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Synthesis of novel furo-pyran derivatives via reaction between an isocyanide and alkylidene-substituted Meldrum's acid

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ABSTRACT

An unexpected four-component (3+1) reaction of an alkyl isocyanide with alkylidene-substituted Meldrum's acid in CH_2Cl_2 at room temperature produces imino-furopyranones in good yields. The structures of the products are deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra and by X-ray analysis. The products are structurally similar to 2*H*-furo[2,3-*c*]pyran-2-one natural products.

1. Introduction

The development of simple synthetic routes for complex organic molecules from readily available reagents is an important task in organic synthesis.[1] Multi-component reactions (MCRs) are significant tools for the rapid and efficient synthesis of a wide variety of organic molecules. These reactions have been investigated extensively in organic and diversity-oriented synthesis; primarily due to their ability to generate complex molecular functionality from simple starting materials via one-pot reactions. In recent years, extensive research on multi-component reactions has been reported.[2–4] In these studies, the type and number of molecules that participate in reactions were varied. In most MCRs, various molecules react in equal molar ratios, for example, the Passerini 3-CR and Ugi 4-CR. Some MCRs occur in which molecules take part more than once. There are several examples where a four-component reaction can be accomplished with 2:2 or 2:1:1 ratios of reactants;[5–7] however, a four-component reaction in which two components react in the ratio 3:1 has not been reported yet.

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione),[8] due to its high acidity (pK_a 7.5)[9] and tendency to generate acetone, is an attractive reagent in organic synthesis. Most applications of this compound are as an alternative for acyclic malonic esters.[10] Also its various derivatives have been used widely for heterocycle and drug synthesis. Useful applications of alkylidene-substituted Meldrum's acids (which are readily accessible from Meldrum's acid and carbonyl compounds) are as dienophiles in Diels–Alder reactions[11] and as Michael acceptors. These are advantages of this system over acyclic analogues;[12–16] however, these derivatives have received little attention in organic synthesis.

As part of our current studies on the reaction between electron-deficient alkenes and isocyanides, we herein report the synthesis of new derivatives of furo-pyrans via (3+1) four-component reactions. Three molecules of isocyanide react with one molecule of alkylidene-substituted Meldrum's acid in one step. The products are structurally similar to 2*H*-furo[2,3-*c*]pyran-2-ones, one such example induces the germination of a variety of wild species from regions as diverse as South Africa, Australia, North America, and Europe, and was synthesized in seven steps in low yield[17,18] (Fig. 1).

The reaction of cyclohexyl isocyanide and alkylidene-substituted Meldrum's acid (ratio 3:1) was carried out in dichloromethane at room temperature, and was complete within 4–6 h in good yield. The products of these reactions were identified as 2,3,7-tris(cyclohexylimino)-3,4-dihydro-4,4-dialkyl-2*H*-furo[3,4-*b*]pyran-5(7*H*)-ones (Scheme 1). The structures of compounds **3a**–**h** were deduced from their elemental analysis and their IR, ^{1}H NMR, and ^{13}C NMR spectra. Identification of **3a** and **3d** was aided by ^{15}N NMR spectroscopy and X-ray analysis, respectively.

The IR spectrum of **3a** shows three bands at 1801 (C=O), 1713 (C=O), and 1697 (C=N) cm^{-1}. There were no absorptions for O–H or N–H bonds. The ^{1}H NMR spectrum of **3a** exhibited one singlet (δ = 1.41 ppm) for the two methyl groups and a complex signal (δ = 1.28–1.77 ppm) for the cyclohexyl protons along with three signals (δ = 3.75, 3.98, and 4.10) due to the three methine protons. The proton-decoupled ^{13}C NMR spectrum of **3a** exhibited 20 distinct resonances in agreement with the furo-pyran structure. Partial assignments of these resonances are given in the experi-

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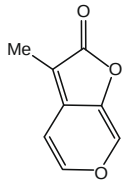


Figure 1. The structure of a 2*H*-furo[2,3-*c*]pyran-2-one.

mental section. The spectral data of **3b**–**h** were similar to **3a** except for differences in the proton resonances of the substituents. The ^{15}N NMR spectrum of **3c** exhibited three signals at 271.9, 287.3, and 353.2 ppm in the imine region.[19] This is consistent with three molecules of isocyanide being incorporated into the product.

