Electronic Supplementary Material (ESI) for MedChemComm.

Supplementary Information

Design and characterization of a heterocyclic electrophilic fragment library for the discovery of cysteine targeted covalent inhibitors

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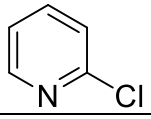
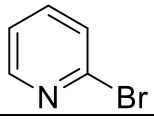
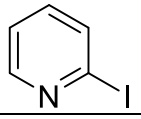
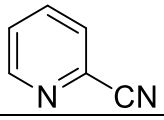
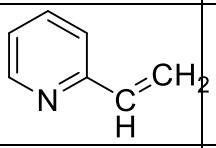
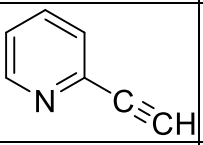
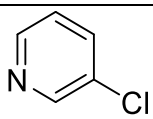
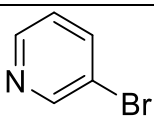
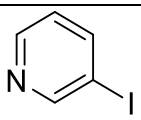
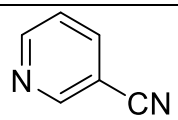
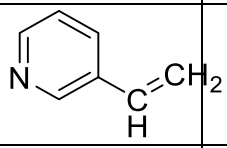
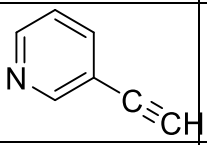
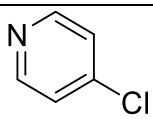
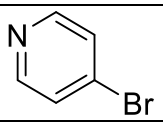
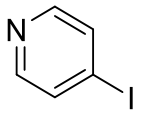
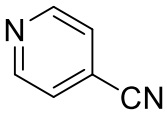
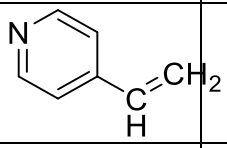
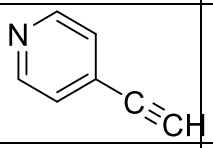
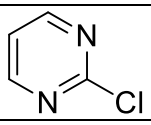
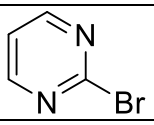
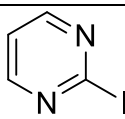
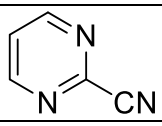
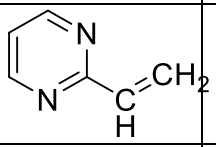
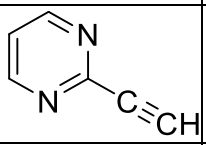
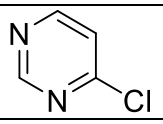
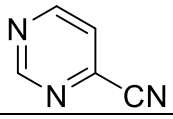
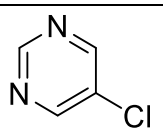
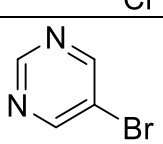
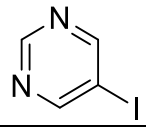
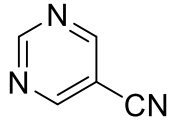
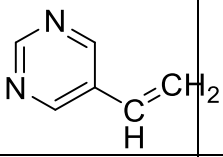
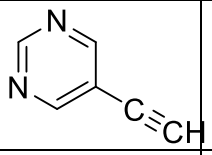
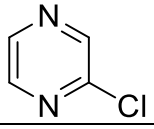
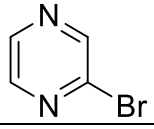
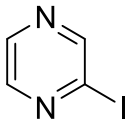
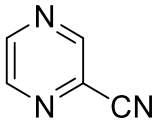
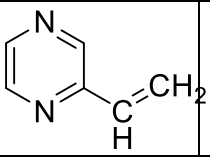
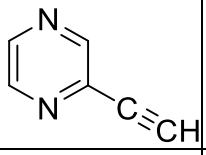
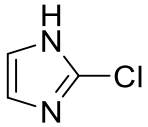
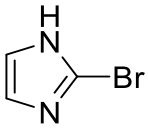
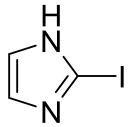
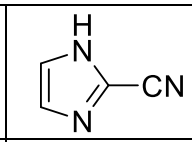
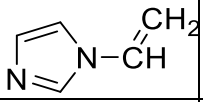
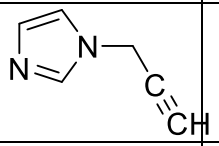
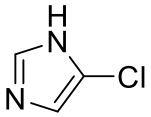
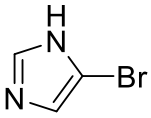
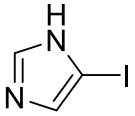
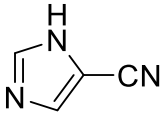
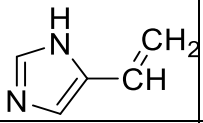
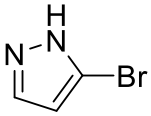
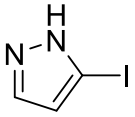
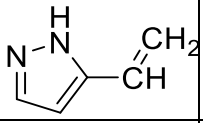
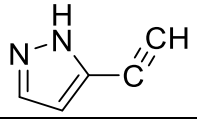
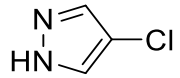
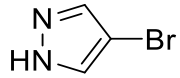
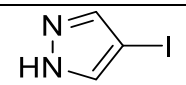
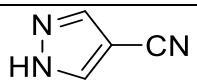
Table S1 Members of the heterocyclic library with the results of the reactivity and stability assay

