an imide ring so that they are hydrophobic and neutral, and can therefore cross biological membranes *in vivo*. Thalidomide is one of them, which was introduced as a sedative drug, was removed from the market because of its teratogenicity.[1,2] Recently, thalidomide proved its activity as potential inhibitor of TNF-α production[3] and this immunosuppressive property led to its use in the treatment of graft-versus-host disease, leprosy, Behcet’s disease, lupus erythematosus, and other related diseases.[4–9] Furthermore, a new pharmacologically interesting compound within the series of phthalimides, NAN-190, is reported as a well-recognized antagonist of postsynaptic receptors 5-HT$_{1A}$[10] (Figure 1). On the basis of these findings, many laboratories are engaged in the synthesis of various phthalimide derivatives.[11–23] For the reasons given above, the synthesis of cyclic imides, especially phthalimide derivatives, is now receiving considerable interest.

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

Dihydrofuran and furan derivatives widely occur as important structural units in a variety of natural products that can be applied as pharmaceuticals, flavor and fragrance compounds.[24–26] Because they are useful and versatile synthetic intermediates for heterocyclic compounds, the development of methodologies for the synthesis of such compounds are of significant interest. Among the most significant examples in the furan chemistry, Diels-Alder cycloadditions using this heterocycle as the 4π diene are of particular interest.[27–29] This pericyclic process is one of the most employed strategies for the construction of six-membered rings. There are only a few cases in the literature where [4 + 2] cycloadditions of 2-aminofurans have been investigated. 2-Aminofurans revealed especially useful partners in the preparation of cyclohexadiene derivatives and polysubstituted anilines. However, the preparation of 2-aminofurans is only scarcely reported and mainly requires several steps such as cyclopropenone ring opening in the presence of carbonyl metals,[30] preparation of nitrofuroate followed by Pd-catalyzed reduction,[31] dinitration of furan and subsequent displacement of one nitro group by an amine,[32] or metal-free amination of bromoheterocycles.[33] In the course of our studies on heterocyclic β-enaminonitriles, we have already reported the synthesis of 2-(cyclic amino)-substituted 4,5-dihydro-3-furancarbonitriles **1**–**4**.[34,35] In this context, we planned the synthesis of a series of 4-(cyclic amino)-substituted phthalimide derivatives in order to expand the scope application of the Diels-Alder reaction of maleimides by using 2-(cyclic amino)-substituted 3-furancarbonitriles as starting materials.

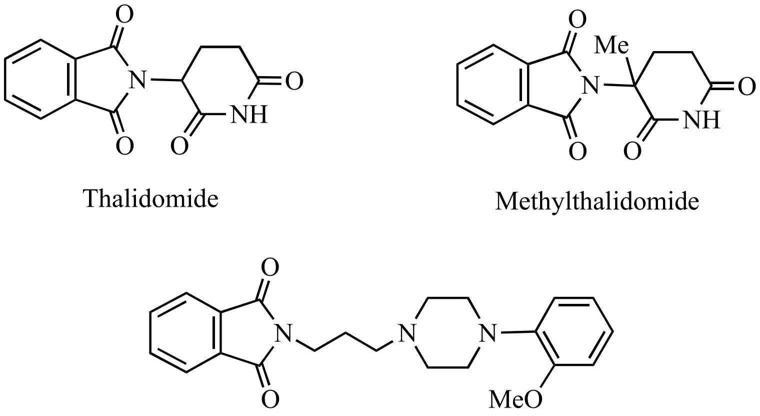
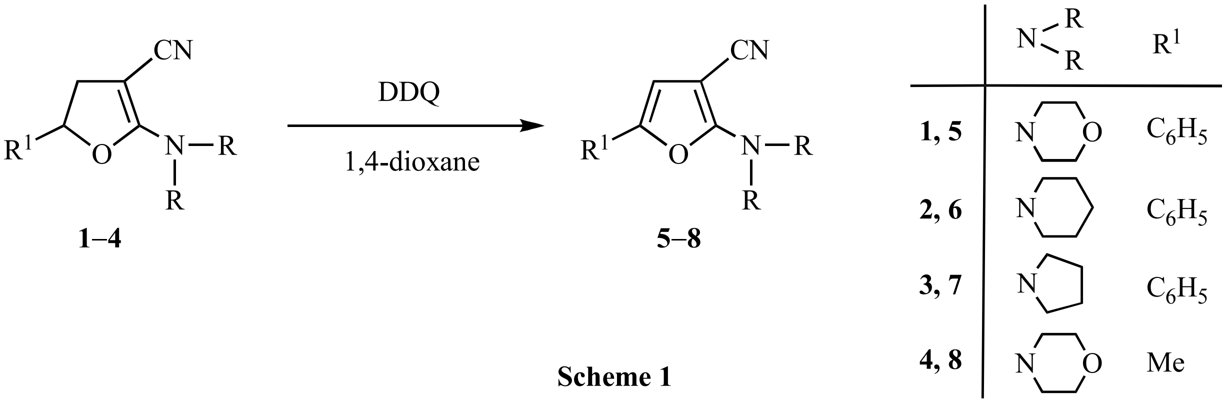


Figure 1. Chemical structures of thalidomide, methylthalidomide, and NAN-190.

RESULTS AND DISCUSSION

In the first step, we tried the dehydrogenation of dihydrofurans **1**–**4** to furans using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). As a consequence, when **1**–**4** were treated with DDQ in refluxing 1,4-dioxane, the expected 2-(cyclic amino)-substituted 3-furancarbonitriles **5**–**8** were obtained in moderate to good yields (**5**: 92%, **6**: 90%, **7**: 96%, **8**: 55%, Scheme 1). Elemental analyses, mass spectra, ^{1}H and ^{13}C NMR spectra of **5–8** are consistent with the assigned structures (see experimental section).

