Synthesis of Nicotinamide and Isonicotinamide Derivatives via Multicomponent Reaction of Alkyl Isocyanides and Acetylenic Compounds in the Presence of Nicotinic or Isonicotinic Acid

Abdolali Alizadeh,* Qasem Oskueyan, Sadegh Rostamnia

Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran
Fax +98(21)88006544; E-mail: abdol_alizad@yahoo.com; E-mail: aalizadeh@modares.ac.ir

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Abstract: An effective route to functionalized nicotinamide and isonicotinamide derivatives is described. This involves the reaction of nicotinic or isonicotinic acid with acetylenic compounds in the presence of alkyl isocyanides. The reactive 1:1 intermediates obtained from the addition of alkyl isocyanides to dialkyl acetylenedicarboxylates or dibenzoylacetylene was trapped by OH-acids such as nicotinic or isonicotinic acid to produce dialkyl 2-(alkylamino)-5-[alkyl(3- or 4-pyridylcarbonyl)amino]-3,4-furandicarboxylate, N^3-(alkyl)-N^3-[3,4-dibenzoyl-5-(alkylamino)-2-furyl]nicotinamide, and N^4-(alkyl)-N^4-[3,4-dibenzoyl-5-(alkylamino)-2-furyl]isonicotinamide derivatives.

Key words: alkyl isocyanide, dialkyl acetylenedicarboxylate, dibenzoylacetylene, nicotinic acid, isonicotinic acid, multicomponent reaction, zwitterion, nicotinamide, isonicotinamide, Dimroth-type rearrangement

We recently reported a new class of isocyanide based multicomponent reaction (IMCRs/DMAD) mediated by zwitterionic intermediates, and Dimroth-Type rearrangement.[1–3] Treatment of benzoic acid and its derivatives with dialkyl acetylenedicarboxylate and alkyl isocyanide in anhydrous CH_2Cl_2 at room temperature led to the formation of the linear imide derivatives (Scheme 1).[3]

In view of the success of the above reaction, we explored the use of nicotinic or isonicotinic acid as the third component in this reaction. In this paper, we present the results of an extended investigation of the reactivity of the intermediate zwitterions with a heteroaromatic acid in THF. To our surprise, the products are 2-furylnicotinamide and 2-furylisonicotinamide derivatives.

In the presence of nicotinic or isonicotinic acid **3**, alkyl isocyanides **1** and dialkyl acetylenedicarboxylates **2** undergo a smooth 2:1:1 addition reaction in THF at ambient temperature, to produce diaminofuran derivatives **4** in 70–95% yields (Table 1). The reaction with dibenzoylacetylene as an acetylenic system led to 2-furylnicotinamide **4h** or 2-furylisonicotinamide **4i** in good yield (Table 1).

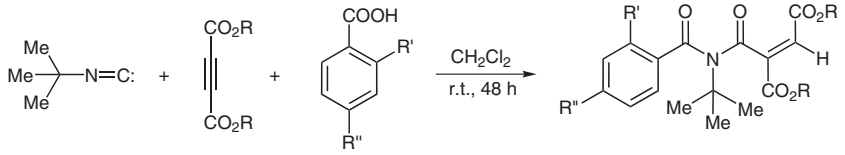
The structure of compounds **4a–i** was deduced from their elemental analyses, IR, and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of **4a** displayed the molecular ion (M^+) peak at 431 *m/z*, which is consistent with the 1:2:1 adduct of dimethyl acetylenedicarboxylate, *tert*-butyl isocyanide, and nicotinic acid. The IR spectrum of **4a** exhibited absorption bands due to the carbonyl group of esters and amide at 1730 and 1667 cm^{-1}, respectively, and a NH group at 3390 cm^{-1}.

The ^{1}H NMR spectrum of **4a** exhibited five single sharp lines readily recognized as arising from *tert*-butyl groups (δ = 1.44 and 1.46), methoxy (δ = 3.63 and 3.79), and NH (δ = 6.90) protons. The pyridyl moiety gave rise to characteristic signals in the aromatic region of the spectrum.

