Efficient One-Pot Synthesis of Triazole-Linked Morpholinone Scaffolds by CuAAC in the Presence of 18-Crown-6

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Abstract A range of bis-heterocyclic derivatives based on novel morpholinone and triazole heterocycles was prepared from iodo-morpholinone. The key step in our strategy is a one-pot procedure based upon copper-catalysed alkyne-azide cycloaddition (CuAAC) from iodo-morpholinone.

Key words click chemistry, iodolactonization, morpholinones, azides, 1,2,3-triazole, one-pot procedure

The synthesis of five- and six-membered nitrogen-containing heterocycles, such as morpholinones and 1,2,3-triazoles, has received considerable attention, and these structures constitute important classes of biologically active compounds.

Various morpholinone-containing compounds have been reported in the past decade with a range of biological properties (Scheme 1). For example, compound A exhibits antifungal and antibacterial activities against four bacteria and seven fungal species1 and morpholinone B was recently found to be an inhibitor of the MDM2–p53 protein–protein interaction. It is important to note that 1,2,3-triazole based heterocycles have become a cornerstone of medicinal chemistry because of their important biological activities. For example, compound C exhibits potent anticancer activity,2 compound D was found to have good TNF-α inhibitory activity,4 antiviral compound E exhibits cytostatic activity in the high micromolar range,3 and compound F shows potent antibacterial activity against both Gram-positive and Gram-negative bacteria.6 In addition, a series of thiazolidinediones with triazole substitution show antidiabetic and anticancer activity properties.7

Given the promising biological properties and synthetic applications of these heterocycles, it appeared interesting to consider the combination of these moieties, with the aim to access novel more biologically effective compounds. As a consequence, the development of effective and practical methods for the construction of morpholines with 1,2,3-triazoles units appeared to be a worthwhile goal.

In our previous work, we have synthesized numerous heterocycles by using coupling/cyclization tandem reactions.8 In a continuation of our research devoted to the development and diversification of new classes of heterocycles, we report herein the construction of iodomorpholine 5 through electrophilic iodocyclization of acid 2. In addition, introduction of an iodo- functionality provides a useful route for the synthesis of novel morpholinones, incorporating the 1,2,3-triazole moiety, with good yields.

Initially, the starting acids 2 and 4 were prepared from allylamine in three steps (Scheme 2). Allylamine was tosylated under standard conditions, providing the corresponding tosyl-functionalized amine. This amine was then alkylated by following Raghunathan’s protocol using ethyl bromoacetate, affording ethyl N-allyl-N-tosyglycinate in 80% yield over two steps.9 Saponification of ester 1 was achieved using 12% KOH, leading to the corresponding acid 3 in quantitative yield. The synthesis of compound 4 was achieved in two steps. First, the N-tosylated allyl amine was reacted with methyl acrylate in MeCN in the presence of a substoichiometric amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), resulting in an aza-Michael addition reaction, as developed by Kim’s group.10 Having synthesized the ester 3 in good yield (88%), the next task was to convert the ester into its corresponding acid. The saponification of ester 3 was achieved with LiOH in a MeOH/H2O mixture to afford the desired acid 4 in quantitative yield. Compounds 3 and 4 were characterized by comparison with the published NMR spectra (see the Supporting Information).11,12
We next explored the reactivity of amino acid 2 in the iodolactonization reaction. Iodocyclization of alkynes or alkenes represents a useful method for the preparation of important heterocycles, and a number of methods have been reported for the construction of functionalized cyclic compounds through halolactonization such as azetidines and pyrrolidines,13 benzo[\(\text{h}\)]phenazines,14 lactones,15 oxazolidin-2-ones,16 and other heterocycles.17 The results of the iodolactonization reaction of alkynes or alkenes were presented in Table 1. Initial experiments were carried out using \(\text{I}_2\) (2 equiv) as the electrophile and \(\text{Na}_2\text{CO}_3\) (3 equiv) as the base in CHCl\(_3\) at room temperature (entry 1). Under these conditions, iodo-mor- pholinone 5 was obtained while some starting material remained (20%). We further tested \(\text{ICl}, \text{I}_2\) (1.5 equiv), Na\(\text{I}\) (1.5 equiv) and AgNO\(_3\) (1 equiv) in CHCl\(_3\) at 25 °C and, after 2 hours, complete iodolactonization was achieved, leading to the intermediate 5’, avoiding the formation of bis-iodinated by-products. Subsequently, regioselective intramolecular nucleophilic attack of the oxygen then proceeds via a 6-exo-tet ring-closing pathway to form iodo-morpholinone 5.