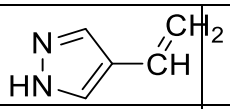
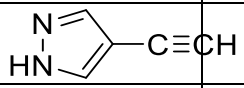
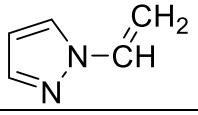
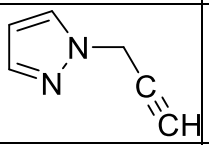
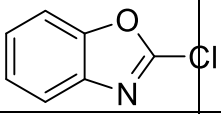
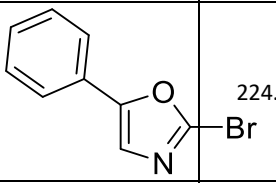
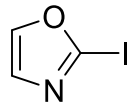
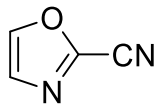
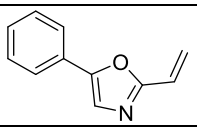
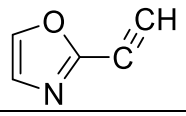
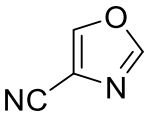
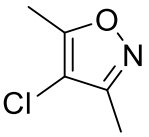
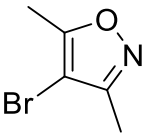
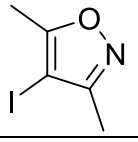
N. A. not available data from the NMR measurements. n.d. not determined (a, in HPLC assay: $k_{GSH+deg} \leq k_{deg}$, b, in NMR assay: $t_{1/2(GSH)} > 72$ h)

ID	Structure	MW	$k_{GSH+deg}$	$t_{1/2(GSH+deg)}$ [h]	k_{deg}	$t_{1/2(deg)}$ [h]	k_{GSH}	$t_{1/2(GSH)}$ [h]
A1		113.54	0.0237	29.4	0.0137	55.7	0.0100	69.4
A2		157.998	0.0228	30.4	0.0128	54.7	0.0100	69.2
A3		204.998	0.0153	45.6	0.0083	84.5	0.0070	98.7
A4		104.112	0.0013	544.3	0.0008	833.2	0.0005	1386.3
A5		105.14	0.7033	1.0	0.0146	47.8	0.6887	1.0
A6		103.124	0.0116	60.6	0.0025	280.1	0.0091	76.4
B1		113.54	0.0222	31.3	0.0253	27.4	-	n.d.
B2		157.998	0.0173	40.1	0.0152	45.7	0.0021	330.1
B3		204.998	0.0144	48.2	0.0151	47.5	-	n.d.
B4		104.112	0.0176	47.8	0.0007	973.7	0.0169	41.0
B5		105.14	N. A.	N. A.	N. A.	N. A.	n.d.	>72
B6		103.124	0.0178	39.2	0.0137	50.7	0.0041	169.5
C1		113.54	0.0189	36.8	0.0165	42.2	0.0024	290.7

C2		157.998	0.0130	53.2	0.0090	76.6	0.0040	174.3
C3		204.998	0.0214	32.4	0.0114	61.2	0.0100	69.0
C4		104.112	0.8892	0.8	0.0056	146.1	0.8837	0.8
C5		105.14	2.4172	0.3	0.0022	367.4	2.4150	0.3
C6		103.124	0.3021	2.3	0.0121	57.3	0.2900	2.4
D1		114.53	0.0013	551.0	0.0017	438.6	-	n.d.
D2		158.986	0.0013	721.9	0.0008	963.1	0.0005	1376.9
D3		205.986	0.0007	1080.3	0.0007	1006.9	-	n.d.
D4		105.1	0.3138	2.2	0.0002	5842.7	0.3136	2.2
D5		106.128	0.0041	167.6	0.0018	392.1	0.0023	292.7
D6		104.112	0.0156	44.9	0.0008	1023.5	0.0148	46.8
E1		114.53	0.0039	177.5	0.0022	318.6	0.0017	400.7
E4		105.1	0.0163	42.7	0.0015	460.4	0.0147	47.1
F1		114.53	0.0126	65.6	0.0056	126.1	0.0070	98.8
F2		158.986	0.0080	90.0	0.0047	149.3	0.0033	209.3

