Supporting Information

Straightforward Synthesis of Biologically Valuable Nonsymmetrical Malonamides Under Mild Conditions

Zhiguo Zhang, a,* Xiyang Cao, a Gang Wang, Guisheng Zhang, a,* Xingjie Zhang

a Key Laboratory of Green Chemical Media and Reactions, Ministry of Education; Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals; NMPA Key Laboratory for Research and Evaluation of Innovative Drug; School of Chemistry and Chemical Engineering, Henan Normal University, 46 East of Construction Road, Xinxiang, Henan 453007, China.
E-mail: zhangzg@htu.edu.cn and zgs6668@yahoo.com Fax: (+86)-373-332-5250.

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I. General Remarks

All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. Petroleum ether (PE) used here refers to the 60–90 °C boiling point fraction of petroleum. Ethyl acetate is abbreviated as EA. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance/600 (¹H: 600 MHz, ¹³C:150 MHz) or Bruker Avance/400 (¹H: 400 MHz, ¹³C: 100 MHz at 25 °C) with tetramethylsilane as the internal standard. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, and m = multiplet), and coupling constants in Hertz (Hz). All high-resolution mass spectra (HRMS) were measured on a mass spectrometer by using electrospray ionization orthogonal acceleration time-of-flight (ESI-OA-TOF), and the purity of all samples used for HRMS (>95%) was confirmed by ¹H NMR and ¹³C NMR spectroscopic analysis. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All reactions were monitored by thin-layer chromatography (TLC) with GF254 silica gel-coated plates. Flash chromatography was carried out on SiO₂ (silica gel 200–300 mesh).
II. General Procedures

1. General Procedure for the Preparation of Reagents

Starting materials isocyanates 1 and β-ketoamides 2a-2l, 2o, 2q, 2t and 2u-2v are obtained from commercial sources. Other starting materials 2 were synthesized following the literatures, and the procedures were described below.

Isocyanates

\[
\begin{align*}
1a & \quad \text{NCO} \quad \text{NCO} \\
1b & \quad \text{MeO} \quad \text{MeO} \\
1c & \quad \text{MeO} \quad \text{MeO} \\
1d & \quad \text{F} \quad \text{NCO} \\
1e & \quad \text{MeO} \quad \text{MeO} \\
1f & \quad \text{Bn} \quad \text{NCO} \\
1g & \quad \text{NCO} \quad \text{NCO} \\
1h & \quad \text{Ts} \quad \text{NCO} \\
1i & \quad \text{Cl} \quad \text{NCO} \\
1j & \quad \text{Cl} \quad \text{NCO} \\
1k & \quad \text{Cl} \quad \text{NCO} \\
1l & \quad \text{OMe} \\
1m & \quad \text{NCO} \quad \text{OMe}
\end{align*}
\]

β-Ketoamides

\[
\begin{align*}
2a & \quad \text{Ph} \quad \text{NMe} \\
2b & \quad \text{Me} \quad \text{NMe} \\
2c & \quad \text{Ph} \quad \text{NMe} \\
2d & \quad \text{OMe} \quad \text{NMe} \\
2e & \quad \text{OMe} \quad \text{NMe} \\
2f & \quad \text{OMe} \quad \text{NMe} \\
2g & \quad \text{OMe} \quad \text{NMe} \\
2h & \quad \text{OMe} \quad \text{NMe} \\
2i & \quad \text{OMe} \quad \text{NMe} \\
2j & \quad \text{OMe} \quad \text{NMe} \\
2k & \quad \text{OMe} \quad \text{NMe} \\
2l & \quad \text{OMe} \quad \text{NMe} \\
2m & \quad \text{OMe} \quad \text{NMe} \\
2n & \quad \text{OMe} \quad \text{NMe} \\
2o & \quad \text{OMe} \quad \text{NMe} \\
2p & \quad \text{OMe} \quad \text{NMe} \\
2q & \quad \text{OMe} \quad \text{NMe} \\
2r & \quad \text{OMe} \quad \text{NMe} \\
2s & \quad \text{OMe} \quad \text{NMe} \\
2t & \quad \text{OMe} \quad \text{NMe} \\
2u & \quad \text{OMe} \quad \text{NMe} \\
2v & \quad \text{OMe} \quad \text{NMe} \\
2w & \quad \text{OMe} \quad \text{NMe} \\
2x & \quad \text{OMe} \quad \text{NMe} \\
2y & \quad \text{OMe} \quad \text{NMe} \\
2z & \quad \text{OMe} \quad \text{NMe}
\end{align*}
\]
Method A: Substrates $2b$, $2c$, $2l$, $2m$, $2s$ and $2w$ were synthesized according to the literature.$^1$

\[
R^3\text{NH}_2 + \begin{array}{c} \text{toluene} \\ \text{reflux, 24 h} \end{array} \rightarrow R^R_\text{C}O \text{C}O \text{H}_N R^1
\]

Anilines (1.0 equiv), β-ketoesters (1.1 equiv) and toluene (0.5 M) in an oven dried round bottom flask equipped with a magnetic stir bar. The resulting mixture was heated under reflux for 24 h. The reaction mixture was allowed to cool to ambient temperature and toluene was removed under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (PE / EA = 3:1) to afford the desired product $2b$, $2c$, $2l$, $2m$, $2s$ and $2w$.

Method B: Substrates $2n$, $2x$, $2y$ and $2z$ were synthesized according to the literature.$^2$

\[
\begin{array}{c} \text{MeO} \\ \text{N} \end{array} + \begin{array}{c} \text{toluene} \\ 100 ^\circ C, 2 h \end{array} \rightarrow O \text{C}O \text{N} I \begin{array}{c} \text{2n} \\ \text{MeO} \end{array}
\]

Diketene (1.1 equiv) was added to a magnetically stirred solution of the substituted anilines (1.0 equiv) in toluene (0.5 M), and the mixture was heated at 100 °C for 2 h. The reaction mixture was monitored by TLC. After completion of the reactions, the solution was evaporated under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (PE / EA = 3:1) to afford the desired product $2n$, $2x$, $2y$ and $2z$.

Method C: The general procedure for the synthesis of $2p$.

\[
\begin{array}{c} \text{EtO}_{2}C - \text{NH}_2 \\ * \text{HCl} \end{array} + \begin{array}{c} \text{NaHCO}_3 (2.0 \text{ equiv}) \\ \text{toluene, 0°C - rt, 4 h} \end{array} \rightarrow \begin{array}{c} \text{O} \\ \text{CO}_{2} \text{Et} \end{array}
\]

Add glycine ethyl ester hydrochloride (1.0 equiv) and NaHCO$_3$ (2.0 equiv) to toluene (0.5 M) and stir at room temperature for 0.5 h, add diketene (1.1 equiv) at 0 °C and the mixture was heated at rt for 4 h. The reaction mixture was monitored by TLC. After completion of the reactions, the solution was evaporated under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (PE / EA = 1:1) to afford the desired product $2p$.