The successful synthesis of iodomorpholinone 5 led us to investigate the iodocyclization of 3-amino propanoic acid 4. Thus, acid 4 was treated with \(\text{I}_2\) (1.5 equiv), Na\(\text{I}\) (2 equiv) and AgNO\(_3\) (1 equiv) in CHCl\(_3\) at 25 °C and, after 2 hours, complete iodolactonization was achieved, leading to the iodo-1,4-oxazepan-7-one 6 in 56% yield (Scheme 3). It should be noted that product 6 is unstable. This product must be immediately purified, and it degrades quickly even when stored in the refrigerator.
We then focused on the installation of 1,2,3-triazole groups into the morpholinone scaffold through CuAAC-based multicomponent reactions (MCR). MCRs are important and effective in carbon–nitrogen bond formation because of their considerable economic and ecological interests.20 These reactions have become important tools for the organic chemist to generate complex molecules that find many applications in drug discovery.21 In this context, the reactivity of halomorpholinones has been widely studied with sodium azide and terminal alkynes by using this one-pot two-step sequence. Although we tested various conditions for the synthesis of 1,2,3-triazoles that are described in the literature, in our case no desired product was observed.22 On the basis of these results, we turned our attention to the preparation of novel morpholinones, incorporating the 1,2,3-triazoles moiety through the more classical two-step route, as shown in Scheme 4.

Thus, we examined nucleophilic substitution of the remaining iodide to introduce the azide group.13,23 In our initial attempt, we tested the influence of the solvent (Table 2, entries 1–3 and entries 6–7) and found that protic solvents, such as H2O and MeOH, led to degradation of product 7, while the use of aprotic solvents, such as acetone, DMF and MeCN resulted in a low yield of 7 (30%). Moreover, we found that heating the reaction only afforded a complex mixture (entries 4 and 8). An increase in the quantity of NaN3 and reaction time did not improve the yield of this reaction (entry 5). In an attempt to increase the yield of 7, we treated iodo-morpholinone 5 with sodium azide in the presence of various additives (entries 9–11)24 and found that product 7 could be obtained from 5 in a very high yield (90%) in the presence of 18-crown-6. However, further investigation showed that, whereas increasing the amount of the latter reduces the reaction time, it did not give a better yield (entries 12 and 13). In this context, it is important to note that various attempts to introduce an azide group into substrates produced by iodolactonization are reported in the literature to result in incomplete reaction.13 Unfortunately, the iodo-1,4-oxazepan-7-one 6, in contrast to iodomorpholinone 5, could not be transformed into the desired

