Pseudo-Five-Component Condensation for the Diversity-Oriented Synthesis of Novel Indoles and Quinolines Containing *pseudo*-Peptides (Tricarboxamides)

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ABSTRACT: *A novel series of indole and quinoline tricarboxamides were synthesized using simple and efficient one-pot pseudo-five-component reactions of 2-formylindole or 2-chloro-3-formyl quinolines, isocyanides, amines, and Meldrum's acid as a CH-acid in CH_2Cl_2 at room temperature. This conversion has been achieved via the construction of new bonds including two C-C bonds, two C-N bonds, and one C=O bond. Remarkably, three peptide bonds were formed through a domino sequence including Knoevenagel reaction, [1+4] cycloaddition, deacetonation and also, aminolysis reaction. Particularly, a number of structurally remarkable and pharmacologically significant products were provided in excellent yields.*

KEYWORDS: *2-formylindole; 2-chloro-3-formyl quinolone; Isocyanides; Meldrum's acid; Multicomponent reaction; Tricarboxamide.*

INTRODUCTION

MultiComponent Reactions (MCRs) wherein at least three different substrates react through covalent bonds have obtained importance in synthetic organic chemistry. The formation of various bonds in a one-pot reaction was provided in MCRs. MCRs give special advantages such as operational simplicity, convergence, reduction in the number of workup steps, extraction, and purification of products [1]. One-pot MCRs frequently provide higher overall chemical yields than multiple-step reactions and decrease the use of manpower and energy.

Remarkable heterocyclic skeletons, which are predominantly valuable for the formation of various chemical libraries of 'drug-like' molecules, can be obtained from various MCRs. In this area, the isocyanide-based MCRs are particularly significant [2].

These MCRs are especially fascinating since they are more varied and useful than other multicomponent reactions [3, 4]. They can increase the diversity of available bond forming methods and increase levels of chemo-, stereo-, and regioselectivity [5-7].

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The isocyanide-based Ugi [8] and the Passerini condensation [9] have been applied extensively in MCRs. Due to the appropriate ability of isocyanides to undergo facile addition with a nucleophile and an electrophile, they are valuable reactants for the formation of new MCRs [10,11]. An efficient route for the synthesis of a highly functionalized dihydrocoumarin derivatives through a four-component reaction was demonstrated in 2008 by Shaabani *et al.* [12].

The 5-arylidene Meldrum's acids are bis-electrophilic classes of compounds that can be used efficiently as suitable precursors in various MCRs [13a, b]. Several methods for the synthesis of amidodiesters and triamides using Meldrum's acid derivatives have been reported and attracted much attention [13c].

These products can be formed by the reaction of aldehydes and Meldrum's acids (5-alkylidene or 5-arylmethylidene Meldrum's acids) with diverse nucleophiles such as alcohols [14a-c], primary amines [14d], and phenols [14c] in dichloromethane. Furthermore, the use of Meldrum's acid derivatives and isocyanides with other nucleophiles in MCRs such as water [15] aryl hydrazines [16], diols [17], arylhydroxylamines [18], 2-hydroxy benzaldehydes [19], urea [20] and sugar hydroxyaldehydes [21] were developed that provided 4-oxobutanoic acids, 1-arylpyrazolidine-3,5-diones, 2-arylisoxazolidine-3,5-diones, 1,4-dioxepane-5,7-diones, 3,4-dihydrocoumarins, barbituric acid and 5-oxo-perhydrofuro-[3,2-*b*]pyran derivatives respectively.

The peptide bond is a significant functional group in organic and medicinal chemistry and biochemistry and peptides play a vital role in all living organisms [22-23]. Di- and tripeptides and their analogues have demonstrated various significant bioactivities such as antitumor [24], anticarcinogenic [25], antibacterial [26], antidiabetic [27] and neuroprotective [28] activities. Peptides show suitable affinity toward cells and nucleic acids and as such, introducing a peptide segment onto drugs, make it possible for the drugs to interact with cells and tissues, affording a forceful approach to design novel drugs.

A significant class of heterocyclic compounds found in natural products [29] are quinolines and indole derivatives. These quinoline derivatives have shown different activities such as anticancer [30], antimicrobial [31], antimalarial [32], antituberculosis, [33] antibiotic [34], anti-inflammatory [35] antihypertensive [36], anticonvulsant [37] and anti HIV [38].

Due to the important properties of these compounds, we decided to combine the indole, quinoline and triamide moieties into one molecular framework. We have combined triamides or 2-formylindole and 2-chloro-3-formyl quinolines as molecular entities *via* carbon-carbon and carbon-heteroatom bond formation to create new hybrid molecules. This was found to be an efficient procedure to form novel classes of tripeptide molecules containing bioactive moieties. In our continued investigation on isocyanide-based MCRs [39], we herein report a *pseudo*-five-component tandem reaction of 2-formylindole or 2-chloro-3-formyl quinolines, Meldrum's acid, and isocyanides with amines, which provides an efficient way to form indole or quinoline-containing *pseudo*-peptides with high yields under mild conditions at ambient temperature.

EXPERIMENTAL SECTION

Apparatus

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Melting points were recorded on an electro thermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu infrared spectrometer IR-435. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz Spectrometer in DMSO-d_6 as solvent and TMS as an internal standard.

General procedure for the synthesis of tricarboxamides

*General procedure for the synthesis of the tripeptide-bound indole derivatives **5**:*

2-Formylindole **1** (1 mmol) and Meldrum's acid **2** (1 mmol) were dissolved in 5 mL of anhydrous CH_2Cl_2, and the mixture stirred for 3h at ambient temperature. The amines **4** (2.0 mmol) and isocyanides **3** (1 mmol) were then added to this mixture and stirred at room temperature for 12 h. This reaction was monitored by TLC (EtOAc / *n*-hexane 1:1). After completion of this reaction, the precipitated product was filtered off and the solid washed with diethyl ether producing **5**. The crude product was recrystallized from hot EtOH to afford the pure products **5a-g**.

General procedure for the synthesis of the tripeptide-bound quinoline derivatives 7a-m:

2-Chloroquinoline-3-carbaldehyde **6** (1 mmol) and Meldrum's acid **2** (1 mmol) were dissolved in 5 mL of anhydrous CH_2Cl_2, and the mixture was stirred at room

the temperature for 3 h. The amines 4 (2 mmol) and isocyanides **3** (1 mmol) were then added and the reaction mixture was stirred at ambient temperature for 12 h. This reaction was monitored by TLC (EtOAc / *n*-hexane 1:1). After completion of this reaction, the precipitated product was filtered off and the solid washed with diethyl ether to give **7a-m**. The crude products were recrystallized from hot EtOH to afford pure products **7a-m**.