F3		205.986	0.0030	235.3	0.0031	235.9	0.0001	n.d.
F4		105.1	0.0013	546.0	0.0009	787.2	0.0004	1732.9
F5		106.128	0.0028	244.0	0.0011	668.3	0.0017	407.7
F6		104.112	0.0065	107.3	0.0055	125.8	0.0010	693.1
G1		114.53	0.0108	64.3	0.0090	77.1	0.0018	387.1
G2		158.986	0.0070	99.6	0.0087	84.9	-	n.d.
G3		205.986	0.0070	98.7	0.0072	96.4	-	n.d.
G4		105.1	0.0314	22.1	0.0006	1209.0	0.0308	22.5
G5		106.128	0.0425	16.9	0.0014	631.8	0.0410	16.9
G6		104.112	0.0040	171.5	0.0002	2934.3	0.0038	182.4
H1		102.52	N. A.	N. A.	N. A.	N. A.	n.d.	>72
H2		146.98	0.0048	145.7	0.0047	149.9	-	6931.5
H3		193.98	N. A.	N. A.	N. A.	N. A.	0.116	6.0

H4		93.09	0.0162	42.8	0.0029	235.5	0.0132	52.3
I5		94.12	N. A.	N. A.	N. A.	N. A.	n.d.	>72
I6		106.13	N. A.	N. A.	N. A.	N. A.	0.0144	48.0
J1		102.52	N. A.	N. A.	N. A.	N. A.	n.d.	>72
J2		146.98	N. A.	N. A.	N. A.	N. A.	n.d.	>72
J3		193.98	N. A.	N. A.	N. A.	N. A.	n.d.	>72
J4		93.09	N. A.	N. A.	N. A.	N. A.	n.d.	>72
J5		94.12	N. A.	N. A.	N. A.	N. A.	n.d.	>72
K2		146.98	N. A.	N. A.	N. A.	N. A.	n.d.	>72
K3		193.98	N. A.	N. A.	N. A.	N. A.	n.d.	>72
K5		94.12	0.0067	105.8	0.0001	6562.5	0.0067	104.0
K6		92.10	0.1511	4.6	0.0099	70.2	0.1412	4.9
L1		102.52	N. A.	N. A.	N. A.	N. A.	n.d.	>72
L2		146.98	N. A.	N. A.	N. A.	N. A.	n.d.	>72
L3		193.98	N. A.	N. A.	N. A.	N. A.	n.d.	>72
L4		93.09	N. A.	N. A.	N. A.	N. A.	n.d.	>72

L5		94.12	0.0030	264.7	0.0003	2643.5	0.0027	256.7
L6		92.10	0.4142	1.7	0.0099	70.2	0.4044	1.7
M5		94.12	0.0084	82.1	0.0093	74.5	-	-
M6		92.13	N. A.	N. A.	N. A.	N. A.	n.d.	>72
N1		153.57	0.1890	3.8	0.0357	19.4	0.1533	4.5
N2		224.06	0.0120	57.8	0.0094	78.1	0.0026	266.6
N3		194.96	6.0689	0.1	0.0116	60.0	6.0573	0.1
N4		94.07	1.4709	0.5	0.0094	73.9	1.4615	0.5
N5		171.20	0.0209	33.4	0.0056	123.7	0.0153	45.2
N6		93.09	0.0227	30.5	0.0100	69.0	0.0127	54.6
O4		94.07	N. A.	N. A.	N. A.	N. A.	0.693	1.0
P1		131.56	N. A.	N. A.	N. A.	n.d.	n.d.	>72
P2		176.01	0.0015	447.4	0.0008	837.0	0.0007	990.2
P3		223.01	0.0163	42.7	0.0130	53.6	0.0033	207.3