Table 1 Optimization of Iodocyclization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile (equiv)</th>
<th>Solvent</th>
<th>Base (equiv)</th>
<th>Temp (°C)</th>
<th>Additive (equiv)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I2 (2)</td>
<td>CHCl3</td>
<td>Na2CO3 (3)</td>
<td>rt</td>
<td>–</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>NBS (2)</td>
<td>CHCl3</td>
<td>Na2CO3 (3)</td>
<td>50</td>
<td>–</td>
<td>–b</td>
</tr>
<tr>
<td>3</td>
<td>ICl (2)</td>
<td>CHCl3</td>
<td>Na2CO3 (3)</td>
<td>rt</td>
<td>50</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>NIS (2)</td>
<td>CHCl3</td>
<td>Na2CO3 (3)</td>
<td>rt</td>
<td>–</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>I2 (2)</td>
<td>CHCl3</td>
<td>Na2CO3 (3)</td>
<td>50</td>
<td>–</td>
<td>tracec</td>
</tr>
<tr>
<td>6</td>
<td>I2 (2)</td>
<td>THF</td>
<td>Na2CO3 (3)</td>
<td>rt</td>
<td>–</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>I2 (2)</td>
<td>CHCl3</td>
<td>NaH (1.5)</td>
<td>0</td>
<td>–</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>I2 (2)</td>
<td>CHCl3</td>
<td>NaOH (3)</td>
<td>50</td>
<td>–</td>
<td>45</td>
</tr>
<tr>
<td>9</td>
<td>I2 (2)</td>
<td>CHCl3</td>
<td>NaH (3)</td>
<td>rt</td>
<td>–</td>
<td>–b</td>
</tr>
<tr>
<td>10</td>
<td>I2 (2)</td>
<td>CHCl3</td>
<td>Na2CO3 (3)</td>
<td>rt</td>
<td>AgNO3 (1)</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
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<td>CHCl3</td>
<td>Na2CO3 (3)</td>
<td>rt</td>
<td>AgNO3 (1.5)</td>
<td>84</td>
</tr>
<tr>
<td>12</td>
<td>I2 (1.5)</td>
<td>CHCl3</td>
<td>Na2CO3 (2)</td>
<td>rt</td>
<td>AgNO3 (1)</td>
<td>86</td>
</tr>
</tbody>
</table>

a Isolated yield after column chromatography.
b Starting material.
c Complex mixture.

Table 2 Optimization Studies of the Reaction between Sodium Azide and Morpholinone 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (equiv)</th>
<th>Solvent</th>
<th>NaN3 (equiv)</th>
<th>Temp (°C)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>MeOH/H2O</td>
<td>3</td>
<td>rt</td>
<td>–b</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>MeOH</td>
<td>3</td>
<td>60</td>
<td>–b</td>
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<tr>
<td>3</td>
<td>–</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>30c</td>
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<td>4</td>
<td>–</td>
<td>acetone</td>
<td>3</td>
<td>45</td>
<td>–b</td>
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<tr>
<td>5</td>
<td>–</td>
<td>acetone</td>
<td>6</td>
<td>rt</td>
<td>30c–d</td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>DMF</td>
<td>3</td>
<td>rt</td>
<td>30c</td>
</tr>
<tr>
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<td>–</td>
<td>MeCN</td>
<td>3</td>
<td>rt</td>
<td>30c</td>
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<tr>
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<td>–</td>
<td>DMF</td>
<td>3</td>
<td>75</td>
<td>–b</td>
</tr>
<tr>
<td>9</td>
<td>18-crown-6 (0.5)</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>TBAI (0.5)</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>72</td>
</tr>
<tr>
<td>11</td>
<td>TBAF (0.5)</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>18-crown-6 (1)</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>90b</td>
</tr>
<tr>
<td>13</td>
<td>18-crown-6 (1.5)</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>90b</td>
</tr>
</tbody>
</table>

a Isolated yield.
b Degradation.
c Starting material 5 was recovered in 30% yield.
d 72 h (time of reaction).
e 18 h (time of reaction).
azide product under these conditions (in the presence of 18-crown-6), presumably because of the instability of the iodo-1,4-oxazepan-7-one 6.

In the next phase of the study, we wished to generate 1,2,3-triazole derivatives involving a 1,3-dipolar cycloaddition using azido morpholinone 7 as the starting material. Many protocols for the synthesis of 1,2,3-triazoles based on copper(I) catalysts have been reported.25 In our initial attempt, CuSO4·5H2O (10 mol%) was used as catalyst in the presence of sodium ascorbate (20 mol%) and phenylacetylene (1.5 equiv) in toluene/H2O (3:1) at room temperature; wherein 8a was obtained in a moderate yield (50%). An attempt to use copper(I) iodide under the same conditions was made, but again afforded moderate yields, as was the case with copper sulfate. We further examined the effect of solvents on the cycloaddition reaction (1:3 THF/H2O, toluene/H2O, DMF/H2O, CHCl3/H2O and CH2Cl2) and the best results were obtained when the reaction was carried out in either CH2Cl2 or CHCl3/H2O (Scheme 5). Under these conditions, compound 8a was obtained in good yield (90%).