Method D: Substrates $2r$ were synthesized according to the literature.$^3$

\[
\begin{array}{c} \text{NH}_2 \\ \text{DMAP, Et}_3\text{N} \\ \text{DCM, N}_2, 0 ^\circ C \end{array} \rightarrow \begin{array}{c} \text{O} \\ \text{N} \end{array}
\]

4-Dimethylaminopyridine (0.45 equiv), triethylamine (1.0 equiv), and S4
(R)-1-phenylethan-1-amine (1.0 equiv) were dissolved in DCM (0.5 M), at 0 °C under an argon atmosphere. The reaction mixture was stirred for 10 min, then diketene (2.0 equiv) was added dropwise. After 4 h, the reaction was quenched with 5% aqueous KOH and extracted with DCM (3 × 20 mL). The combined extracts were dried (Na₂SO₄) and evaporated under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (PE / EA = 3:1) to afford the desired product 2r.

2. General Procedure for the Synthesis of Nonsymmetrical Malonamides

![Diagram]

To a 15 mL tube was added 2a (103.5 mg, 0.5 mmol), MgCl₂ (57 mg, 1.2 equiv), KOH (40 mg, 1.2 equiv, 85%+), EtOH (3 mL), and stirred at 25 °C for 0.5 h before 1a (80 mg, 0.6 mmol) was added. Then the reaction mixture was stirred at 25 °C for 1 h (the whole process was closely monitored by TLC). After completion of the reactions, the solution was evaporated under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (EA : DCM : PE : Et₃N = 50 : 100 : 50 : 1) to give primary amide 3a as white solid (135 mg, 91%).

3. General Procedure for the Gram-Scale Synthesis of 3s

N¹,N¹⁺-[(1,4-phenylene)bis(N³-(p-tolyl)malonamide) (3s): To a 250 mL round-bottom flask was added N¹,N¹⁺-(1,4-phenylene)bis(3-oxobutanamide) (2u) (5.52 g, 20 mmol), MgCl₂ (4.19 g, 2.2 equiv), KOH (2.90 g, 1.2 equiv, 85%+). Then the mixture was stirred well in EtOH (120 mL) at 25 °C for 0.5 h, then 1-isocyanato-4-methylbenzene (1a) (5.86 g, 44 mmol) was added and stir at room temperature for 4 h, After the completion of the reaction, 300 mL of distilled water was added to the reaction, suction filtered under reduced pressure and the crude product was washed with a large amount of water and dried in vacuum to give 3s as a white solid (8.59 g, 94%).
4. General Procedure for the Synthetic Applications (3\textit{ab} as the example)

Synthesis of 2\textit{w}: 4-((6,7-dimethoxyquinolin-4-yl)oxy) aniline (20 mmol, 1.0 equiv), ethyl acetoacetate (22 mmol, 1.1 equiv) and toluene (100 mL) in an oven dried round bottom flask (250 mL) equipped with a magnetic stir bar. The resulting mixture was heated under reflux for 24 h. The reaction mixture was allowed to cool to ambient temperature and toluene was removed under reduced pressure to give crude product 2\textit{w} (Figure S1).

To the crude product 2\textit{w} was added MgCl\textsubscript{2} (24 mmol, 1.2 equiv), KOH (24 mmol, 1.2 equiv, 85%+) and EtOH (120 mL) (Figure S2) and stirred well for 0.5 h (Figure S3) before 1-fluoro-4-isocyanatobenzene (1\textit{j}) (24 mmol, 1.2 equiv) was added. Then the mixture stirred at 25 °C for 3 hours (the whole process was closely monitored by TLC). After the completion of the reaction (Figure S4), the crude reaction mixture was purified by flash silica gel column chromatography (DCM : MeOH = 30 : 1) to give 3\textit{ab} as yellow solid (7.5 g, 79%) (Figure S5).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{s1.png}
\caption{The status of the completion of the reaction.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{s2.png}
\caption{Add MgCl\textsubscript{2}, KOH, and EtOH.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{s3.png}
\caption{After stirring for 0.5 h.}
\end{figure}
Figure S4: The status of the completion of the reaction.
Figure S5: Product properties
III. Dosage Screening of MgCl₂

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>MgCl₂ (x equiv)</th>
<th>Yield of 3a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>19\textsuperscript{b}</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>45\textsuperscript{c}</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>91\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Unless otherwise indicated, all reactions were conducted with 1\textsubscript{a} (1.2 equiv), 2\textsubscript{a} (0.5 mmol), KOH (1.2 equiv) in 3 mL of EtOH at 25 °C in 1 h. \textsuperscript{b} 72\% of 2\textsubscript{a} was recovered. \textsuperscript{c} 48\% of 2\textsubscript{a} was recovered. \textsuperscript{d} Table 1, entry 1 in manuscript.

The experiment showed that 1.2 equivalent of MgCl₂ was necessary for the reaction, because we only got 19\% and 45\% product 3\textsubscript{a}, respectively, when 0.2 and 0.5 equivalents of MgCl₂ were employed to the reaction, even if we prolonged the reaction time to 3 h.
IV. Analytical Data of Compounds

\[
\begin{array}{c}
\text{N}^1-(4\text{-methoxyphenyl})-N^3-(p\text{-tolyl})\text{malonamide (3a): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and } N-(4\text{-methoxyphenyl})-3\text{-oxobutanamide (2a) in presence of magnesium chloride and potassium hydroxide to afford 3a as white solid (135 mg, 91\%); } Mp = 173-174^\circ\text{C. } ^1\text{H NMR (600 MHz, DMSO) } \delta 10.06 (s, 1H), 10.01 (s, 1H), 7.50 (dd, } J = 15.6, 8.4 \text{ Hz, 4H), 7.11 (d, } J = 7.8 \text{ Hz, 2H), 6.89 (d, } J = 9.0 \text{ Hz, 2H), 3.72 (s, 3H), 3.41 (s, 2H), 2.25 (s, 3H). } ^13\text{C NMR (151 MHz, DMSO) } \delta 165.7, 165.4, 136.9, 132.7, 132.6, 129.6, 121.1, 119.6, 114.3, 55.6, 46.2, 20.9. \text{ HRMS (ESI) (m/z) calculated for C}_{17}\text{H}_{18}\text{N}_{2}\text{NaO}_{3} [M+Na]^+: 321.1210, found: 321.1201. }
\end{array}
\]

