Mechanochemical IMCR and post-MCR transformation-based domino strategies: Towards the sustainable DOS of dipeptides-like and heterocyclic peptidomimetics.

Shrikant G. Pharande, Manuel A. Rentería-Gómez and Rocío Gámez-Montaño *

Departamento de Química, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, Guanajuato, C.P. 36050, Gto., México.
e-mail (R.G.-M.): rociogm@ugto.mx

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General information

All reactions were carried out in 10 mL stoppered glass tube. Reactions were monitored by silica gel TLC on precoated silica gel Kieselgel 60 F254 plates and the spots were visualized under UV light at 254 or 365 nm, using mixture of hexane and ethyl acetate (AcOEt) as eluents. Column chromatography was performed using silica gel (230-400 mesh) and mixtures of hexane with AcOEt in different proportions (v/v) as mobile phase. Melting points were determined on an Electrothermal apparatus and were uncorrected. $^1$H NMR spectra were recorded on Bruker Advance III spectrometer (500 MHz) at 295 K in CDCl$_3$; chemical shifts ($\delta$ in ppm) and coupling constants ($J$/Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) ($\delta_{\text{TMS}} = 0$ ppm) or CHCl$_3$ ($\delta_{\text{CHCl}_3} = 7.26$ ppm). $^{13}$C NMR spectra were recorded on Bruker Advance III spectrometer (126 MHz) at room temperature in CDCl$_3$; chemical shifts ($\delta$ in ppm) are reported relative to CHCl$_3$ ($\delta_{\text{C}} = 77.00$ ppm). In $^1$H NMR, the following abbreviations were used throughout: s = singlet, d = doublet, dd = doublet of doublet, m = multiplet and bs = broad singlet. The assignment of signals was confirmed by $^1$H and $^{13}$C spectral data. NMR spectra were analyzed using the MestreNova software version 10.0.1-14719. HRMS spectra were acquired on a Bruker Daltonics Maxis Impact ESI-qTOF MS spectrometer. HRMS samples were ionized by ESI$^+$ mode and recorded via the TOF method. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package.
General procedure for Ugi-4CR (GP)

A mixture of aldehyde 1 (1.0 equiv.), amine 2 (1.0 equiv.), isocyanide 3 (1.0 equiv.) and carboxylic acid 4 (1.0 equiv.) was thoroughly mixed in an agate mortar and grinded with a pestle manually for 3 minutes (a mixture which was initially particulate liquefied and eventually solidified to generate the Ugi product (5)). The resultant crude product was washed with hexane:EtOAc (9:1) mixture to remove the traces of isocyanide and imine and was recrystallized in hot EtOH to afford pure Ugi products (5).

N-(tert-Butyl)-2-(2-chloro-N-phenylacetamido)-2-phenylacetamide (5a)

Based on GP, 0.048 mL benzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 0.053 mL tert-butyl isocyanide (0.47 mmol) and 44.0 mg monochloroacetic acid (0.47 mmol) were grinded together to afford 154.0 mg (91%) as a light brown needle shaped crystals; mp 110–112 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ = 7.58 – 6.95 (m, 10H), 5.93 (s, 1H), 5.54 (bs, 1H), 3.87 (d, J = 13.7 Hz, 2H), 3.83 (d, J = 13.7 Hz, 2H), 1.35 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ = 168.3, 166.8, 138.8, 134.2, 130.6, 130.5, 129.2, 128.8, 128.7, 128.6, 66.3, 51.9, 42.7, 28.8; HRMS (ESI$^+$): m/z calcd. for C$_{20}$H$_{24}$ClN$_2$O$_2$ $^{[M + H]^+}$ 359.152, found 359.1529.

$^1$H NMR spectra of the compound 5a
$^{13}$C NMR spectra of the compound 5a

HRMS spectra of the compound 5a
2-Chloro-N-(2-((4-methoxyphenyl)amino)-2-oxo-1-phenylethyl)-N-phenylacetamide (5b)

Based on GP, 0.048 mL benzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 62.0 mg 4-methoxyphenyl isocyanide (0.47 mmol) and 44.0 mg monochloroacetic acid (0.47 mmol) were grinded together to afford 174.0 mg (90%) as a light yellow needle shaped crystals; mp 118-119 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ = 7.77 (s, 2H), 7.47 – 7.14 (m, 10H), 6.81 (s, 2H), 6.27 (s, 1H), 3.89 (d, $J$ = 6.7 Hz, 2H), 3.77 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ = 167.5, 167.2, 156.7, 138.6, 133.5, 130.8, 129.3, 129.0(2), 128.7, 122.1, 114.2, 66.4, 55.6, 42.7; HRMS (ESI$^+$): m/z calcd. for C$_{23}$H$_{22}$ClN$_2$O$_3$ $^{[M + H]}$ 409.1313, found 409.1310.