The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 18 distinct resonances in agreement with the furan structure. Partial assignments of these resonances are given in experimental section. The ^{1}H and ^{13}C NMR spectra of compounds **4b–g** are similar to those of **4a**, except for the aromatic moiety, the ester groups, and alkyl group of isocyanide which exhibit characteristic signals with appropriate chemical shifts (see experimental section).

Although we have not yet established the mechanism of the reaction between the alkyl isocyanide and the acetylenic system in the presence of nicotinic or isonicotinic acid **3** in an experimental manner, a possible explanation is proposed in Scheme 2.

On the basis of the well-established chemistry of isocyanides,[4–9] it is reasonable to assume that the functionalized diaminofurans **4** apparently result from initial addition of



Scheme 1

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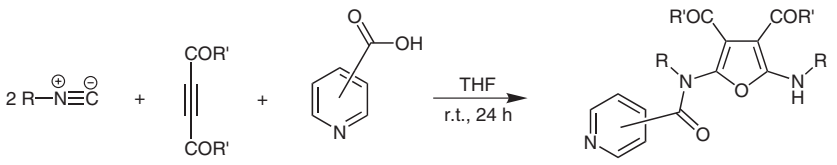
Table 1 Reaction of Alkyl Isocyanide **1** with Acetylenic Compound **2** in the Presence of Nicotinic or Isonicotinic Acid **3**

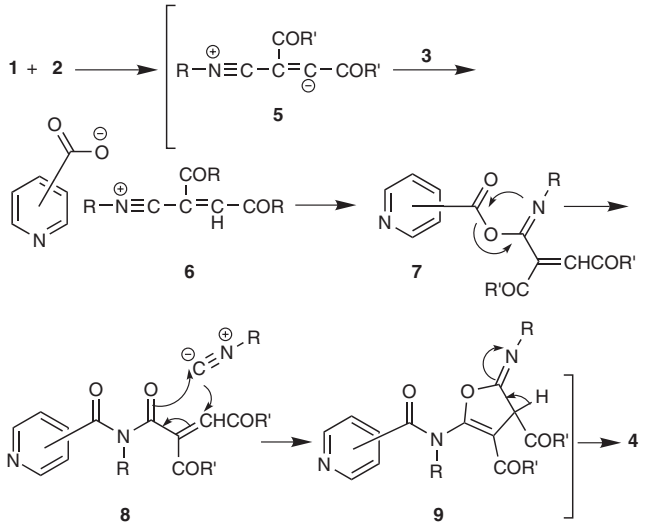


1 2 3 4

4	R	R′	3	Yield (%) of 4
a	*t*-Bu	OMe	nicotinic acid	70
b	*t*-Bu	OMe	isonicotinic acid	95
c	*t*-Bu	OEt	isonicotinic acid	80
d	*c*-C_6H_{11}	OMe	nicotinic acid	75
e	*c*-C_6H_{11}	OMe	isonicotinic acid	80
f	*c*-C_6H_{11}	OEt	nicotinic acid	80
g	*c*-C_6H_{11}	OEt	isonicotinic acid	85
h	*c*-C_6H_{11}	Ph	nicotinic acid	75
i	*c*-C_6H_{11}	Ph	isonicotinic acid	70

the isocyanide to the acetylenic system and subsequent protonation of the 1:1 adduct **5** by compound **3**, followed by attack of the carboxylate anion on the positively charged ion of **6** to form imidoyl carboxylate **7** as an intermediate. This intermediate rearranges[10,11] under the reaction conditions employed to produce the intermediate **8**, followed by its trapping with isocyanide,[12] to give the intermediate **9**, which produces compound **4** (Scheme 2) by a 1,5-H shift.

In summary, the reaction between isocyanides and acetylenic system in the presence of nicotinic or isonicotinic acid provides a simple one-pot entry into the synthesis of polyfunctional furyl nicotinamide and furyl isonicotinamide derivatives of potential synthetic and pharmaceutical interest. The present method carries the advantage that it can be performed under neutral conditions and requires no activation or modification of the reactants.



