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Synthesis and evaluation of novel heterocyclic MMP inhibitors

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Abstract—A variety of novel heterocyclic compounds were synthesized and evaluated for MMP inhibition. Broad spectrum inhibition of MMPs 1, 2, 9, and 12 was found with pyridinone-based compounds while *N*-heterocyclic triazoles and tetrazoles were largely ineffective. A highly selective tetrazole inhibitor for MMP-2 was discovered.

Extracellular proteolysis plays a key role in many biological processes. Angiogenesis, wound healing, inflammatory reactions, management of the blood–brain barrier, general maintenance of joints, organ development, ovulation, fetus implantation in the uterus, embryogenesis, and many others all depend on enzymes which remodel connective tissues in the extracellular matrix. A family of enzymes known as the matrix metalloproteinases (MMPs) are, at least in part, responsible for these functions. The important role of MMPs in extracellular degradation has been clearly demonstrated in many diseases including arthritis, multiple sclerosis, osteoporosis, Alzheimer's disease, cancer growth and metastasis, and periodontal disease.[1] For example, MMPs mediate extracellular matrix and basement-membrane degradation during the early stages of tumor growth particularly the gelatinases.[2] Abnormal levels of MMPs are observed for patients of these diseases and thus inhibition of MMPs offers a potential for new therapeutics. There are more than 24 known MMPs. The MMP family of enzymes is structurally related with a zinc-containing catalytic site. There are metalloproteinases that utilize a zinc (II) metal for catalysis of the proteolysis, and therefore, zinc binding groups (ZBGs) are crucial for designing MMP inhibitors (MMPIs). As a consequence, there has been a great deal of effort in recent years to design and prepare inhibitors of MMPs, mostly targeted at the prime side of the active site, which contains a hydrophobic S1′ pocket (Fig. 1a). Key to the activity of almost all MMPIs is the functional group that binds the zinc atom in the sctive site and the P1′ substituent.[3,4] To date, the only medically approved MMPI is a tetracycline derivative with μM range inhibitions used in the treatment of periodontal disease. In the last few decades, hydroxamate-based MMPIs have been mainly studied and fair amount of structure–activity data is available on these compounds. Many small molecule MMPIs with hydroxamic acid as a ZBG have shown outstanding inhibition in preclinical tests. Moreover, MMPIs with other ZBGS, such as thiols, carboxylates, mercaptoalcohols,[1e] and dithiols, have shown good inhibition in vitro.[5] However, clinical tests for these compounds have been disappointing. Some of the reasons for this include low oral availability, poor in vivo stability, pharmacokinetic problems,[6] and undesirable side effects associated with hydroxamates. Therefore, the discovery of new MMPIs with better properties and non-toxic ZBGs is critical. Recent reports demonstrate a continued optimism that MMPI therapy might be beneficial.[7–9] Thus, we have been focused on the development of MMPIs with non-hydroxamate ZBGs, better drug-like properties, and efficient and economical

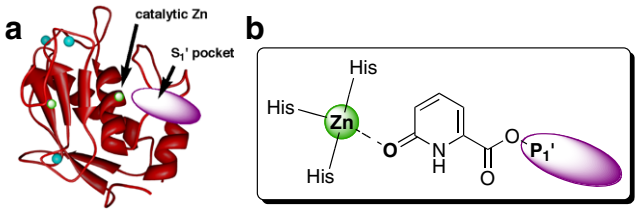

Fig. 1. (a) MMP-2 catalytic domain.[11] (b) Hypothetical binding of pyridinone-based MPIs.

Keywords: Matrix metalloproteinase inhibitors; Pyridinones; bis-Heterocycles.
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synthetic routes.[10] Herein, we disclose the synthesis of novel heterocyclic MMPIs and results of their biological examination.