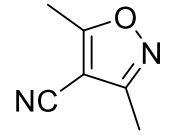
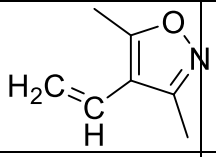
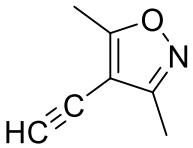
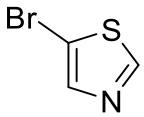
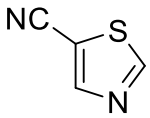
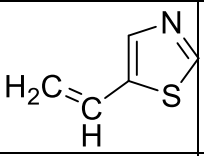
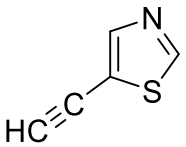
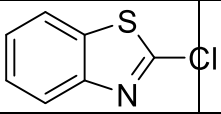
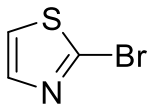
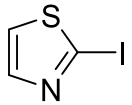
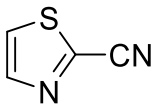
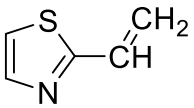
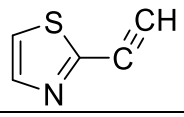
P4		122.13	0.0121	57.3	0.0040	177.6	0.0081	85.1
P5		123.16	0.0563	12.3	0.0479	14.5	0.0084	82.9
P6		121.14	0.1699	4.1	0.0415	16.7	0.1284	5.4
Q2		164.02	0.0322	22.1	0.0212	32.8	0.011	63.0
Q4		110.13	0.0054	127.9	0.0020	349.9	0.0034	201.5
Q5		111.16	0.0364	19.6	0.0208	33.4	0.0156	44.5
Q6		109.15	0.0333	24.1	0.0203	34.3	0.0130	53.1
R1		169.63	0.0505	13.7	0.0422	17.1	0.0083	83.5
R2		164.02	0.0153	45.4	0.0152	45.5	0	n.d.
R3		211.02	0.7999	0.9	0.0127	54.8	0.7872	0.9
R4		110.13	0.0923	7.5	0.0056	125.3	0.0868	8.0
R5		111.16	0.2729	2.7	0.0147	48.1	0.2583	2.7
R6		109.15	0.0119	58.1	0.0086	80.9	0.0034	205.4

Table S2 Calculated descriptors for the GSH-active members of the library

ID	ε_H (ht)	ε_L (ht)	$\rho_{e^-}^0$	$\rho_{e^-}^{-1}$	η	μ	$\rho(e^-)$	ω	$f^+(\vec{r})$	$\omega(\vec{r})$	$t_{1/2(GSH)}$ [h]	log $t_{1/2(GSH)}$	ΔH	ΔG	σ_{ind}
A1	-0.27	-0.05	0.20	0.18	5.92	-4.41	-0.20	1.65	0.02	0.04	69.40	1.84	85.56	133.08	0.25
A2	-0.27	-0.05	0.15	0.13	5.76	-4.36	-0.15	1.65	0.02	0.04	69.20	1.84			0.25
A3	-0.25	-0.05	0.07	0.06	5.46	-4.20	-0.07	1.62	0.01	0.01					
A4	-0.29	-0.08	0.28	0.28	5.76	-5.11	-0.28	2.26	0.00	-0.01					
A5	-0.24	-0.06	-0.31	-0.56	5.04	-4.12	0.31	1.68	0.25	0.42	1.00	0.00	69.54	112.37	0.25
A6	-0.26	-0.06	-0.17	-0.44	5.39	-4.33	0.17	1.74	0.27	0.47					
B1	-0.26	-0.07	-0.09	-0.10	5.25	-4.52	0.09	1.94	0.01	0.01					
B2	-0.27	-0.05	-0.14	-0.16	5.77	-4.38	0.14	1.66	0.02	0.03					
B3	-0.26	-0.05	-0.24	-0.31	5.55	-4.25	0.24	1.62	0.07	0.12					
B4	-0.30	-0.08	0.29	0.29	5.88	-5.10	-0.29	2.22	0.00	0.01	39.50	1.60			0.22
B5	-0.25	-0.06	-0.35	-0.61	5.26	-4.15	0.35	1.64	0.26	0.43					
B6	-0.25858	-0.06013	-0.177	-0.441	5.399963415	-4.336161099	0.177	1.740964857	0.264	0.459614722					
C1	-0.27869	-0.05242	-0.013	-0.21	6.156965089	-4.504867439	0.013	1.648038469	0.197	0.324663578					
C2	N.A.														