\[
\begin{array}{c}
\text{N}^1-(3\text{-methoxyphenyl})-N^3-(p\text{-tolyl})\text{malonamide (3b): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and } N-(3\text{-methoxyphenyl})-3\text{-oxobutanamide (2d) in presence of magnesium chloride and potassium hydroxide to afford 3b as white solid (127 mg, 85\%); } Mp = 175-177^\circ\text{C. } ^1\text{H NMR (600 MHz, DMSO) } \delta 10.16 (s, 1H), 10.08 (s, 1H), 7.49 (d, } J = 8.4 \text{ Hz, 2H), 7.32 (s, 1H), 7.21 (t, } J = 7.8 \text{ Hz, 1H), 7.12 (t, } J = 8.4 \text{ Hz, 3H), 6.64 (d, } J = 8.4 \text{ Hz, 1H), 3.73 (s, 3H), 3.45 (s, 2H), 2.25 (s, 3H). } ^13\text{C NMR (151 MHz, DMSO) } \delta 166.0, 165.6, 160.0, 140.6, 136.9, 132.8, 130.04, 129.6, 119.6, 111.8, 109.3, 105.4, 55.4, 46.4, 20.9. \text{ HRMS (ESI) (m/z) calculated for C}_{17}\text{H}_{18}\text{N}_{2}\text{NaO}_{3} [M+Na]^+: 321.1210, found: 321.1205. }
\end{array}
\]

\[
\begin{array}{c}
\text{N}^1-(2\text{-methoxyphenyl})-N^3-(p\text{-tolyl})\text{malonamide (3c): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and } N-(2\text{-methoxyphenyl})-3\text{-oxobutanamide (2e) in presence of magnesium chloride and potassium hydroxide to afford 3c as white solid (138 mg, 93\%); } Mp = 171-172^\circ\text{C. } ^1\text{H NMR (400 MHz, DMSO) } \delta 10.12 (s, 1H), 9.68 (s, 1H), 8.10 (d, } J = 8.0 \text{ Hz, 1H), 7.48 (d, } J = 8.4 \text{ Hz, 2H), 7.13 (d, } J = 8.0 \text{ Hz, 2H), 7.09 – 7.03 (m, 2H), 6.93 – 6.89 (m, 1H), 3.85 (s, 3H), 3.58 (s, 2H), 2.25 (s, 3H). } ^13\text{C NMR (101 MHz, DMSO) } \delta 166.4, 165.7, 149.4, 136.7, 133.0, 129.6, 127.7, 124.6, 121.2, 120.8, 119.8, 111.5,
\end{array}
\]
56.3, 45.5, 20.9. HRMS (ESI) (m/z) calculated for C_{17}H_{18}N_{2}NaO_{3} [M+Na]^+: 321.1210, found: 321.1209.

\[
N^1-(2,5\text{-dimethoxyphenyl})-N^3-(p\text{-tolyl})\text{malonamide} \quad (3d): \quad \text{According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and } N(2,5\text{-dimethoxyphenyl})-3\text{-oxobutanamide (2f) in presence of magnesium chloride and potassium hydroxide to afford 3d as white solid (146 mg, 90%); Mp = 146-147 °C.} \quad \text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \quad \delta 10.13 (s, 1H), 9.71 (s, 1H), 7.84 (s, 1H), 7.48 (d, \textit{J} = 8.4 Hz, 2H), 7.13 (d, \textit{J} = 8.4 Hz, 2H), 6.96 (d, \textit{J} = 8.8 Hz, 1H), 6.62 (dd, \textit{J} = 8.8, 2.8 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.59 (s, 2H), 2.25 (s, 3H).} \\
\text{\textsuperscript{13}C NMR (150 MHz, DMSO)} \quad \delta 166.4, 165.7, 153.4, 143.4, 136.7, 133.0, 129.7, 128.6, 119.8, 112.3, 108.2, 107.7, 56.8, 55.8, 45.5, 20.9. \quad \text{HRMS (ESI) (m/z) calculated for C_{18}H_{20}N_{2}NaO_{4} [M+Na]^+: 351.1315, found: 351.1307.}
\]

\[
N^1-(4\text{-ethoxyphenyl})-N^3-(p\text{-tolyl})\text{malonamide} \quad (3e): \quad \text{According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and } N(4\text{-ethoxyphenyl})-3\text{-oxobutanamide (2g) in presence of magnesium chloride and potassium hydroxide to afford 3e as white solid (135 mg, 87%); Mp = 218-220 °C.} \quad \text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \quad \delta 10.05 (s, 1H), 10.00 (s, 1H), 7.51 – 7.47 (m, 4H), 7.11 (d, \textit{J} = 8.0 Hz, 2H), 6.87 (d, \textit{J} = 9.2 Hz, 2H), 3.98 (q, \textit{J} = 6.8 Hz, 2H), 3.41 (s, 2H), 2.25 (s, 3H), 1.30 (t, \textit{J} = 6.8 Hz, 3H).} \\
\text{\textsuperscript{13}C NMR (150 MHz, DMSO)} \quad \delta 165.8, 165.4, 155.0, 137.0, 132.7, 132.5, 129.6, 121.1, 119.5, 114.9, 63.5, 46.2, 20.9, 15.2. \quad \text{HRMS (ESI) (m/z) calculated for C_{18}H_{20}N_{2}NaO_{3} [M+Na]^+: 335.1366, found: 335.1360.}
\]

\[
N^1-(2\text{-chlorophenyl})-N^3-(p\text{-tolyl})\text{malonamide} \quad (3f): \quad \text{According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and } N(2\text{-chlorophenyl})-3\text{-oxobutanamide (2h) in presence of magnesium chloride and potassium hydroxide to afford 3f as white solid (142 mg, 95%); Mp = 186-188 °C.} \quad \text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \quad \delta 10.15 (s, 1H), 10.03 (s, 1H), 7.97 (d, \textit{J} = 8.4 Hz, 1H), 7.52 – 7.48 (m, 3H), 7.36 – 7.31 (m, 1H), 7.19 – 7.12 (m, 3H), 3.60 (s, 2H), 2.26 (s, 3H).} \\
\text{\textsuperscript{13}C NMR (151 MHz, DMSO)} \quad \delta 166.2, 166.1, 136.7, 135.3, 133.1, 129.9,

**N1-(5-chloro-2-methoxyphenyl)-N3-(p-tolyl)malonamide (3g):** According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and N-(5-chloro-2-methoxyphenyl)-3-oxobutanamide (2i) in presence of magnesium chloride and potassium hydroxide to afford 3g as white solid (150 mg, 91%); Mp = 189-190 °C. 

\[ ^1H\text{ NMR (400 MHz, DMSO)} \delta 10.13 \text{ (s, 1H), 9.88 \text{ (s, 1H), 8.22 \text{ (d, J = 2.0 Hz, 1H), 7.47 \text{ (d, J = 8.0 Hz, 2H), 7.14 – 7.06 \text{ (m, 4H), 3.87 (s, 3H), 3.61 (s, 2H), 2.26 (s, 3H).}} \]

\[ ^{13}C\text{ NMR (101 MHz, DMSO)} \delta 166.3, 166.2, 148.0, 136.7, 133.0, 129.7, 129.0, 124.4, 123.7, 120.1, 119.8, 112.9, 56.8, 45.3, 20.9. \]