Scheme 2

Dimethyl, diethyl and di(*tert*-butyl) acetylenedicarboxylates, and *tert*-butyl and cyclohexyl isocyanides were obtained from Merck (Germany) and Fluka (Switzerland), and were used without further purification. Dibenzoylacetylene was prepared according to a published procedure.[13,14] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were recorded (in $CDCl_3$ solution with TMS as internal standard) on a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel (230–240 mesh).

Dimethyl 2-(*tert*-Butylamino)-5-[*tert*-butyl(3-pyridylcarbonyl)amino]-3,4-furandicarboxylate (4a); Typical Procedure

To a magnetically stirred solution of dimethyl acetylenedicarboxylate (**2a**; 0.14 g, 1 mmol) and nicotinic acid (**3**; 0.12 g, 1 mmol) in anhyd THF (5 mL), was added dropwise a solution of *tert*-butyl isocyanide (**1a**; 0.083 g, 1 mmol) in anhyd THF (3 mL) at r.t. over 10 min. The mixture was then allowed to stir for 24 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using hexane–EtOAc mixture as eluent; yield: 0.3 g, (70%); red oil.

IR (KBr): 3325 (NH), 1730 (CO_2Me), 1667 (CON), 1596 and 1535 (Ar), 1266 and 1214 cm^{-1} (C–O).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.43 (9 H, s, *t*-C_4H_9), 1.46 (9 H, s, *t*-C_4H_9), 3.63 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 6.90 (1 H, s, NH), 7.17 (1 H, m, CH of py), 7.72 (1 H, dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.9 Hz, CH of py), 8.51 (1 H, dd, $^3J_{H,H}$ = 3.7 Hz, $^4J_{H,H}$ = 1.0 Hz, CH of py), 8.60 (1 H, d, $^4J_{H,H}$ = 1.1 Hz, CH of py).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 27.93 [C(*C*H)$_3$], 29.71 [C(*C*H)$_3$], 50.98 (*C*Me$_3$), 51.99 (*C*Me$_3$), 52.57 (OCH$_3$), 61.54 (OCH$_3$), 85.81 (C-3 of furan), 114.90 (C-4 of furan), 122.70 (CH of py), 134.73 (CH of py), 138.91 (C_{ipso}-CO), 147.62 (CH of py), 150.35 (CH of py), 152.82 (C-5 of furan), 159.30 (C-2 of furan), 162.38 (*C*O$_2$Me), 164.87 (*C*O$_2$Me), 169.97 (CON).

MS: *m*/*z* (%) = 433 (M$^+$ + 2, 3), 432 (M$^+$ + 1, 13), 431 (M$^+$, 12), 395 (2), 375 (53), 344 (3), 319 (46), 287 (40), 269 (7), 255 (7), 240 (2), 228 (2), 213 (31), 196 (5), 182 (5), 181 (20), 156 (7), 140 (4), 138 (11), 123 (15), 106 (100), 84 (41), 78 (40), 57 (52), 51 (13), 41 (47).

Anal. Calcd for $C_{22}H_{29}N_3O_6$ (431.48): C, 61.24; H, 6.77; N, 9.74. Found: C, 60.90; H, 6.90; N, 9.84.

Dimethyl 2-(*tert*-Butylamino)-5-[*tert*-butyl(4-pyridylcarbonyl)amino]-3,4-furandicarboxylate (4b)
Yield: 0.41 g (95%); red oil.

