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

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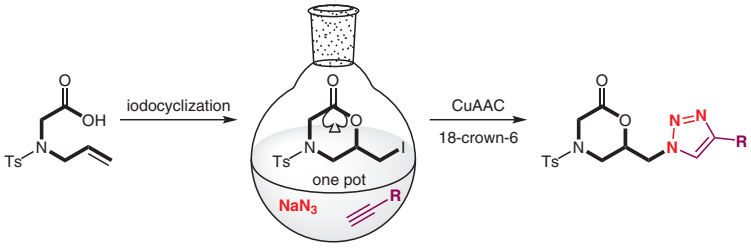

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Abstract A range of bis-heterocyclic derivatives based on novel morpholinone and triazole heterocycles was prepared from iodomorpholinone. The key step in our strategy is a one-pot procedure based upon copper-catalysed alkyne-azide cycloaddition (CuAAC)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

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

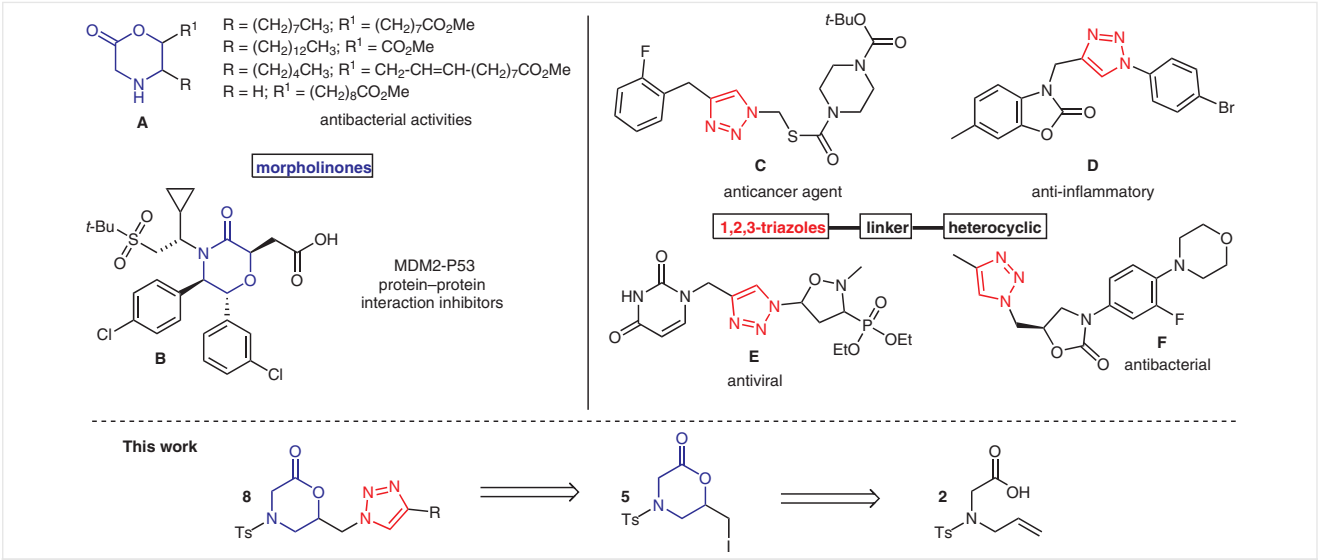
The synthesis of five- and six-membered nitrogen-containing heterocycles, such as morpholinones and 1,2,3-triazoles, has received considerable attention, and these structures constitute important classes of biologically active compounds.

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 species[1] and morpholinone **B** was recently found to be an inhibitor of the MDM2–p53 protein–protein interaction.[2] 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,[3] compound **D** was found to have good TNF-α inhibitory activity,[4] antiviral compound **E** exhibits cytostatic activity in the high micromolar range,[5] 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]