Recently, Cohen reported the investigation of pyridinone-based ZBGs for MMP inhibition and these potentially have better drug-like properties for MMPIs.[11] Based partly on this work and work ongoing in our laboratories, we envisioned that a strongly basic pyridinone carbonyl oxygen might efficiently coordinate to the catalytic Zn(II) in the active site of MMPs and the ester substituent could play the role of a hydrophobic P_1'.

In order to provide proof of principle for our proposed pyridinone ester-based MMPIs, we prepared a library of pyridinones containing different P_1' substituents. One of the important challenges of drug synthesis is how economical and simple the synthesis of the target molecule is. All of our novel pyridinone-ester MMPIs were prepared in one step from commercially available **1**. The results of the biological screening of pyridinone-ester structures for MMP antagonist activity are summarized in Table 1.

In general, most pyridinone-based MMPIs showed better inhibition for MMP-1 over MMP-2, MMP-9, or MMP-12. Alkyl R-groups (**3–1**, **3–2**, **3–5**) provided good inhibition (25–32 μM) for MMP-1. In the case of aromatic R-groups, simple benzyl R-group (**3–6**) inhibits MMP-1 (30 μM). Longer alkyl chains with aromatic R-group showed diminished inhibitions for MMP-1 (**3–7**, **3–13**, **3–14**, **3–30**). Electron-rich benzyl R-groups (**3–8**, **3–11**, **3–12**) were also found to be less effective. Interestingly, placing $-CF_3$ in either the *p*- or *m*-position (**3–9** and **3–10**) resulted in selective inhibition of MMP-1. These benzyl R-groups with electron-withdrawing substitutions showed better inhibition (28 and 24 μM) over electron-rich benzyl R-groups for MMP-1. Since **3–11** and **3–12** showed good inhibition towards MMP-1, fluorinated benzyl R-groups were tested. Fluorine substitution on the *o*-position (**3–15**) showed moderate inhibition for MMPs. Fluorine substitution on both *m*- (**3–16**) and *p*-positions (**3–17**) showed good inhibition for MMP-1 (28, 23 μM). We also tested other fluorinated compounds and in particular, **3–21** displayed the best inhibition toward MMP-1 among all of inhibitors tested (13 μM). Compound **3–23** also showed good inhibition towards MMP-1 (19 μM). In addition, we tested other halogen substituted aromatic rings. Chlorinated groups performed similar to fluorinated compounds with the *o*-substituted compound (**3–24**) less effective. Chlorine substitution on both *m*- (**3–25**) and *p*-positions (**3–25**) afforded good inhibition for MMP-1 (21, 26 μM). In contrast, the *o*-brominated benzyl group (**3–27**) showed increased inhibition over the *m*-substituted analog (**3–28**) for MMP-1 (19, 22 μM). Larger aromatic R-groups (**3–31**, **3–32**, **3–33**) resulted in diminished inhibition for MMPs. Notably, **3–34** showed good inhibition for MMP-1 (42 μM) and MMP-2 (33 μM). Additionally, heteroaromatic rings were also tested (**3–36**, **3–37**, **3–38**) and they showed moderate inhibitions for MMP-1.

Since sulfides are known to be good ZBGs for MMPs, pyridylthiol-based MMPIs[12] (**4**) were synthesized and tested (Table 2). Compared to pyridinone-based MMPIs, the pyridylthiols proved to be generally worse for inhibition of MMPs. The only exception was observed in **4–25** and **4–26**, which inihibited MMP-2 over MMP-1, MMP-9, or MMP-12.