IR (KBr): 3320 (NH), 1728 (CO$_2$Me), 1667 (CON), 1595 and 1542 (Ar), 1267 and 1211 cm^{-1} (C–O).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.44 (9 H, s, *t*-C$_4$H$_9$), 1.47 (9 H, s, *t*-C$_4$H$_9$), 3.65 (3 H, s, OCH$_3$), 3.80 (3 H, s, OCH$_3$), 6.91 (1 H, s, NH), 7.25 (2 H, d, $^3J_{H,H}$ = 5.9 Hz, 2 CH of py), 8.51 (2 H, d, $^3J_{H,H}$ = 5.9 Hz, 2 CH of py).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 27.91 [C(*C*H)$_3$], 29.73 [C(*C*H)$_3$], 51.02 (*C*Me$_3$), 51.99 (*C*Me$_3$), 52.55 (OCH$_3$), 61.62 (OCH$_3$), 85.96 (C-3 of furan), 115.37 (C-4 of furan), 121.01 (2 CH of py), 138.38 (C_{ipso}-CO), 145.46 (C-5 of furan), 149.49 (2 CH of py), 159.24 (C-2 of furan), 162.40 (*C*O$_2$Me), 164.83 (*C*O$_2$Me), 170.07 (CON).

MS: *m*/*z* (%) = 433 (M$^+$ + 2, 2), 432 (M$^+$ + 1, 8), 431 (M$^+$, 11), 375 (73), 344 (5), 319 (70), 304 (3), 287 (50), 269 (5), 255 (2), 213 (30), 196 (5), 182 (3), 181 (27), 165 (8), 149 (2), 138 (12), 123 (3), 106 (100), 84 (2), 78 (3), 57 (50), 41 (3).

Anal. Calcd for $C_{22}H_{29}N_3O_6$ (431.48): C, 61.24; H, 6.77; N, 9.74. Found: C, 61.50; H, 6.90; N, 10.00.

Diethyl 2-(*tert*-Butylamino)-5-[*tert*-butyl(4-pyridylcarbonyl)amino]-3,4-furandicarboxylate (4c)
Yield: 0.36 g (80%); red oil.

IR (KBr): 3325 (NH), 1726 (CO$_2$Et), 1665 (CON), 1619 and 1594 (Ar), 1241 and 1208 cm^{-1} (C–O).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.19 (3 H, t, $^3J_{H,H}$ = 7.1 Hz, 2 OCH$_2$C*H*$_3$), 1.31 (3 H, t, $^3J_{H,H}$ = 7.1 Hz, 2 OCH$_2$C*H*$_3$), 1.42 (9 H, s, *t*-C$_4$H$_9$), 1.46 (9 H, s, *t*-C$_4$H$_9$), 4.19 (2 H, q, $^3J_{H,H}$ = 7.1 Hz, OC*H*$_2$CH$_3$), 4.24 (2 H, q, $^3J_{H,H}$ = 7.1 Hz, OC*H*$_2$CH$_3$), 6.86 (1 H, s, NH), 7.26 (2 H, d, $^3J_{H,H}$ = 4.7 Hz, 2 CH of py), 8.49 (2 H, d, $^3J_{H,H}$ = 4.3 Hz, 2 CH of py).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.12 (OCH$_2$*C*H$_3$), 14.21 (OCH$_2$*C*H$_3$), 27.97 [C(*C*H)$_3$], 29.75 [C(*C*H)$_3$], 52.49 (*C*Me$_3$), 59.76 (O*C*H$_2$CH$_3$), 61.31 (O*C*H$_2$CH$_3$), 61.63 (*C*Me$_3$), 86.27 (C-3 of furan), 115.81 (C-4 of furan), 121.13 (2 CH of py), 137.68 (C_{ipso}-CO), 145.45 (C-5 of furan), 149.48 (2 CH of py), 159.14 (C-2 of furan), 162.33 (*C*O$_2$Et), 164.46 (*C*O$_2$Et), 170.09 (CON).

MS: *m*/*z* (%) = 461 (M$^+$ + 2, 2), 460 (M$^+$ + 1, 10), 459 (M$^+$, 10), 403 (57), 358 (3), 347 (44), 318 (3), 301 (46), 273 (3), 241 (20), 225 (3), 217 (3), 196 (4), 195 (10), 179 (8), 167 (15), 151 (5), 127 (2), 123 (13), 106 (100), 91 (5), 78 (36), 57 (41), 51 (7), 41 (20).