$^1$H NMR spectra of the compound 5b
$^{13}$C NMR spectra of the compound 5b

HRMS spectra of the compound 5b
**Ethyl (E)-4-{(2-(tert-butylamino)-2-oxo-1-phenylethyl)(phenyl)amino}-4-oxobut-2-enoate (5c)**

Based on GP, 0.048 mL benzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 0.053 mL tert-butyl isocyanide (0.47 mmol) and 67.0 mg (E)-4-ethoxy-4-oxobut-2-enoic acid (0.47 mmol) were grinded together to afford 160.0 mg (83%) as a white needle shaped crystals; mp 148-150 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.35 – 6.99 (m, 10H), 6.85 (d, $J$ = 15.3 Hz, 1H), 6.70 (d, $J$ = 15.3 Hz, 1H), 5.98 (s, 1H), 5.62 (bs, 1H), 4.12 (q, $J$ = 7.1 Hz, 2H), 1.35 (s, 9H), 1.21 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 168.3, 165.6, 164.7, 139.0, 134.5, 134.5, 131.6, 130.5, 130.4, 129.1, 128.6, 128.6, 128.6, 66.4, 61.0, 51.8, 28.8, 14.2; HRMS (ESI$^+$): m/z calcd. for C$_{24}$H$_{29}$N$_2$O$_4$ $^{[M + H]}$ 409.2122, found 409.2121.

$^1$H NMR spectra of the compound 5c
$^{13}$C NMR spectra of the compound 5c

HRMS spectra of the compound 5c
2-Chloro-N-(2-((2,6-dimethylphenyl)amino)-2-oxo-1-phenylethyl)-N-phenylacetamide (5d)

Based on GP, 0.048 mL benzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 61.0 mg 2,6-dimethylphenyl isocyanide (0.47 mmol) and 44.0 mg monochloroacetic acid (0.47 mmol) were grinded together to afford 169.0 mg (88%) as a light yellow needle shaped crystals; mp 115-118 °C; \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.30 - 7.17\) (m, 8H), 7.13 - 6.95 (m, 5H), 6.22 (s, 1H), 3.86 (d, \(J = 13.7\) Hz, 1H), 3.84 (d, \(J = 13.7\) Hz, 1H), 2.16 (s, 6H); \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) \(\delta = 168.0, 167.0, 138.6, 135.7, 133.5, 133.4, 130.7, 130.6, 129.3, 129.1, 129.0, 128.7, 128.3, 127.5, 66.1, 42.7, 18.6\); HRMS (ESI\(^{+}\)): m/z calcd. for C\(_{24}\)H\(_{24}\)ClN\(_2\)O\(_2\)\(^{+}\) [M + H\(^{+}\)] 407.1521, found 407.1527.

\(^{1}H\) NMR spectra of the compound 5d
$^{13}$C NMR spectra of the compound 5d

HRMS spectra of the compound 5d
**N-(4-Methoxyphenyl)-N-(2-((4-methoxyphenyl)amino)-2-oxo-1-phenylethyl)benzamide (5e)**

Based on GP, 0.048 mL benzaldehyde (0.47 mmol), 58.0 mg 4-methoxyaniline (0.47 mmol), 62.0 mg 4-methoxyphenyl isocyanide (0.47 mmol) and 57.0 mg benzoic acid (0.47 mmol) were grinded together to afford 176.0 mg (80%) as a light brown needle shaped crystals; mp 128-129 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta = 8.00 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 7.3 Hz, 4H), 7.29 (d, J = 5.8 Hz, 3H), 7.22 (t, J = 7.1 Hz, 1H), 7.16 (t, J = 7.4 Hz, 2H), 6.93 (bs, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.55 (d, J = 8.4 Hz, 2H), 6.38 (s, 1H), 3.79 (s, 3H), 3.68 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta = 171.6, 167.9, 158.4, 156.5, 156.0, 134.4, 133.8, 131.4, 130.9, 130.2, 129.4, 128.6, 128.5, 127.6, 121.9, 114.1, 113.5, 67.4, 55.6, 55.3; HRMS (ESI\(^+\)): m/z calcd. for C\(_{29}\)H\(_{27}\)N\(_2\)O\(_4^+\) [M + H]\(^+\) 467.1965, found 467.1962.

\(^1\)H NMR spectra of the compound 5e
$^{13}$C NMR spectra of the compound 5e

HRMS spectra of the compound 5e
Based on GP, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 0.032 mL aniline (0.35 mmol), 0.040 mL tert-butyl isocyanide (0.35 mmol) and 33.0 mg monochloroacetic acid (0.35 mmol) were grinded together to afford 110.0 mg (78%) as a brown needle shaped crystals; mp 108-111 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 8.13 – 7.19 (m, 5H), 7.16 (d, $J$ = 8.1 Hz, 2H), 7.08 (d, $J$ = 8.0 Hz, 2H), 5.90 (s, 1H), 5.63 (s, 1H), 3.90 – 3.79 (m, 2H), 1.35 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 168.0, 167.0, 138.5, 134.9, 132.7, 131.8, 130.5, 129.4, 129.1, 128.8, 65.3, 52.0, 42.5, 28.8; HRMS (ESI$^+$): m/z calcd. for C$_{20}$H$_{23}$Cl$_2$N$_2$O$_2$ $^{[M + H]^+}$ 393.1131, found 393.1135.
$^{13}$C NMR spectra of the compound 5f