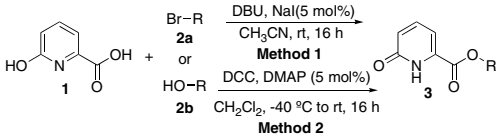
As histidine imidazoles serve as ligands for the catalytic zinc in the active site of MMPs, this heterocycle should be ideal for binding the catalytic Zn. We envisioned the readily accessible triazole to be similar. Oxazoline heterocycles are also well known as ligands for Lewis acids[13] and we have previously utilized them for MMP inhibition.[10] We hypothesized the combination of oxazoline and triazole would be useful for chelating to Zn(II). Thus, oxazolinyl triazole compounds were prepared (Scheme 1). Their synthesis started from trimethylsilyl propiolic acid (**5**). Peptide coupling with the aid of *N*-hydroxysuccinimide and DCC was followed by dehydration facilitated by methanesulfonyl chloride to form trimethylsilanylethynyl oxazoline (**8**). Removal of the silyl protecting group with tetrabutylammonium fluoride was followed by copper-catalyzed [3+2] cycloaddition[14] to afford the desired triazole (**12**). Results of the biological assay are presented in Table 3. To our disappointment, these compounds were largely ineffective for inhibition of all four MMPs tested. Only the cinnamyl derivative (**12–7**) showed any activity at all with modest inhibition of MMP-2 and slightly improved inhibition of MMP-12.

We also synthesized and tested tetrazole templates as well. Using [2+3] cycloaddition mediated by Zn(II), tetrazoles were prepared in high yields (Scheme 2). Since it has been shown that bidentate ligands have much better inhibitory potency than monodentate ligands, an additional potentially chelating heterocycle was incorporated into the design. We synthesized furanyl, thiophenyl, and pyridyl substituted tetrazoles (**15** and **18**). However, these compounds were completely ineffective. Interestingly, compound **18a**, which possesses a long flexible substituent, showed selective inhibition for MMP-2 (32 μM).

We next investigated MMPIs with potentially larger six-membered ring chelation as illustrated by **19a** (Scheme 3). Pyridylmethyl tetrazoles **21** were prepared from cyanomethyl pyridine (**19**) in a rapid two-step sequence of [3+2] cycloaddition followed by alkylation. The biological assay results are summarized in Table 4. Unfortunately compounds **21–1** through **4** showed no inhibition of MMPs. Interestingly the unsubstituted pyridylmethyl tetrazole **20** afforded complete selectivity for MMP-2 with a good level of inhibition.

In conclusion, we have prepared and evaluated novel heterocyclic MMPIs with good levels of inhibitory activity with non-hydroxamate ZBGs. Pyridinone esters afforded broad spectrum low micro molar inhibition of MMPs 1, 2, 9, and 12. These compounds are advantageous as they are small and readily accessible in one synthetic step from commercially available materials. We have also synthesized and tested a variety of chelating bis-heterocycles