A single crystal X-ray diffraction study confirmed the structure of compound **3d** (Fig. 2).[20] The X-ray structure indicated that all the atoms of the furo-pyran ring are in the same plane except for the sp^3 carbon atom.

On the basis of the well-established chemistry of isocyanides[2–4,21,22], it is reasonable to assume that the furo-pyran **3** results from an initial [4+1] cycloaddition reaction of the electron-deficient heterodiene moiety of **2** with cyclohexyl isocyanide to produce an iminolactone intermediate **4**. Nucleophilic attack of a second isocyanide on the imine carbon of **4** followed by cleavage of the five-membered ring and subsequent cyclization gives di-imino pyran intermediate **5**. Addition of a third isocyanide to the carbonyl of intermediate **5** gives unstable intermediate **6** that easily loses an acetone molecule and cyclizes to give furo-pyran **3** (see Scheme 2).

In conclusion, we have established a novel and efficient (3+1) four-component reaction, which gives new furo-pyran derivatives. The advantage of this procedure is that not only the reaction is performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification. The one-pot nature of the present method makes it an interesting alternative to multistep approaches for the synthesis of new derivatives of furo-pyran.

2. General procedure for the synthesis of 3a–h. Exemplified for 3a

To a magnetically stirred solution of 1 mmol of alkylidene-substituted Meldrum's acid **2** in 10 ml of CH_2Cl_2, a mixture of

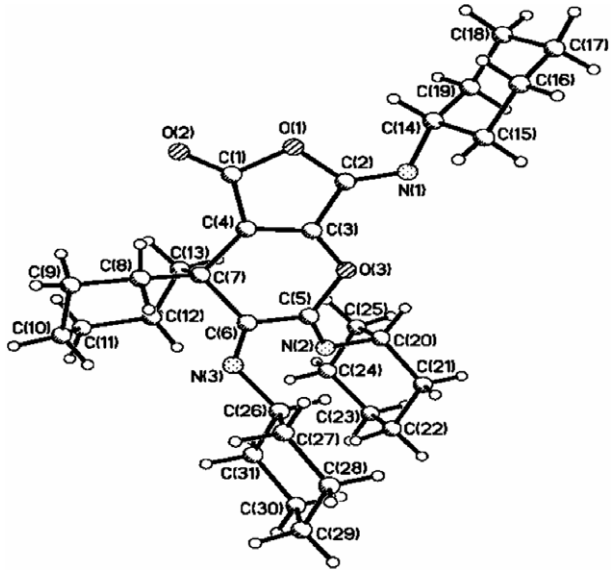
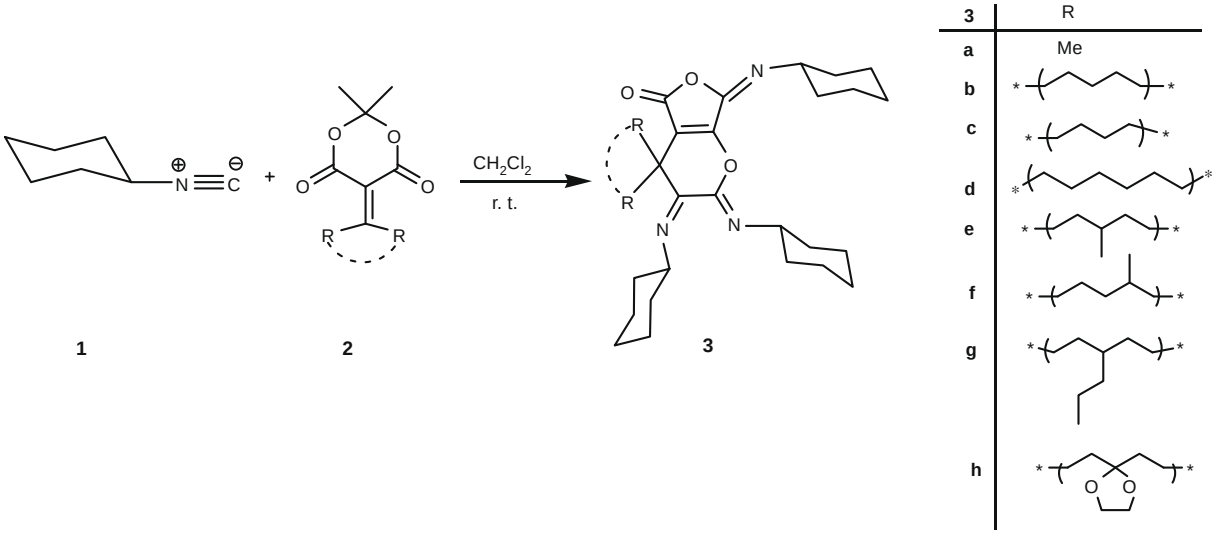


Figure 2. X-Ray crystal structure of **3d** (ORTEP-III plot; arbitrary numbering of atoms).