Anal. Calcd for $C_{24}H_{33}N_3O_6$ (459.54): C, 62.73; H, 7.24; N, 9.14. Found: C, 62.70; H, 7.26; N, 9.15.

Dimethyl 2-(Cyclohexylamino)-5-[cyclohexyl(3-pyridylcarbonyl)amino]-3,4-furandicarboxylate (4d)
Yield: 0.36 g (75%); red oil.

IR (KBr): 3330 (NH), 1727 (CO$_2$Me), 1664 (CON), 1626 and 1598 (Ar), 1255 and 1229 cm^{-1} (C–O).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.14–1.90 (20 H, m, 10 CH$_2$ of 2 cyclohexyl), 3.48 (1 H, m, CHN), 3.60 (3 H, s, OCH$_3$), 3.66 (3 H, s, OCH$_3$), 4.40 (1 H, m, CHN), 6.61 (1 H, d, $^3J_{H,H}$ = 8.0 Hz, NH), 7.16 (1 H, m, CH of py), 7.71 (1 H, dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.7 Hz, CH of py), 8.48 (1 H, dd, $^3J_{H,H}$ = 4.7 Hz, $^4J_{H,H}$ = 1.3 Hz, CH of py), 8.54 (1 H, d, $^4J_{H,H}$ = 1.6 Hz, CH of py).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 24.41–33.26 (10 CH$_2$ of 2 cyclohexyl), 50.97 (CHN), 51.60 (OCH$_3$), 51.95 (CHN), 56.94 (OCH$_3$), 85.36 (C-3 of furan), 114.73 (C-4 of furan), 122.82 (CH of py),132.60 (C-5 of furan) 135.19 (CH of py), 137.65 (C_{ipso}-CO), 147.83 (CH of py), 150.66 (CH of py), 159.48 (C-2 of furan), 162.21 (*C*O$_2$Me), 164.67 (*C*O$_2$Me), 168.99 (CON).

MS: *m*/*z* (%) = 484 (M$^+$ + 1, 3), 483 (M$^+$, 8), 452 (3), 401 (6), 378 (2), 369 (8), 295 (40), 285 (6), 263 (6), 213 (19), 196 (3), 187 (3), 181 (27), 165 (17), 149 (3), 138 (19), 123 (12), 106 (100), 84 (33), 78 (55), 56 (13), 55 (53), 41 (57).

Anal. Calcd for $C_{26}H_{33}N_3O_6$ (483.56): C, 64.58; H, 6.88; N, 8.69. Found: C, 64.60; H, 7.00; N, 9.00.

Dimethyl 2-(Cyclohexylamino)-5-[cyclohexyl(4-pyridylcarbonyl)amino]-3,4-furandicarboxylate (4e)
Yield: 0.38 g (80%); red oil.

IR (KBr): 3390 (NH), 1729 (CO$_2$Me), 1690 (CON), 1615 and 1542 (Ar), 1253 and 1202 cm^{-1} (C–O).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ= 1.01–2.23 (20 H, m, 10 CH$_2$ of 2 cyclohexyl), 3.50 (1 H, m, CHN), 3.65 (3 H, s, OCH$_3$), 3.72 (3 H, s, OCH$_3$), 4.42 (1 H, m, CHN), 6.64 (1 H, d, $^3J_{H,H}$ = 8.1 Hz, NH), 7.26 (2 H, d, $^3J_{H,H}$ = 6.0 Hz, 2 CH of py), 8.52 (2 H, d, $^3J_{H,H}$ = 6.0 Hz, 2 CH of py).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 19.67–33.30 (10 CH$_2$ of 2 cyclohexyl), 51.03 (CHN), 51.64 (CHN), 51.98 (OCH$_3$), 56.95 (OCH$_3$), 85.60 (C-3 of furan), 115.15 (C-4 of furan), 121.31 (2 CH of py), 137.05 (C_{ipso}-CON), 144.05 (C-5 of furan), 149.58 (2 CH of py), 159.46 (C-2 of furan), 162.27 (*C*O$_2$Me), 164.68 (*C*O$_2$Me), 169.21 (CON).