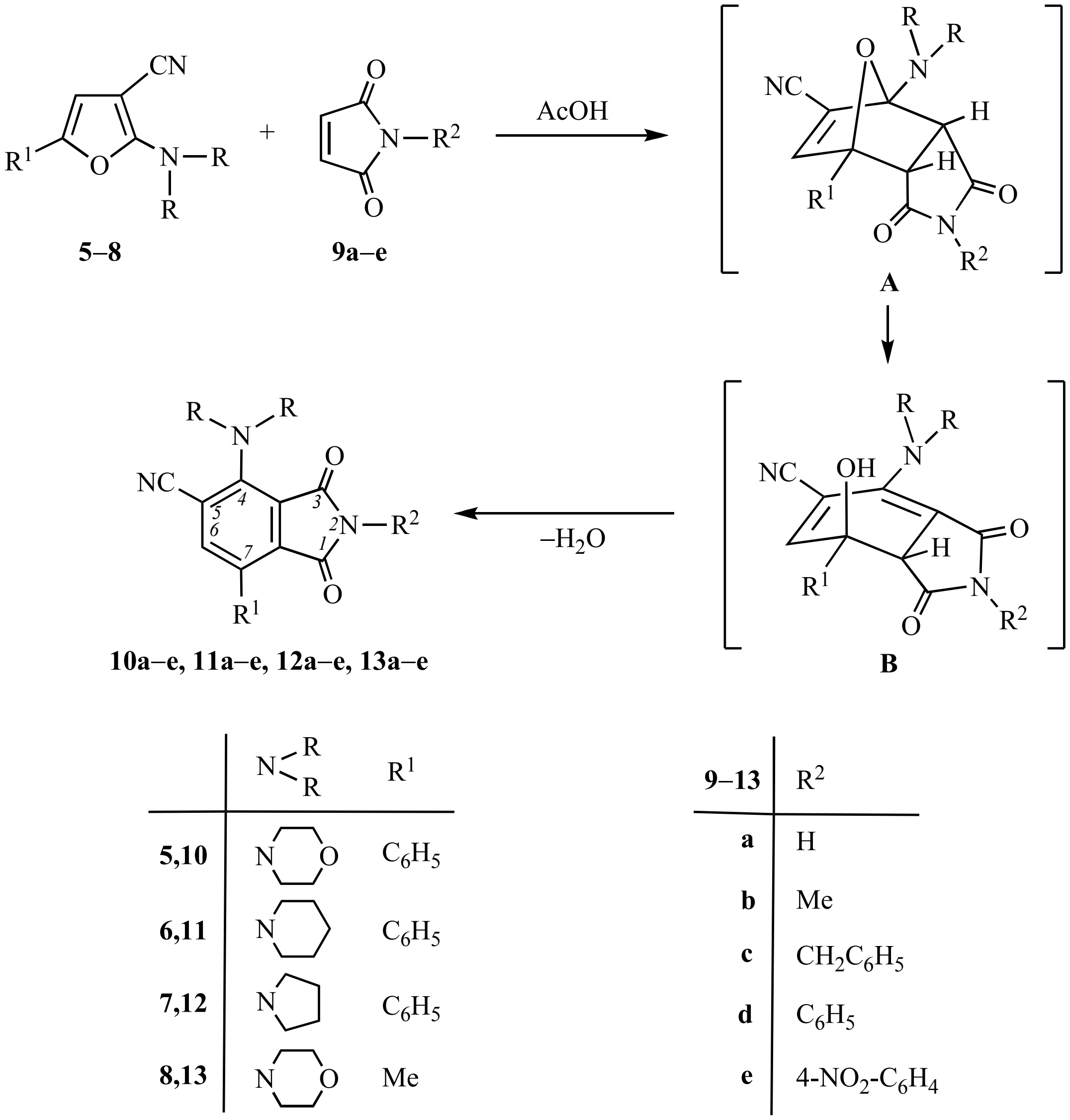


Scheme 1

In the next step, we examined the cycloaddition reaction of 2-(cyclic amino)-substituted 3-furancarbonitriles **5–8** with maleimides **9a–e** to phthalimide derivatives **10–13**. The best results are shown in Scheme 2 and Table 1. Indeed, when a mixture of **5–8** and maleimides **9a–e** in acetic acid was refluxed for 8 h, the desired phthalimides **10a–e**, **11a–e**, **12a–e**, and **13a–e** were obtained in moderate to good yields. The IR spectra of **10–13** display bands near 2220 cm^{-1} due to a conjugated cyano group, and in the range of 1770–1702 cm^{-1} due to two imido carbonyl groups. The ^{13}C NMR spectra of **10–13** show a signal near δ 116 due to the cyano carbon, and two signals near δ 166 due to the imido carbonyl carbon. By comparison of the IR spectra, NMR spectra, mass spectra and elemental analyses of **10–13**, it seems that the structural assignments given to these compounds are correct.

These Diels-Alder reactions are assumed to proceed through the formation of the oxabridged cycloadducts **A**. The literature has only a few examples of the isolation of the oxabridged cycloadducts.[32,36,37] In this reaction, such intermediates **A** were not observed. In all cases, aromatization into phthalimide derivatives **10–13** spontaneously results from a ring-opening reaction of cycloadducts **A** with an acid and subsequent dehydration of the ring-opening intermediates **B**. It is a fact that when these cycloadditions were carried out under the milder reaction conditions, the intermediary of [4 + 2] cycloadducts **A** and/or **B** could not be isolated but instead 2-(cyclic amino)-substituted 3-furancarbonitriles **5–8** were recovered unchanged. It makes us believe that the ring-opening reaction of cycloadducts **A** and dehydration of the ring-opening intermediates **B** can be promoted by using acetic acid not only as a solvent but also as a catalyst.

In conclusion, the Diels-Alder reaction of 2-(cyclic amino)-substituted 3-furancarbonitriles with maleimides proceeds smoothly to furnish the corresponding phthalimide derivatives. Functionalized phthalimide derivatives are important synthons in organic synthesis and for the preparation of biologically active compounds with interest in medicinal chemistry.