Having established that morpholinone 5 can be transformed into 1,2,3-triazole derivatives in a two-step procedure, we decided to investigate the ‘one-pot’ cascade (Scheme 6) of the two previously defined steps (Scheme 4) and we found the presence of 18-crown-6 to be crucial for the azide substitution reaction to take place. In this context, iodomorpholinone 5 was subjected to the copper-catalyzed-multicomponent reaction in the presence of 18-crown-6 using phenylacetylene and sodium azide under the previously defined conditions. As expected, under these conditions (Scheme 6), the multicomponent click reaction worked well and the targeted 1,2,3-triazole 8a was obtained in 82% yield. It was found that 18-crown-6 is indispensable for this three-component reaction. This one-pot reaction led to the isolation of the desired product 8a with a similar yield to the two-step procedure (81%). To demonstrate the generality of this one-pot morpholinone-triazole synthesis reaction, a range of substituted 1,2,3-triazoles derivatives 8a–k were prepared in moderate to excellent yields by using the multicomponent reaction of iodomorpholinone 5 and sodium azide with various terminal alkynes.

\[
\begin{align*}
\text{Scheme 5} & \quad 1,3\text{-Dipolar cycloaddition between 7 and phenylacetylene} \\
\text{Scheme 6} & \quad \text{Synthesis of morpholinone-triazoles 8 through a CuAAC one-pot procedure}
\end{align*}
\]
In summary, we have developed an efficient and general methodology for the synthesis of novel six- and seven-membered iodo heterocycles through electrophilic iodocyclization. We have also demonstrated that the resulting six-membered iodoazomorpholine 5 afforded a novel series of heterocyclic derivatives based on morpholine and triazole heterocycles, prepared using a CuAAC one-pot procedure in the presence of 18-crown-6. Further investigations concerning the scope of applications are ongoing in our laboratory.

All reactions were carried out under an argon atmosphere in dried glassware. THF was distilled under argon from sodium benzophenone ketyl. Dimethylformamide was dried and freshly distilled from calcium hydride. Other chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Fluorochem or ABCR and used without further purification. Reactions were monitored by TLC with Merck silica gel 60 F254. TLC plates were visualized using UV light (254 nm) or staining with KMnO4. Column chromatography was performed on silica gel (40–63 μm) using mixtures of EtOAc and petroleum ether (35–60 °C fraction) as eluent. 1H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer, using as internal deuterium lock the solvent 39.52 ppm). 19F NMR spectra were recorded at 282 MHz on the same instrument. Absorption maxima (νmax) are quoted in wavenumbers. Melting points are uncorrected.

Synthesis of 6-(Iodomethyl)-4-tosylmorpholin-2-one (5)

In a round-bottom flask containing carboxylic acid 4 (1 equiv, 300 mg, 1.059 mmol) and CHCl3 (25 mL) were added sodium carbonate (2 equiv, 224 mg, 2.12 mmol), iodine (1.5 equiv, 403 mg, 1.59 mmol) and silver nitrate (1.5 equiv, 180 mg, 1.06 mmol). The mixture was stirred for 2 h at r.t., quenched with a saturated solution of Na2S2O3 (30 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over MgSO4, filtered and evaporated under reduced pressure.

1H NMR (300 MHz, DMSO-d6): δ = 7.68 (d, J = 8.17 Hz, 2 H), 7.38 (d, J = 8.17 Hz, 2 H), 4.48–4.54 (m, 1 H), 4.24–4.3 (dd, J = 1.8 Hz, J = 14.47 Hz, 1 H), 4.03–4.11 (m, 1 H), 3.28–3.41 (m, 2 H, 2.71–3.04 (m, 4 H), 2.47 (s, 3 H). 11C NMR (75 MHz, DMSO-d6): δ = 163.51, 145.21, 131.39, 130.35, 127.81, 77.27, 53.57, 46.71, 46.48, 21.6, 1.76.