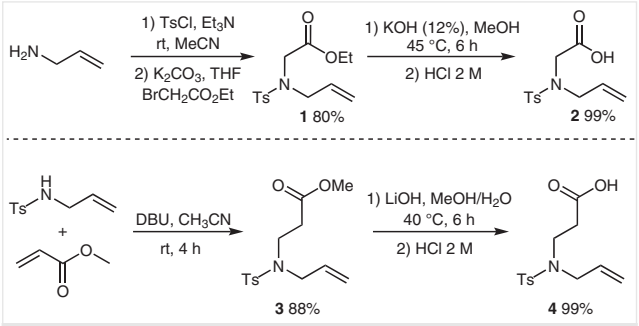
Given the promising biological properties and synthetic applications of these heterocycles, it appeared interesting to consider the combination of these moieties, with the aim to access novel more biologically effective compounds. As a consequence, the development of effective and practical methods for 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 iodomorpholinone **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*-tosylglycinate **1** in 80% yield over two steps.[9] Saponification of ester **1** was achieved using 12% KOH, leading to the corresponding acid **2** 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/H_2O 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]



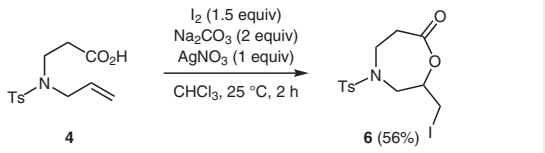
Scheme 1 Selected biologically active triazole and morpholinone units and retrosynthetic strategy for the sequential synthesis of morpholinones incorporating the 1,2,3-triazole moiety



Scheme 2 Preparation of acids **2** and **4**

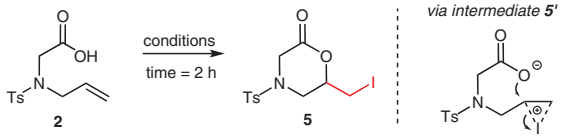
We next explored the reactivity of amino acid **2** in the iodolactonization reaction. Iodocyclization of alkynes or alkenes represents a useful method for the preparation of important heterocycles, and a number of methods have been reported for the construction of functionalized cyclic compounds through halolactonization such as azetidines and pyrrolidines,[13] benzo[*a*]phenazines,[14] lactones,[15] oxazolidin-2-ones,[16] and other heterocycles.[17] The results of the iodolactonization of **2** are presented in Table 1. Initial experiments were carried out using I_2 (2 equiv) as the electrophile and Na_2CO_3 (3 equiv) as the base in $CHCl_3$ at room temperature (entry 1). Under these conditions, iodo-morpholinone **5** was obtained while some starting material remained (20%). We further tested ICl, *N*-bromosuccinimide (NBS) and NIS as electrophiles instead of iodine in this reaction without changing other factors (entries 2–4) but a decrease in the yield of the desired product **5** was noted along with 20% of starting material remaining. Only a complex mixture was obtained on increasing the temperature and only traces of the desired product **5** were isolated (entry 5). Changing $CHCl_3$ to tetrahydrofuran (THF) gave a similar result (entry 6). Different bases, such as NaH and NaOH (entries 7–8) gave similar results, while no reaction occurred when Et_3N was used as the base. However, we were pleased to find that the addition of $AgNO_3$ (1 equiv) provided **5** selectively and in high yield (86%) (entry 10).[18] Subsequent testing showed that increasing the quantity of $AgNO_3$ did not improve the yield (entry 11). On the basis of these results, the optimum conditions were established as Na_2CO_3 (2 equiv), I_2 (1.5 equiv) and $AgNO_3$ (1 equiv) in $CHCl_3$ at room temperature (entry 12). Addition of silver nitrate probably allows an ionic reaction,[19] and precipitation of AgI from the reaction medium will prevent iodide attacking 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-aminopropanoic acid **4**. Thus, acid **4** was treated with I_2 (1.5 equiv), Na_2CO_3 (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.