Scheme 2

Table 1. Synthesis of phthalimide derivatives **10–13** according to Scheme 2.

Entry	Sustrate	Product	Yield (%)
1	**5**	**10a**	91
2	**5**	**10b**	90
3	**5**	**10c**	78
4	**5**	**10d**	73
5	**5**	**10e**	85
6	**6**	**11a**	86
7	**6**	**11b**	94
8	**6**	**11c**	92
9	**6**	**11d**	88
10	**6**	**11e**	77
11	**7**	**12a**	62
12	**7**	**12b**	82
13	**7**	**12c**	77
14	**7**	**12d**	81
15	**7**	**12e**	52
16	**8**	**13a**	80
17	**8**	**13b**	88
18	**8**	**13c**	75
19	**8**	**13d**	81
20	**8**	**13e**	82

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 sifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. Positive FAB mass spectra were obtained on a JEOL JMS-700T spectrometer. Elemental analyses were performed on YANACO MT-6 CHN analyzer. The starting compounds, 2-(cyclic amino)-substituted 4,5-dihydro-3-furancarbonitriles **1-4**, were prepared in this laboratory according to the procedure reported in literature.[34,35]

General procedure for the preparation of 2-(cyclic amino)-substituted 3-furancarbonitriles 5–8.

A mixture of **1-4** (20 mmol) and DDQ (4.99 g, 22 mmol) in 1,4-dioxane (40 mL) was refluxed for 1 h (in the case of the preparation of **5**–**7**) or 30 min (in the case of the preparation of **8**). The solid was removed by filtration and washed with 1,4-dioxane. The combined filtrates were concentrated *in vacuo*. The residue was purified by column chromatography on alumina with CH_2Cl_2 as the eluent to give **5**–**8**.

2-(4-Morpholinyl)-5-phenyl-3-furancarbonitrile (5)

Colorless columns (4.65 g, 92%), mp 107–108 °C (acetone/petroleum ether); IR (KBr): 2202 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.64 (t, J = 4.9 Hz, 4H, $2NCH_2$), 3.84 (t, J = 4.9 Hz, 4H, $2OCH_2$), 6.58 (s, 1H, 4-H), 7.21–7.25 (m, 1H, aryl H), 7.32–7.36 (m, 2H, aryl H), 7.44–7.47 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 46.4 ($2NCH_2$), 66.0 ($2OCH_2$), 70.4 (C-3), 106.8 (C-4), 116.4 (CN), 122.9, 127.4, 128.8, 129.2 (C aryl), 144.5 (C-5), 161.3 (C-2); MS: *m/z* 255 [M+H]$^+$; Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.93; H, 5.59; N, 11.02.

5-Phenyl-2-(1-piperidinyl)-3-furancarbonitrile (6)

Colorless prisms (4.54 g, 90%), mp 117–118 °C (CH_2Cl_2/petroleum ether); IR (KBr): 2195 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.64–1.75 (m, 6H, $3CH_2$), 3.58–3.66 (m, 4H, $2NCH_2$), 6.56 (s, 1H, 4-H), 7.19–7.22 (m, 1H, aryl H), 7.31–7.35 (m, 2H, aryl H), 7.45–7.47 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 23.9 (piperidine C-4), 25.2 (piperidine C-3, 5), 47.5 ($2NCH_2$), 68.9 (C-3), 107.1 (C-4), 117.2 (CN), 122.7 127.0, 128.7, 129.5 (C aryl), 143.4 (C-5), 161.7 (C-2); MS: *m/z* 253 [M+H]$^+$; Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.14; H, 6.41; N, 11.06.

5-Phenyl-2-(1-pyrrolidinyl)-3-furancarbonitrile (7)

Colorless columns (4.58 g, 96%), mp 133–134 °C (acetone/petroleum ether); IR (KBr): 2194 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.01–2.04 (m, 4H, $2CH_2$), 3.68–3.71 (m, 4H, $2NCH_2$), 6.56 (s, 1H, 4-H), 7.17–7.21 (m, 1H, aryl H), 7.30–7.35 (m, 2H, aryl H), 7.43–7.46 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 25.4 ($2CH_2$), 47.8 ($2NCH_2$), 66.9 (C-3), 107.0 (C-4), 117.5 (CN), 122.5 126.7, 128.7, 129.7 (C aryl), 143.3 (C-5), 160.5 (C-2); MS: *m/z* 239 [M+H]$^+$; Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.67; H, 6.03; N, 11.67.

5-Methyl-2-(4-morpholinyl)-3-furancarbonitrile (8)

Colorless columns (2.11 g, 55%), mp 56−57 °C (Et_2O/petroleum ether); IR (KBr): 2204 (CN) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 3.05−3.51 (m, 4H, $2NCH_2$), 3.78−3.80 (m, 4H, $2OCH_2$), 5.91−5.92 (m, 1H, 4-H); ^{13}C NMR ($CDCl_3$): δ 12.9 (CH_3), 46.6 ($2NCH_2$), 66.0 ($2OCH_2$), 68.8 (C-3), 107.0 (C-4), 116.8 (CN), 142.7 (C-5), 161.3 (C-2); MS: *m/z* 193 $[M+H]^+$; Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.46; H, 6.31; N, 14.51.

General procedure for the preparation of phthalimide derivatives 10-13 from 5-8 and maleimides 9. A mixture of **5-8** (5 mmol) and maleimide (0.97 g, 10 mmol), *N*-methylmaleimide (1.11 g, 10 mmol), *N*-benzylmaleimide (1.87 g, 10 mmol), *N*-phehylmaleimide (1.73 g, 10 mmol), or *N*-(4-nitrophenyl)maleimide (2.18 g, 10 mmol) in acetic acid (5 mL) was refluxed for 8 h. After removal of the solvent *in vacuo*, cold water was added to the residue. The precipitate was isolated by filtration, washed with water, dried and recrystallized from an appropriate solvent to yield **10-13**.