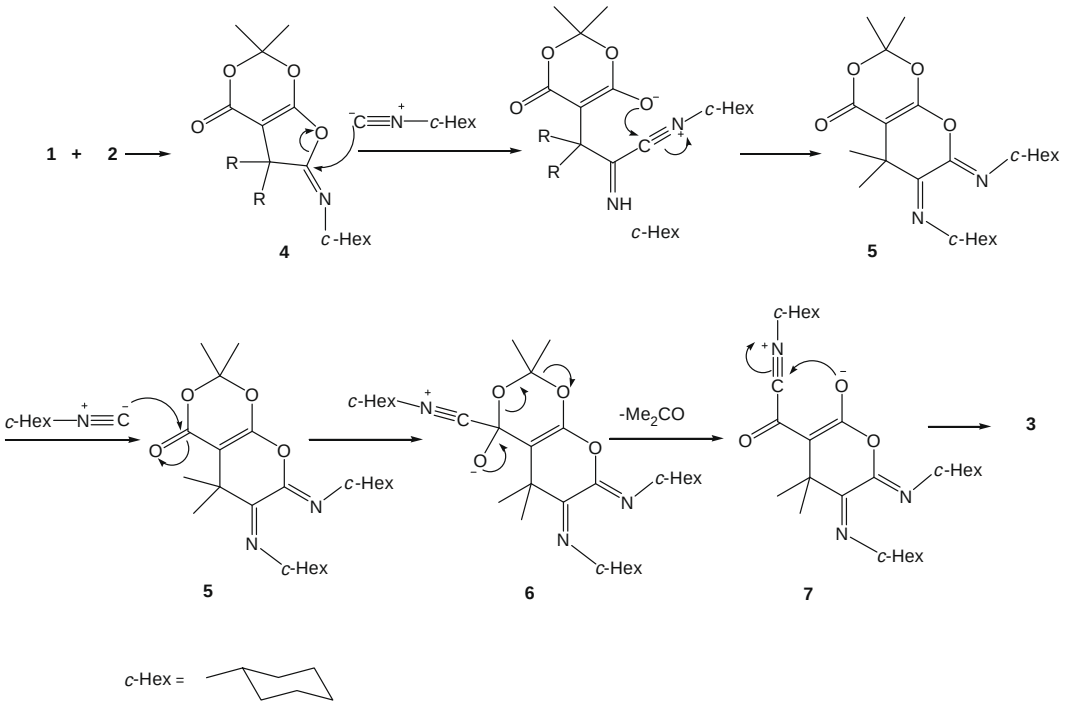
3 mmol of cyclohexyl isocyanide in 2 ml of CH_2Cl_2 was added dropwise at room temperature. The reaction mixture was stirred for 3–5 h after which the solvent was removed under reduced pressure. The product was precipitated by addition of ethanol and standing for a few hours, then collected by filtration and recrystallized from ethanol.

2.1. 2,3,7-Tris(cyclohexylimino)-3,4-dihydro-4,4-dimethyl-2*H*-furo[3,4-*b*]pyran-5(7*H*)-one (3a, $C_{27}H_{39}N_3O_3$)

White powder; mp 128 °C; yield: 58%. IR (KBr) (ν_{max}/cm^{-1}): 1801 (C=O), 1713, 1697 and 1671 (3C=N). ^1H NMR (300.1 MHz, CD_6CO): $\delta = 1.41$ (6H, s, 2 CH_3) 1.28–1.77 (30H, m, 15CH_2 of 3 cyclohexyls), 3.75 (1H, m, HC–N), 3.98 (1H, m, HC–N), 4.1 (1H, m, HC–N) ppm. ^{13}C NMR (75.47 MHz, CD_6CO): $\delta = 24.12$, 24.41, 24.93, 26.15, 26.31, 26.41, 34.01, 34.07, 34.28 (15CH_2 of 3 cyclohexyls), 24.93 (2CH_3), 41.05 (C), 55.62, 58.35, 61.97 (3CH), 117.63 and 136.56 (C=C), 143.22, 155.43 and 155.30 (3C=N), 163.36 (C=O) ppm. MS (EI) *m/z* (%): 453 (M^+, 20), 410 (25), 371



Scheme 1. The (3+1) multi-component reaction of **1** and **2**.