Scheme 3 Iodocyclization of acid **4**

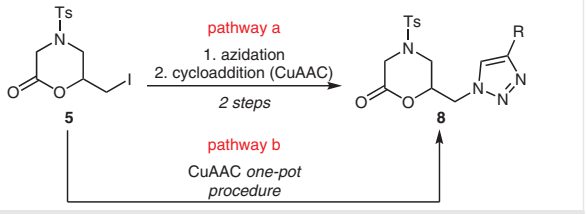
Table 1 Optimization of Iodocyclization



Entry	Electrophile (equiv)	Solvent	Base (equiv)	Temp (°C)	Additive (equiv)	Yield (%)[a]
1	I_2 (2)	$CHCl_3$	Na_2CO_3 (3)	rt	–	55
2	NBS (2)	$CHCl_3$	Na_2CO_3 (3)	50	–	–[b]
3	ICl (2)	$CHCl_3$	Na_2CO_3 (3)	rt	–	50
4	NIS (2)	$CHCl_3$	Na_2CO_3 (3)	rt	–	43
5	I_2 (2)	$CHCl_3$	Na_2CO_3 (3)	50	–	trace[c]
6	I_2 (2)	THF	Na_2CO_3 (3)	rt	–	51
7	I_2 (2)	$CHCl_3$	NaH (1.5)	0	–	48
8	I_2 (2)	$CHCl_3$	NaOH (3)	50	–	45
9	I_2 (2)	$CHCl_3$	Et_3N (3)	rt	–	–[b]
10	I_2 (2)	$CHCl_3$	Na_2CO_3 (3)	rt	$AgNO_3$ (1)	86
11	I_2 (2)	$CHCl_3$	Na_2CO_3 (3)	rt	$AgNO_3$ (1.5)	84
12	I_2 (1.5)	$CHCl_3$	Na_2CO_3 (2)	rt	$AgNO_3$ (1)	86

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

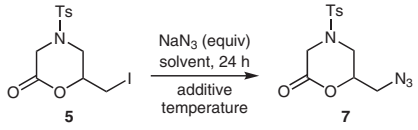
We then focused on the installation of 1,2,3-triazole groups into the morpholinone scaffold through CuAAC-based multicomponent reactions (MCR). MCRs are important and effective in carbon–nitrogen bond formation because of their considerable economic and ecological interests.[20] These reactions have 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.



Scheme 4 Synthetic routes towards triazole-linked morpholinone **8**

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 H_2O 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 NaN_3 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 2 Optimization Studies of the Reaction between Sodium Azide and Morpholinone **5**

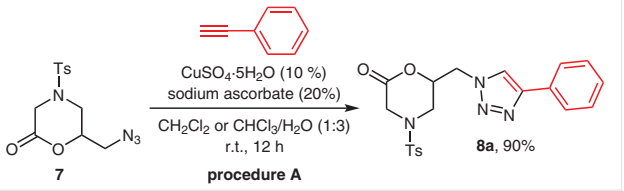


Entry	Additive (equiv)	Solvent	NaN_3 (equiv)	Temp (°C)	Yield (%)[a]
1	–	$MeOH/H_2O$	3	rt	–[b]
2	–	MeOH	3	60	–[b]
3	–	acetone	3	rt	30[c]
4	–	acetone	3	45	–[b]
5	–	acetone	6	rt	30[c,d]
6	–	DMF	3	rt	30[c]
7	–	MeCN	3	rt	30[c]
8	–	DMF	3	75	–[b]
9	**18-crown-6 (0.5)**	**acetone**	**3**	**rt**	**90**
10	TBAI (0.5)	acetone	3	rt	72
11	TBAF (0.5)	acetone	3	rt	70
12	18-crown-6 (1)	acetone	3	rt	90[e]
13	18-crown-6 (1.5)	acetone	3	rt	90[e]

[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).

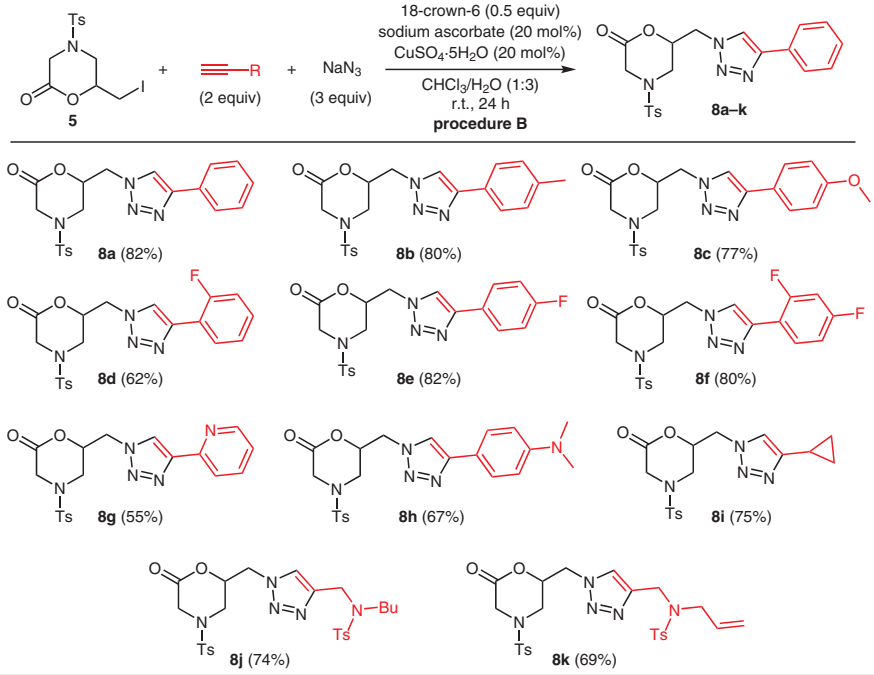
azide product under these conditions (in the presence of 18-crown-6), presumably because of the instability of the iodo-1,4-oxazepan-7-one **6**.