C3	-0.27	-0.05	-0.17	-0.25	5.81	-4.38	0.17	1.65	0.08	0.13	69.00	1.84		0.25
C4	-0.29	-0.09	0.28	0.28	5.49	-5.20	-0.28	2.47	0.00	0.00	0.80	-0.10		0.25
C5	-0.26	-0.07	-0.33	-0.59	5.22	-4.47	0.33	1.92	0.26	0.50	0.30	-0.52	56.88	99.73	0.25
C6	-0.27	-0.07	-0.17	-0.44	5.55	-4.63	0.17	1.93	0.27	0.52	2.40	0.38		0.25
D1	-0.28	-0.07	0.41	0.42	5.67	-4.81	-0.41	2.04	-0.01	-0.02				
D2	-0.28	-0.07	0.36	0.37	5.54	-4.77	-0.36	2.05	-0.02	-0.03				
D3	-0.26	-0.07	0.28	0.31	5.11	-4.54	-0.28	2.02	-0.04	-0.07				
D4	-0.30	-0.09	0.27	0.28	5.49	-5.29	-0.27	2.55	-0.01	-0.01	2.20	0.34		0.23
D5	-0.26	-0.07	-0.30	-0.55	5.25	-4.45	0.30	1.88	0.26	0.48				
D6	-0.27	-0.07	-0.14	-0.42	5.42	-4.63	0.14	1.98	0.28	0.55	46.10	1.66		0.23
E1	-0.29	-0.07	0.22	0.05	5.90	-4.80	-0.22	1.95	0.18	0.35				
E2	N.A.													
E3														
E4	-0.30	-0.10	0.27	0.28	5.21	-5.46	-0.27	2.86	-0.01	-0.03	47.10	1.67		0.26
E5	N.A.													
E6														
F1	-0.28	-0.07	-0.12	-0.10	5.60	-4.77	0.12	2.04	-0.03	-0.05				
F2	-0.28	-0.07	-0.19	-0.15	5.59	-4.78	0.19	2.04	-0.04	-0.07				

F3	-0.27	-0.07	-0.29	-0.24	5.43	-4.66	0.29	2.00	-0.05	-0.10					
F4	-0.29	-0.09	0.28	0.28	5.40	-5.27	-0.28	2.57	0.00	0.00					
F5	-0.26	-0.07	-0.33	-0.59	5.15	-4.55	0.33	2.01	0.26	0.52					
F6	-0.27	-0.07	-0.16	-0.43	5.41	-4.66	0.16	2.00	0.27	0.55					
G1	-0.28	-0.08	0.16	0.16	5.48	-4.91	-0.16	2.19	0.01	0.01					
G2	-0.28	-0.08	0.11	0.07	5.40	-4.88	-0.11	2.21	0.04	0.08					
G3	-0.27	-0.08	0.02	0.00	5.07	-4.70	-0.02	2.18	0.02	0.04					
G4	-0.29	-0.10	0.27	0.29	5.15	-5.38	-0.27	2.82	-0.02	-0.06	22.10	1.34			0.25
G5	-0.26	-0.08	-0.31	-0.53	4.86	-4.55	0.31	2.13	0.23	0.48	16.70	1.22	50.90	92.53	0.25
G6	-0.27	-0.08	-0.15		5.16	-4.77	0.15	2.20	-0.15	-0.33					
H1	N.A.														
H2	-0.24	-0.02	0.27	0.25	5.97	-3.63	-0.27	1.10	0.02	0.02					
H3	-0.24	-0.05	0.17	0.11	5.21	-3.92	-0.17	1.48	0.07	0.10	6.00	0.78			0.27
H4	-0.27	-0.06	0.25	0.28	5.70	-4.42	-0.25	1.72	-0.03	-0.04	52.30	1.72			0.27
H5	N.A.														
H6	-0.24	-0.04	-0.16	-0.22	5.46	-3.69	0.16	1.25	0.06	0.08					
I1	N.A.														
I2															

I3														
I4														
I5														
I6	-0.24	-0.02	-0.20	-0.26	6.00	-3.53	0.20	1.04	0.06	0.07	48.00	1.68			0.51
J1	N.A.													
J2														
J3														
J4														
J5														
J6														
K1														
K2														
K3														
K4														
K5	-0.24	-0.05	-0.36	-0.62	5.11	-3.93	0.36	1.51	0.26	0.39	104.00	2.02			
K6	-0.25	-0.04	-0.16	-0.53	5.69	-3.94	0.16	1.37	0.37	0.50	4.90	0.69			0.13
L1	N.A.													
L2														
L3														
L4														
L5	-0.23	-0.03	-0.37	-0.41	5.56	-3.49	0.37	1.10	0.04	0.05					
L6	-0.24	-0.02	-0.20	-0.26	6.04	-3.60	0.20	1.07	0.07	0.07	1.70	0.23			0.16
M1	N.A.													
M2														
M3														