Synthesis of 6-(Azidomethyl)-4-tosylmorpholin-2-one (7)

A mixture of the appropriate 6-(iodomethyl)-4-tosylmorpholin-2-one 5 (300 mg, 0.76 mmol), sodium azide (148 mg, 2.28 mmol), 18-crown-6 (100 mg, 0.38 mmol) and acetone (20 mL) was stirred at r.t. until completion of the reaction (TLC). The solvents were evaporated under reduced pressure, and the crude product was then poured into water, extracted with CH2Cl2 (3 × 40 mL), dried (MgSO4), filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using PE/EtOAc (6:1) mixture as eluent.

1H NMR (300 MHz, CDCl3): δ = 7.67 (d, J = 8.3 Hz, 2 H), 7.40 (d, J = 8.3 Hz, 2 H), 4.68–4.61 (m, 1 H), 4.11 (dd, J = 1.1, 17.6 Hz, 1 H), 3.67–3.58 (m, 3 H), 3.53 (dd, J = 4.4, 13.2 Hz), 2.94 (dd, J = 8.6, 12.7 Hz, 1 H), 2.47 (s, 3 H). 13C NMR (75 MHz, CDCl3): δ = 163.52, 145.29, 131.34, 130.43, 130.28, 127.91, 76.77, 51.68, 46.97, 46.25, 21.71.


Synthesis of Triazoles; General Procedures

Method A

Finely powdered CuSO4·5H2O (16 mg, 0.10 mol%) and sodium ascorbate (20 mg, 0.20 mol%) were slowly added to a stirred solution of 6-(azidomethyl)-4-tosylmorpholin-2-one 7 (200 mg, 0.64 mmol) and terminal alkyne (0.96 mmol, 1.5 equiv) in H2O/CHCl3 (3:1 = 15 mL/5 mL) at 0–10 °C. The mixture was then allowed to reach r.t. and TLC monitoring was used to follow reaction progress. The mixture was filtered, evaporated to dryness at r.t. and the residual crude product was purified by flash chromatography over silica gel (eluent CHCl3/MeOH = 88:12) to afford the desired pure triazole 8.

1H NMR (300 MHz, DMSO-d6): δ = 7.68 (d, J = 7.7, 12.9 Hz, 1 H), 3.68 (d, J = 17.7 Hz, 1 H), 3.39–3.27 (m, 2 H), 3.07 (dd, J = 7.7, 12.9 Hz, 1 H), 2.47 (s, 3 H). 13C NMR (75 MHz, DMSO-d6): δ = 163.6, 145.26, 131.55, 130.44, 127.91, 77.16, 46.79, 46.56, 21.73, 1.74.

um ascorbate (79 mg, 0.4 mmol, 0.2 equiv) and CuSO₄·5H₂O (100 mg, 0.4 mmol, 0.2 equiv) were added to the mixture which was then stirred for 24 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl (20 mL) and the mixture was stirred for further 15 min. The mixture was filtered through a pad of Celite® and the filtrate was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was then purified by recrystallization or by flash chromatography on silica gel using PE/EtOAc as the eluent.

6-[(4-Phenyl-1H-1,2,3-triazol-1-yl)methyl]-4-tosylmorpholin-2-one (8a)

According to general procedure B, compound 8a was isolated after recrystallization (EtOH).

Yield: 675 mg (82%); white solid; mp 213–214 °C; R₆ = 0.35 (EtOAC/PE = 4:1).

1H NMR (300 MHz, DMSO-d₆): δ = 8.54 (s, 1 H), 7.83 (d, J = 7.75 Hz, 2 H), 7.69 (d, J = 7.75 Hz, 2 H), 7.45 (d, J = 4.80 Hz, 4 H), 7.34 (t, J = 7.3 Hz, 1 H), 6.00–5.05 (m, 1 H), 4.80 (d, J = 3.5, 14.6 Hz, 1 H), 4.72 (d, J = 7.3, 14.6 Hz, 1 H), 4.03 (d, J = 17.2 Hz, 1 H), 3.77 (dd, J = 3.0, 12.3 Hz, 1 H), 3.73 (d, J = 17.2 Hz, 1 H), 3.07 (dd, J = 8.9, 12.5 Hz, 1 H), 2.38 (s, 3 H).