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, $CuSO_4{\cdot}5H_2O$ (10 mol%), was used as catalyst in the presence of sodium ascorbate (20 mol%) and phenylacetylene (1.5 equiv) in toluene/H_2O (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/H_2O, toluene/H_2O, DMF/H_2O, $CHCl_3$/H_2O and CH_2Cl_2) and the best results were obtained when the reaction was carried out in either CH_2Cl_2 or $CHCl_3$/H_2O (Scheme 5). Under these conditions, compound **8a** was obtained in good yield (90%).



Scheme 5 1,3-Dipolar cycloaddition between **7** and phenylacetylene

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.



Scheme 6 Synthesis of morpholinone-triazoles **8** through a CuAAC one-pot procedure

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 iodomorpholinone **5** afforded a novel series of heterocyclic derivatives based on morpholinone 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 $KMnO_4$. Column chromatography was performed on silica gel (40–63 μm) using mixtures of EtOAc and petroleum ether (35–60 °C fraction) as eluent. ^{1}H NMR spectra were recorded with a Bruker Avance 300 (300 MHz) NMR spectrometer, using as internal deuterium lock the solvents $CDCl_3$ (δ 7.26 ppm), $(CD_3)_2CO$ (δ = 2.05 ppm) or $(CD_3)_2SO$ (δ = 2.54 ppm). Chemical shifts are quoted in ppm (δ_H, δ_C). Peak multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet and br = broad. Coupling constants (*J*) are reported in Hz. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument, using the solvent peak at as reference $CDCl_3$ (δ = 77.16 ppm), $(CD_3)_2CO$ (δ = 29.85 ppm) or $(CD_3)_2SO$ (δ = 39.52 ppm). ^{19}F NMR spectra were recorded at 282 MHz on the same instrument, using the $CFCl_3$ as the internal reference (δ = 0.0 ppm). Mass spectra were obtained with a Hewlett Packard 5988A by direct inlet at 70 eV. HRMS were obtained with a LCMS-IT-TOF mass spectrometer under ESI. Infrared spectra were recorded with a Perkin–Elmer Spectrum One spectrophotometer with the sample being prepared as a thin film on a diamond ATR module. Absorption maxima (ν_{max}) 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 **2** (1 equiv, 300 mg, 1.11 mmol) and $CHCl_3$ (25 mL) were added sodium carbonate (2 equiv, 236 mg, 2.23 mmol), iodine (1.5 equiv, 424 mg, 1.67 mmol) and silver nitrate (1 equiv, 189 mg, 1.11 mmol). The mixture was stirred 2 h at r.t., quenched with a saturated solution of $Na_2S_2O_3$ (30 mL) then extracted with dichloromethane (3 × 25 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield **5**.

Yield: 258 mg (86%); yellow solid; mp 174–175 °C; R_f = 0.53 (EtOAC/PE = 1:4).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7. 68 (d, *J* = 7.8 Hz, 2 H), 7.40 (d, *J* = 7.8 Hz, 2 H), 4.52–4.58 (m, 1 H), 4.03 (d, *J* = 17.7 Hz, 1 H), 3.76 (d, *J* = 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).