HRMS spectra of the compound 5f
2-Chloro-N-(1-(4-chlorophenyl)-2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-N-phenylacetamide (5g)

Based on GP, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 0.032 mL aniline (0.35 mmol), 47.0 mg 2,6-dimethylphenyl isocyanide (0.35 mmol) and 33.0 mg monochloroacetic acid (0.35 mmol) were grinded together to afford 141.0 mg (90%) as a light yellow needle shaped crystals; mp 123-125 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta = 7.32 – 7.28\) (m, 3H), \(7.25 – 7.19\) (m, 5H), \(7.18 – 7.02\) (m, 5H), 6.20 (s, 1H), 3.89 (d, \(J = 13.7\) Hz, 1H), 3.85 (d, \(J = 13.7\) Hz, 1H), 2.18 (s, 6H); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta = 167.5, 167.0, 138.2, 135.5, 135.2, 133.1, 131.9, 131.8, 130.5, 129.4, 129.1, 128.8, 128.2, 127.5, 65.1, 42.3, 18.5; HRMS (ESI\(^+\)): m/z calcd. for C\(_{24}\)H\(_{23}\)Cl\(_2\)N\(_2\)O\(_2\)\(^+\) [M + H]\(^+\) 441.1131, found 441.1136.

\(^1\)H NMR spectra of the compound 5g
$^{13}$C NMR spectra of the compound 5g

HRMS spectra of the compound 5g
2-(4-Chlorophenyl)-2-(N-(4-chlorophenyl)formamido)-N-(4-methoxyphenyl)acetamide (5h)

Based on GP, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 45.0 mg 4-chloroaniline (0.35 mmol), 47.0 mg 4-methoxyphenyl isocyanide (0.35 mmol) and 0.013 mL formic acid (0.35 mmol) were grinded together to afford 125.0 mg (82%) as a white needle shaped crystals; mp 134-136 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ = 8.35 (s, 1H), 8.07 (bs, 1H), 7.36 (d, $J = 8.7$ Hz, 2H), 7.25 – 7.16 (m, 6H), 7.11 (d, $J = 8.3$ Hz, 2H), 6.80 (d, $J = 8.7$ Hz, 2H), 6.22 (s, 1H), 3.76 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ = 166.6, 163.1, 156.7, 136.9, 135.1, 134.3, 131.7, 131.2, 130.1, 129.3, 129.0, 121.8, 114.1, 62.9, 55.4; HRMS (ESI$^+$): m/z calcd. for C$_{22}$H$_{19}$Cl$_2$N$_2$O$_3$ $[M + H]^+$ 429.0767, found 429.0770.

$^1$H NMR spectra of the compound 5h
$^{13}$C NMR spectra of the compound 5h

HRMS spectra of the compound 5h
Ethyl (E)-4-((4-chlorophenyl)(1-(4-chlorophenyl)-2-((2,6-dimethylphenyl)amino)-2-oxoethyl)amino)-4-oxobut-2-enoate (5i)

Based on GP, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 45.0 mg 4-chloroaniline (0.35 mmol), 47.0 mg 2,6-dimethylphenyl isocyanide (0.35 mmol) and 51.0 mg (E)-4-ethoxy-4-oxobut-2-enoic acid (0.35 mmol) were grinded together to afford 151.0 mg (80%) as a light yellow needle shaped crystals; mp 131-133 °C; 

$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.29 - 7.20$ (m, 6H), 7.16 - 7.04 (m, 5H), 6.90 (d, $J = 15.3$ Hz, 1H), 6.70 (d, $J = 15.3$ Hz, 1H), 6.28 (s, 1H), 4.19 (d, $J = 7.1$ Hz, 2H), 4.17 (d, $J = 7.1$ Hz, 2H), 2.18 (s, 6H), 1.26 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 167.7, 165.4, 164.9, 136.8, 135.6, 135.5, 135.1, 133.7, 133.2, 132.4, 132.2, 132.0, 131.9, 129.6, 129.2, 128.4, 127.7, 64.7, 61.3, 18.6, 14.2; HRMS (ESI$^+$): m/z calcd. for C$_{28}$H$_{27}$Cl$_2$N$_2$O$_4$ $[M + H]^+$ 525.1342, found 525.1339.