**N1-phenyl-N3-(p-tolyl)malonamide (3h):** According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and 3-oxo-N-phenylbutanamide (2j) in presence of magnesium chloride and potassium hydroxide to afford 3h as white solid (123 mg, 92%); Mp = 224-227 °C. 

\[ ^1H\text{ NMR (400 MHz, DMSO)} \delta 10.15 \text{ (s, 1H), 10.07 \text{ (s, 1H), 7.60 \text{ (d, J = 8.0 Hz, 2H), 7.49 \text{ (d, J = 8.4 Hz, 2H), 7.31 \text{ (t, J = 7.6 Hz, 2H), 7.11 \text{ (d, J = 8.0 Hz, 2H), 7.05 \text{ (t, J = 7.6 Hz, 1H), 3.45 (s, 2H), 2.25 (s, 3H).}} \]

\[ ^{13}C\text{ NMR (151 MHz, DMSO)} \delta 165.9, 165.7, 139.5, 136.9, 132.8, 129.6, 129.2, 123.9, 119.6, 119.5, 46.4, 20.9. \]


**N1-(3-nitrophenyl)-N3-(p-tolyl)malonamide (3i):** According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and N-(3-nitrophenyl)-3-oxobutanamide (2k) in presence of magnesium chloride and potassium hydroxide to afford 3i as light yellow solid (117 mg, 75%); Mp = 196-197 °C. 

\[ ^1H\text{ NMR (600 MHz, DMSO)} \delta 10.70 \text{ (s, 1H), 10.13 \text{ (s, 1H), 8.65 \text{ (s, 1H), 7.94 – 7.91 \text{ (m, 2H), 7.63 \text{ (t, J = 8.4 Hz, 1H), 7.49 \text{ (d, J = 7.8 Hz, 2H), 7.12 \text{ (d, J = 8.4 Hz, 2H), 3.51 (s, 2H), 2.25 (s, 3H).}} \]

\[ ^{13}C\text{ NMR (151 MHz, DMSO)} \delta 166.8, 165.3, 148.5, 140.5, 136.9, 132.9, 130.7, 129.6, 125.5, 119.6, 118.4, 113.6, 46.5, 20.9. \]

ethyl 4-(3-oxo-3-(p-tolylamino)propanamido)benzoate (3j): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and ethyl 4-(3-oxobutanamido)benzoate (2l) in presence of magnesium chloride and potassium hydroxide to afford 3j as white solid (133 mg, 79%); Mp = 195-196 °C. **1H NMR** (400 MHz, DMSO) δ 10.51 (s, 1H), 10.09 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.50 (s, 2H), 2.25 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H). **13C NMR** (101 MHz, DMSO) δ 166.6, 165.8, 165.4, 143.7, 136.9, 132.8, 130.8, 129.6, 124.9, 119.6, 118.9, 60.9, 46.5, 20.9, 14.7. **HRMS** (ESI) (m/z) calculated for C_{19}H_{20}N_{2}NaO_{4} [M+Na]^+: 363.1315, found: 363.1313.

N^1-(quinolin-8-yl)-N^3-(p-tolyl)malonamide (3k): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and 3-oxo-N-(quinolin-8-yl)butanamide (2m) in presence of magnesium chloride and potassium hydroxide to afford 3k as white solid (101 mg, 63%); Mp = 172-173 °C. **1H NMR** (400 MHz, DMSO) δ 10.94 (s, 1H), 10.24 (s, 1H), 8.96 – 8.94 (m, 1H), 8.69 (d, J = 7.6 Hz, 1H), 8.41 – 8.39 (m, 1H), 7.68 – 7.62 (m, 2H), 7.58 (t, J = 8.0 Hz, 1H), 7.53 – 7.50 (m, 2H), 7.14 (d, J = 8.4 Hz, 2H), 3.77 (s, 2H), 2.25 (s, 3H). **13C NMR** (151 MHz, DMSO) δ 166.3, 166.0, 149.5, 138.6, 137.0, 136.7, 134.9, 133.1, 129.7, 128.3, 127.4, 122.6, 122.5, 119.9, 116.9, 46.2, 20.9. **HRMS** (ESI) (m/z) calculated for C_{19}H_{17}N_{3}NaO_{2} [M+Na]^+: 342.1213, found: 342.1208.

N^1-(4-methoxyphenyl)-N^3-methyl-N^3-(p-tolyl)malonamide (3l): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and N-(4-methoxyphenyl)-N-methyl-3-oxobutanamide (2n) in presence of magnesium chloride and potassium hydroxide to afford 3l as white solid (131 mg, 84%); Mp = 136-137 °C. **1H NMR** (400 MHz, DMSO) δ 9.78 (s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.15 (s, 3H), 3.14 (s, 2H), 2.24 (s, 3H). **13C NMR** (151 MHz,
DMSO) δ 167.3, 165.6, 158.9, 136.9, 136.7, 132.6, 129.5, 119.5, 115.2, 55.8, 43.5, 37.5, 20.9. HRMS (ESI) (m/z) calculated for C_{18}H_{20}N_{2}NaO_{3} [M+Na]^+: 335.1366, found: 335.1362.

$N^1,N^1$-dimethyl-$N^3$-(p-toly)malonamide (3m): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and $N,N$-dimethyl-3-oxobutanamide (2o) in presence of magnesium chloride and potassium hydroxide to afford 3m as white solid (101 mg, 92%); Mp = 105-106 °C. $^1$H NMR (400 MHz, DMSO) δ 10.02 (s, 1H), 7.46 (d, $J$ = 8.4 Hz, 2H), 7.10 (d, $J$ = 8.4 Hz, 2H), 3.46 (s, 2H), 3.01 (s, 3H), 2.84 (s, 3H), 2.24 (s, 3H). $^{13}$C NMR (101 MHz, DMSO) δ 167.6, 165.8, 137.1, 132.6, 129.6, 119.5, 43.2, 37.8, 35.4, 20.9.