13C NMR (75 MHz, DMSO-d₆): δ = 164.21, 146.39, 144.46, 131.71, 130.54, 130.21, 128.98, 128.01, 127.71, 125.2, 122.42, 75.75, 50.71, 46.49, 43.53, 21.04.


6-[(4-(4-Methoxyphenyl)-1H-1,2,3-triazol-1-yl)methyl]-4-tosylmorpholin-2-one (8d)

According to general procedure B, compound 8d was isolated after recrystallization (EtOH).

Yield: 533 mg (62%); white solid; mp 191–192 °C; R₆ = 0.38 (EtOAC/PE = 4:1).

1H NMR (300 MHz, DMSO-d₆): δ = 8.45 (d, J = 3.81 Hz, 1 H), 8.15 (td, J = 1.7, 7.4 Hz, 1 H), 7.17 (d, J = 8.15 Hz, 2 H), 7.47 (d, J = 8.15 Hz, 2 H), 7.42–7.31 (m, 3 H), 5.08–5.00 (m, 1 H), 4.87–4.74 (m, 2 H), 4.01 (d, J = 17.0 Hz, 1 H), 3.78 (d, J = 17.0 Hz, 1 H), 3.73 (dd, J = 3.3, 12.3 Hz, 1 H), 3.10 (d, J = 8.4, 12.6 Hz, 1 H), 2.39 (s, 3 H).

13C NMR (75 MHz, DMSO-d₆): δ = 164.14, 158.46 (d, J = 247 Hz), 144.42, 139.72 (d, J = 2.3 Hz, 2 H), 131.70, 130.18, 127.27 (d, J = 3.4 Hz, 4 H), 125.0 (d, J = 3.15 Hz), 124.77 (d, J = 11.7 Hz), 118.21 (d, J = 21.3 Hz), 116.05 (d, J = 21.3 Hz), 75.80, 50.71, 46.52, 43.49, 21.01.

19F NMR (282 MHz, DMSO-d₆): δ = –114.65.


6-[(4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl)methyl]-4-tosylmorpholin-2-one (8c)

According to general procedure B, compound 8c was isolated after recrystallization (EtOH).

Yield: 705 mg (82%); white solid; mp 207–208 °C; R₆ = 0.38 (EtOAC/PE = 4:1).

1H NMR (300 MHz, DMSO-d₆): δ = 8.53 (s, 1 H), 7.87 (dd, J = 5.5, 8.8 Hz, 2 H), 7.70 (d, J = 8.2 Hz, 2 H), 7.46 (d, J = 8.2 Hz, 2 H), 7.30 (t, J = 8.9 Hz, 2 H), 5.00–4.05 (m, 5 H), 4.80 (d, J = 3.8, 14.6 Hz, 1 H), 4.71 (dd, J = 7.3, 14.6 Hz, 1 H), 4.03 (d, J = 17.15 Hz, 1 H), 3.77 (dd, J = 3.1, 12.8 Hz, 1 H), 3.76 (d, J = 17.15 Hz, 1 H), 3.04 (dd, J = 8.8, 12.7 Hz, 1 H), 2.38 (s, 3 H).

13C NMR (75 MHz, DMSO-d₆): δ = 164.33, 161.95 (d, J = 244.5 Hz), 145.65, 144.6, 131.76, 130.32, 127.8, 127.43, 127.35 (d, J = 8.2 Hz, 4 H), 127.17 (d, J = 3.1 Hz), 122.44, 116.02 (d, J = 22 Hz, 2 H), 75.83, 50.82, 46.56, 43.61, 21.13.

19F NMR (282 MHz, DMSO-d₆): δ = –113.84.