$^1$H NMR spectra of the compound 5i
$^{13}$C NMR spectra of the compound 5i

HRMS spectra of the compound 5i
**N-Benzyl-2-{2-chloro-N-(4-methoxyphenyl)acetamido}-2-(4-chlorophenyl)acetamide (5j)**

Based on GP, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 44.0 mg 4-methoxyaniline (0.35 mmol), 46.0 mg benzyl isocyanide (0.35 mmol) and 33.0 mg monochloro acetic acid (0.35 mmol) were grinded together to afford 140.0 mg (86%) as a light brown needle shaped crystals; mp 111-112 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta = 7.57 \text{(bs, 1H)}, 7.35 - 7.30 \text{ (m, 2H)}, 7.29 - 7.23 \text{ (m, 3H)}, 7.19 \text{ (d, } J = 8.1 \text{ Hz, 2H)}, 7.10 \text{ (d, } J = 8.0 \text{ Hz, 2H)}, 6.87 - 6.42 \text{ (m, 3H)}, 6.16 \text{ (sb, 1H)}, 6.08 \text{ (s, 1H)}, 4.50 \text{ (qd, } J = 14.8, 5.7 \text{ Hz, 2H)}, 3.90 - 3.81 \text{ (m, 2H)}, 3.79 \text{ (s, 3H)}; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta = 168.8, 167.4, 159.7, 137.7, 134.9, 132.2, 131.9, 131.6, 131.4, 130.5, 128.7, 127.6, 127.5, 114.4, 64.5, 55.4, 43.9, 42.5\); HRMS (ESI\(^+\)): m/z calcd. for C\(_{24}\)H\(_{23}\)Cl\(_2\)N\(_2\)O\(_3\) \([M + H]^+\) 457.1080, found 457.1079.

\(^1\)H NMR spectra of the compound 5j
$^{13}$C NMR spectra of the compound 5j

HRMS spectra of the compound 5j
**N-(2-(tert-Butylamino)-1-(2,4-dimethoxyphenyl)-2-oxoethyl)-N-phenylbenzamide (5k)**

Based on GP, 50.0 mg 2,4-dimethoxybenzaldehyde (0.30 mmol), 0.028 mL aniline (0.30 mmol), 0.034 mL tert-butyl isocyanide (0.30 mmol) and 36.0 mg benzoic acid (0.30 mmol) were grinded together to afford 101.0 mg (75%) as a white solid; mp 142-143 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta = 7.30\) (d, \(J = 7.6\) Hz, 2H), 7.20 – 7.12 (m, 2H), 7.12 – 7.07 (m, 2H), 7.07 – 6.98 (m, 2H), 6.98 – 6.89 (m, 3H), 6.38 – 6.20 (m, 3H), 5.68 (s, 1H), 3.73 (s, 6H), 1.38 (s, 9H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta = 171.0, 169.4, 161.1, 158.5, 141.2, 136.7, 131.7, 130.2, 129.1, 128.5, 127.8, 127.5, 126.7, 115.6, 104.0, 98.0, 60.6, 55.3, 55.2, 51.5, 28.7; HRMS (ESI\(^+\)): \(m/z\) calcd. for C\(_{27}\)H\(_{31}\)N\(_2\)O\(_4\) [M + H]\(^+\) 447.2278, found 447.2279.

\(^1\)H NMR spectra of the compound 5k
$^{13}$C NMR spectra of the compound 5k

HRMS spectra of the compound 5k
2-Chloro-N-(4-methoxyphenyl)-N-(1-(4-methoxyphenyl)-2-((4-methoxyphenyl)amino)-2-oxoethyl)acetamide (5l)

Based on GP, 0.044 mL 4-methoxybenzaldehyde (0.36 mmol), 45.0 mg 4-methoxyaniline (0.36 mmol), 49.0 mg 4-methoxyphenyl isocyanide (0.36 mmol) and 34.0 mg monochloro acetic acid (0.36 mmol) were ground together to afford 144.0 mg (83%) as a light white crystals; mp 118-119 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.78 – 7.57 (m, 2H), 7.35 (d, $J$ = 8.6 Hz, 2H), 7.08 (d, $J$ = 8.3 Hz, 2H), 6.87 – 6.76 (m, 3H), 6.72 (d, $J$ = 8.2 Hz, 2H), 6.65 – 6.52 (m, 1H), 6.52 – 6.35 (m, 1H), 6.23 (s, 1H), 3.89 (d, $J$ = 13.7 Hz, 2H), 3.84 (d, $J$ = 13.8 Hz, 2H), 3.78 – 3.72 (m, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 168.0, 167.6, 160.1, 159.8, 156.8, 132.2, 131.9, 131.0(2), 125.6, 122.1, 114.5, 114.3, 114.2, 65.4, 55.7, 55.6, 55.5, 42.9; HRMS (ESI$^+$): m/z calcd. for C$_{25}$H$_{26}$ClN$_2$O$_5^+$ [M + H]$^+$ 469.1525, found 469.1525.