Table 1. Inhibition of MMPs with pyridinone-based inhibitors



Entry	Product	R	% Yield	IC_{50}[a] (μM)			
				MMP-1	MMP-2	MMP-9	MMP-12
1	**3–1**	Isopropyl	64[b]	31	67	67	67
2	**3–2**	Cyclobutyl	76[b]	25	66	62	51
3	**3–3**	$CH_2CHC(CH_3)_2$	71	37	72	69	67
4	**3–4**	CH_2CCCH_3	56	50	70	68	71
5	**3–5**	Cyclohexyl	64[b]	32	101	94	71
6	**3–6**	Benzyl	76	30	65	69	69
7	**3–7**	$(CH_2)_2C_6H_5$	74[b]	47	69	81	68
8	**3–8**	4-Me-Benzyl	35	65	73	68	69
9	**3–9**	3-CF_3-Benzyl	73	28	na	na	82
10	**3–10**	3-CF_3-Benzyl	51	24	112	101	64
11	**3–11**	3-OMe-Benzyl	60	69	70	88	69
12	**3–12**	4-OMe-Benzyl	60	99	110	100	105
13	**3–13**	$(CH_2)_2OC_6H_4$	35[b]	59	na	127	79
14	**3–14**	$(CH_2)_4OC_6H_4$	65[b]	67	90	94	82
15	**3–15**	2-F-Benzyl	41	64	71	76	68
16	**3–16**	3-F-Benzyl	59	28	70	50	16
17	**3–17**	4-F-Benzyl	66	23	71	3	65
18	**3–18**	2,6-F-Benzyl	59	35	66	60	60
19	**3–19**	2,5-F-Benzyl	19	70	70	85	100
20	**3–20**	3,5-F-Benzyl	67	41	69	71	20
21	**3–21**	2,4,6-F-Benzyl	13	16	39	33	31
22	**3–22**	2,4,5-F-Benzyl	40[c]	30	86	67	56
23	**3–23**	$CH_2C_6F_5$	70	19	64	69	63
24	**3–24**	2-Cl-Benzyl	38	51	69	81	68
25	**3–25**	3-Cl-Benzyl	47	25	5	67	46
26	**3–26**	4-Cl-Benzyl	46c	26	69	68	47
27	**3–27**	2-Br-Benzyl	47	19	57	59	44
28	**3–28**	3-Br-Benzyl	38	22	68	67	31
29	**3–29**	4-Br-Benzyl	40	81	107	114	105
30	**3–30**	Cinnamyl	71	86	90	73	70
31	**3–31**	1-Napthalyl	36	115	109	109	111
32	**3–32**	2-Napthalyl	42	75	125	103	97
33	**3–33**	Piperonyl	60[d]	128	107	114	105
34	**3–34**	3-Ph-Benzyl	50	42	33	na	99
35	**3–35**	3-OPh-Benzyl	78[d]	68	na	na	118
36	**3–36**	2-Thiophenyl	52[d]	56	73	70	65
37	**3–37**	3-Thiophenyl	65[d]	39	65	67	62
38	**3–38**	2-Furyl	62[d]	46	111	90	76
39	**3–39**	$(CH_2)_4CH_3$	49	50	103	66	68

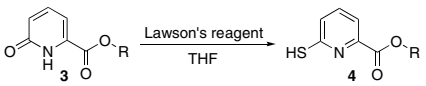
[a] na, not active (IC_{50} > 150 nM).
[b] Method 1 under 70 °C.
[c] Alkyl-Cl was used.
[d] Method 2.

possessing triazole and tetrazole functionality with some displaying highly selective MMP inhibition.

General experimental procedure.[15] Thin layer chromatography (TLC) was performed on silica gel Whatman-60F glass plates, and components were visualized by illumination with UV light or by staining with potassium permanganate solution. Chromatography was performed using silica E. Merck silica gel 60 (230–400 mesh). NMR spectra were recorded in $CDCl_3$ on a Varian Inova 500 MHz, 400 MHz, or Varian Mercury 300 MHz spectrometer. ^{13}C NMR was recorded using broad band proton decoupling. Chemical shifts are reported in relative to TMS and coupling constants in Hz. Melting points were determined without correction. Reactions were carried out under an inert atmosphere of nitrogen or argon. Solvents were dried using a nitrogen pressurized alumina column system from Solvtek.

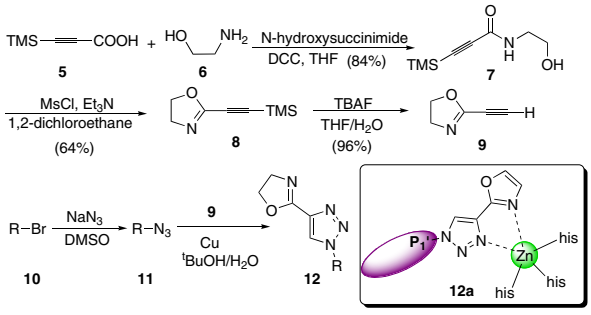
General procedure of biological assay. The compounds were tested for inhibition on MMP-1, MMP-2, MMP-9, and MMP-12[16] by using the fluorogenic MMP substrate 7-(methoxycoumarin-4-yl)acetyl-Pro-Leu-Gly-Leu(*N*-3-[2,4-dinitrophenyl]-L-2,3-diamino-propio-