N^2-cyclohexyl-2-(1H-indol-2-yl)-N^1,N'^1-bis(2-iodophenyl) ethane-1,1,2-tricarboxamide **(5a):**

$C_{31}H_{30}I_4N_4O_3$ (MW: 760.40), White powder, m.p.: 294 °C; FT-FT-IR (KBr): ν_{max} = 3294, 3064, 3015, 2932, 2855, 1703, 1627, 1525, 1463, 1430 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.02-1.76 (m, 10H), 3.41-3.43 (m,1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 6.47 (s, 1H), 6.86-7.54 (m, 10H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 2H), 9.39 (s, 1H), 9.61 (s, 1H), 10.57 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 24.4, 25.2, 32.0, 32.3, 44.9, 47.8, 55.2, 94.3, 99.7, 111.2, 118.9, 119.7, 120.9, 126.1, 126.55, 127.6, 127.9, 128.6, 128.9, 135.6, 135.8, 138.6, 138.9, 139.0, 139.3, 165.6, 165.8, 168.9 ppm.

N^2-cyclohexyl-2-(1H-indol-2-yl)-N^1,N'^1-di-p-tolylethane-1,1,2-tricarboxamide **(5b):**

$C_{33}H_{36}N_4O_3$ (MW: 536.66), white powder, m.p.: > 300 °C; FT-FT-IR (KBr): ν_{max} = 3272, 3124, 2929, 2855, 1662, 1537, 1449, 1412 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.99-1.69 (m, 10H), 2.17 (s, 3H), 2.25 (s, 3H), 3.41-3.43 (m,1H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.66 (d, *J* = 11.4 Hz, 1H), 6.27 (s, 1H), 6.87-7.46 (m, 12H), 7.96 (d, *J* = 7.9 Hz, 1H), 9.77 (s, 1H), 9.83 (s, 1H), 10.63 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 24.2 24.3, 25.1, 31.9, 32.2, 44.6, 47.7, 56.7, 99.1, 111.2, 118.8, 119.2, 119.5, 120.6, 127.8, 129.2, 132.6, 135.9, 136.2, 165.1, 165.3, 169.1 ppm.

N^2-(tert-butyl)-2-(1H-indol-2-yl)-N^1,N'^1-di-p-tolylethane-1,1,2-tricarboxamide **(5c):**

$C_{31}H_{34}N_4O_3$ (MW: 510.63), white powder, m.p.: > 300 °C; FT-FT-IR (KBr): ν_{max} = 3312, 3127, 2969, 2872, 1663, 1532, 1453, 1409 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.16 (s, 9H), 2.18 (s, 3H), 2.25 (s, 3H), 4.31 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 6.27 (s, 1H), 6.88-7.47 (m, 12H), 7.69 (s, 1H), 9.75 (s, 1H), 9.82 (s, 1H), 10.60 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 20.4, 28.3, 45.2, 50.2, 56.9, 98.9, 111.2, 118.7, 119.2, 119.4, 120.5, 127.7, 129.2, 132.6, 135.8, 135.9, 136.1, 136.2, 165.2, 165.3, 169.4 ppm.

N^1,N'^1-bis(4-chlorophenyl)-N^2-cyclohexyl-2-(1H-indol-2-yl)ethane-1,1,2-tricarboxamide **(5d):**

$C_{31}H_{30}Cl_2N_4O_3$ (MW: 577.50), white powder, m.p.: > 300 °C; FT-FT-IR (KBr): ν_{max} = 3290, 3124, 2931, 2855, 1670, 1615, 1536, 1496, 1453 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.00 -1.68 (m, 10H), 3.41-3.43 (m, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.68 (d, *J* = 11.3 Hz, 1H), 6.29 (s, 1H), 6.88-7.62 (m, 12H), 7.96 (d, *J* = 7.9 Hz, 1H), 9.99 (s, 1H), 10.09 (s, 1H), 10.63 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 24.2, 25.1, 31.9, 32.2, 44.6, 47.7, 56.8, 99.3, 111.2, 118.8, 119.5, 120.6, 120.8, 127.3, 127.7, 128.6, 128.7, 135.5, 135.8, 137.2, 137.5, 165.3, 165.5, 168.9 ppm.

N^1,N'^1-dibenzyl-N^2-cyclohexyl-2-(1H-indol-2-yl)ethane-1,1,2- tricarboxamide **(5e):**

$C_{33}H_{36}N_4O_3$ (MW: 536.66), white powder, m.p.: 299-300 °C; FT-FT-IR (KBr): ν_{max} =3282, 3124, 3068, 2929, 2855, 1656, 1550, 1451, 1422 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.97-1.68 (m, 10H), 3.42-3.44 (m, 1H), 4.01-4.06 (m, 1H), 4.19-4.30 (m, 2H), 4.38 (d, *J* = 6.0 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 6.25 (s, 1H), 6.75-7.45 (m, 14H), 7.87 (d, *J* = 7.8 Hz, 1H), 8.17 (s, 1H), 8.18 (s, 1H), 10.57 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 24.3, 25.2, 31.9, 32.2, 41.9, 42.3, 44.8, 47.7, 55.2, 99.5, 111.3, 118.8, 119.4, 120.5, 126.5, 126.8, 127.8, 126.9, 127.9, 128.2, 128.6, 135.8, 136.2, 138.6, 139.2, 167.24, 167.25, 169.2 ppm.

N^2-cyclohexyl-2-(1H-indol-2-yl)-N1,N'^1-bis(4-methoxyphenyl) ethane-1,1,2-tricarboxamide **(5f):**

$C_{33}H_{36}N_4O_5$ (MW: 568.66), white powder, m.p.: > 300 °C; FT-FT-IR (KBr): ν_{max} = 3291, 3076, 2931, 2852, 1658, 1619, 1541, 1517, 1453, 1416 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.00-1.69 (m, 10H), 3.41-3.43 (m,1H), 3.65 (s, 3H), 3.72 (s, 3H), 4.34 (d, *J* = 11.4 Hz, 1H), 4.66 (d, *J* = 11.4 Hz, 1H), 6.28 (s, 1H), 6.77-7.49 (m, 12H), 7.94 (d, *J* = 7.9 Hz, 1H), 9.72 (s, 1H), 9.77 (s, 1H), 10.62 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 24.3, 25.1, 31.9, 32.2, 44.6, 47.6, 55.2, 56.5, 99.1, 111.2, 113.9, 118.7, 119.4, 120.5, 120.7, 127.8, 131.5, 131.9, 135.8, 135.9, 155.4, 164.9, 165.1, 169.1 ppm.