2,3-Dihydro-4-(4-morpholinyl)-1,3-dioxo-7-phenyl-1*H*-isoindole-5-carbonitrile (10a)

Yellow needles (1.52 g, 91%), mp 310−311 °C (acetone); IR (KBr): 3160 (NH), 2224 (CN), 1766, 1722 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.48−3.52 (m, 4H, $2NCH_2$), 3.78−3.81 (m, 4H, $2OCH_2$), 7.39−7.44 (m, 3H, aryl H), 7.45−7.52 (m, 2H, aryl H), 7.98 (s, 1H, 6-H), 11.39 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 51.9 ($2NCH_2$), 66.7 ($2OCH_2$), 111.1 (C aryl), 117.6 (CN), 123.9, 127.7, 128.2, 129.4, 132.8, 134.0, 134.8 (C aryl), 142.8 (C-6), 148.9 (C aryl), 166.5, 167.1 (CO); MS: *m/z* 334 $[M+H]^+$; Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.49; H, 4.62; N, 12.62.

2,3-Dihydro-2-methyl-4-(4-morpholinyl)-1,3-dioxo-7-phenyl-1*H*-isoindole-5-carbonitrile (10b)

Yellow prisms (1.56 g, 90%), mp 192−193 °C (acetone); IR (KBr): 2224 (CN), 1761, 1712 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.97 (s, 3H, CH_3), 3.51 (t, *J* = 4.6 Hz, 4H, $2NCH_2$), 3.81 (t, *J* = 4.6 Hz, 4H, $2OCH_2$), 7.42−7.44 (m, 3H, aryl H), 7.50−7.53 (m, 2H, aryl H), 8.00 (s, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 23.8 (CH_3), 51.9 ($2NCH_2$), 66.7 ($2OCH_2$), 111.1 (C aryl), 117.6 (CN), 123.0, 127.7, 128.2, 129.4, 132.6, 133.3, 134.7 (C aryl), 142.9 (C-6), 148.5 (C aryl), 165.4, 165.9 (CO); MS: *m/z* 348 $[M+H]^+$; Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.16; H, 5.03; N, 12.07.

2,3-Dihydro-4-(4-morpholinyl)-1,3-dioxo-7-phenyl-2-(phenylmethyl)-1*H*-isoindole-5-carbonitrile (10c)

Orange needles (1.65 g, 78%), mp 183−184 °C (acetone); IR (KBr): 2221 (CN), 1760, 1706 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.53 (t, *J* = 4.6 Hz, 4H, $2NCH_2$), 3.80 (t, *J* = 4.6 Hz, 4H, $2OCH_2$), 4.70 (s, 2H, $C\underline{H}_2C_6H_5$), 7.24−7.32 (m, 5H, aryl H), 7.42−7.44 (m, 3H, aryl H), 7.51−7.53 (m, 2H, aryl H), 8.03 (s, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 41.0 ($\underline{C}H_2C_6H_5$), 51.9 ($2NCH_2$), 66.7 ($2OCH_2$), 111.1 (C aryl), 117.6 (CN), 122.5, 127.3, 127.4, 127.7, 128.3, 128.4, 129.4, 132.7, 132.9, 134.6, 136.4 (C aryl), 143.2 (C-6), 148.8 (C aryl), 165.1, 165.7 (CO); MS: *m/z* 424 $[M+H]^+$; Anal. Calcd for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92. Found: C, 73.74; H, 5.09; N, 9.93.

2,3-Dihydro-4-(4-morpholinyl)-1,3-dioxo-2,7-diphenyl-1*H*-isoindole-5-carbonitrile (10d)

Orange prisms (1.50 g, 73%), mp 197−198 °C (acetone); IR (KBr): 2222 (CN), 1768, 1717 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.55−3.58 (m, 4H, $2NCH_2$), 3.79−3.82 (m, 4H, $2OCH_2$), 7.38−7.45 (m, 6H, aryl H), 7.47−7.51 (m, 2H, aryl H), 7.56−7.58 (m, 2H, aryl H), 8.08 (s, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 52.0 ($2NCH_2$), 66.7 ($2OCH_2$), 110.8 (C aryl), 117.6 (CN), 122.5, 127.5, 127.7, 128.0, 128.3, 128.6, 129.5, 131.7, 132.8, 133.0, 134.7 (C aryl), 143.3 (C-6), 148.9 (C aryl), 164.4, 164.9 (CO); MS: *m/z* 410 $[M+H]^+$; Anal. Calcd for $C_{25}H_{19}N_3O_3$: C, 73.34; H, 4.68; N, 10.26. Found: C, 73.71; H, 4.79; N, 10.22.

2,3-Dihydro-4-(4-morpholinyl)-2-(4-nitrophenyl)-1,3-dioxo-7-phenyl-1*H*-isoindole-5-carbonitrile (10e)

Orange needles (1.91 g, 85%), mp 234−235 °C (acetone); IR (KBr): 2222 (CN), 1770, 1722 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.58 (t, *J* = 4.6 Hz, 4H, $2NCH_2$), 3.82 (t, *J* = 4.6 Hz, 4H, $2OCH_2$), 7.43−7.46 (m, 3H, aryl H), 7.57−7.60 (m, 2H, aryl H), 7.73−7.75 (m, 2H, aryl H), 8.11 (s, 1H, 6-H), 8.35−8.38 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 52.0 ($2NCH_2$), 66.7 ($2OCH_2$), 110.8 (C aryl), 117.6 (CN), 122.3, 123.9, 127.8, 127.9, 128.3, 129.4, 132.8, 134.6, 137.5 (C aryl), 143.6 (C-6), 146.2, 149.0 (C aryl), 163.8, 164.3 (CO); MS: *m/z* 455 $[M+H]^+$; Anal. Calcd for $C_{25}H_{18}N_4O_5$: C, 66.08; H, 3.99; N, 12.33. Found: C, 66.09; H, 4.11; N, 12.27.