Table 2. Inhibition of MMP's with pyridithiol-based inhibitors



Entry	Product	R	% Yield	IC_{50}[a] (μM)			
				MMP-1	MMP-2	MMP-9	MMP-12
1	**4–1**	Isopropyl	50	121	na	132	146
2	**4–2**	Cyclobutyl	60	135	na	137	na
3	**4–3**	Cyclohexyl	52	102	73	91	87
4	**4–4**	Benzyl	56	101	85	88	82
5	**4–5**	$(CH_2)_2C_6H_5$	47	120	119	107	117
6	**4–6**	$(CH_2)_3C_6H_5$	60	95	100	112	85
7	**4–7**	3-Me-Benzyl	32	na	7	7	70
8	**4–8**	4-Me-Benzyl	43	na	98	119	81
9	**4–9**	3-CF_3-Benzyl	11	134	110	126	134
10	**4–10**	4-CF_3-Benzyl	46	na	125	141	94
11	**4–11**	3-OMe-Benzyl	30	86	90	93	78
12	**4–12**	4-OMe-Benzyl	30	108	91	95	96
13	**4–13**	$(CH_2)_4OC_6H_5$	33	138	63	83	78
14	**4–14**	3-F-Benzyl	20	119	124	107	151
15	**4–15**	4-F-Benzyl	58	120	108	120	112
16	**4–16**	2,6-F-Benzyl	32	92	66	101	127
17	**4–17**	2,5-F-Benzyl	30	114	79	140	17
18	**4–18**	2,4,5-F-Benzyl	27	124	90	105	106
19	**4–19**	$CH_2C_6F_6$	20	78	70	100	81
20	**4–20**	4-Cl-Benzyl	16	126	96	112	115
21	**4–21**	2-Br-Benzyl	10	na	108	na	na
22	**4–22**	1-Napthalyl	51	na	98	na	na
23	**4–23**	2-Napthalyl	59	99	100	119	101
24	**4–24**	4-Ph-Benzyl	65	119	110	150	135
25	**4–25**	3-Ph-Benzyl	30	75	42	50	52
26	**4–26**	3-OPh-Benzyl	45	78	46	75	71
27	**4–27**	4-OPh-Benzyl	44	114	93	110	109
28	**4–28**	3-Thiophenyl	35	108	77	90	93
29	**4–29**	$(CH)_5CH_3$	60	115	85	109	105

[a] na, not active (IC_{50} > 150 μM).



Scheme 1. Synthesis of oxazolinyl triazoles and their hypothetical binding to MMPs (**12a**).

nyl)-Ala-Arg-NH_2 (Biomol International, Plymouth Meeting, PA), in wellplate experiments with the catalytic domains (Biomol International, Plymouth Meeting, PA) in 384-well format. The catalytic domains of MMPs (MMP-1, final concentration 85 nM; MMP-2, final concentration 24 nM; MMP-9, final concentration 18 nM; MMP-12, final concentration, 84 nM) and various concentrations (150 μM to 1.2 μM using 1:2 dilutions) of the test compounds were pre-mixed and incubated at 37 °C for 30 min prior to start of experiment. To the mixture of MMP and the test compound was added the substrate (final concentration 7 μM) in Hepes buffer (50 mM, 5 mM $CaCl_2$, 0.05% w/w Brij-35 at pH 7.5) and incubated for 30 min. After incubation fluorescence intensity measurements were taken by a Molecular Devices Gemini EM microplate reader (Sunnyvale, CA), excitation at 328 nm was used, and the time course of emission at 393 nm was monitored for 45 min at 50-s intervals.