HRMS (ESI) (m/z) calculated for C_{12}H_{16}N_{2}NaO_{2} [M+Na]^+: 243.1104, found: 243.1101.

ethyl (3-oxo-3-($p$-tolylamino)propanoyl)glycinate (3n): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and ethyl (3-oxobutanoyl)glycinate (2p) in presence of magnesium chloride and potassium hydroxide to afford 3n as white solid (131 mg, 95%); Mp = 107-108 °C. $^1$H NMR (400 MHz, DMSO) δ 9.99 (s, 1H), 8.48 (t, $J$ = 5.6 Hz, 1H), 7.46 (d, $J$ = 8.0 Hz, 2H), 7.10 (d, $J$ = 7.6 Hz, 2H), 4.09 (qd, $J$ = 7.2, 1.6 Hz, 2H), 3.30 (s, 2H), 2.24 (s, 3H). $^{13}$C NMR (151 MHz, DMSO) δ 170.2, 167.6, 165.6, 136.9, 132.8, 129.6, 119.6, 60.9, 44.7, 41.3, 20.9, 14.5. HRMS (ESI) (m/z) calculated for C_{14}H_{18}N_{2}NaO_{4} [M+Na]^+: 301.1159, found: 301.1154.

$N^1$-benzyl-$N^3$-(p-toly)malonamide (3o): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and $N$-benzyl-3-oxobutanamide (2q) in presence of magnesium chloride and potassium hydroxide to afford 3o as white solid (132 mg, 94%); Mp = 184-185 °C. $^1$H NMR (400 MHz, DMSO) δ 10.02 (s, 1H), 8.55 (t, $J$ = 5.6 Hz, 1H), 7.47 (d, $J$ = 8.4 Hz, 2H), 7.34 – 7.28 (m, 4H), 7.26 – 7.22 (m, 1H), 7.11 (d, $J$ = 8.4 Hz, 2H), 4.31 (d, $J$ = 6.0 Hz, 2H), 3.29 (s, 2H), 2.25 (s, 3H). $^{13}$C NMR (151 MHz, DMSO) δ 167.1, 165.9, 139.6, 136.9, 132.7, 129.6, 128.8, 127.7, 127.3, 119.6, 45.1, 42.7, 20.9. HRMS (ESI) (m/z) calculated for C_{17}H_{18}N_{2}NaO_{2} [M+Na]^+: 305.1260, found: 305.1256.
(R)-N\textsuperscript{1}-(1-phenylethyl)-N\textsuperscript{3}-(p-tolyl)malonamide (3p): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and (R)-3-oxo-N-(1-phenylethyl)butanamide (2r) in presence of magnesium chloride and potassium hydroxide to afford 3p as white solid (136 mg, 92%); Mp = 176-177 \degree C. \textsuperscript{1}H NMR (400 MHz, DMSO) δ 9.99 (s, 1H), 8.52 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.35 – 7.30 (m, 4H), 7.24 – 7.20 (m, 1H), 7.10 (d, J = 8.0 Hz, 2H), 4.93 (p, J = 7.2 Hz, 1H), 3.27 (s, 2H), 2.24 (s, 3H), 1.37 (d, J = 7.2 Hz, 3H). \textsuperscript{13}C NMR (151 MHz, DMSO) δ 166.2, 165.9, 144.8, 136.9, 132.7, 129.6, 128.7, 127.1, 126.5, 119.5, 48.6, 45.1, 23.0, 20.9. HRMS (ESI) (m/z) calculated for C\textsubscript{18}H\textsubscript{20}N\textsubscript{2}NaO\textsubscript{2} [M+Na]\textsuperscript{+}: 319.1417, found: 319.1413.

N\textsuperscript{1}-(benzo[d]thiazol-2-yl)-N\textsuperscript{3}-(p-tolyl)malonamide (3q): According to the general procedure, combining 1-isocyanato-4-methylbenzene (1a) and N-(benzo[d]thiazol-2-yl)-3-oxobutanamide (2s) in presence of magnesium chloride and potassium hydroxide to afford 3q as white solid (153 mg, 94%); Mp = 259-261 \degree C. \textsuperscript{1}H NMR (600 MHz, DMSO) δ 12.42 (s, 1H), 10.16 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.8 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 3.65 (s, 2H), 2.26 (s, 3H). \textsuperscript{13}C NMR (101 MHz, DMSO) δ 167.1, 164.8, 158.2, 149.0, 136.8, 132.9, 131.9, 129.7, 126.6, 124.1, 122.2, 121.1, 119.6, 45.2, 20.9. HRMS (ESI) (m/z) calculated for C\textsubscript{17}H\textsubscript{15}N\textsubscript{3}NaO\textsubscript{2}S [M+Na]\textsuperscript{+}: 348.0777, found: 348.0773.

N\textsuperscript{1}-(p-tolyl)malonamide (3r): According to the general procedure, combining 1-isocyanato-4–methylbenzene (1a) and 3-oxobutanamide (2t) in presence of magnesium chloride and potassium hydroxide to afford 3r as white solid (68 mg, 68%); Mp = 99-101 \degree C. \textsuperscript{1}H NMR (600 MHz, DMSO) δ 9.98 (s, 1H), 7.49 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 3H), 3.19 (s, 2H), 2.24 (s, 3H). \textsuperscript{13}C NMR (101 MHz, DMSO) δ 169.2, 166.0, 137.0, 132.7, 129.6, 119.5, 44.9, 20.9. HRMS (ESI) (m/z) calculated for C\textsubscript{10}H\textsubscript{12}N\textsubscript{2}NaO\textsubscript{2} [M+Na]\textsuperscript{+}: 215.0791, found: 215.0783.
N\(^1\),N\(^1\)'-(1,4-phenylene)bis(N\(^3\)-(p-tolyl)malonamide) (3s): According to the general procedure, combining isocyanatocyclohexane (1a) and N,N\(^1\)-(1,4-phenylene)bis(3-oxobutanamide) (2u) in presence of magnesium chloride and potassium hydroxide to afford 3s as white solid (8.59 g, 94%); Mp >320 °C. \(^1\)H NMR (400 MHz, DMSO) δ 10.12 (s, 2H), 10.06 (s, 2H), 7.54 (s, 4H), 7.48 (d, \(J = 8.4\) Hz, 4H), 7.11 (d, \(J = 8.4\) Hz, 4H), 3.43 (s, 4H), 2.25 (s, 6H). \(^{13}\)C NMR (151 MHz, DMSO) δ 165.7, 165.7, 137.0, 135.0, 132.8, 129.6, 120.0, 119.6, 46.3, 20.9. HRMS (ESI) (m/z) calculated for C\(_{26}\)H\(_{26}\)N\(_4\)NaO\(_4\) [M+Na]^+: 481.1846, found: 481.1841.