$^1$H NMR spectra of the compound 5l
$^{13}$C NMR spectra of the compound 5l

HRMS spectra of the compound 5l
2-(N-(4-Chlorophenyl)formamido)-N-(2,6-dimethylphenyl)-2-(4-methoxyphenyl)acetamide (5m)

Based on GP, 0.044 mL 4-methoxybenzaldehyde (0.36 mmol), 46.0 mg 4-chloroaniline (0.36 mmol), 48.0 mg 2,6-dimethylphenyl isocyanide (0.36 mmol) and 0.014 mL formic acid (0.36 mmol) were grinded together to afford 130.0 mg (84%) as a light white crystals; mp 110-111 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ = 8.33 (s, 1H), 7.23 – 7.14 (m, 4H), 7.10 (d, J = 8.2 Hz, 2H), 7.06 – 7.00 (m, 3H), 6.78 (d, J = 8.2 Hz, 2H), 6.20 (s, 1H), 3.81 (s, 3H), 2.19 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ = 167.7, 162.8, 160.0, 137.3, 135.5, 134.0, 133.2, 131.4, 130.6, 129.0, 128.2, 127.4, 125.2, 114.2, 62.8, 55.2, 18.4; HRMS (ESI$^+$): m/z calcd. for C$_{24}$H$_{23}$ClN$_2$O$_3^+$ [M + H]$^+$ 423.1470, found 423.1479.

$^1$H NMR spectra of the compound 5m
$^{13}$C NMR spectra of the compound $\text{5m}$

HRMS spectra of the compound $\text{5m}$
*N*-\((2\text{-}(\text{tert}-\text{Butylamino})\text{-}1\text{-}(2\text{-}3\text{-dimethoxyphenyl})\text{-}2\text{-oxoethyl})\text{-}N\text{-}(4\text{-chlorophenyl})\text{-}3\text{-enamide (5n)}

Based on GP, 50.0 mg 2,3-dimethoxybenzaldehyde (0.30 mmol), 38.0 mg 4-chloroaniline (0.30 mmol), 0.034 mL *tert*-butyl isocyanide (0.30 mmol) and 25.0 mg 3-butenolic acid (0.30 mmol) were grinded together to afford 107.0 mg (80%) as a light white crystals; mp 105-107 °C; \(^1\text{H NMR} (500 \text{ MHz, CDCl}_3) \delta = 7.25 – 6.91 \text{(m, 3H)}, 6.79 – 6.71 \text{(m, 2H)}, 6.55 \text{(d, J = 7.0 Hz, 1H)}, 6.25 \text{(s, 1H)}, 5.93 – 5.80 \text{(m, 1H)}, 5.41 \text{(s, 1H)}, 5.05 \text{(d, J = 10.2 Hz, 1H)}, 4.93 \text{(d, J = 17.2 Hz, 1H)}, 3.84 \text{(s, 3H)}, 3.82 \text{(s, 3H)}, 2.88 – 2.76 \text{(m, 2H)}, 1.31 \text{(s, 9H)}; \(^{13}\text{C NMR} (126 \text{ MHz, CDCl}_3) \delta = 171.1, 169.2, 152.4, 147.8, 138.8, 134.0, 132.0, 131.7, 128.9, 128.5, 123.8, 122.6, 117.9, 113.0, 61.1, 59.1, 55.9, 51.7, 39.9, 28.8; \text{HRMS (ESI\(^+\))}: m/z \text{calcd. for C}_{24}\text{H}_{30}\text{ClN}_{2}\text{O}_{4}^{+} \text{[M + H]}^{+} 445.1889, \text{found} 445.1890.

\(^1\text{H NMR spectra of the compound 5n}
$^{13}$C NMR spectra of the compound 5n

HRMS spectra of the compound 5n
Ethyl (E)-4-{benzyl(2-((4-methoxyphenyl)amino)-2-oxo-1-phenylethyl)amino)-4-oxobut-2-enate (5o)

Based on GP, 0.048 mL benzaldehyde (0.47 mmol), 0.051 mL benzylamine (0.47 mmol), 62.0 mg 4-methoxyphenyl isocyanide (0.47 mmol) and 67.0 mg (E)-4-ethoxy-4-oxobut-2-enoic acid (0.47 mmol) were grinded together to afford 113.0 mg (51%) as a light yellow solid; mp 121-122 °C; \( ^1H \text{NMR} \) (500 MHz, CDCl\(_3\)) \( \delta = 7.92 \) (bs, 1H), 7.45 – 7.35 (m, 3H), 7.32 (d, \( J = 8.1 \) Hz, 2H), 7.25 – 7.20 (m, 3H), 7.15 (d, \( J = 6.9 \) Hz, 2H), 6.97 (d, \( J = 6.6 \) Hz, 2H), 6.83 – 6.75 (m, 3H), 6.13 (s, 1H), 4.85 (d, \( J = 17.5 \) Hz, 1H), 4.67 (d, \( J = 17.6 \) Hz, 1H), 4.15 (q, \( J = 6.9 \) Hz, 2H), 3.74 (s, 3H), 1.22 (t, \( J = 7.1 \) Hz, 4H); \( ^{13}C \text{NMR} \) (126 MHz, CDCl\(_3\)) \( \delta = 167.5, 166.8, 165.4, 156.7, 137.0, 134.0, 133.8, 132.9, 130.8, 129.9, 129.1, 129.0, 128.7, 127.5, 126.5, 122.0, 114.2, 64.1, 61.2, 55.6, 50.4, 14.2; \( \text{HRMS (ESI)^+} \): m/z calcd. for C\(_{28}\)H\(_{29}\)N\(_2\)O\(_5\)\(^{+}\) [M + H]^+ 473.2071, found 473.2069.