M4															
M5	-0.26	-0.03	-0.33	-0.36	6.14	-3.88	0.33	1.22	0.02	0.03					
M6	N.A.														
N1	-0.26	-0.05	0.49	0.35	5.58	-4.15	-0.49	1.54	0.14	0.22	4.50	0.65	59.81	102.06	0.28
N2	-0.23	-0.06	0.42	0.33	4.69	-4.02	-0.42	1.72	0.09	0.15					
N3	N.A.														
N4	-0.29	-0.08	0.24	0.20	5.62	-5.06	-0.24	2.28	0.04	0.08	0.50	-0.30			0.28
N5	-0.24	-0.06	-0.32	-0.64	5.00	-4.10	0.32	1.68	0.32	0.53	45.20	1.66	54.39	94.28	0.28
N6	-0.26	-0.06	-0.12	-0.46	5.39	-4.25	0.12	1.68	0.34	0.56	54.60	1.74			0.28
O1	N.A.														
O2															
O3															
O4	-0.29	-0.06	0.27	0.28	6.18	-4.84	-0.27	1.89	-0.01	-0.01	1.00	0.00			0.31
O5	N.A.														
O6															
P1	-0.26	-0.03	-0.19	-0.19	6.22	-3.91	0.19	1.23	0.00	0.00					
P2	-0.26	-0.03	-0.26	-0.27	6.16	-3.89	0.26	1.23	0.02	0.02					
P3	-0.25	-0.05	-0.36		5.55	-4.05	0.36	1.47	-0.36	-0.53					
P4	-0.28	-0.06	0.29	0.28	6.20	-4.60	-0.29	1.71	0.00	0.01					
P5	-0.24	-0.03	-0.37	-0.38	5.52	-3.70	0.37	1.24	0.02	0.02					

P6	-0.25	-0.04	-0.19	-0.24	5.81	-3.86	0.19	1.28	0.04	0.06	5.40	0.73			0.22
Q1	N.A.														
Q2	-0.26	-0.05	-0.39	-0.52	5.58	-4.26	0.39	1.62	0.14	0.22	63.00	1.80			0.23
Q3	N.A.														
Q4	-0.29	-0.09	0.26	0.27	5.38	-5.11	-0.26	2.43	-0.01	-0.02					
Q5	-0.24	-0.07	-0.35	-0.61	4.76	-4.19	0.35	1.84	0.26	0.47	44.50	1.65	70.63	107.92	0.23
Q6	-0.25	-0.07	-0.16	-0.42	5.05	-4.33	0.16	1.85	0.26	0.49	53.10	1.73			0.23
R1	-0.26	-0.06	0.02	-0.13	5.40	-4.25	-0.02	1.67	0.15	0.25					
R2	-0.26	-0.05	-0.09	-0.26	5.64	-4.24	0.09	1.59	0.17	0.27					
R3	-0.25	-0.06	-0.18		5.26	-4.28	0.18	1.74	-0.18	-0.32	0.90	-0.05			0.34
R4	-0.28	-0.09	0.25	0.26	5.20	-5.12	-0.25	2.52	-0.01	-0.01	8.00	0.90			0.34
R5	-0.24	-0.07	-0.33	-0.59	4.67	-4.21	0.33	1.89	0.26	0.49	2.70	0.43	52.07	91.29	0.34
R6	-0.25	-0.07	-0.14	-0.42	4.97	-4.36	0.14	1.91	0.28	0.54					

Experimental section

Instruments

^{1}H NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ solution at room temperature, on a Varian Unity Inova 500 spectrometer (500 MHz for ^{1}H NMR spectra), with the deuterium signal of the solvent as the lock and TMS as the internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and Hz, respectively.

HPLC-MS measurements were performed using a Shimadzu LCMS-2020 device equipped with a Reprospher 100 C18 (5 µm; 100x3mm) column and positive-negative double ion source (DUIS) with a quadrupole MS analysator in a range of 50-1000 m/z. Sample was eluted with gradient elution using eluent A (0.1% formic acid in water:acetonitrile 19:1) and eluent B (0.1% formic acid in water:acetonitrile 1:4). Flow rate was set to 1.5 ml/min. The initial condition was 0% B eluent, followed by a linear gradient to 100% B eluent by 1 min, from 1 to 3.5 min 100% B eluent was retained; and from 3.5 to 4.5 min back to initial condition with 5% B eluent and retained to 5 min. The column temperature was kept at room temperature and the injection volume was 10 µl. Purity of compounds was assessed by HPLC with UV detection at 215 nm; all tested compounds were >95% pure.