N^1,N'^1-bis(4-bromophenyl)-N^2-cyclohexyl-2-(1H-indol-2-yl)ethane-1,1,2-tricarboxamide **(5g):**

$C_{31}H_{30}Br_2N_4O_3$ (MW: 666.40), white powder, m.p.: > 300 °C; FT-FT-IR (KBr): ν_{max} = 3289, 3117, 2929, 2853, 1672, 1626, 1533, 1450, cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.00-1.68 (m, 10H), 3.41-3.43 (m, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.71 (d, *J* = 11.2 Hz, 1H), 6.30 (s, 1H), 6.88-7.57 (m, 12H), 7.97 (d, *J* = 7.8 Hz, 1H), 10.04 (s, 1H), 10.10 (s, 1H), 10.65 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 24.3, 25.1, 31.9, 32.2, 44.6, 47.7, 56.8, 99.3, 111.2, 115.3, 118.9, 119.5, 120.6, 121.2, 127.7, 131.6, 135.5, 135.8, 137.6, 137.9, 165.3, 165.5, 168.9 ppm.

N^2-(tert-butyl)-2-(2-chloro-6-methylquinolin-3-yl)-N^1,N'^1-di-p-tolylethane-1,1,2-tricarboxamide **(7a):**

$C_{33}H_{35}ClN_4O_3$ (MW: 571.11), white powder, m.p.: 285-286 °C; FT-FT-IR (KBr): ν_{max} = 3250, 3039, 2971, 2923, 1674, 1604, 1524, 1453, 1407 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.12 (s, 9H), 2.15 (s, 3H), 2.26 (s, 3H), 2.49 (s, 3H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.96 (d, *J* = 11.6 Hz, 1H), 6.97-7.79 (m, 12H), 8.45 (s, 1H), 9.81 (s, 1H), 9.87 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 20.4, 21.0, 28.2, 47.9, 50.5, 58.2, 119.3, 119.6, 126.4, 126.7, 127.1, 129.1, 129.8, 132.7, 135.6, 136.1, 137.1, 144.4, 149.4, 164.9, 165.2, 168.6 ppm.

N^1,N'^1-bis(4-bromophenyl)-2-(2-chloroquinolin-3-yl)-N^2-cyclohexylethane-1,1,2-tricarboxamide **(7b):**

$C_{32}H_{29}Br_2ClN_4O_3$ (MW: 712.86), white powder, m.p.: 259-260 °C; FT-FT-IR (KBr): ν_{max} = 3279, 3067, 2928, 2853, 1683, 1645, 1596, 1496, 1450 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.99-1.56 (m, 10H), 3.40-3.46 (m, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.96 (d, *J* = 11.4 Hz, 1H), 7.27-8.01 (m, 13H), 8.55 (s, 1H), 9.99 (s, 1H), 10.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 25.1, 31.9, 47.5, 48.1, 57.9, 115.4, 121.4, 126.6, 127.4, 127.9, 129.5, 130.8, 131.5, 137.4, 138.0, 145.9, 150.2, 165.1, 165.6, 168.3 ppm.

N^1,N'^1-dibenzyl-2-(2-chloroquinolin-3-yl)-N^2-cyclohexylethane-1,1,2-tricarboxamide **(7c):**

$C_{34}H_{35}ClN_4O_3$ (MW: 583.12), white powder, m.p.: 255-257 °C; FT-FT-IR (KBr): ν_{max} = 3281, 3064, 2928, 2854, 1656, 1548, 1449, 1391 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.04-1.62 (m, 10H), 3.40-3.44 (m, 1H), 3.86-4.33 (m, 4H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.87 (d, *J* = 11.7 Hz, 1H), 6.63-7.98 (m, 15H), 8.36 (s, 1H), 8.51 (s, 1H), 8.53 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 24.5, 25.1, 31.9, 41.9, 42.4, 47.1, 48.0, 126.2, 126.3, 126.7, 126.9, 127.3, 127.8, 128.3, 130.2, 130.6, 139.1, 145.8, 150.5, 166.8, 166.9, 168.4 ppm.

2-(2-chloro-6-methylquinolin-3-yl)-N^1,N'^1-bis(4-chlorophenyl)-N^2-cyclohexylethane-1,1,2-tricarboxamide **(7d):**

$C_{33}H_{31}Cl_3N_4O_3$ (MW: 637.98), white powder, m.p.: 248-250 °C; FT-FT-IR (KBr): ν_{max} = 3285, 3075, 2929, 2853, 1683, 1647, 1601, 1527, 1451, 1394 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.99-1.58 (m, 10H), 2.48 (s, 3H), 3.42-3.45 (m, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.95 (d, *J* = 11.3 Hz, 1H), 7.21-7.95 (m, 12H), 8.42 (s, 1H), 9.98 (s, 1H), 10.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 21.1, 24.4, 25.1, 31.9, 47.5, 48.1, 57.8, 120.9, 126.5, 126.7, 127.3, 128.5, 129.5, 132.9, 137.6, 144.5, 149.3, 165.1, 165.6, 168.3 ppm.

2-(2-chloroquinolin-3-yl)-N^2-cyclohexyl-N^1,N'^1-bis(4-methoxyphenyl)ethane-1,1,2-tri-carboxamide **(7e):**

$C_{34}H_{35}ClN_4O_5$ (MW: 615.12), white powder, m.p.: 280-281 °C; FT-FT-IR (KBr): ν_{max} = 3277, 3077, 2929, 2848, 1676, 1646, 1518, 1452, 1406 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.03-1.60 (m, 10H), 3.40-3.45 (m, 1H), 3.62 (s, 3H), 3.73 (s, 3H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.95 (d, *J* = 11.4 Hz, 1H), 6.72-8.01 (m, 13H), 8.57 (s, 1H), 9.76 (s, 1H), 9.79 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 25.1, 31.9, 47.5, 48.0, 55.1, 57.6, 113.8, 121.0, 126.7, 127.4, 127.9, 129.9, 130.7, 131.2, 131.8, 145.8, 150.3, 155.51, 155.53, 164.7, 165.1, 168.3 ppm.