2,3-Dihydro-1,3-dioxo-7-phenyl-4-(1-piperidinyl)-1*H*-isoindole-5-carbonitrile (11a)

Orange needles (1.44 g, 86%), mp 256−257 °C (acetone); IR (KBr): 3186 (NH), 2222 (CN), 1767, 1715 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.60−1.75 (m, 6H, $3CH_2$), 3.40−3.48 (m, 4H, $2NCH_2$), 7.40−7.43 (m, 3H, aryl H), 7.49−7.51 (m, 2H, aryl H), 7.93 (s, 1H, 6-H), 11.31 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 23.2 (piperidine C-4), 26.1 (piperidine C-3, 5), 53.0 ($2NCH_2$), 111.1 (C aryl), 117.6 (CN), 123.3, 127.6, 128.0, 129.4, 131.9, 134.1, 134.9 (C aryl), 142.8 (C-6), 149.9 (C aryl), 166.4, 167.1 (CO); MS: *m/z* 332 $[M+H]^+$; Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.48; H, 5.23; N, 12.64.

2,3-Dihydro-2-methyl-1,3-dioxo-7-phenyl-4-(1-piperidinyl)-1*H*-isoindole-5-carbonitrile (11b)

Orange needles (1.62 g, 94%), mp 189−190 °C (acetone); IR (KBr): 2224 (CN), 1763, 1713 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.69−1.74 (m, 2H, piperidine 4-CH_2), 1.81−1.86 (m, 4H, piperidine 3, 5-CH_2), 3.09 (s, 3H, CH_3), 3.53−3.56 (m, 4H, $2NCH_2$), 7.41−7.44 (m, 5H, aryl H), 7.74 (s, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 23.8 (piperidine C-4), 24.0 (CH_3), 26.6 (piperidine C-3, 5), 53.9 ($2NCH_2$), 111.8 (C aryl), 117.9 (CN), 122.1, 128.1, 128.7, 129.3, 132.8, 133.5, 134.9 (C aryl), 143.5 (C-6), 150.6 (C aryl), 165.9, 166.4 (CO); MS: *m/z* 346 $[M+H]^+$; Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 73.01; H, 5.59; N, 12.18.

2,3-Dihydro-1,3-dioxo-7-phenyl-2-(phenylmethyl)-4-(1-piperidinyl)-1*H*-isoindole-5-carbonitrile (11c)

Orange prisms (1.93 g, 92%), mp 181−182 °C (acetone); IR (KBr): 2224 (CN), 1761, 1712 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.62−1.66 (m, 2H, piperidine 4-CH_2), 1.70−1.76 (m, 4H, piperidine 3, 5-CH_2), 3.45−3.48 (m, 4H, 2NCH_2), 4.69 (s, 2H, $C\underline{H}_2C_6H_5$), 7.23−7.32 (m, 5H, aryl H), 7.40−7.44 (m, 3H, aryl H), 7.50−7.53 (m, 2H, aryl H), 7.98 (s, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 23.2 (piperidine C-4), 26.1 (piperidine C-3, 5), 41.0 ($\underline{C}H_2C_6H_5$), 53.1 (2NCH_2), 111.3 (C aryl), 117.6 (CN), 122.0, 127.3, 127.4, 127.7, 128.2, 128.4, 129.4, 132.0, 133.0, 134.7, 136.5 (C aryl), 143.2 (C-6), 149.8 (C aryl), 165.0, 165.7 (CO); MS: *m/z* 422 [M+H]$^+$; Anal. Calcd for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97. Found: C, 76.89; H, 5.57; N, 9.94.

2,3-Dihydro-1,3-dioxo-2,7-diphenyl-4-(1-piperidinyl)-1*H*-isoindole-5-carbonitrile (11d)

Orange needles (1.79 g, 88%), mp 200−201 °C (acetone); IR (KBr): 2223 (CN), 1767, 1718 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.64−1.67 (m, 2H, piperidine 4-CH_2), 1.71−1.76 (m, 4H, piperidine 3, 5-CH_2), 3.49−3.51 (m, 4H, 2NCH_2), 7.38−7.43 (m, 6H, aryl H), 7.47−7.51 (m, 2H, aryl H), 7.55−7.57 (m, 2H, aryl H), 8.03 (s, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 23.2 (piperidine C-4), 26.1 (piperidine C-3, 5), 53.1 (2NCH_2), 111.0 (C aryl), 117.7 (CN), 122.0, 127.5, 127.7, 128.0, 128.1, 128.6, 129.4, 131.8, 132.1, 133.0, 134.8 (C aryl), 143.3 (C-6), 149.9 (C aryl), 164.4, 165.0 (CO); MS: *m/z* 408 [M+H]$^+$; Anal. Calcd for $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.19; N, 10.31. Found: C, 76.73; H, 5.27; N, 10.26.

2,3-Dihydro-2-(4-nitrophenyl)-1,3-dioxo-7-phenyl-4-(1-piperidinyl)-1*H*-isoindole-5-carbonitrile (11e)

Orange needles (1.74 g, 77%), mp 192−193 °C (acetone/petroleum ether); IR (KBr): 2222 (CN), 1767, 1720 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.63−1.69 (m, 2H, piperidine 4-CH_2), 1.72−1.78 (m, 4H, piperidine 3, 5-CH_2), 3.51−3.54 (m, 4H, 2NCH_2), 7.42−7.45 (m, 3H, aryl H), 7.56−7.59 (m, 2H, aryl H), 7.73−7.76 (m, 2H, aryl H), 8.07 (s, 1H, 6-H), 8.34−8.37 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 23.2 (piperidine C-4), 26.1 (piperidine C-3, 5), 53.1 (2NCH_2), 111.0 (C aryl), 117.6 (CN), 121.7, 123.9, 127.7, 127.9, 128.2, 129.4, 132.1, 132.9, 134.7, 137.6 (C aryl), 143.6 (C-6), 146.1, 150.0 (C aryl), 163.7, 164.4 (CO); MS: *m/z* 453 [M+H]$^+$; Anal. Calcd for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.01; H, 4.57; N, 12.27.