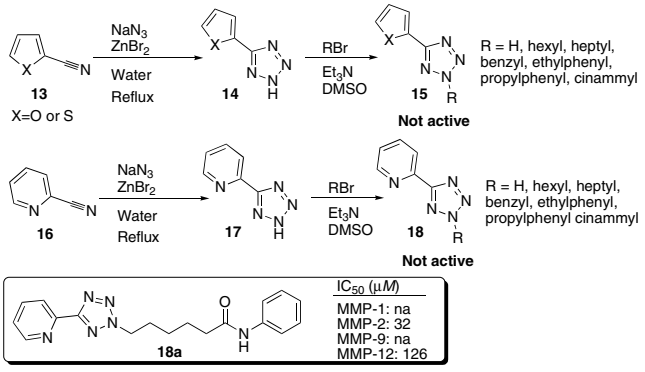
General procedure for synthesis of pyridinone-based MMPIs.

Method 1. DBU (2.4 mmol) was added to a solution of 2-hydroxy-6-picolinic acid (2.0 mmol) and bromide (2.2 mmol) in CH_3CN (10 mL). The mixture was stirred overnight at the appropriate temperature. When the reaction mixture was completed (monitored by TLC) the mixture was quenched by addition of water (20 mL) and extracted with CH_2Cl_2 (2× 20 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent and purification by flash silica gel chromatography (Hexane–EtOAc 3:7) afforded the desired pyridinones.

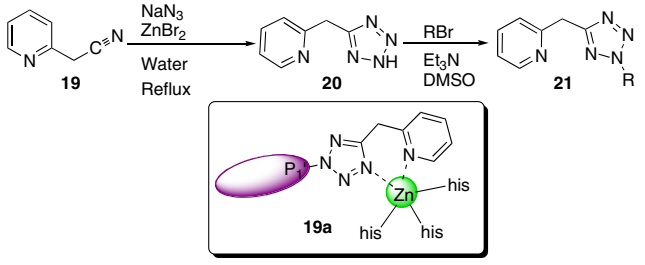
Table 3. Inhibition of MMPs with oxazolinyl triazoles based inhibitors

Entry	Product	R	% Yield	IC_{50}[a] (μ/M)			
				MMP-1	MMP-2	MMP-9	MMP-12
1	**12–1**	cyclohexene	42	na	na	na	na
2	**12–2**	hexyl	34	na	na	na	na
3	**12–3**	heptyl	35	na	na	na	na
4	**12–4**	benzyl	48	na	na	na	na
5	**12–5**	$(CH_2)_2C_6H_5$	41	na	na	na	na
6	**12–6**	$(CH_2)_3C_6H_5$	33	na	na	na	na
7	**12–7**	cinnamyl	42	na	**149**	na	**61**

[a] na, not active (IC_{50} > 150 μM).



Scheme 2. Synthesis of furanyl-, thiophenyl-, and pyridyl-substituted tetrazoles.



Scheme 3. Synthesis of pyridylmethyl tetrazoles and its hypothetical binding to MMPs (**19a**).

Method 2. Alcohol (2.0 mmol) was added to the solution of 2-hydroxy-6-picolinic acid (2.0 mmol), DCC (2.0 mmol), and DMAP (0.2 mmol) in CH_2Cl_2 (10 mL) at −40 °C. The mixture was allowed to warm to room temperature and stirred overnight. When the reaction was completed (monitored by TLC) the mixture was quenched by addition of water (20 mL) and extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent and purification by flash silica gel chromatography (Hexane–EtOAc 3:7) afforded the desired pyridinones.

General procedure for synthesis of thiopyridine-based MMPIs. A mixture of **3** (1.0 mmol) and Lawson's reagent (0.6 mmol) was stirred at room temperature in THF (5 mL) overnight. Upon completion of reaction, the mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent and purification by flash silica gel chromatography (Hexane–EtOAc 8:2) afforded the desired thiopyridines.