MS: *m*/*z* (%) = 484 (M$^+$ + 1, 3), 483 (M$^+$, 8), 452 (3), 401 (6), 378 (8), 369 (8), 295 (40), 285 (6), 263 (6), 239 (3), 213 (19), 195 (6), 181 (21), 165 (17), 149 (3), 138 (19), 123 (24), 106 (100), 84 (19), 83 (33), 56 (19), 55 (73), 41 (55).

Anal. Calcd for $C_{26}H_{23}N_3O_6$ (483.56): C, 64.58; H, 6.88; N, 8.69. Found: C, 65.00; H, 7.10; N, 8.80.

Diethyl 2-(Cyclohexylamino)-5-[cyclohexyl(3-pyridylcarbonyl)amino]-3,4-furandicarboxylate (4f)
Yield: 0.41 g (80%); red oil.

IR (KBr): 3330 (NH), 1722 (CO$_2$Et), 1662 (CON), 1626 and 1597 (Ar), 1227 and 1200 cm^{-1} (C–O).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.13–2.23 (20 H, m, 10 CH$_2$ of 2 cyclohexyl), 1.25 (3 H, t, $^3J_{H,H}$ = 7.1 Hz, OCH$_2$C*H*$_3$), 1.29 (3 H, t, $^3J_{H,H}$ = 7.1 Hz, OCH$_2$C*H*$_3$), 3.75 (1 H, m, CHN), 4.14 (1 H, m, CHN), 4.19 (2 H, q, $^3J_{H,H}$ = 7.1 Hz, O*C*H$_2$CH$_3$), 4.27 (2 H, q, $^3J_{H,H}$ = 7.1 Hz, O*C*H$_2$CH$_3$), 7.05 (1 H, d, $^3J_{H,H}$ = 8.1 Hz, NH), 7.33 (1 H, m, CH of py), 7.95 (1 H, dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.8 Hz, CH of py), 8.71 (1 H, dd, $^3J_{H,H}$ = 4.8 Hz, $^4J_{H,H}$ = 1.6 Hz, CH of py), 8.87 (1 H, d, $^4J_{H,H}$ = 1.9 Hz, CH of py).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.95 (OCH$_2$*C*H$_3$), 13.99 (OCH$_2$*C*H$_3$), 24.31–34.05 (10 CH$_2$ of 2 cyclohexyl), 60.83 (O*C*H$_2$CH$_3$), 61.26 (CHN), 61.61 (O*C*H$_2$CH$_3$), 62.38 (CHN), 84.44 (C-3 of furan), 122.44 (C-4 of furan), 123.27 (CH of py), 131.71 (C_{ipso}-CON), 135.80 (CH of py),142.34 (C-5 of furan), 149.17 (CH

of py), 152.78 (CH of py), 162.49 (C-2 of furan), 164.19 (*C*O_2Et), 165.92 (*C*O_2Et), 172.94 (CON).

MS: *m*/*z* (%) = 513 (M^+ + 2, 5), 512 (M^+ + 1, 17), 511 (M^+, 45), 465 (10), 429 (22), 406 (4), 405 (12), 383 (30), 323 (62), 299 (20), 284 (11), 272 (12), 241 (16), 225 (8), 213 (7), 197 (8), 195 (18), 168 (9), 151 (9), 123 (12), 106 (100), 83 (42), 56 (6), 55 (78), 41 (29).

Anal. Calcd for $C_{28}H_{37}N_3O_6$ (511.61): C, 65.73; H, 7.29; N, 8.21. Found: C, 65.40; H, 7.15; N, 8.30.

Diethyl 2-(Cyclohexylamino)-5-[cyclohexyl(4-pyridylcarbonylamino]-3,4-furandicarboxylate (4g)
Yield: 0.43 g (85%); red oil.