\( ^1H \text{NMR} \) spectra of the compound 5o
$^{13}$C NMR spectra of the compound 5o

HRMS spectra of the compound 5o
1-(2,6-Dimethylphenyl)-3,4-diphenylpiperazine-2,5-dione (6a)

Based on GP, 0.048 mL benzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 61.0 mg 2,6-dimethylphenyl isocyanide (0.47 mmol) and 44.0 mg monochloroacetic acid (0.47 mmol) were grinded for three minutes together to afford Ugi adducts. Further, 230.0 mg of Cs$_2$CO$_3$ (0.70 mmol) was added with 0.2 µL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na$_2$SO$_4$. The obtained crude product was purified via column using EtOAc: hexane (30:70) mixture to afford 116.0 mg (66%) of pure product as white solid; mp 145-147 ºC; $^1$H NMR (500 MHz, CDCl$_3$) δ = 7.64 (d, J = 7.8 Hz, 2H), 7.53 – 7.48 (m, 2H), 7.47 – 7.37 (m, 5H), 7.33 – 7.29 (m, 1H), 7.21 – 7.15 (m, 2H), 7.07 – 7.03 (m, 1H), 5.69 (s, 1H), 4.46 (d, J = 17.4 Hz, 1H), 4.00 (d, J = 17.4 Hz, 1H), 2.35 (s, 3H), 1.78 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ = 165.5, 164.9, 140.2, 137.2, 136.0, 135.1, 134.5, 129.5, 129.4, 129.1, 129.0(2), 128.9, 127.4, 125.9, 125.0, 68.2, 52.5, 17.7, 17.0; HRMS (ESI$^+)$: m/z calcd. for C$_{33}$H$_{21}$N$_2$O$_3$ $^[M + H]^+$ 373.1547, found 373.1548.

$^1$H NMR spectra of the compound 6a
$^{13}\text{C}$ NMR spectra of the compound 6a

HRMS spectra of the compound 6a
3-(3,4-Dimethoxyphenyl)-1-(2,6-dimethylphenyl)-4-phenylpiperazine-2,5-dione (6b)

Based on GP, 0.048 mL 3,4-dimethoxybenzaldehyde (0.47 mmol), 0.043 mL aniline (0.47 mmol), 61.0 mg 2,6-dimethylphenyl isocyanide (0.47 mmol) and 44.0 mg 4-chloro acetic acid (0.47 mmol) were grinded for three minutes together to afford Ugi adducts. Further, 230.0 mg of Cs$_2$CO$_3$ (0.70) was added with 0.2 µL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na$_2$SO$_4$. The obtained crude product was purified via column using EtOAc:hexane (30:70) mixture to afford 116.0 mg (60%) of pure product as white solid; mp 139-140 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.42 – 7.36 (m, 4H), 7.31 – 7.27 (m, 1H), 7.18 – 7.09 (m, 4H), 7.04 (d, $J$ = 6.6 Hz, 1H), 6.94 (d, $J$ = 8.0 Hz, 1H), 5.59 (s, 1H), 4.43 (d, $J$ = 17.4 Hz, 1H), 3.97 (d, $J$ = 17.2 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 2.31 (s, 3H), 1.81 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 165.6, 165.1, 149.9, 149.5, 140.2, 137.1, 136.0, 135.1, 129.4, 129.1, 129.0, 128.9, 128.3, 127.4, 126.5, 124.8, 117.4, 111.3, 109.1, 67.8, 56.2, 56.1, 52.5, 17.8, 17.3; HRMS (ESI$^+$): m/z calcd. for C$_{24}$H$_{23}$N$_2$O$_2$+ [M + H]$^+$ 371.1754, found 371.1755.