Scheme 2. A suggested mechanism.

(25), 370 (31), 326 (20), 288 (28), 262 (16), 245 (15), 235 (78), 167 (35), 149 (75), 123 (15), 98 (37), 83 (46), 69 (40), 55 (100), 41 (48). Anal. Calcd for $C_{27}H_{39}N_3O_3$ (453.61): C, 71.50; H, 8.60; N, 9.26. Found: C, 71.25; H, 8.90; N, 9.01.

2.2. 2,3,7-Tris(cyclohexylimino)-3,4-dihydro-4-spirocyclohexan-2*H*-furo[3,4-*b*]pyran-5(7*H*)-one (3b, $C_{30}H_{43}N_3O_3$)

White powder; mp 165 °C; yield: 67%. IR (KBr) (ν_{max}/cm^{-1}): 1790 (C=O), 1694 and 1653 (3C=N). ^{1}H NMR (300.1 MHZ, $CDCl_3$): δ = 1.24–1.93 (40H, m, 20CH_2 of 4 cyclohexyls), 3.75 (2H, m, 2HC–N), 4.15 (1H, m, HC–N) ppm. ^{13}C NMR (75.47 MHZ, $CDCl_3$): δ = 21.64, 25.03, 31.25 (5CH_2), 23.76, 24.20, 24.50, 25.74, 25.62, 25.71, 33.34, 33.40, 33.73 (15CH_2 of 3 cyclohexyls); 43.91 (C), 52.41, 52.62, 52.71, (3CH), 117.12 and 134.90, (C=C), 141.25, 155.01 and 155.26 (3C=N), 162.03 (C=O) ppm. MS (EI) *m/z* (%): 493 (M$^+$, 25), 450 (17), 410 (32), 368 (14), 329 (27), 328 (30), 275 (82), 167 (38), 149 (100), 121 (14), 109 (22), 98 (32), 83 (48), 81 (37), 69 (42), 57 (40), 55 (87), 41 (42). Anal. Calcd for $C_{30}H_{43}N_3O_3$ (493.68): C, 72.90; H, 8.78; N, 8.51. Found: C, 72.96; H, 9.03; N, 8.50.

2.3. 2,3,7-Tris(cyclohexylimino)-3,4-dihydro-4-spirocyclopentan-2*H*-furo[3,4-*b*] pyran-5(7*H*)-one (3c, $C_{29}H_{41}N_3O_3$)

White powder; mp 155 °C; yield: 60%. IR (KBr) (ν_{max}/cm^{-1}): 1793 (C=O), 1699 and 1660 (3C=N). ^{1}H NMR (300.1 MHZ, $CDCl_3$): δ = 1.26–2.16 (38H, m, 19CH_2), 3.80 (2H, m, 2HC–N), 4.16 (1H, m, HC–N) ppm. ^{13}C NMR (75.47 MHZ, $CDCl_3$): δ = 25.08, 34.2 (4CH_2) 23.78, 24.23, 24.49, 25.41, 25.61, 25.71, 33.34, 33.43, 33.57 (15CH_2 of 3cyclohexyls), 50.69 (C), 54.87, 58.08, 61.30, (3CH), 162.96 (C=O), 116.88 and 135.42 (C=C), 142.4, 152.59 and 155.27 (3C=N) ppm. ^{15}N NMR (30 MHZ): δ = 271.9, 287.3 and 353.2 ppm (3C=N). MS (EI) *m/z* (%): 479 (M$^+$, 22), 436 (20), 397 (12), 353 (25), 352 (67), 315 (23), 314 (26), 270 (72), 261 (100), 167 (30), 149 (80), 108 (17), 98 (22), 95 (22), 83 (40), 81 (28), 67 (27), 55 (88), 41 (38). Anal. Calcd for $C_{29}H_{41}N_3O_3$ (479.66): C, 72.62; H, 8.62; N, 8.76. Found: C, 72.36; H, 8.22; N, 8.59.