^{13}C NMR (75 MHz, DMSO–d_6): δ = 163.6, 145.26, 131.55, 130.44, 127.91, 77.16, 46.79, 46.56, 21.73, 1.74.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}INO_4S$: 395.97610; found: 395.97568.

Synthesis of 2-(Iodomethyl)-4-tosyl-1,4-oxazepan-7-one (6)

In a round-bottom flask containing carboxylic acid **4** (1 equiv, 300 mg, 1.059 mmol) and $CHCl_3$ (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 $Na_2S_2O_3$ (30 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure.

^{1}H NMR (300 MHz, DMSO-d_6): 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).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.51, 145.21, 131.39, 130.35, 127.81, 77.27, 53.57, 46.71, 46.48, 21.6, 1.76.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}INO_4S$: 409.99175; found: 409.99147.

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 CH_2Cl_2 (3 × 40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using PE/EtOAc (6:1) mixture as eluent.

^{1}H NMR (300 MHz, $CDCl_3$): 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).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.52, 145.29, 131.34, 130.43, 130.28, 127.91, 76.77, 51.68, 46.97, 44.25, 21.71.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}IN_4O_4S$: 311.08085; found: 311.08011.

Synthesis of Triazoles; General Procedures

Method A

Finely powdered $CuSO_4{\cdot}5H_2O$ (16 mg, 10 mol%) and sodium ascorbate (26 mg, 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 $H_2O/CHCl_3$ (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, concentrated and diluted with water (30 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL), the combined organic layers were washed with H_2O and then with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude products were crystallized from various solvents or purified by flash chromatography over silica gel (eluent $CHCl_3$/MeOH = 88:12) to afford the desired pure triazole product.

Method B

6-(Iodomethyl)-4-tosylmorpholin-2-one **5** (789 mg, 2 mmol) was dissolved in $H_2O/CHCl_3$ (3:1 = 22.5 mL/7.5 mL). Sodium azide (390 mg, 6 mmol) and 18-crown-6 (264 mg, 1 mmol) were then added to the solution and the suspension was stirred for 30 min. The mixture was degassed at 0 °C, then the terminal alkyne (4.0 mmol, 2 equiv), sodi-

um ascorbate (79 mg, 0.4 mmol, 0.2 equiv) and $CuSO_4·5H_2O$ (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 NH_4Cl (20 mL) and the mixture was stirred for a 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 Na_2SO_4, 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-1*H*-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; R_f = 0.35 (EtOAC/PE = 4:1).

^{1}H NMR (300 MHz, DMSO-d_6): 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 (m, 4 H), 7.34 (t, *J* = 7.3 Hz, 1 H), 5.00–5.05 (m, 1 H), 4.80 (dd, *J* = 3.5, 14.6 Hz, 1 H), 4.72 (dd, *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).

^{13}C NMR (75 MHz, DMSO-d_6): 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.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}N_4O_4S$: 413.12780; found: 431.12656.

6-{[4-(*p*-Tolyl)-1*H*-1,2,3-triazol-1-yl]methyl}-4-tosylmorpholin-2-one (8b)

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

Yield: 681 mg (80%); white solid; mp 191–192 °C; R_f = 0.38 (EtOAC/PE = 4:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.47 (s, 1 H), 7. 72 (d, *J* = 6.4 Hz, 2 H), 7.69 (d, *J* = 6.4 Hz, 2 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 7.26 (d, *J* = 8.1 Hz, 2 H), 5.03–4.98 (m, 1 H), 4.02 (d, *J* = 18.1 Hz, 1 H), 3.76 (dd, *J* = 3.5, 11.7 Hz, 1 H), 3.75 (d, *J* = 18.1 Hz, 1 H), 3.06 (dd, *J* = 8.9, 12.5 Hz, 1 H), 2.38 (s, 3 H), 2.32 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.28, 145.52, 137.41, 131.75, 130.28, 129.58, 127.8, 127.77, 125.2, 122.04, 75.82, 50.73, 46.53, 43.59, 21.1, 20.91.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}N_4O_4S$: 427.14345; found: 427.14241.