Computational methods

In all quantum chemical calculations, the B3LYP/6-311++g(2d,2p) method and basis set was used under the Gaussian09 program package. The calculations were performed at 298 K and 1 bar. No solvent model was used. All the geometries were optimized and frequency calculations were made to assure that the structures are in a local minimum.

GSH-assay based on HPLC

For glutathione assay 500 µM solution of the fragment (PBS buffer pH 7.4, 10 % acetonitrile, 250 µL) with 200 µM solution of indoprofen as internal standard was added to 10 mM glutathione solution (dissolved in PBS buffer, 250 µL) in 1:1 ratio. The final contentration was 250 µM fragment, 100 µM indoprofen, 5 mM glutathione and 5 % acetonitrile (500 µL). The final mixture was analyzed by HPLC-MS after 0, 1, 2, 4, 8, 12, 24, 48, 72 h time intervals. In the case of fragments that were not detectable in a concentration of 250 µM, the final concentrations were reversed, as 5 mM for the fragment and 250 µM for GSH. Degradation kinetic was also investigated respectively using the previously described method, applying pure PBS buffer instead of the glutathione solution. In this experiment the final concentration of the mixture was 250 µM fragment, 100 µM indoprofen and 5 % acetonitrile. The AUC (area under the curve) values were determined via integration of HPLC spectra then corrected with internal standard. The fragments AUC values were applied for ordinary least squares (OLS) linear regression and for computing the important parameters (kinetic rate constant, half-life time) a programmed excel (Visual Basic for Applications) was utilized. The data are expressed as means of duplicate determinations, and the standard deviations were within 10% of the given values.

The calculation of the kinetic rate constant for the degradation and corrected GSH-reactivity is the following. Reaction half-life for pseudo-first order reactions is $t_{1/2}$=ln2/k, where k is the reaction rate. In the case of competing reactions (reaction with GSH and degradation), the effective rate for the consumption of the starting compound is $k_{eff} = k_{deg} + k_{GSH}$. When measuring half-lives experimentally, the $t_{1/2(eff)} = \ln2/k_{eff} = \ln2/(k_{deg} + k_{GSH})$. In our case, the corrected k_{deg} and k_{eff} (regarding to blank and GSH containing samples, respectively) can be calculated by linear regression of the datapoints of the kinetic measurements. The corrected k_{GSH} is calculated by k_{eff}-k_{deg}, and finally half-life time is determined using the equation $t_{1/2(GSH)} = \ln2/k_{GSH}$.

GSH-assay based on NMR

For glutathione assay, the fragment stock was initially prepared as a 400 mM solution in dimethyl sulfoxide DMSO-d6. Then a 4.0 mM electrophile standard solution was prepared by taking a 20 µL aliquot of the concentrated stock solution and diluting it 100 fold into a 100 mM potassium phosphate buffer solution pH = 7.4 (8/2, H_2O/D_2O). 0.5mL of this electrophile standard solution was added to NMR tube and these NMR's where considered as the 0 h or reference peaks for the kinetic study. For the reaction measurements a 20 mM GSH solution was prepared in 100 mM phosphate buffer solution. The final concentration 0.5mL of the electrophile standard solution was added to 0.5mL of the 20 mM GSH solution. The sample vile was shaken vigorously and transferred to an NMR tube. The final mixture was analyzed by ^{1}H NMR (D_2O, 500 MHz). after 0, 1, 2, 4, 8, 12, 24, 48, 72 h time intervals. The AUC (area under the curve) values were determined via integration of NMR spectra. The fragments AUC values were applied for ordinary least squares (OLS) linear regression and for computing the important parameters (kinetic rate constant, half-life time) a programmed excel (Visual Basic for Applications) was utilized.

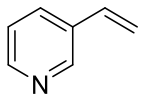
General synthetic procedures

Air sensitive reactions were performed in anhydrous solvents that were purged by dry argon gas. Glassware was either dried in the oven or flame dried before use, assembled hot and cooled to room temperature under a stream of nitrogen. All reactions were monitored using TLC (and/or LCMS spectroscopy) to ensure reactions had gone to completion. Anhydrous dimethylformamide, toluene , dichloromethane and acetonitrile were purchased from Sigma Aldrich. Reagents and fragments from commercial sources (Sigma Aldrich, Combi Blocks, Fluorochem) were used without further purification. Thin layer chromatography (TLC) was carried out on Merck silica gel aluminium sheets (60 F_{254}). UV light and a mixture of 1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10 % NaOH in 200 mL water were used as a visualising stain. Merck silica gel (60, 0.040-0.063) was used for the flash column chromatography. The microwave reactions were conducted in an Anton Paar Monowave 300 microwave reactor.