2.4. 2,3,7-Tris(cyclohexylimino)-3,4-dihydro-4-spirocycloheptan-2*H*-furo[3,4-*b*] pyran-5(7*H*)-one (3d, $C_{31}H_{45}N_3O_3$)

White powder; mp 150 °C; yield: 75%. IR (KBr) (ν_{max}/cm^{-1}): 1788 (C=O), 1690 and 1649 (3C=N). ^{1}H NMR (300.1 MHZ, $CDCl_3$): δ = 1.27–2.15 (42H, m, 21CH_2), 3.79 (2H, m, 2HC–N), 4.15 (1H, m, HC–N) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 23.48, 30.46, 33.36 (6CH_2), 23.74, 24.22, 24.50, 25.44, 25.65, 25.76, 33.36, 33.67, 34.32 (15CH_2 of 3 cyclohexyls); 47.63 (C), 54.75, 58.06, 61.50 (3CH), 119.19 and 135.50 (C=C), 142.64, 153.87 and 154.61 (3C=N), 163.12 (C=O) ppm. MS (EI) *m/z* (%): 507 (M$^+$, 25), 464 (12), 450 (10), 425 (27), 424 (47), 343 (21), 342 (32), 299 (24), 289 (95), 167 (18), 149 (50), 123 (16), 98 (34), 83 (50), 69 (28), 67 (30), 55 (100), 41 (43). Anal. Calcd for $C_{31}H_{45}N_3O_3$ (507.70): C, 73.30; H, 8.93; N, 8.2. Found: C, 72.98; H, 8.77; N, 8.28.

2.5. 2,3,7-Tris(cyclohexylimino)-3,4-dihydro-4-spiro-4′-methylcyclohexan-2*H*-furo[3,4-*b*]pyran-5(7*H*)-one (3e, $C_{31}H_{45}N_3O_3$)

White powder; mp 154 °C; yield: 63%. IR (KBr) (ν_{max}/cm^{-1}): 1790 (C=O), 1662, 1669 and 1651 (3C=N). ^{1}H NMR (300.1 MHZ, $CDCl_3$): δ = 0.87 (3H, d, $^3J_{HH}$ = 4.69 Hz, Me), 1.28–2.09 (39H, m, 19CH_2 and CH), 3.78 (2H, m, 2HC–N), 4.15 (1H, m, HC–N) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 22.54 (Me), 30.18, 31.20 (4CH_2), 23.75, 24.15, 24.50, 25.41, 25.62, 25.72, 33.34, 33.40, 33.69 (15CH_2 of 3 cyclohexyls), 31.30 (CH), 43.91 (C), 54.71, 58.12, 61.80 (3CH), 116.45 and 135.29 (C=C) 142.14, 155.21 and 155.40 (3C=N), 162.39 (C=O) ppm. MS (EI) *m/z* (%): 507 (M$^+$, 20), 464 (15), 425 (30), 424 (40), 382 (15), 343 (30), 342 (42), 289 (78), 167 (34), 149 (80), 123 (22), 108 (18), 98 (38), 83 (55), 81 (42), 69 (35), 67 (20), 55 (100), 43 (25), 41 (45). Anal. Calcd for $C_{31}H_{45}N_3O_3$ (507.70): C, 73.30; H, 8.93; N, 8.27. Found: C, 72.96; H, 8.57; N, 8.28.

2.6. 2,3,7-Tris(cyclohexylimino)-3,4-dihydro-4-spiro-3′-methyl-cyclohexan-2*H*-furo[3,4-*b*]pyran-5(7*H*)-one (3f, $C_{31}H_{45}N_3O_3$)