IR (KBr): 3330 (NH), 1724 (CO_2Et), 1664 (CON), 1627 and 1596 (Ar), 1252 and 1228 cm^{-1} (C–O).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.23–1.90 (20 H, m, 10 CH_2 of 2 cyclohexyl), 1.21 (3 H, t, $^3J_{H,H}$ = 7.1 Hz, OCH_2CH_3), 1.27 (3 H, t, $^3J_{H,H}$ = 7.2 Hz, OCH_2CH_3), 3.49 (1 H, m, CHN), 4.14 (2 H, q, $^3J_{H,H}$ = 7.1 Hz, OCH_2CH_3), 4.20 (2 H, q, $^3J_{H,H}$ = 7.2 Hz, OCH_2CH_3), 4.23 (1 H, m, CHN), 6.63 (1 H, d, $^3J_{H,H}$ = 8.1 Hz, NH), 7.28 (2 H, d, $^3J_{H,H}$ = 4.5 Hz, 2 CH of py), 8.52 (2 H, d, $^3J_{H,H}$ = 5.9 Hz, 2 CH of py).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.10 (OCH_2CH_3), 14.25 (OCH_2CH_3), 24.41–33.30 (10 CH_2 of 2 cyclohexyl), 51.58 (CHN), 56.98 (CHN), 59.77 (OCH_2CH_3), 61.22 (OCH_2CH_3), 85.87 (C-3 of furan), 115.58 (C-4 of furan), 121.45 (2 CH of py), 136.41 (C_{ipso}-CON), 144.02 (C-5 of furan), 149.57 (2 CH of py), 159.39 (C-2 of furan), 162.15 (*C*O_2Et), 164.36 (*C*O_2Et), 169.23 (CON).

MS: *m*/*z* (%) = 513 (M^+ + 2, 6), 512 (M^+ + 1, 18), 511 (M^+, 37), 465 (8), 429 (28), 406 (8), 405 (15), 383 (27), 323 (50), 299 (17), 284 (10), 277 (12), 256 (2), 241 (15), 225 (7), 213 (6), 197 (7), 195 (17), 179 (8), 167 (32), 151 (7), 126 (2), 123 (11), 106 (100), 96 (4), 83 (36), 78 (41), 67 (8), 55 (78), 41 (32).

Anal. Calcd for $C_{28}H_{37}N_3O_6$ (511.61): C; 65.73, H; 7.29, N; 8.21. Found: C; 65.87, H; 7.33, N; 8.20.

N^3-Cyclohexyl-N^3-[3,4-dibenzoyl-5-(cyclohexylamino)-2-furyl]nicotinamide (4h)
Yield: 0.43 g (75%); yellow powder; mp 197–199 °C.

IR (KBr): 3405 (NH), 1700 (C=O), 1659 (CON), 1583 and 1550 cm^{-1} (Ar).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.23–2.29 (20 H, m, 10 CH_2 of 2 cyclohexyl), 3.78 (1 H, m, CHN), 3.90 (1 H, m, CHN), 6.92 (1 H, t, $^3J_{H,H}$ = 7.5 Hz, CH of Ph), 7.05 (2 H, t, $^3J_{H,H}$ = 7.6 Hz, 2 CH of Ph), 7.16 (1 H, t, $^3J_{H,H}$ = 7.4 Hz, CH of Ph), 7.29 (2 H, d, $^3J_{H,H}$ = 8.2 Hz, 2 CH of Ph), 7.30 (2 H, d, $^3J_{H,H}$ = 7.5 Hz, 2 CH of Ph), 7.48 (2 H, t, $^3J_{H,H}$ = 8.3 Hz, 2 CH of Ph), 7.98 (1 H, d, $^3J_{H,H}$ = 7.9 Hz, CH of py), 8.22 (1 H, dd, $^3J_{H,H}$ = 5.3 Hz, $^4J_{H,H}$ = 3.9 Hz, CH of py), 8.45 (1 H, d, $^3J_{H,H}$ = 8.0 Hz, NH), 8.75 (1 H, dd, $^3J_{H,H}$ = 5.5 Hz, $^4J_{H,H}$ = 1.6 Hz, CH of py), 8.98 (1 H, d, $^4J_{H,H}$ = 1.5 Hz, CH of py).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 24.55–33.31 (10 CH_2 of 2 cyclohexyl), 48.69 (CHN), 50.95 (CHN), 94.59 (C-3 of furan), 123.07 (CH of Ph), 123.24 (2 CH of Ph), 124.33 (C-4 of furan), 126.71 (CH of Ph), 127.20 (2 CH of Ph), 127.79 (2 CH of Ph), 128.75 (2 CH of Ph), 128.96 (C_{ipso}-CON), 129.58 (CH of Py), 129.85 (C_{ipso}-CO), 130.10 (C_{ipso}-CO), 137.43 (CH of Py), 150.90 (CH of py), 151.14 (C-5 of furan), 153.75 (CH of py), 161.62 (C-2 of furan), 162.00 (CON), 188.09 (*C*OPh), 190.00 (*C*OPh).