$^1$H NMR spectra of the compound 6b
$^{13}$C NMR spectra of the compound 6b

HRMS spectra of the compound 6b
3-(4-chlorophenyl)-1-(2,6-dimethylphenyl)-4-(4-methoxyphenyl)piperazine-2,5-dione (6c)

Based on GP, 57.0 mg 4-chlorobenzaldehyde (0.406 mmol), 50.0 mg 4-methoxyaniline (0.406 mmol), 53.0 mg 2,6-dimethylphenyl isocyanide (0.406 mmol) and 38.0 mg monochloroacetic acid (0.406 mmol) were grinded for three minutes together to afford Ugi adducts. Further, 198.0 mg of Cs₂CO₃ (0.608) was added with 0.2 µL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na₂SO₄. The obtained crude product was purified via column using EtOAc:hexane (30:70) mixture to afford 103.0 mg (58%) of pure product as white solid; mp 144-145 °C; \(^1\)H NMR (500 MHz, CDCl₃) δ = 7.53 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.18 – 7.10 (m, 2H), 7.05 – 6.99 (m, 1H), 6.88 (d, J = 8.9 Hz, 1H), 5.54 (s, 1H), 4.44 (d, J = 17.5 Hz, 1H), 3.99 (d, J = 17.5 Hz, 1H), 3.77 (s, 3H), 2.30 (s, 3H), 1.79 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl₃) δ = 164.9, 164.3, 158.7, 136.9, 135.8, 135.0, 134.9, 133.4, 132.4, 129.5, 129.1, 128.9, 128.9, 127.4, 126.6, 114.6, 67.9, 55.5, 52.0, 17.6, 17.1; HRMS (ESI\(^{+}\)): m/z calcd. for C_{28}H_{24}ClN₂O₃ [M + H]\(^{+}\) 435.1470, found 435.1496.

\(^1\)H NMR spectra of the compound 6c
$^{13}$C NMR spectra of the compound 6c

HRMS spectra of the compound 6c
3,4-bis(4-chlorophenyl)-1-(2,6-dimethylphenyl)piperazine-2,5-dione (6d)

Based on GP, 50.0 mg 55.0 mg 4-chloroaniline (0.392 mmol), 4-chlorobenzaldehyde (0.392 mmol), 51.0 mg 2,6-dimethylphenyl isocyanide (0.392 mmol) and 37.0 mg monochloroacetic acid (0.392 mmol) were grinded for three minutes together to afford Ugi adducts. Further, 191.0 mg of Cs₂CO₃ (0.388) was added with 0.2 µL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na₂SO₄. The obtained crude product was purified via column using EtOAc:hexane (30:70) mixture to afford 97.0 mg (56%) of pure product as white solid; mp 150-151 °C; ¹H NMR (500 MHz, CDCl₃) δ = 7.51 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.18 – 7.12 (m, 2H), 7.06 – 7.01 (m, 1H), 5.58 (s, 1H), 4.40 (d, J = 17.6 Hz, 1H), 3.99 (d, J = 17.6 Hz, 1H), 2.29 (s, 3H), 1.78 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ = 165.0, 164.0, 138.1, 136.8, 135.8, 135.2, 134.8, 133.0, 132.7, 129.7, 129.5, 129.1, 129.0, 127.2, 126.1, 67.4, 52.1, 17.65, 17.1; HRMS (ESI⁺): m/z calcd. for C₂₄H₂₁Cl₂N₂O₂⁺ [M + H]⁺ 439.0975, found 439.0986.

¹H NMR spectra of the compound 6d
$^{13}$C NMR spectra of the compound 6d

HRMS spectra of the compound 6d
(S)-3-Amino-1,2-bis(4-chlorophenyl)-N-(2,6-dimethylphenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxamide (7a)

Based on GP, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 45.0 mg 4-chloroaniline (0.35 mmol), 46.0 mg 2,6-dimethylphenyl isocyanide (0.35 mmol) and 30.0 mg cyanoacetic acid (0.35 mmol) were grinded for three minutes together to afford crude Ugi adducts. Further, 28.0 mg of NaOH (0.71 mmol) was added with 0.2 µL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na₂SO₄. The obtained crude product was purified via column using EtOAc:hexane (50:50) mixture to afford 137.0 mg (64 %) of pure product as white solid; mp 159-160 °C; ¹H NMR (500 MHz, CDCl₃) δ = 8.10 (s, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.32 – 7.28 (m, 4H), 7.20 – 7.16 (m, 3H), 7.11 (d, J = 7.5 Hz, 2H), 5.26 (s, 1H), 5.01 (s, 2H), 2.18 (s, 6H); ¹³C NMR (126 MHz, DMSO-d₆) δ = 173.8, 166.9, 164.2, 135.6, 135.4, 134.6, 133.7, 132.5, 130.1, 129.6, 128.7(2), 128.3, 127.9, 124.7, 89.9, 75.7, 18.1; HRMS (ESI⁺): m/z calcd. for C₂₅H₂₂Cl₂N₃O₂⁺ [M + H]⁺ 466.1083, found 466.1090.