N\(^1\),N\(^3\)-bis(4-methoxyphenyl)malonamide (3t): According to the general procedure, combining 1-isocyanato-4-methoxybenzene (1b) and N-(4-methoxyphenyl)-3-oxobutanamide (2a) in presence of magnesium chloride and potassium hydroxide to afford 3t as white solid (149 mg, 95%); Mp = 230-232 °C. \(^1\)H NMR (600 MHz, DMSO) δ 10.01 (s, 2H), 7.51 (d, \(J = 8.8\) Hz, 4H), 6.90 – 6.87 (m, 4H), 3.72 (s, 6H), 3.40 (s, 2H). \(^{13}\)C NMR (151 MHz, DMSO) δ 165.5, 155.7, 132.6, 121.1, 114.3, 55.6, 46.1. HRMS (ESI) (m/z) calculated for C\(_{17}\)H\(_{18}\)N\(_2\)NaO\(_4\) [M+Na]^+: 337.1159, found: 337.1159.

N\(^1\)-(2-methoxyphenyl)-N\(^3\)-(4-methoxyphenyl)malonamide (3u): According to the general procedure, combining 1-isocyanato-3-methoxybenzene (1c) and N-(4-methoxyphenyl)-3-oxobutanamide (2a) in presence of magnesium chloride and potassium hydroxide to afford 3u as white solid (141 mg, 90%); Mp = 120-122 °C. \(^1\)H NMR (600 MHz, DMSO) δ 10.08 (s, 1H), 9.70 (s, 1H), 8.10 (d, \(J = 7.8\) Hz, 1H), 7.51 (d, \(J = 9.0\) Hz, 2H), 7.08 – 7.04 (m, 2H), 6.92 – 6.89 (m, 3H), 3.85 (s, 3H), 3.72 (s, 3H), 3.56 (s, 2H). \(^{13}\)C NMR (151 MHz, DMSO) δ 166.2, 165.7, 155.9, 149.3, 132.3, 127.8, 124.6, 121.4, 121.1, 120.8, 114.4, 111.5, 56.3, 55.6, 45.3. HRMS (ESI) (m/z) calculated for C\(_{17}\)H\(_{18}\)N\(_2\)NaO\(_4\) [M+Na]^+: 337.1159, found: 337.1153.
**N¹-(4-methoxyphenyl)-N³-(4-(trifluoromethyl)phenyl)malonamide (3v):** According to the general procedure, combining 1-isocyanato-4-(trifluoromethyl)benzene (1d) and N-(4-methoxyphenyl)-3-oxobutanamide (2a) in presence of magnesium chloride and potassium hydroxide to afford 3v as white solid (150 mg, 85%); Mp = 233-234 °C. ¹H NMR (600 MHz, DMSO) δ 10.53 (s, 1H), 10.05 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.72 (s, 3H), 3.48 (s, 2H). ¹³C NMR (101 MHz, DMSO) δ 166.7, 165.1, 155.8, 143.0, 132.6, 126.6 (q, J_C-F = 3.4 Hz), 124.8 (q, J_C-F = 269.4 Hz), 123.9 (q, J_C-F = 31.8 Hz), 121.1, 119.5, 114.4, 55.6, 46.3. HRMS (ESI) (m/z) calculated for C₁₇H₁₅F₃N₂NaO₃ [M+Na]⁺: 375.0927, found: 375.0925.

**methyl 4-(3-((4-methoxyphenyl)amino)-3-oxopropanamido)benzoate (3w):** According to the general procedure, combining methyl 4-isocyanatobenzoate (1e) and N-(4-methoxyphenyl)-3-oxobutanamide (2a) in presence of magnesium chloride and potassium hydroxide to afford 3w as white solid (151 mg, 89%); Mp = 202-203 °C. ¹H NMR (600 MHz, DMSO) δ 10.51 (s, 1H), 10.05 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H), 3.72 (s, 3H), 3.49 (s, 2H). ¹³C NMR (151 MHz, DMSO) δ 166.6, 166.3, 165.1, 155.8, 143.8, 132.6, 130.8, 124.6, 121.1, 118.9, 114.4, 55.6, 52.4, 46.4. HRMS (ESI) (m/z) calculated for C₁₈H₁₈N₂NaO₅ [M+Na]⁺: 365.1108, found: 365.1101.

**N¹-benzyl-N³-(4-methoxyphenyl)malonamide (3x):** According to the general procedure, combining methyl (isocyanatomethyl)benzene (1f) and N-(4-methoxyphenyl)-3-oxobutanamide (2a) in presence of magnesium chloride and potassium hydroxide to afford 3x as white solid (145 mg, 97%); Mp = 148-149 °C. ¹H NMR (400 MHz, DMSO) δ 9.98 (s, 1H), 8.56 (t, J = 5.6 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.35 – 7.29 (m, 4H), 7.26 – 7.22 (m, 1H), 6.89 (d, J = 8.8 Hz, 2H), 4.32 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H), 3.29 (s, 2H). ¹³C NMR (151
MHz, DMSO) \( \delta \) 167.2, 165.7, 155.7, 139.7, 132.6, 128.8, 127.7, 127.3, 121.1, 114.3, 55.6, 45.0, 42.7. HRMS (ESI) (m/z) calculated for C\(_{17}\)H\(_{18}\)N\(_2\)NaO\(_3\) [M+Na]\(^+\): 321.1210, found: 321.1204.

\( \text{N}^1\)-ethyl-\( \text{N}^3\)-(4-methoxyphenyl)malonamide (3y): According to the general procedure, combining isocyanatoethane (1g) and \( \text{N} \)-(4-methoxyphenyl)-3-oxobutanamide (2a) in presence of magnesium chloride and potassium hydroxide to afford 3y as white solid (100 mg, 85%); Mp = 151-153 °C. \(^1\text{H NMR}\) (400 MHz, DMSO) \( \delta \) 9.94 (s, 1H), 8.03 (s, 1H), 7.48 (d, \( J = 8.8 \) Hz, 2H), 6.88 (d, \( J = 9.2 \) Hz, 2H), 3.72 (s, 3H), 3.18 (s, 2H), 3.14 – 3.07 (m, 2H), 1.03 (t, \( J = 7.2 \) Hz, 3H). \(^{13}\text{C NMR}\) (101 MHz, DMSO) \( \delta \) 166.8, 165.7, 155.7, 132.6, 121.0, 114.3, 55.6, 44.9, 34.1, 15.1. HRMS (ESI) (m/z) calculated for C\(_{12}\)H\(_{16}\)N\(_2\)NaO\(_3\) [M+Na]\(^+\): 259.1053, found: 259.1046.