MS: *m*/*z* (%) = 361 (3), 272 (6), 205 (3), 190 (3), 147 (3), 123 (25), 105 (100), 84 (6), 77 (58), 56 (9), 51 (4), 41 (21).

Anal. Calcd for $C_{36}H_{37}N_3O_4$ (575.70): C, 75.11; H, 6.48; N, 7.30. Found: C, 75.00; H, 6.70; N, 7.40.

N^4-Cyclohexyl-N^4-[3,4-dibenzoyl-5-(cyclohexylamino)-2-furyl]isonicotinamide (4i)
Yield: 0.40 g (70%); yellow powder; mp 195–197 °C.

IR (KBr): 3405 (NH), 1721 (C=O), 1666 (CON), 1625 and 1571 cm^{-1} (Ar).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.09–2.15 (20 H, m, 10 CH_2 of 2 cyclohexyl), 3.72 (1 H, m, CHN of cyclohexyl), 4.44 (1 H, m, CHN of cyclohexyl), 6.61 (2 H, t, $^3J_{H,H}$ = 7.2 Hz, CH of Ph), 6.89 (2 H, t, $^3J_{H,H}$ = 7.8 Hz, 2 CH of Ph), 6.94–6.98 (4 H, m, 4 CH of 2 Ph), 7.08 (1 H, t, $^3J_{H,H}$ = 7.5 Hz, CH of Ph), 7.18 (1 H, t, $^3J_{H,H}$ = 7.1 Hz, CH of Ph), 7.36 (2 H, d, $^3J_{H,H}$ = 4.6 Hz, 2 CH of py), 7.97 (1 H, d, $^3J_{H,H}$ = 7.8 Hz, NH), 8.51 (2 H, d, $^3J_{H,H}$ = 5.7 Hz, 2 CH of py).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 24.4–33.22 (10 CH_2 of 2 cyclohexyl), 51.86 (CHN), 56.88 (CHN), 97.40 (C-3 of furan), 120.69 (C-4 of furan), 121.61 (2 CH of py), 126.96 (2 CH of Ph), 127.79 (2 CH of Ph), 127.95 (2 CH of Ph), 127.96 (2 CH of Ph), 130.59 (CH_{para} of Ph), 132.18 (CH_{para} of Ph), 137.62 (C_{ipso}-CO), 140.30 (C_{ipso}-CO), 144.67 (C_{ipso}-CON), 149.44 (2 CH of py), 159.54 (C-5 of furan), 169.20 (C-2 of furan), 172.15 (CON), 186.50 (*C*OPh), 189.58 (*C*OPh).

MS: *m*/*z* (%) = 576 (M^+, 8), 453 (14), 371 (65), 289 (17), 262 (14), 211 (11), 105 (100), 78 (38), 77 (34), 56 (9), 41 (31).

Anal. Calcd for $C_{36}H_{37}N_3O_4$ (575.70): C, 75.11; H, 6.48; N, 7.30. Found: C, 75.10; H, 6.70; N, 7.20.

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