¹H NMR spectra of the compound 7a
\(^{13}\)C NMR spectra of the compound 7a

HRMS spectra of the compound 7a
3-Amino-2-(4-chlorophenyl)-N-(2,6-dimethylphenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-2-carboxamide (7b)

Based on GP, 50.0 mg 4-chlorobenzaldehyde (0.35 mmol), 0.032 mL aniline (0.35 mmol), 46.0 mg 2,6-dimethylphenyl isocyanide (0.35 mmol) and 30.0 mg cyanoacetic acid (0.35 mmol) were grinded for three minutes together to afford crude Ugi adducts. Further, 28.0 mg of NaOH (0.71 mmol) was added with 0.2 µL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na₂SO₄. The obtained crude product was purified via column using EtOAc:hexane (50:50) mixture to afford 127.0 mg (51%) of pure product as white solid; mp 151-152 °C; ¹H NMR (500 MHz, DMSO-d₆) δ = 8.29 (bs, 1H), 7.37 (d, J = 7.4 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.25 – 7.17 (m, 4H), 7.17 – 7.12 (m, 1H), 7.11 – 7.04 (m, 3H), 5.23 (s, 1H), 2.54 (bs, 2H), 2.14 (s, 6H); ¹³C NMR (126 MHz, CDCl₃ + DMSO-d₆) δ = 174.2, 167.0, 164.5, 136.6, 135.5, 134.9, 134.0, 132.6, 129.9(2), 128.9, 128.5, 128.1, 125.8, 124.3, 90.2, 76.4, 18.2; HRMS (ESI⁺): m/z calcd. for C₂₅H₂₃ClN₃O₂ [M + H]⁺ 432.1473, found 432.1473.

¹H NMR spectra of the compound 7b
$^{13}$C NMR spectra of the compound 7b

HRMS spectra of the compound 7b
3-amino-2-(4-chlorophenyl)-N-(2,6-dimethylphenyl)-1-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxamide (7c)

Based on GP, 50.0 mg 4-chlorobenzaldehyde (0.36 mmol), 43.0 mg aniline (0.36 mmol), 46.0 mg 2,6-dimethylphenyl isocyanide (0.36 mmol) and 30.0 mg cyanoacetic acid (0.35 mmol) were grinded for three minutes together to afford crude Ugi adducts. Further, 28.0 mg of NaOH (0.71 mmol) was added with 0.2 µL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na₂SO₄. The obtained crude product was purified via column using EtOAc:hexane (50:50) mixture to afford 91.0 mg (55%) of pure product as white solid; mp 160-161 °C; \( ^1\)H NMR (500 MHz, CDCl₃) \( \delta = 8.26 \) (s, 1H), 7.32 (d, \( J = 8.7 \) Hz, 2H), 7.26 (d, \( J = 8.7 \) Hz, 2H), 7.16 – 7.12 (m, 1H), 7.10 – 7.07 (m, 2H), 7.01 (d, \( J = 9.0 \) Hz, 2H), 6.72 (d, \( J = 9.0 \) Hz, 2H), 5.27 (s, 1H), 5.00 (s, 2H), 3.72 (s, 3H), 2.16 (s, 6H); \( ^{13}\)C NMR (126 MHz, CDCl₃) \( \delta = 174.1, 167.7, 163.2, 157.6, 135.3, 134.8, 134.5, 132.6, 130.1, 129.6, 128.8, 128.5, 128.0, 127.0, 114.3, 91.0, 55.4, 18.2; HRMS (ESI⁺): m/z calcd. for C₂₆H₂₅ClN₃O₃ [M + H]⁺ 462.1579, found 462.1607.

\( ^1\)H NMR spectra of the compound 7c
$^{13}$C NMR spectra of the compound 7c

3-amino-$N$-(2,6-dimethylphenyl)-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-2-carboxamide (7d)
Based on GP, 50.0 mg 4-nitrobenzaldehyde (0.33 mmol), 0.031 mL aniline (0.33 mmol), 43.0 mg 2,6-dimethylphenyl isocyanide (0.33 mmol) and 28.0 mg cyanoacetic acid (0.33 mmol) were grinded for three minutes together to afford crude Ugi adducts. Further, 26.0 mg of NaOH (0.66 mmol) was added with 0.2 µL EtOH and grinded for three minutes more. The obtained crude product was extracted with EtOAc and water then organic layer was dried over Na$_2$SO$_4$. The obtained crude product was purified via column using EtOAc:hexane (50:50) mixture to afford 78.0 mg (53%) of pure product as white solid; mp 166-167 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ = 8.27 (d, J = 8.7 Hz, 1H), 7.99 (s, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.10 – 7.06 (m, 1H), 7.04 – 6.99 (m, 2H), 6.90 – 6.84 (m, 1H), 6.76 – 6.71 (m, 1H), 5.09 (d, J = 2.7 Hz, 1H), 4.82 (d, J = 3.1 Hz, 1H), 1.99 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ = 13C NMR (126 MHz, CDCl3) δ 168.1, 148.0, 145.9, 145.6, 135.2, 132.6, 129.6, 128.4, 128.3, 127.7, 124.4, 120.0, 114.2, 63.6, 18.3; HRMS (ESI$^+$): m/z calcd. for C$_{25}$H$_{23}$N$_4$O$_4$ [M + H]$^+$ 443.1714, found 443.1707.

$^1$H NMR spectra of the compound 7d
$^{13}$C NMR spectra of the compound 7d

HRMS spectra of the compound 7d