6-[(4-(2,4-Difluorophenyl)-1H-1,2,3-triazol-1-yl)methyl]-4-tosylmorpholin-2-one (8f)

According to general procedure B, compound 8f was isolated after recrystallization (EtOH).

Yield: 716 mg (80%); white solid; mp 213–214 °C; R₆ = 0.35 (EtOAC/PE = 4:1).

1H NMR (300 MHz, DMSO-d₆): δ = 8.44 (d, J = 3.55 Hz, 1 H), 8.20–8.12 (m, 1 H), 7.70 (d, J = 7.8 Hz, 2 H), 7.46 (d, J = 7.8 Hz, 2 H), 7.43–7.37 (m, 1 H), 7.27–7.20 (m, 1 H), 5.06–5.00 (m, 1 H), 4.84–4.76 (m, 2 H), 4.00 (d, J = 10.1 Hz, 1 H), 3.77 (d, J = 17.1 Hz, 1 H), 3.73 (dd, J = 2.8, 12.05 Hz, 1 H), 3.10 (dd, J = 8.5, 12.6 Hz, 1 H), 2.39 (s, 3 H).

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According to general procedure B, compound 8h was isolated after recrystallization (EtOH).

Yield: 851 mg (74%); white solid; mp 179–180 °C; Rf = 0.33 (EtOAc/PE = 4:1).

1H NMR (300 MHz, DMSO-d$_6$): δ = 7.83 (s, 1 H), 7.72 (d, J = 8.0 Hz, 2 H), 7.69 (d, J = 8.0 Hz, 2 H), 7.48 (d, J = 8.4 Hz, 2 H), 7.37 (d, J = 8.4 Hz, 2 H), 5.05 (dd, J = 1.6, 10.2 Hz, 1 H), 5.03–4.96 (m, 1 H), 4.84–4.71 (m, 2 H), 4.43 (s, 2 H), 4.03 (d, J = 17.3 Hz, 2 H), 3.84–3.76 (m, 2 H), 3.10 (dd, J = 8.3, 12.8 Hz, 2 H), 2.42 (s, 3 H), 2.39 (s, 3 H).

13C NMR (75 MHz, acetone-d$_6$): δ = 163.27, 145.67, 144.29, 138.44, 133.51, 131.1, 130.62, 128.89, 128.18, 119.14, 77.28, 70.82, 51.93, 50.73, 47.58, 44.95, 42.48, 21.85, 21.49.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{30}$H$_{30}$N$_5$O$_5$: 560.19450; found: 560.19292.

**N-Allyl-4-methyl-N-{(1-[6-oxo-4-tosylmorpholin-2-yl]methyl)-1H-1,2,3-triazol-4-yl}benzenesulfonamide (8k)**

According to general procedure B, compound 8k was isolated after flash chromatography.

Yield: 771 mg (69%); white solid; mp 157–158 °C; Rf = 0.35 (EtOAc/PE = 4:1).

1H NMR (300 MHz, acetone-d$_6$): δ = 7.83 (s, 1 H), 7.72 (d, J = 8.0 Hz, 2 H), 7.69 (d, J = 8.0 Hz, 2 H), 7.48 (d, J = 8.4 Hz, 2 H), 7.37 (d, J = 8.4 Hz, 2 H), 5.05 (dd, J = 1.6, 10.2 Hz, 1 H), 5.03–4.96 (m, 1 H), 4.84–4.71 (m, 2 H), 4.43 (s, 2 H), 4.03 (d, J = 17.3 Hz, 2 H), 3.84–3.76 (m, 2 H), 3.10 (dd, J = 8.3, 12.8 Hz, 2 H), 2.42 (s, 3 H), 2.39 (s, 3 H).

13C NMR (75 MHz, acetone-d$_6$): δ = 164.27, 145.67, 144.29, 138.44, 133.51, 131.1, 130.62, 128.89, 128.18, 119.14, 77.28, 70.82, 51.93, 50.73, 47.58, 44.95, 42.48, 21.85, 21.49.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{30}$H$_{30}$N$_5$O$_5$: 560.19450; found: 560.16186.

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**Supporting Information**

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**References**