2-(2-chloroquinolin-3-yl)-N^2-cyclohexyl-N^1,N'^1-di-p-tolylethane-1,1,2-tricarboxamide **(7f):**

$C_{34}H_{35}ClN_4O_3$ (MW: 583.12), white powder, m.p.: 298-299 °C; FT-FT-IR (KBr): ν_{max} = 3309, 3071, 2929, 2853, 1650, 1602, 1517, 1449, 1403 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.07-1.59 (m, 10H), 2.14 (s, 3H), 2.26 (s, 3H), 3.40-3.44 (m, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.96 (d, *J* = 11.4 Hz, 1H), 6.95-8.01 (m, 13H), 8.56 (s, 1H), 9.79 (s, 1H), 9.85 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 20.4, 24.5, 25.0, 31.9, 47.5, 48.1, 57.8, 119.4, 126.7, 127.4, 127.9, 129.0, 129.8, 130.7, 132.7, 135.6, 136.1, 145.8, 150.3, 164.8, 165.2, 168.3 ppm.

2-(2-chloroquinolin-3-yl)-N^2-cyclohexyl-N^1,N'^1-bis(2-iodophenyl)ethane-1,1,2-tricarboxamide **(7g):**

$C_{32}H_{29}ClI_2N_4O_3$ (MW: 807.86), white powder, m.p.: 289-290 °C; FT-FT-IR (KBr): ν_{max} = 3281, 3066, 2926, 2851, 1687, 1643, 1569, 1523, 1474, 1431, 1399 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.01-1.71 (m, 10H), 3.45-3.50 (m, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.92 (d, *J* = 11.4 Hz, 1H), 6.84-8.09 (m, 13H), 8.54 (s, 1H), 9.45 (s, 1H), 9.63 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 24.5, 25.1, 32.0, 48.2, 126.7, 127.4, 128.2, 128.6, 128.7, 130.8, 138.3, 138.8, 139.1, 145.9, 150.3, 165.0, 168.1 ppm.

2-(2-chloro-6-methoxyquinolin-3-yl)-N^2-cyclohexyl-N^1,N'^1-di-p-tolylethane-1,1,2-tricarboxamide **(7h):**

$C_{35}H_{37}ClN_4O_4$ (MW: 613.15), white powder, m.p.: 295-296 °C; FT-FT-IR (KBr): ν_{max} = 3281, 3079, 2927, 2855, 1678, 1643, 1606, 1522, 1450, 1396 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.00-1.60 (m, 10H), 2.15 (s, 3H), 2.26 (s, 3H), 3.44-3.46 (m, 1H), 3.90 (s, 3H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.92 (d, *J* = 11.4 Hz, 1H), 6.96-7.88 (m, 12H), 8.45 (s, 1H), 9.74 (s, 1H), 9.85 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 20.4, 24.4, 25.1, 31.9, 47.5, 48.0, 55.6, 57.8, 105.7, 119.4, 122.9, 127.9, 129.0, 129.9, 132.7, 135.6, 136.1, 141.8, 147.5, 157.8, 164.7, 165.3, 168.4 ppm.

N^1,N'^1-dibenzyl-2-(2-chloro-6-methoxyquinolin-3-yl)-N^2-cyclohexylethane-1,1,2-tricarboxamide **(7i):**

$C_{35}H_{37}ClN_4O_4$ (MW: 613.15), white powder, m.p.: 275-276 °C; FT-FT-IR (KBr): ν_{max} = 3282, 3070, 2928, 2854, 1656, 1540, 1452 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.04-1.61 (m, 10H), 3.42-3.44 (m, 1H), 3.90 (s, 3H), 4.26-4.42 (m, 4H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 1H), 6.65-7.42 (m, 14H), 8.40 (s, 2H), 8.52 (s, 1H) ppm^{13}C NMR (100 MHz, DMSO-d_6): 20.6, 24.0, 24.6, 31.4, 41.5, 41.9, 46.6, 47.5, 55.6, 125.8, 126.2, 126.6, 127.2, 127.9, 129.6, 132.2, 136.4, 138.1, 138.6, 143.9, 149.0, 166.3, 166.4, 167.9 ppm.

2-(2-chloro-6-methylquinolin-3-yl)-N^2-cyclohexyl-N^1,N'^1-di-p-tolylethane-1,1,2-tricarboxamide **(7j):**

$C_{35}H_{37}ClN_4O_4$ (MW: 597.15), white powder, m.p.: 249-251 °C; FT-FT-IR (KBr): ν_{max} = 3282, 3072, 2926, 2855, 1679, 1645, 1603, 1523, 1449, 1406 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.00-1.59 (m, 10H), 2.14 (s, 3H), 2.26 (s, 3H), 2.5 (s, 3H), 3.43-3.45 (m, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.94 (d, *J* = 11.4 Hz, 1H), 6.96-7.89 (m, 12H), 8.42 (s, 1H), 9.79 (s, 1H), 9.87 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 20.4, 21.0, 24.5, 25.1, 31.9, 47.5, 48.0, 57.7, 119.5, 126.4, 126.7, 127.1, 129.0, 129.7, 132.7, 135.6, 136.1, 137.1, 144.4, 149.4, 164.7, 165.2, 168.4 ppm.

N^1,N'^1-bis(4-chlorophenyl)-2-(2-chloroquinolin-3-yl)-N^2-cyclohexylethane-1,1,2-tricarboxamide **(7k):**

$C_{32}H_{29}Cl_3N_4O_3$ (MW: 623.96), white powder, m.p.: 248-250 °C; FT-FT-IR (KBr): ν_{max} = 3282, 3068, 2929, 2854, 1683, 1645, 1600, 1525, 1450, 1395 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.99-1.57 (m, 10H), 3.41-3.45 (m, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.96 (d, *J* = 11.4 Hz, 1H), 7.21-8.01 (m, 13H), 8.55 (s, 1H), 9.99 (s, 1H), 10.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 24.5, 25.1, 31.9, 47.5, 48.1, 57.8, 121.0, 126.7, 127.4, 127.9, 128.6, 129.5, 130.8, 136.9, 137.6, 145.9, 150.2, 165.1, 165.6, 168.3 ppm.