2,3-Dihydro-1,3-dioxo-7-phenyl-4-(1-pyrrolidinyl)-1*H*-isoindole-5-carbonitrile (12a)

Orange needles (0.98 g, 62%), mp 220−221 °C (acetone); IR (KBr): 3195 (NH), 2212 (CN), 1756, 1704 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.92−1.96 (m, 4H, 2CH_2), 3.79−3.83 (m, 4H, 2NCH_2), 7.37−7.42 (m, 3H, aryl H), 7.47−7.49 (m, 2H, aryl H), 7.82 (s, 1H, 6-H), 11.14 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 25.4 (2CH_2), 53.2 (2NCH_2), 102.2 (C aryl), 116.8 (CN), 119.4, 127.6, 127.7, 127.8, 129.3, 134.3, 135.1

(C aryl), 143.9 (C-6), 145.5 (C aryl), 167.0, 167.2 (CO); MS: *m/z* 318 $[M+H]^+$; Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.87; H, 4.81; N, 13.26.

2,3-Dihydro-2-methyl-1,3-dioxo-7-phenyl-4-(1-pyrrolidinyl)-1*H*-isoindole-5-carbonitrile (12b)

Orange needles (1.37 g, 82%), mp 185–186 °C (acetone); IR (KBr): 2214 (CN), 1752, 1702 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.93–1.96 (m, 4H, $2CH_2$), 2.93 (s, 3H, CH_3), 3.81–3.84 (m, 4H, $2NCH_2$), 7.38–7.42 (m, 3H, aryl H), 7.48–7.50 (m, 2H, aryl H), 7.85 (s, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 23.8 (CH_3), 25.4 ($2CH_2$), 53.2 ($2NCH_2$), 102.6 (C aryl), 115.9 (CN), 119.3, 127.6, 127.8, 127.9, 129.3, 133.6, 135.0 (C aryl), 143.9 (C-6), 145.4 (C aryl), 165.9, 166.1 (CO); MS: *m/z* 332 $[M+H]^+$; Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.51; H, 5.24; N, 12.73.

2,3-Dihydro-1,3-dioxo-7-phenyl-2-(phenylmethyl)-4-(1-pyrrolidinyl)-1*H*-isoindole-5-carbonitrile (12c)

Red needles (1.57 g, 77%), mp 161–162 °C (acetone); IR (KBr): 2216 (CN), 1754, 1706 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.93–1.96 (m, 4H, $2CH_2$), 3.82–3.85 (m, 4H, $2NCH_2$), 4.67 (s, 2H, $C\underline{H_2}C_6H_5$), 7.23–7.32 (m, 5H, aryl H), 7.38–7.41 (m, 3H, aryl H), 7.48–7.50 (m, 2H, aryl H), 7.88 (s, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 25.4 ($2CH_2$), 40.9 ($\underline{C}H_2C_6H_5$), 53.3 ($2NCH_2$), 102.8 (C aryl), 115.4 (CN), 119.2, 127.2, 127.3, 127.6, 127.8, 128.0, 128.4, 129.4, 133.2, 134.9, 136.6 (C aryl), 144.2 (C-6), 145.5 (C aryl), 165.6, 165.7 (CO); MS: *m/z* 408 $[M+H]^+$; Anal. Calcd for $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.19; N, 10.31. Found: C, 76.74; H, 5.34; N, 10.23.

2,3-Dihydro-1,3-dioxo-2,7-diphenyl-4-(1-pyrrolidinyl)-1*H*-isoindole-5-carbonitrile (12d)

Red needles (1.59 g, 81%), mp 216–217 °C (acetone); IR (KBr): 2216 (CN), 1758, 1712 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.94–1.97 (m, 4H, $2CH_2$), 3.85–3.88 (m, 4H, $2NCH_2$), 7.37–7.41 (m, 6H, aryl H), 7.46–7.49 (m, 2H, aryl H), 7.53–7.56 (m, 2H, aryl H), 7.94 (s, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 25.4 ($2CH_2$), 53.4 ($2NCH_2$), 102.6 (C aryl), 115.5 (CN), 119.3, 127.5, 127.7, 127.8, 128.1, 128.6, 129.4, 131.9, 133.2, 135.0 (C aryl), 144.2 (C-6), 145.7 (C aryl), 164.9, 165.0 (CO); MS: *m/z* 394 $[M+H]^+$; Anal. Calcd for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68. Found: C, 76.38; H, 5.01; N, 10.60.

2,3-Dihydro-2-(4-nitrophenyl)-1,3-dioxo-7-phenyl-4-(1-pyrrolidinyl)-1*H*-isoindole-5-carbonitrile (12e)

Orange prisms (1.13 g, 52%), mp 177–178 °C (acetone); IR (KBr): 2212 (CN), 1749, 1702 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.95–1.98 (m, 4H, $2CH_2$), 3.86–3.89 (m, 4H, $2NCH_2$), 7.39–7.44 (m, 3H, aryl H), 7.55–7.57 (m, 2H, aryl H), 7.72–7.75 (m, 2H, aryl H), 7.96 (s, 1H, 6-H), 8.32–8.36 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 25.4 ($2CH_2$), 53.4 ($2NCH_2$), 102.5 (C aryl), 115.1 (CN), 119.2, 123.9, 127.69, 127.72, 127.9, 128.1, 129.4, 133.1, 134.9, 137.7 (C aryl), 144.5 (C-6), 145.8, 145.9 (C aryl), 164.1, 164.5 (CO); MS: *m/z* 439 $[M+H]^+$; Anal. Calcd for $C_{25}H_{18}N_4O_4$: C, 68.49; H, 4.14; N, 12.78. Found: C, 68.42; H, 4.42; N, 12.86.