6-{[4-(4-Methoxyphenyl)-1*H*-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: 680 mg (77%); white solid; mp 225–226 °C; R_f= 0.37 (EtOAc/PE = 4:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.42 (s, 1 H), 7.75 (d, *J* = 8.8 Hz, 2 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 5.04–4.96 (m, 1 H), 4.77 (dd, *J* = 3.9, 14.5 Hz, 1 H), 4.69 (dd, *J* = 7.4, 14.5 Hz, 1 H), 4.03 (d, *J* = 17.1 Hz, 1 H), 3.78 (s, 3 H), 3.77 (dd, *J* = 3.2, 12.4 Hz, 1 H), 3.75 (d, *J* = 17.1 Hz, 1 H), 3.06 (dd, *J* = 9.0, 12.6 Hz, 1 H), 2.39 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.29, 159.15, 146.39, 144.54, 131.74, 130.28, 127.76, 126.62, 123.15, 121.5, 114.43, 75.82, 55.23, 50.7, 46.52, 43.59, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}N_4O_5S$: 443.13837; found: 443.13705.

6-{[4-(2-Fluorophenyl)-1*H*-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; R_f = 0.38 (EtOAc/PE = 4:1).

^{1}H NMR (300 MHz, DMSO-d_6): 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 (dd, *J* = 8.4, 12.6 Hz, 1 H), 2.39 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.14, 158.46 (d, *J* = 247 Hz), 144.42, 139.72 (d, *J* = 2.3 Hz), 131.70, 130.18, 127.27 (d, *J* = 3.4 Hz), 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.

^{19}F NMR (282 MHz, DMSO-d_6): δ = –114.65.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}FN_4O_4S$: 431.11893; found: 431.11709.

6-{[4-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]methyl}-4-tosylmorpholin-2-one (8e)

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

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

^{1}H NMR (300 MHz, DMSO-d_6): 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), 5.00–5.05 (m, 1 H), 4.80 (dd, *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).

^{13}C NMR (75 MHz, DMSO-d_6): 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), 127.17 (d, *J* = 3.1 Hz), 122.44, 116.02 (d, *J* = 22 Hz), 75.83, 50.82, 46.56, 43.61, 21.13.

^{19}F NMR (282 MHz, DMSO-d_6): δ = –113.84.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_2H_{20}FN_4O_4S$: 431.11838; found: 431.11736.

6-{[4-(2,4-Difluorophenyl)-1*H*-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; R_f = 0.35 (EtOAc/PE = 4:1).

^{1}H NMR (300 MHz, DMSO-d_6): 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).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.1, 161.78 (dd, J = 12.5, 247.3 Hz), 158.49 (dd, J = 12.7, 248.6 Hz), 144.41, 139.12 (d, J = 2.2 Hz), 131.70, 130.15, 128.50 (dd, J = 5.2, 9.7 Hz), 127.68, 124.41 (d, J = 11.1 Hz), 115.03 (dd, J = 3.75, 13.4 Hz), 112.30 (dd, J = 3.25, 21.3 Hz), 104.56 (t, J = 26 Hz), 75.79, 50.74, 46.51, 43.48, 20.99.

^{19}F NMR (282 MHz, DMSO-d_6): δ = –110.56 (d, J = 7.7 Hz), –110.35 (d, J = 7.7 Hz).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{22}N_4O_4S$: 449.10896; found: 449.10778.

6-{[4-(Pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]methyl}-4-tosylmorpholin-2-one (8g)

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

Yield: 454 mg (55%); white solid; mp 225–226 °C; R_f = 0.37 (EtOAc/PE = 4:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.65–8.59 (m, 2 H), 8.05 (d, J = 7.6 Hz, 1 H), 7.91 (t, J = 7.2 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 2 H), 7.47 (d, J = 8.1 Hz, 2 H), 7.39–7.35 (m, 1 H), 5.06–5.00 (m, 1 H), 4.87–4.74 (m, 2 H), 4.02 (d, J = 17.1 Hz, 1 H), 3.79 (d, J = 17.1 Hz, 1 H), 3.75 (dd, J = 3.1, 12.5 Hz, 1 H), 3.11 (dd, J = 8.6, 12.5 Hz, 1 H), 2.39 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 175.38, 155.16, 148.33, 145.94, 141.92, 141.82, 137.66, 134.85, 132.63, 132.17, 128.94, 124.34, 88.25, 85.08, 55.78, 52.53, 26.13.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{20}N_5O_4S$: 414.12305; found: 414.12213.