2-(2-chloro-6-methylquinolin-3-yl)-N^2-cyclohexyl-N^1,N'^1-bis(2-iodophenyl)ethane-1,1,2-tricarboxamide **(7l):**

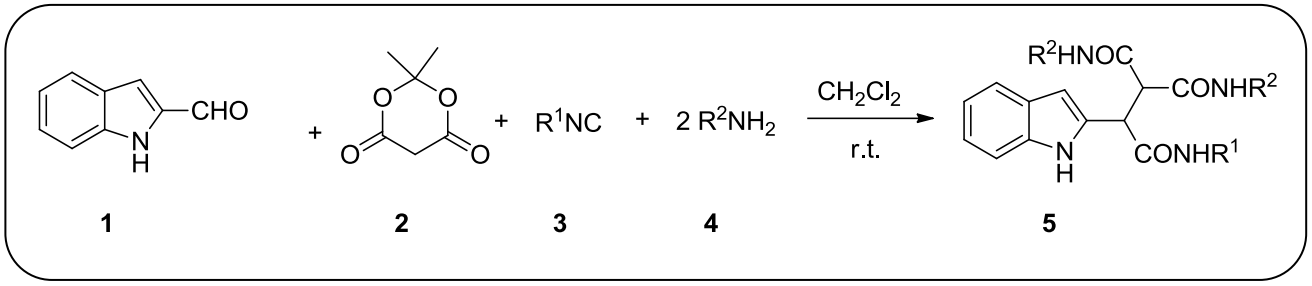
$C_{33}H_{31}ClI_2N_4O_3$ (MW: 820.89), white powder, m.p.: 273-275 °C; FT-FT-IR (KBr): ν_{max} = 3270, 3063, 2924, 2851, 1685, 1648, 1574, 1520, 1429 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.00-1.69 (m, 10H), 2.34 (s, 3H), 3.41-3.45 (m, 1H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.89 (d, *J* = 11.6 Hz, 1H), 6.83-7.94 (m, 12H), 8.42 (s, 1H), 9.49 (d, *J* = 5.6 Hz, 1H), 9.63 (d, *J* = 13.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 21.0, 24.5, 25.1, 32.0, 47.3, 48.2, 54.0, 94.3, 114.8, 118.9, 126.0, 126.7, 127.4, 129.2, 132.8, 135.6, 137.0, 138.5, 139.1, 165.03, 168.2, 168.9 ppm.

2-(2-chloro-6-methylquinolin-3-yl)-N^2-cyclohexyl-N^1,N'^1-bis(4-methoxyphenyl)ethane-1,1,2-tricarboxamide **(7m):**

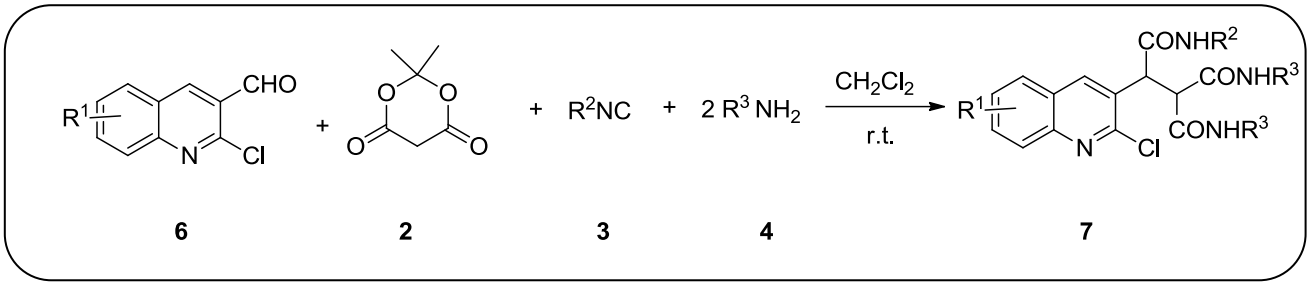
$C_{35}H_{37}ClN_4O_5$ (MW: 629.15), white powder, m.p.: 292-294 °C; FT-IR (KBr): ν_{max} = 3277, 3078, 2929, 2849, 1677, 1518, 1452, 1408 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.04-1.58 (m, 10H), 2.5 (s, 3H), 3.41-3.45 (m, 1H), 3.63 (s, 3H), 3.73 (s, 3H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.94 (d, *J* = 11.4 Hz, 1H), 6.73-7.89 (m, 12H), 8.43 (s, 1H), 9.76 (s 1H), 9.82 (s, 1H) ppm.

RESULTS AND DISCUSSION

Initially, optimal reaction conditions were examined by adding together a mixture of 2-formylindole **1**,



Scheme 1: Synthesis of the tripeptide-bound indole derivatives 5a-g.



Scheme 2: Synthesis of the tripeptide-bound quinoline derivatives 7a-m.

Meldrum's acid **2** as the acid component in dry dichloromethane (instead of the carboxylic acid in Ugi reactions), cyclohexyl isocyanide **3** and 4-methylaniline **4** at room temperature without any catalyst to provide *N*^{2}-cyclohexyl-2-(1*H*-indol-2-yl)-*N*^{1},*N*^{1}-di-*p*-tolylethane-1,1,2-tricarboxamide **5b** (Scheme **1**). This reaction provides the formation of three peptide bonds in a one-pot reaction. Significantly, this reaction was studied in different solvents such as aprotic (CH_3CN and CH_2Cl_2) and protic (MeOH and EtOH) solvents. The best result was obtained at room temperature in CH_2Cl_2. EtOH and MeOH produced side products.

Using the optimal reaction conditions, the scope and generality of the one-pot *pseudo*-five-component reaction were further examined using 2-formylindole, aromatic and aliphatic amines, and cyclohexyl or *tert*-butyl isocyanides for the preparation of a variety of tripeptide derivatives. The results are demonstrated in Table **1**.The reaction was efficient with both the sterically hindered *tert*-butyl isocyanide and the less hindered cyclohexyl isocyanide. A wide range of aromatic anilines containing electron-donating and withdrawing groups for example methyl, methoxy, ethyl, phenyl, fluoro, iodo, and bromo as well as benzylamine were also used in the reaction. In all cases, the corresponding products **5a-g** were obtained in yields in excess of 90%.

In the second round of reactions, the 2-formylindole was replaced with 2-chloroquinoline-3-carbaldehyde **6** under optimal conditions without the use of catalysts to provide 2-(2-chloroquinolin-3-yl)-*N*^{2}-cyclohexyl-*N*^{1},*N*^{1}-di-*p*-tolylethane-1,1,2-tricarboxamide **7f** in 95% yield (Scheme **2**). With various amines as mentioned above and cyclohexyl and *tert*-butyl isocyanides, a range of 2-chloroquinoline-3-carbaldehyde derivatives were prepared in good yields of between 85-95%. The results are shown in Table **2**.