2,3-Dihydro-7-methyl-4-(4-morpholinyl)-1,3-dioxo-1*H*-isoindole-5-carbonitrile (13a)

Yellow needles (1.09 g, 80%), mp 227–228 °C (acetone); IR (KBr): 3168 (NH), 2225 (CN), 1761, 1720 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.51 (d, *J* = 0.6 Hz, 3H, CH_3), 3.39–3.41 (m, 4H, $2NCH_2$), 3.75–3.77 (m, 4H, $2OCH_2$), 7.94 (q, *J* = 0.6 Hz, 1H, 6-H), 11.47 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 15.9 (CH_3), 51.6 ($2NCH_2$), 66.7 ($2OCH_2$), 111.4 (C aryl), 117.7 (CN), 123.6, 130.3, 134.7 (C aryl), 143.2 (C-6), 148.3 (C aryl), 166.7, 168.5 (CO); MS: *m/z* 272 [M+H]$^+$; Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.99; H, 4.93; N, 15.42.

2,3-Dihydro-2,7-dimethyl-4-(4-morpholinyl)-1,3-dioxo-1*H*-isoindole-5-carbonitrile (13b)

Yellow needles (1.26 g, 88%), mp 183−184 °C (acetone); IR (KBr): 2220 (CN), 1755, 1704 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.53 (d, *J* = 0.6 Hz, 3H, 7-CH_3), 2.29 (s, 3H, 2-CH_3), 3.42 (t, *J* = 4.6 Hz, 4H, $2NCH_2$), 3.77 (t, *J* = 4.6 Hz, 4H, $2OCH_2$), 7.97 (q, *J* = 0.6 Hz, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 16.0 (7-CH_3), 23.7 (2-CH_3), 51.6 ($2NCH_2$), 66.6 ($2OCH_2$), 111.3 (C aryl), 117.6 (CN), 122.7, 130.1, 134.0 (C aryl), 143.3 (C-6), 148.0 (C aryl), 165.6, 167.2 (CO); MS: *m/z* 286 [M+H]$^+$; Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.12; H, 5.29; N, 14.63.

2,3-Dihydro-7-methyl-4-(4-morpholinyl)-1,3-dioxo-2-(phenylmethyl)-1*H*-isoindole-5-carbonitrile (13c)

Yellow needles (1.36 g, 75%), mp 146−147 °C (acetone); IR (KBr): 2221 (CN), 1762, 1712 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.54 (d, *J* = 0.6 Hz, 3H, CH_3), 3.43 (t, *J* = 4.6 Hz, 4H, $2NCH_2$), 3.76 (t, *J* = 4.6 Hz, 4H, $2OCH_2$), 4.73 (s, 2H, $C\underline{H_2}C_6H_5$), 7.24–7.34 (m, 5H, aryl H), 8.00 (q, *J* = 0.6 Hz, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 16.0 (CH_3), 40.8 ($\underline{C}H_2C_6H_5$), 51.7 ($2NCH_2$), 66.6 ($2OCH_2$), 111.4 (C aryl), 117.6 (CN), 122.2, 127.28, 127.34, 128.4, 130.3, 133.6, 136.4 (C aryl), 143.6 (C-6), 148.2 (C aryl), 165.2, 167.0 (CO); MS: *m/z* 362 [M+H]$^+$; Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.84; H, 5.34; N, 11.48.

2,3-Dihydro-7-methyl-4-(4-morpholinyl)-1,3-dioxo-2-phenyl-1*H*-isoindole-5-carbonitrile (13d)

Yellow columns (1.40 g, 81%), mp 171−172 °C (acetone); IR (KBr): 2219 (CN), 1765, 1711 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.58 (d, *J* = 0.6 Hz, 3H, CH_3), 3.47 (t, *J* = 4.6 Hz, 4H, $2NCH_2$), 3.77 (t, *J* = 4.6 Hz, 4H, $2OCH_2$), 7.40–7.46 (m, 3H, aryl H), 7.50–7.54 (m, 2H, aryl H), 8.05 (q, *J* = 0.6 Hz, 1H, 6-H); ^{13}C NMR (DMSO-d_6): δ 16.2 (CH_3), 51.7 ($2NCH_2$), 66.6 ($2OCH_2$), 111.0 (C aryl), 117.7 (CN), 122.2, 127.5, 128.1, 128.7, 130.3, 131.6, 133.7 (C aryl), 143.7 (C-6), 148.3 (C aryl), 164.6, 166.3 (CO); MS: *m/z* 348 [M+H]$^+$; Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.32; H, 5.04; N, 12.01.

2,3-Dihydro-7-methyl-4-(4-morpholinyl)-2-(4-nitrophenyl)-1,3-dioxo-1*H*-isoindole-5-carbonitrile (13e)

Orange needles (1.60 g, 82%), mp 204−205 °C (acetone); IR (KBr): 2219 (CN), 1764, 1715 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.59 (d, *J* = 0.6 Hz, 3H, CH_3), 3.49 (t, *J* = 4.6 Hz, 4H, $2NCH_2$), 3.78 (t, *J* = 4.6

Hz, 4H, 2OCH$_2$), 7.74–7.78 (m, 2H, aryl H), 8.08 (q, J = 0.6 Hz, 1H, 6-H), 8.37–8.40 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 16.2 (CH$_3$), 51.7 (2NCH$_2$), 66.6 (2OCH$_2$), 111.1 (C aryl), 117.7 (CN), 121.9, 124.0, 127.9, 130.4, 133.6, 137.4 (C aryl), 144.0 (C-6), 146.2, 148.4 (C aryl), 163.9, 165.6 (CO); MS: *m/z* 393 $[M+H]^+$; Anal. Calcd for $C_{20}H_{16}N_4O_5$: C, 61.22; H, 4.11; N, 14.28. Found: C, 61.27; H, 4.15; N, 14.25.