White powder; mp 155 °C; yield: 60%. IR (KBr) (ν_{max}/cm^{-1}): 1791 (C=O), 1696, 1659 and 1650 (3C=N). ^1H NMR (300.1 MHz, $CDCl_3$): δ = 0.85–2.18 (42H, m, 19CH_2, CH and Me), 3.75 (2H, m, 2HC–N), 4.10 (1H, m, HC–N) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 23.73, 24.16, 24.33, 25.62, 25.70, 25.89, 33.36, 33.68, 33.81(15 CH_2 of 3 cyclohexyls), 21.24, 21.10, 24.49, 27.52, 30.11, 39.98, (4CH_2, CH, Me), 44.62 (C), 54.68, 58.07, 61.78 (HC–N), 118.07 and 135.43 (C=C), 142.49 155.52 and 155.33 (3C=N), 162.54 (C=O) ppm. MS (EI) *m/z* (%): 507 (M^+, 28), 464 (16), 425 (33), 424 (38), 382 (20), 343 (25), 342 (38), 289 (88), 167 (34), 149 (90), 123 (20), 108 (15), 98 (38), 83 (56), 81 (42), 69 (40), 67 (32), 55 (100), 43 (25), 41 (50). Anal. Calcd for $C_{31}H_{45}N_3O_3$ (507.70): C, 73.30; H, 8.93; N, 8.27. Found: C, 72.92; H, 8.59; N, 8.05.

2.7. 2,3,7-Tris(cyclohexylimino)-3,4-dihydro-4-spiro-4′-propyl-cyclohexan-2*H*-furo[3,4-*b*]pyran-5(7*H*)-one (3g, $C_{33}H_{49}N_3O_3$)

White powder; mp 130 °C; yield: 59%. IR (KBr) (ν_{max}/cm^{-1}): 1792 (C=O), 1698, 1655 and 1648 (3C=N). ^1H NMR (300.1 MHz, $CDCl_3$): δ = 0.89–1.94 (46H, m, 21CH_2, CH and Me), 3.76 (2H, m, 2HC–N), 4.15 (1H, m, HC–N) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.25, 19.77, 28.20, 31.22 (4CH_2), 24.49 (Me), 35.71 (CH), 43.87 (C), 23.75, 24.16, 24.26, 25.42, 25.63, 25.71, 33.34, 33.40, 33.69 (15CH_2 of 3 cyclohexyls), 54.73, 58.07, 61.70 (3HC–N), 118.80, 135.33, (C=C and C=N), 142.49, 153.31 and 155.49 (3C=N), 162.60 (C=O) ppm. MS (EI) *m/z* (%): 535 (M^+, 22), 507 (27), 464 (17), 425 (20), 424 (28), 382 (18), 342 (32), 299 (16), 289 (80), 167 (20), 149 (44), 123 (13), 98 (31), 83 (40), 69 (32), 55 (100), 43 (19), 41 (50). Anal. Calcd for $C_{33}H_{49}N_3O_3$ (535.72): C, 73.98; H, 9.22; N, 7.83. Found: C, 74.13; H, 9.16; N, 7.81.

2.8. 2,3,7-Tris(cyclohexylimino)-3,4-dihydro-4-spiro-4′-acetal-cyclohexan-2*H*-furo[3,4-*b*]pyran-5(7*H*)-one (3h, $C_{32}H_{45}N_3O_5$)

White powder; mp 160 °C; yield: 59%. IR (KBr) (ν_{max}/cm^{-1}): 1798 (C=O), 1700, 1694 and 1657 (3C=N). ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.26–2.43 (38H, m, 19CH_2), 3.76 (2H, m, 2HC–N), 3.95 (4H, t, $^3J_{HH}$ = 6.42 Hz, H2C–O), 4.17 (1H, m, HC–N) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 23.69, 24.18, 24.49, 25.42, 25.61, 25.67, 33.33, 33.40, 33.69 (15CH_2 of 3 cyclohexyls), 29.08, 30.66, (4CH_2), 42.90 (C), 54.8, 56.16, 62.05 (HC–N), 64.29 (2H_2C–O), 108.05 (C), 117.08, 134.89, (C=C), 142.2, 152.78 and 155.76 (3C=N), 162.24 (C=O) ppm. MS (EI) *m/z* (%): 551 (M^+, 17), 507 (29), 469 (15), 464 (10), 425 (24), 424 (39), 342 (28), 342 (32), 299 (21), 289 (72), 167 (17), 149 (37), 123 (15), 98 (30), 83 (42), 69 (20), 55 (100), 41 (50). Anal. Calcd for $C_{32}H_{45}N_3O_5$ (551.73): C, 69.66; H, 8.22; N, 7.62. Found: C, 68.98; H, 8.34; N, 7.56.

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