A plausible reaction pathway is depicted in Scheme **3** for the synthesis of the tripeptide-bound indoles **5** or quinolines **7**. An initial Knoevenogel condensation of the aldehyde **1** or **6** and Meldrum's acid **2**, occurs forming an imine intermediate. It was followed by a [1 + 4] cycloaddition reaction [40] with isocyanide **3** resulting in an iminolactone intermediate **9**. Arylidene Meldrum's acids [21] and acylated Meldrum's acids [41] can easily lose acetone with the addition of nucleophiles. An arylamine then reacts with the fused iminolactone **9** with loss of acetone to produce **10**, which further reacts with a second molecule of amine at the activated lactone carbonyl group to form the desired products **5** or **7** (Scheme **3**).

CNOCLUSIONS

A *pseudo*-five-component condensation procedure for the synthesis of indoles and quinolines containing peptidomimetics through a one-pot and multicomponent

Table 1: Components and yields of the pseudo-five-component reaction between 2-formylindole, Meldrum's acid, isocyanides and amines.

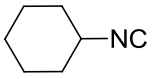
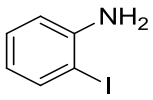
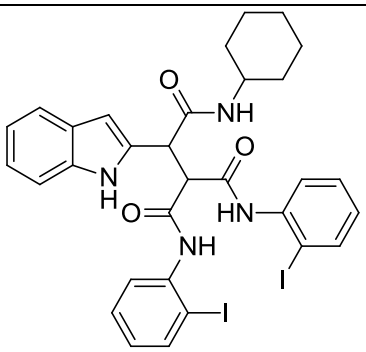
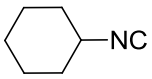
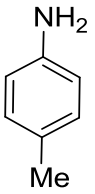
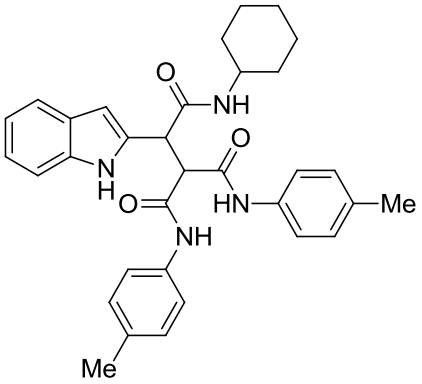
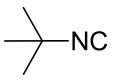
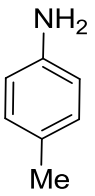
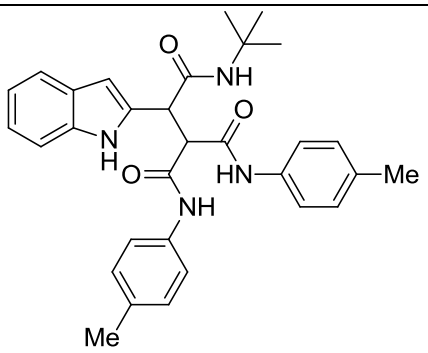
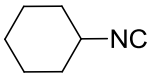
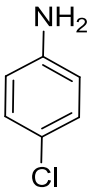
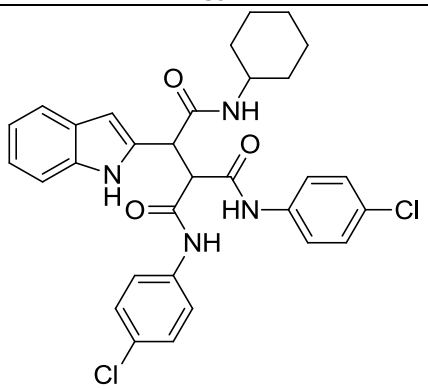
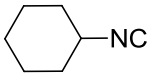
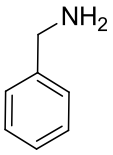
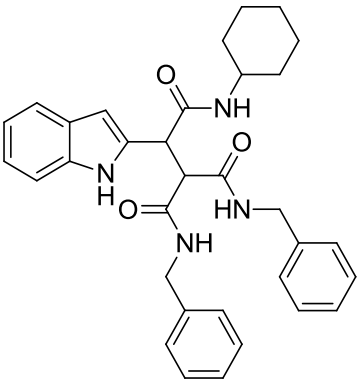
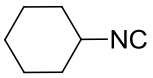
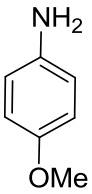
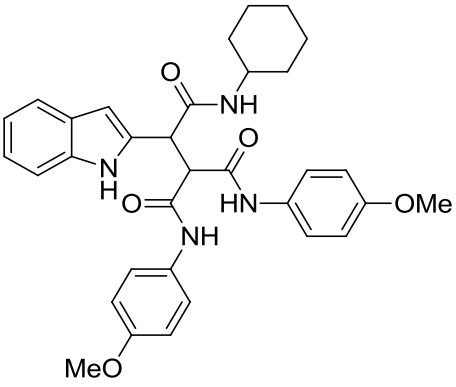
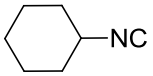
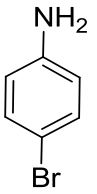
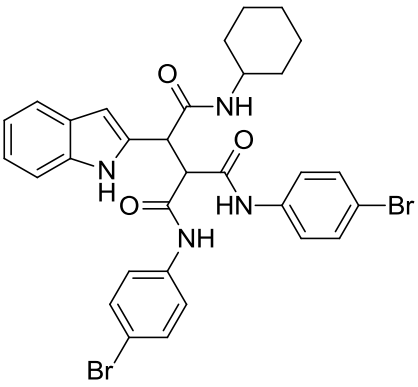
Entry	Isocyanide	Amine	Product	Isolated Yield %
1			 **5a**	94
2			 **5b**	98
3			 **5c**	93
4			 **5d**	95

Table 1: Components and yields of the pseudo-five-component reaction between 2-formylindole, Meldrum's acid, isocyanides and amines.

Entry	Isocyanide	Amine	Product	IsolatedYield %
5			 **5e**	92
6			 **5f**	96
7			 **5g**	93

the reaction of 2-formylindole or 2-chloro-3-formyl quinolines, isocyanides, and amines using Meldrum's acid at room temperature in the absence of any catalyst was developed. The resulting compounds were produced in excellent yields of >90% for the indole derivatives and > 85% for the quinoline derivatives. This synthetic procedure provides several advantages including high bond efficiency, good yields, and the use of mild reaction

Table 2: Pseudo-five-component reaction between of 2-chloro-3-formyl quinoline, Meldrum's acid, isocyanides and amines.