\( \text{N}^1\)-cyclohexyl-\( \text{N}^3\)-(4-methoxyphenyl)malonamide (3z): According to the general procedure, combining isocyanatocyclohexane (1h) and \( \text{N} \)-(4-methoxyphenyl)-3-oxobutanamide (2a) in presence of magnesium chloride and potassium hydroxide to afford 3z as white solid (127 mg, 87%); Mp = 162-163 °C. \(^1\text{H NMR}\) (600 MHz, DMSO) \( \delta \) 9.92 (s, 1H), 7.93 (d, \( J = 7.8 \) Hz, 1H), 7.48 (d, \( J = 8.4 \) Hz, 2H), 6.87 (d, \( J = 7.2 \) Hz, 2H), 3.71 (s, 3H), 3.56 – 3.53 (m, 1H), 1.74 (d, \( J = 10.2 \) Hz, 2H), 1.67 (d, \( J = 13.2 \) Hz, 2H), 1.54 (d, \( J = 12.0 \) Hz, 1H), 1.29 – 1.23 (m, 2H), 1.19 – 1.13 (m, 3H). \(^{13}\text{C NMR}\) (151 MHz, DMSO) \( \delta \) 166.1, 165.7, 155.7, 132.6, 121.0, 114.3, 55.6, 48.1, 44.9, 32.8, 25.7, 24.9. HRMS (ESI) (m/z) calculated for C\(_{16}\)H\(_{22}\)N\(_2\)NaO\(_3\) [M+Na]\(^+\): 313.1523, found: 313.1514.

\( \text{N}^1\)-(4-((6,7-dimethoxyquinolin-4-y1)oxy)phenyl)-\( \text{N}^3\)-(4-fluorophenyl)malonamide (3ab): According to the general procedure, combining 1-fluoro-4-isocyanatobenzene (1j) and \( \text{N} \)-(4-((6,7-dimethoxyquinolin-4-y1)oxy)phenyl)-3-oxobutanamide (2w) in presence of
magnesium chloride and potassium hydroxide to afford 3ad as yellow solid (206 mg, 87%); Mp = 119-121 °C. $^1$H NMR (400 MHz, DMSO) δ 10.36 (s, 1H), 10.28 (s, 1H), 8.46 (d, $J = 5.2$ Hz, 1H), 7.76 (d, $J = 9.2$ Hz, 2H), 7.66 – 7.62 (m, 2H), 7.51 (s, 1H), 7.39 (s, 1H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.17 (t, $J = 8.8$ Hz, 2H), 6.45 (d, $J = 5.2$ Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H). 19F NMR (376 MHz, DMSO) δ -119.17 (s). $^{13}$C NMR (151 MHz, DMSO) δ 165.8, 165.8, 160.4, 158.5 (d, $J_{C-F} = 239.9$ Hz), 153.0, 149.8, 149.8, 149.3, 146.9, 137.0, 135.9, 122.0, 121.3 (d, $J_{C-F} = 7.9$ Hz), 121.3, 115.8 (d, $J_{C-F} = 22.2$ Hz), 115.6, 108.3, 103.5, 99.6, 56.2, 56.2, 46.2. HRMS (ESI) (m/z) calculated for C$_{26}$H$_{23}$FN$_{3}$O$_{5}$ [M+H]$^+$: 476.1616, found: 476.1611.

$N^1$-(benzyloxy)-$N^3$-(3,4-dichlorophenyl)malonamide (3ac): According to the general procedure, combining 1,2-dichloro-4-isocyanatobenzene (1k) and $N$-(benzyloxy)-3-oxobutanamide (2x) in presence of magnesium chloride and potassium hydroxide to afford 3ac as white solid (107 mg, 61%); Mp = 117-119 °C. $^1$H NMR (400 MHz, DMSO) δ 11.24 (s, 1H), 10.43 (s, 1H), 7.98 (d, $J = 2.4$ Hz, 1H), 7.57 (d, $J = 8.8$ Hz, 1H), 7.48 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.42 – 7.34 (m, 5H), 4.82 (s, 2H), 3.16 (s, 2H). $^{13}$C NMR (101 MHz, DMSO) δ 166.0, 163.8, 139.4, 136.4, 131.5, 131.2, 129.3, 128.8, 128.5, 125.4, 120.8, 119.6, 77.4, 42.6. HRMS (ESI) (m/z) calculated for C$_{16}$H$_{14}$Cl$_2$N$_2$NaO$_3$ [M+Na]$^+$: 375.0274, found: 375.0270.

$N^1$-(3-fluoro-4-methoxyphenyl)-$N^3$-phenylmalonamide (3ad): According to the general procedure, combining isocyanatobenzene (1l) and $N$-(3-fluoro-4-methoxyphenyl)-3-oxobutanamide (2y) in presence of magnesium chloride and potassium hydroxide to afford 3ad as white solid (137 mg, 90%); Mp = 182-184 °C. $^1$H NMR (400 MHz, DMSO) δ 10.20 (s, 1H), 10.16 (s, 1H), 7.62-7.58 (m, 3H), 7.31 (t, $J = 7.6$ Hz, 2H), 7.28 – 7.25 (m, 1H), 7.12 (t, $J = 9.6$ Hz, 1H), 7.06 (t, $J = 7.2$ Hz, 1H), 3.80 (s, 3H), 3.45 (s, 2H). 19F NMR (376 MHz, DMSO) δ -133.82. $^{13}$C NMR (101 MHz, DMSO) δ 165.8, 165.7, 151.3 (d, $J_{C-F} = 242.3$ Hz), 143.5 (d, $J_{C-F} = 10.8$ Hz), 139.4, 132.9 (d, $J_{C-F} = 9.4$ Hz), 129.2, 123.9, 119.5, 115.5 (d, $J_{C-F} = 3.4$ Hz), 114.6 (d, $J_{C-F} = 2.6$ Hz), 108.0 (d, $J_{C-F} = 22.6$ Hz), 56.6, 46.3. HRMS (ESI) (m/z) calculated for C$_{16}$H$_{15}$FN$_2$NaO$_3$ [M+Na]$^+$: 325.0959, found: 325.0954.
N^1-(5-chloro-2-methoxyphenyl)-N^2-octylmalonamide (3ae): According to the general procedure to afford 3ae as white solid (170 mg, 96%); Mp = 45-46 °C. $^1$H NMR (400 MHz, DMSO) δ 10.08 (s, 1H), 8.24 (d, $J = 2.4$ Hz, 1H), 8.17 (t, $J = 5.2$ Hz, 1H), 7.10 – 6.04 (m, 2H), 3.85 (s, 3H), 3.36 (s, 2H), 3.08 (q, $J = 2.8$ Hz, 2H), 1.41 (t, $J = 6.4$ Hz, 2H), 1.24 (s, 10H), 0.84 (t, $J = 6.8$ Hz, 3H). $^{13}$C NMR (101 MHz, DMSO) δ 167.7, 166.2, 147.8, 129.1, 124.5, 123.5, 119.7, 112.8, 56.7, 43.9, 39.2, 31.7, 29.3, 29.2, 29.1, 26.8, 22.5, 14.4. HRMS (ESI) (m/z) calculated for C$_{18}$H$_{27}$ClN$_2$NaO$_3$ [M+Na]$^+$: 377.1602, found: 377.1592.