General for the synthesis of triazoles. Alkyne (10.0 mmol) was added dropwise to the solution of organic azide (10.0 mmol) in *t*-BuOH/H_2O (3:1, 15 mL). Copper metal was added and the mixture was stirred overnight at 40 °C. Once the reaction was complete, it was quenched with water (30 mL), extracted with EtOAc (2×30 mL) and dried over Na_2SO_4. Removal of the solvent and purification by flash silica gel chromatography (Hexane–EtOAc 1:1) afforded the desired triazoles.

Synthesis of compound **7**. To a solution of 3-(trimethylsilyl) propynoic acid (5.0 mmol) in 25 mL of THF, *N*-hydrosuccinimide (6.0 mmol and DCC (6.0 mmol) were added sequentially. After 2.5 h of stirring at room temperature, hydroxylamine (5.0 mmol) was added via a syringe. Stirring was maintained for additional 10 h until completion of the reaction. The precipitation was filtered, and the filtrate was evaporated at reduced pressure. The residue was taken up in EtOAc and was washed with saturated NaCl solution. The aqueous phase was extracted with EtOAc twice, the combined organic extracts were dried over Na_2SO_4 and the solvent

Table 4. Inhibition of MMPs with pyridylmethyl tetrazoles

Entry	Product	**R**	% Yield	IC_{50}[a] (μM)			
				MMP-1	MMP-2	MMP-9	MMP-12
1	**20**	H	86	na	**48**	na	na
2	**21–1**	Benzyl	48	na	na	na	na
3	**21–2**	$(CH_2)_2C_6H_5$	35	na	na	na	na
4	**21–3**	$(CH_2)_3C_6H_5$	38	na	na	na	na
5	**21–4**	Cinnamyl	12	na	na	na	na

[a] na, not active (IC_{50} > 150 μM).

removed under reduced pressure. Flash silica gel chromatography afforded the product as white solid.

Synthesis of compound **8**. To a stirred solution of the ynamide **7** (3.5 mmol), triethylamine (17.3 mmol) and DMAP (0.10 mmol) in 1,2-dichloroethane (20 mL) was added methanesulfonyl chloride (5.2 mmol). The resulting mixture was heated to reflux until the disappearance of the starting amide was noted. After cooling, the solvent and the excess triethylamine were evaporated at reduce pressure. The residue was purified by flash silica gel chromatography with hexane/ethyl acetate as eluent.

Synthesis of compound **9**. To a stirred solution of **8** (2.05 mmol) in 5 ml of THF was added sequentially a solution of tetrabutylammonium fluoride in THF (0.05 mmol) and 0.05-ml distilled water were added. After 30 min, the reaction mixture was diluted with 20 mL of dichloromethane and washed with 20 mL of a saturated NaCl solution. The aqueous phase, after separation, was washed with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and the residue was purified by flash silica gel chromatography.

General procedure for tetrazoles synthesis. A mixture of nitrile (5.0 mmol), sodium azide (5.5 mmol), zinc bromide (5.0 mmol), and water was refluxed overnight with vigorous stirring. HCl (9.0 mL, 3N) and ethyl acetate (25 mL) were added and the mixture was stirred until no solid was present and the aqueous layer had a pH of 1. The organic layer was separated and the aqueous layer extracted with 2×25 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. 50 mL of 0.25N NaOH was added and the mixture was stirred for 30 min until the original precipitate was dissolved and a suspension of zinc hydroxide was formed. The suspension was filtered and the solid washed with 5 mL of 1N NaOH. To the filtrate was added 10 mL of 3N HCl with vigorous stirring until pH of 3. The precipitate was filtered, collected, and dried in the oven.

General procedure for alkyl substitution[17] A solution of tetrazole (0.71 mmol) in DMSO was added dropwise into a suspension of NaH (0.71 mmol) in THF (10 mL) under nitrogen at room temperature. After 15 min alkyl bromide (1.06 mmol) was added via a syringe. After 5 h, the reaction mixture was quenched with water and extracted by ethyl acetate twice. The organic phase was washed by water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The product was isolated purified by flash silica gel chromatography.

Acknowledgments

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References and notes

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