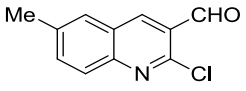
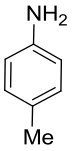
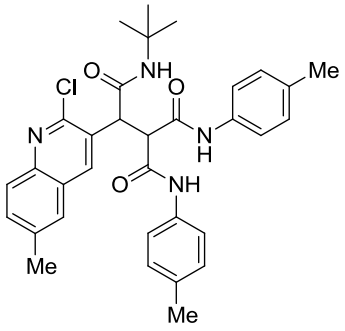
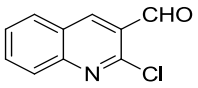
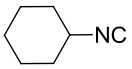
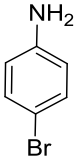
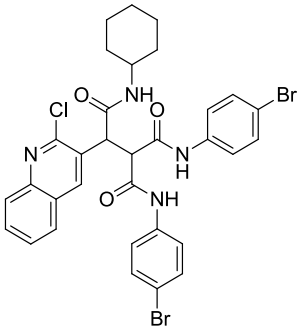
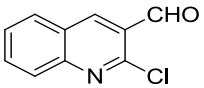
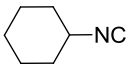
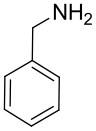
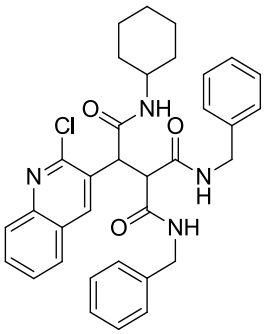
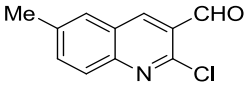
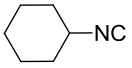
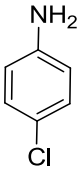
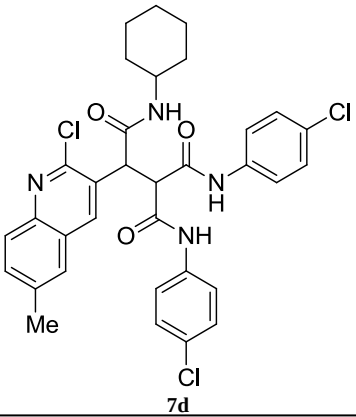
Entry	Aldehyde	Isocyanide	Amine	Product	Isolated Yield %
1				 **7a**	89
2				 **7b**	88
3				 **7c**	87
4				 **7d**	91

Table 2: Pseudo-five-component reaction between of 2-chloro-3-formyl quinoline, Meldrum's acid, isocyanides and amines.

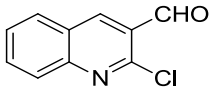
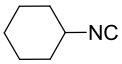
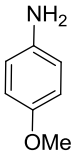
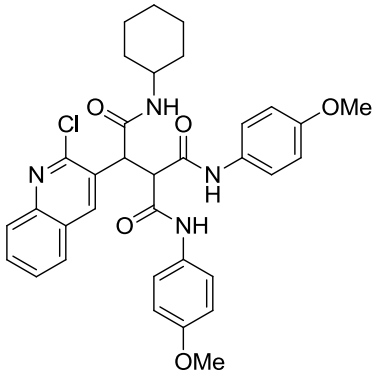
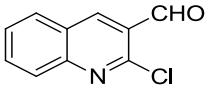
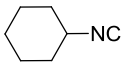
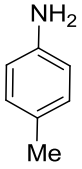
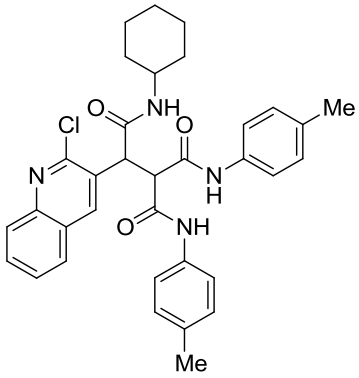
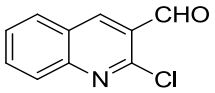
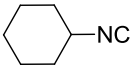
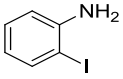
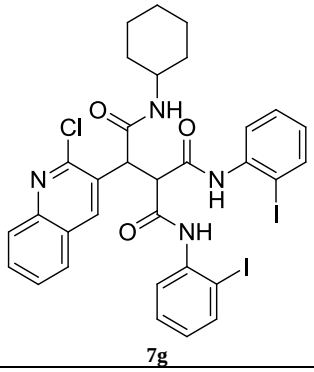
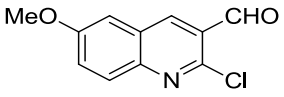
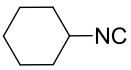
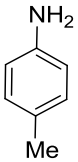
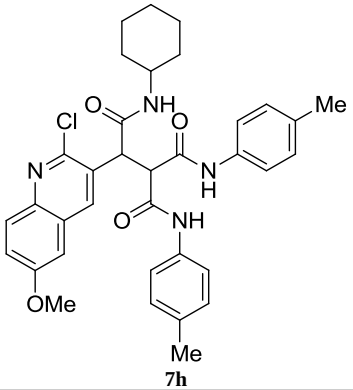
Entry	Aldehyde	Isocyanide	Amine	Product	Isolated Yield %
5				 **7e**	94
6				 **7f**	95
7				 **7g**	90
8				 **7h**	88

Table 2: Pseudo-five-component reaction between of 2-chloro-3-formyl quinoline, Meldrum's acid, isocyanides and amines.