3-ethyl 5-methyl 4-(2-chlorophenyl)-6-methyl-2-((2-(3-oxo-3-(p-tolylamino)propanamido)ethoxy)methyl)-1,4-dihydropyridine-3,5-dicarboxylate (3af): According to the general procedure to afford 3af as white solid (281 mg, 96%); Mp = 188-190 °C. $^1$H NMR (600 MHz, DMSO) δ 10.01 (s, 1H), 8.43 (s, 1H), 8.25 (t, $J = 5.4$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 7.8$ Hz, 1H), 7.26 (d, $J = 7.8$ Hz, 1H), 7.21 (t, $J = 7.8$ Hz, 1H), 7.12–7.08 (m, 3H), 5.30 (s, 1H), 4.60 (dd, $J = 51.0$, 13.8 Hz, 2H), 4.00 – 3.90 (m, 2H), 3.54 – 3.50 (m, 5H), 3.35 – 3.34 (m, 2H), 3.27 (s, 2H), 2.28 (s, 3H), 2.24 (s, 3H), 1.10 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (151 MHz, DMSO) δ 167.6, 167.4, 166.8, 165.918, 146.3, 145.938, 145.4, 136.9, 13 2.7, 131.6, 131.5, 129.6, 129.4, 128.2, 127.9, 119.5, 102.8, 102.2, 69.7, 66.9, 59.9, 51.0, 45.1, 39.1, 37.2, 20.9, 18.7, 14.6. HRMS (ESI) (m/z) calculated for C$_{30}$H$_{34}$ClN$_3$NaO$_7$ [M+Na]$^+$: 606.1977, found: 606.1967.

$\textit{tert-}$butyl2-((4R,6R)-2,2-dimethyl-6-(2-(3-oxo-3-(p-tolylamino)propanamido)ethyl)-1,3-dioxan-4-yl)acetate (3ag): According to the general procedure to afford 3ag as colorless oil (199 mg, 89%). $^1$H NMR (600 MHz, DMSO) δ 9.99 (s, 1H), 8.00 (t, $J = 5.4$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 7.8$ Hz, 2H), 4.19 – 4.15 (m, 1H), 3.94 – 3.90 (m, 1H), 3.20 (s, 2H), 3.15 – 3.11 (m, 2H), 2.35 (dd, $J = 15.0$, 4.8 Hz, 1H), 2.24 (s, 3H), 2.21 (dd, $J = 15.0$, 7.8 Hz, 1H), 1.55 – 1.50 (m, 3H), 1.39 (s, 9H), 1.37 (s, 3H), 1.24 (s, 3H), 1.05 (dd, $J = 24.0$, 12.0 Hz, 3H).
Hz, 1H). $^{13}$C NMR (151 MHz, DMSO) $\delta$ 170.1, 166.9, 165.9, 136.9, 132.7, 129.6, 119.5, 98.6, 80.2, 66.8, 66.5, 45.1, 42.7, 36.2, 36.0, 35.5, 30.4, 28.2, 20.9, 20.1. HRMS (ESI) (m/z) calculated for C$_{20}$H$_{30}$N$_{2}$NaO$_{6}$ [M+Na]$^+$: 471.2466, found: 471.2452.

**tert-butyl (S)-2-(2-oxo-3-(3-oxo-3-(p-tolylamino)propanamido)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)acetate (3ah):** According to the general procedure to afford 3ah as white solid (214 mg, 92%); Mp = 94-96 $^\circ$C. $^1$H NMR (600 MHz, DMSO) $\delta$ 9.90 (s, 1H), 8.48 (s, 1H), 7.44 (d, $J$ = 7.2 Hz, 2H), 7.36 – 7.32 (m, 3H), 7.23 (t, $J$ = 7.2 Hz, 1H), 7.09 (d, $J$ = 7.8 Hz, 2H), 4.58 (d, $J$ = 17.4 Hz, 1H), 4.35 (d, $J$ = 17.4 Hz, 1H), 4.28 (s, 1H), 3.27 – 3.20 (m, 3H), 2.65 (dd, $J$ = 13.2, 6.6 Hz, 1H), 2.27 (d, $J$ = 7.8 Hz, 1H), 2.24 (s, 3H), 2.05 – 1.99 (m, 1H), 1.36 (s, 9H). $^{13}$C NMR (151 MHz, DMSO) $\delta$ 171.1, 168.4, 166.5, 165.7, 141.3, 136.8, 135.8, 132.7, 129.8, 129.6, 128.3, 127.1, 123.3, 119.6, 81.7, 51.3, 49.5, 44.6, 35.5, 28.1, 27.9, 20.9. HRMS (ESI) (m/z) calculated for C$_{26}$H$_{31}$N$_{3}$NaO$_{5}$ [M+Na]$^+$: 488.2156, found: 488.2146.

**1-(4-methoxyphenyl)-5-((1-((p-tolyl)-1H-tetrazol-5-yl)methyl)-1H-tetrazole (5):** Phosphorus oxychloride (1.53 g, 10 mmol) and NaN$_3$ (0.195 g, 3 mmol) were added to a vigorously stirred solution of amide 3a (0.298 g, 1 mmol) in 3 mL of acetonitrile. The mixture was refluxed for 8 h (the whole process was closely monitored by TLC). After the completion of the reaction, acetonitrile was evaporated, the residue was dissolved in water with ice, and the solution was neutralized with saturated soda solution. The precipitate that formed was filtered off. Liquid tetrazoles were extracted with methylene chloride, and the solvent was evaporated in a vacuum. The crude reaction mixture was purified by flash silica gel column chromatography. (PE : EA = 3 : 1) as eluent to give 5 as a yellow oil (184 mg, 53%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.47 – 7.45 (m, 2H), 7.42 (d, $J$ = 8.4 Hz, 2H), 7.36 (d, $J$ = 8.4 Hz, 2H), 7.05 – 7.03 (m, 2H), 4.47 (s, 2H), 3.88 (s, 3H), 2.45 (s, 3 H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.4, 149.8, 149.7, 141.6, 130.7, 130.4, 126.8, 125.5, 125.0, 115.2, 55.8, 21.3, 19.2.
HRMS (ESI) (m/z) calculated for C_{17}H_{16}N_{8}NaO [M+Na]^+: 371.1339, found: 371.1335.
V. References


VI. $^1$H and $^{13}$C NMR Spectra

Compound 3a
Compound 3b
Compound 3d
Compound 3e
Compound 3f
Compound 3g
Compound 3h
Compound 3i

[Chemical structure image]

[Graph and data analysis]

S31
Compound 3k
Compound 3m
Compound 3n
Compound 36
Compound 3p
Compound 3q
Compound 3r
Compound 3v

S44
Compound 3w
Compound 3ab
Compound 3ac
Compound 3ad
Compound 3ae
Compound 3af
Compound 3ag
Compound 3ah
Compound 5