6-[{4-[4-(Dimethylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}methyl]-4-tosylmorpholin-2-one (8h)

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

Yield: 609 mg (67%); white solid; mp 237–238 °C; R_f = 0.35 (EtOAc/PE = 4:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.32 (s, 1 H), 7.70 (d, J = 8.2 Hz, 2 H), 7.64 (d, J = 8.7 Hz, 2 H), 7.46 (d, J = 8.2 Hz, 2 H), 6.78 (d, J = 8.7 Hz, 2 H), 5.05–4.97 (m, 1 H), 4.74 (dd, J = 3.8, 14.6 Hz, 1 H), 4.67 (dd, J = 7.3, 14.6 Hz), 4.04 (d, J = 17.1 Hz, 1 H), 3.77 (dd, J = 8.9, 12.6 Hz, 1 H), 3.75 (d, J = 17.1 Hz, 1 H), 3.06 (dd, J = 8.9, 12.6 Hz, 1 H), 2.93 (s, 6 H), 2.39 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.22, 150.09, 147.02, 144.44, 131.73, 130.2, 127.7, 126.1, 120.47, 118.4, 112.36, 75.81, 50.56, 46.47, 43.56, 21.04.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{26}N_5O_4S$: 456.17000; found: 456.16862.

6-[(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)methyl]-4-tosylmorpholin-2-one (8i)

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

Yield: 564 mg (75%); white solid; mp 177–178 °C; R_f = 0.35 (EtOAc/PE = 4:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.80 (s, 1 H), 7.70 (d, J = 8.2 Hz, 2 H), 7.48 (d, J = 8.2 Hz, 2 H), 4.95–4.88 (m, 1 H), 4.65 (dd, J = 3.9, 14.6 Hz, 1 H), 4.57 (dd, J = 7.5, 14.6 Hz, 1 H), 4.01 (d, J = 17.1 Hz, 1 H), 3.72 (d, J = 17.1 Hz, 1 H), 3.70 (dd, J = 3.2, 12.6 Hz, 1 H), 3.00 (dd, J = 8.8, 12.6 Hz, 1 H), 2.42 (s, 3 H), 1.98–1.88 (m, 1 H), 0.92–0.86 (m, 2 H), 0.72–0.67 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.16, 148.91, 144.45, 131.71, 130.2, 127.7, 121.78, 75.85, 69.69, 50.4, 46.45, 43.53, 21.06, 7.61, 6.44.

HRMS (ESI$^+$): m/z [M + H]$^+$ calcd for $C_{17}H_{21}N_4O_4S$: 377.12830; found: 377.12731.

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

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

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

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.95 (s, 1 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.66 (d, J = 8.2 Hz, 2 H), 7.48 (d, J = 8.1 Hz, 2 H), 7.37 (d, J = 8.1 Hz, 2 H), 4.93–4.87 (m, 1 H), 4.73–4.61 (m, 2 H), 4.37 (s, 2 H), 4.03 (d, J = 17.2 Hz, 1 H), 3.72 (dd, J = 2.9, 12.4 Hz, 1 H), 3.71 (d, J = 17.2 Hz, 1 H), 2.95–3.07 (m, 3 H), 2.42 (s, 3 H), 2.38 (s, 3 H), 1.40–1.30 (m, 2 H), 1.15–1.07 (m, 2 H), 0.74 (t, J = 7.27 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.98, 144.48, 143.08, 142.94, 136.29, 131.7, 130.21, 129.72, 127.68, 126.93, 124.89, 75.91, 50.54, 47.32, 46.84, 43.52, 42.33, 29.54, 21.04, 20.94, 19.05, 13.39.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{34}N_5O_6S_2$: 576.19450; found: 576.19292.

N-Allyl-4-methyl-*N*-{1-[(6-oxo-4-tosylmorpholin-2-yl)methyl]-1*H*-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; R_f = 0.35 (EtOAc/PE = 4:1).

^{1}H 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), 5.60 (ddt, J = 6.3, 10.2, 17.1 Hz, 1 H), 5.15 (dq, J = 1.5, 17.1 Hz, 1 H), 5.05 (dq, 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).

^{13}C 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 $C_{25}H_{30}N_5O_6S_2$: 560.16320; found: 560.16186.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610399.

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