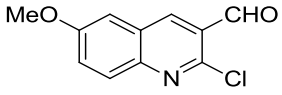
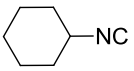
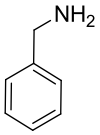
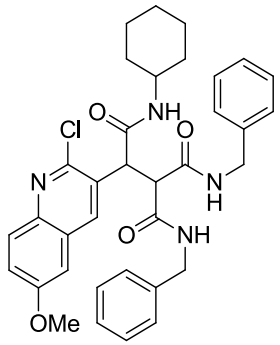
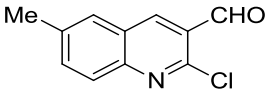
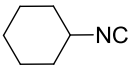
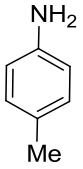
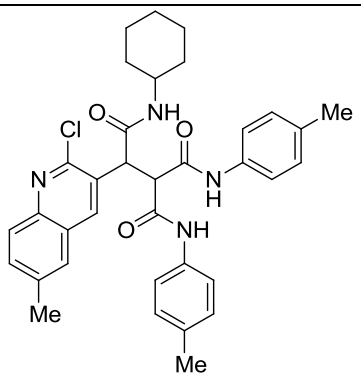
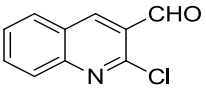
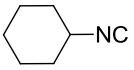
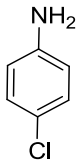
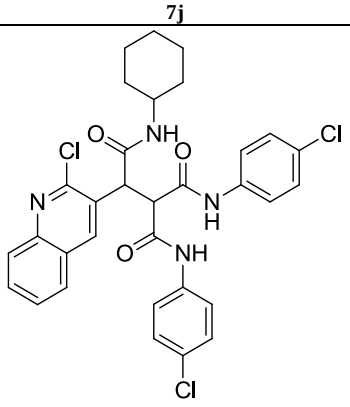
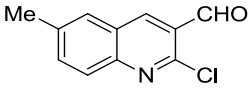
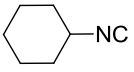
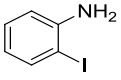
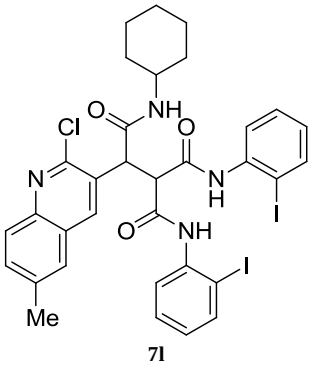
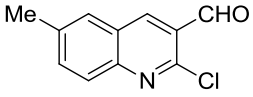
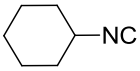
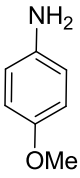
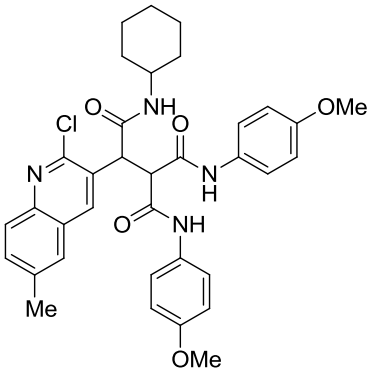
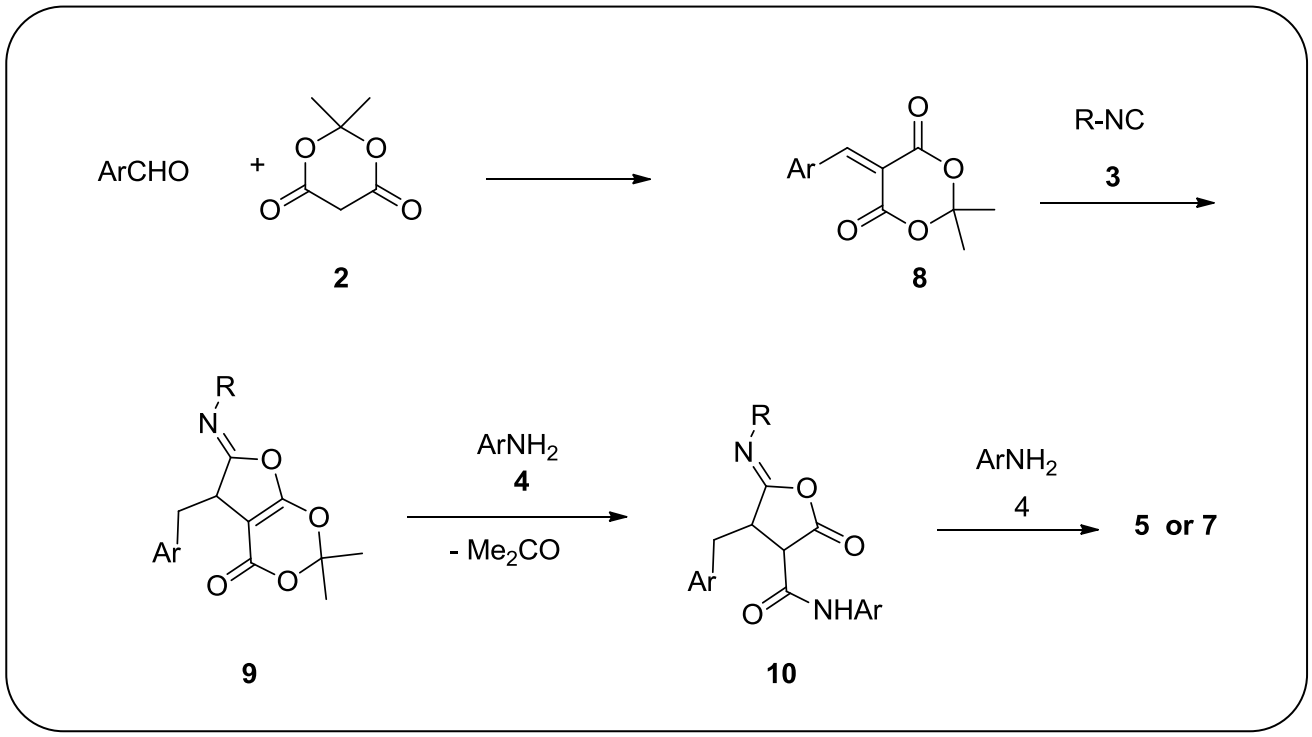
Entry	Aldehyde	Isocyanide	Amine	Product	Isolated Yield %
9				 **7i**	88
10				 **7j**	85
11				 **7k**	92
12				 **7l**	89

Table 2: Pseudo-five-component reaction between of 2-chloro-3-formyl quinoline, Meldrum's acid, isocyanides and amines.

Entry	Aldehyde	Isocyanide	Amine	Product	Isolated Yield %
13				 **7m**	90



Scheme 3: Suggested mechanism for the synthesis of the tripeptide-bound indole and quinoline derivatives.

conditions, operational simplicity, and simple workup procedure. Significantly, five new carbon-carbon and C-heteroatom bonds were constructed in a single operation and three amide bonds were formed using this reaction.

Acknowledgments

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Supplementary material

The ^{1}H-NMR and ^{13}C-NMR spectra for all compounds (**5** and **7**) are presented as supplementary material.

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