REFERENCES

1. F. O. Kelsey, *Teratology,* 1988, **38**, 221.
2. Y. Shibata, K. Sasaki, Y. Hashimoto, and S. Iwasaki, *Chem. Pharm. Bull.,* 1996, **44**, 156.
3. E. P. Sampaio, E. N. Sarno, R. Galilly, Z. A. Cohn, and G. Kaplan, *J. Exp. Med.,* 1991, **173**, 699.
4. T. Randall, *J. Am. Med. Assoc*., 1990, **263**, 1467.
5. M. Siadak and K. M. Sullivan, *Blood. Rev.,* 1994, **8**, 154.
6. R. Feldmann, D. Salomon, and J.-H. Saurat, *Dermatology,* 1994, **189**, 425.
7. Y. Hashimoto, *Chemistry Today,* 1994, **283**, 38.
8. G. Kaplan, *Immunobiol.,* 1994, **191**, 564.
9. P. M. Parker, N. Chao, A. Nademanee, M. R. O'Donnell, G. M. Schmidt, D. S. Snyder, A. S. Stein, E. P. Smith, A. Molina, D. E. Stepan, A. Kashyap, I. Planas, R. Spielberger, G. Somlo, K. Margolin, K. Zwingenberger, K. Wilsman, R. S. Negrin, G. D. Long, J. C. Niland, K. G. Blume, and S. J. Forman, *Blood*, 1995, **86**, 3604.
10. R. K. Raghupathi, L. Rydelek-Fitzgerald, M. Teitler, and R. A. Glennon, *J. Med. Chem.,* 1991, **34**, 2638.
11. Y. Shibata, M. Shichita, K. Sasaki, K. Nishimura, Y. Hashimoto, and S. Iwasaki, *Chem. Pharm. Bull.,* 1995, **43**, 177.
12. M. S. Khajavi, F. Nikpour, and M. Hajihadi, *J. Chem. Res. (S),* 1996, 96.
13. D. Bogdal, J. Pielichowski, and A. Boron, *Synlett,* 1996, 873.
14. H. Miyachi, A. Azuma, A. Ogasawara, E. Uchimura, N. Watanabe, Y. Kobayashi, F. Kato, M. Kato, and Y. Hashimoto, *J. Med. Chem.,* 1997, **40**, 2858.
15. H. Miyachi, A. Ogasawara, A. Azuma, and Y. Hashimoto, *Bioorg. Med. Chem.,* 1997, **5**, 2095.
16. Y. Peng, G. Song, and X. Qian, *Synth. Commun.,* 2001, **31**, 1927.
17. B. Martin, H. Sekljic, and C. Chassaing, *Org. Lett.,* 2003, **5**, 1851.
18. L. M. Lima, P. Castro, A. L. Machado, C. A. M. Fraga, C. Lugnier, V. L. G. de Moraes, and E. J. Barreiro, *Bioorg. Med. Chem.,* 2002, **10**, 3067.
19. K. Kacprzak, *Synth. Commun.,* 2003, **33**, 1499.
20. K. Mogilaiah and G. R. Reddy, *Indian J. Chem.,* 2004, **43B**, 882.
21. F. Nikpour, S. Kazemi, and D. Sheikh, *Heterocycles,* 2006, **68**, 1559.

22. E. P. S. Falcão, S. J. de Melo, R. M. Srivastava, M. T. J. A. Catanho, and S. C. D. Nascimento, *Eur. J. Med. Chem.*, 2006, **41**, 276.
23. S. H. L. Kok, R. Gambari, C. H. Chui, M. C. W. Yuen, E. Lin, R. S. M. Wong, F. Y. Lau, G. Y. M. Cheng, W. S. Lam, S. H. Chan, K. H. Lam, C. H. Cheng, P. B. S. Lai, M. W. Y. Yu, F. Cheung, J. C. O. Tang, and A. S. C. Chan, *Bioorg. Med. Chem.*, 2008, **16**, 3626.
24. F. M. Dean, 'Advances in Heterocyclic Chemistry: Recent Advances in Furan Chemistry. Part II,' Vol. 31, ed. by A. R. Katritzky, Academic Press, Inc., New York, 1982, pp. 237−344.
25. M. V. Sargent and F. M. Dean, 'Comprehensive Heterocyclic Chemistry: Furans and their Benzo Derivatives: (ii) Reactivity,' Vol. 4, eds. by C. W. Bird and G. W. H. Cheeseman, Pergamon Press, Oxford, 1984, pp. 599−656.
26. H. Heaney and J. S. Ahn, 'Comprehensive Heterocyclic Chemistry II: Furans and their Benzo Derivatives: Reactivity,' Vol. 2, eds. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon Press, Oxford, 1996, pp. 297−350.
27. J. L. Isidor, M. S. Brookhart, and R. L. McKee, *J. Org. Chem.*, 1973, **38**, 612.
28. A. O. Abdelhamid, A. M. Negm, and I. M. Abbas, *J. Prakt. Chem.*, 1989, **331**, 31.
29. R. Medimagh, S. Marque, D. Prim, S. Chatti, and H. Zarrouk, *J. Org. Chem.*, 2008, **73**, 2191.
30. N. Chatani and T. Hanafusa, *J. Org. Chem.*, 1987, **52**, 4408.
31. J. E. Cochran, T. Wu, and A. Padwa, *Tetrahedron Lett.*, 1996, **37**, 2903.
32. A. Padwa, M. Dimitroff, A. G. Waterson, and T. Wu, *J. Org. Chem.*, 1997, **62**, 4088.
33. D. Prim and G. Kirsch, *Tetrahedron*, 1999, **55**, 6511.
34. K. Yamagata, M. Takaki, and M. Yamazaki, *Liebigs Ann. Chem.*, 1992, 1109.
35. K. Yamagata, K. Akizuki, and M. Yamazaki, *J. Prakt. Chem.*, 1998, **340**, 51.
36. R. H. Schlessinger, T. R. R. Pettus, J. P. Springer, and K. Hoogsteen, *J. Org. Chem.*, 1994, **59**, 3246.
37. R. H. Schlessinger, and C. P. Bergstrom, *Tetrahedron Lett.*, 1996, **37**, 2133.