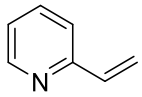
Purchased fragments: **A1**-**A4**, **B1**-**B4**, **C1**-**C4**, **D1**-**D4**, **E1** and **E4**, **F1**-**F4**, **G1**-**G4**, **H1**-**H4**, **I5**, **J1**-**J4**, **K2**, **K3**, and **K6**, **L1**-**L4**, and **L6**, **M5**, **N1**, **N2** and **N4**, **O4**, **P1**-**P4**, **Q2** and **Q4**, **R1**, **R2** and **R4**.

General procedure for the vinylation reactions

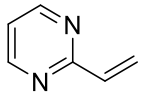
Compounds **A5**, **B5**, **D5**, and **P5** where synthesized using the following procedure



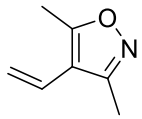
Example **B5**; A solution of potassium vinyltrifluoroborate (1 g, 7.59 mmol, 1.2 eq), palladium(II) acetate (56.8 mg, 0.25 mmol), triphenylphosphine (132.8 mg, 0.506 mmol), potassium carbonate (2.6 g, 18.9 mmol), and 3-bromopyridine (610 µL, 6.33 mmol, 1 eq) in DMF (20 mL) was heated at 110 ^{0}C in a microwave reactor for 80 minutes or in a sealed screw cap reaction vial and oil bath for 18 h. The reaction mixture was cooled to room temperature, diluted with water (30 mL), and extracted with ethyl acetate (4x15 mL). The combined organic extracts were washed with brine, then dried over $MgSO_4$, filtered, concentrated, and the crude material was purified by flash chromatography (silica gel, 5-100 percent DCM in hexanes) to afford the title compound **B5**,[S1] 600 µL 90%: ^{1}H NMR ($CDCl_3$, 500 MHz) δH (ppm) = 8.63 (br s, 1H), 7.64 (t, J= 7.56 Hz, 1H), 7.34 (d, J= 7.56 Hz, 1H), 7.15 (m, 1H), 6.82 (dd, J= 17.9, 11.0 Hz, 1H), 6.20 (d, J= 17.9 Hz, 1H), 5.48 (d, J= 11.0 Hz, 1H).



A5;[S2] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 8.57 (d, J= 4.3 Hz, 1H), 7.64 (td, J= 7.8, 1.6 Hz, 1H), 7.34 (d, J= 7.8 Hz, 1H), 7.17-7.12 (m, 1H), 6.82 (dd, J= 17.5, 10.8 Hz, 1H), 6.20 (d, J= 17.5 Hz, 1H), 5.48 (d, J= 10.8 Hz, 1H).

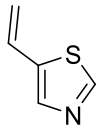


D5;[S3] ^{1}H NMR (DMSO-d_6, 500 MHz) δH(ppm) = 8.77- 8.75 (d, J = 4.4 Hz, 2H), 7.36-7.34 (m, 1H), 6.83-6.76 (m, 1H), 6.54-6.5 (d, J = 17.2 Hz, 1H), 5.74-5.71 (d, J = 10.4 Hz, 1H).

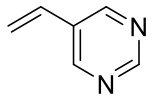


P5;[S4] ^{1}H NMR (, 500 MHz) δH(ppm) = 6.38 (dd, J = 17.9, 11.6 Hz, 1H), 5.40 (d, J = 17.9 Hz, 1H), 5.28 (d, J = 11.6 Hz, 1H), 2.40 (s, 3H), 2.31 (s, 3H).

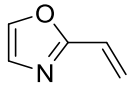
Compounds **F5**, **N5**, **Q5**, and **R5** where synthesized using following the procedure



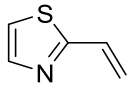
Example **Q5**; 5-Bromoisothiazole (436 µL, 4.88 mmol, 1 eq) was dissolved in anhydrous THF (25 mL), to this solution, tributylvinyltin (2,280 µL, 7.8 mmol, 1.6 eq) and Bis(triphenylphosphine)palladium chloride (340 mg, 0.49 mmol) was added at RT under nitrogen and was heated in a sealed screw cap reaction vial and oil bath for 110 ^{0}C for 18 h. The reaction mixture was cooled to RT and passed through a glass sinter funnel containing celite, and concentrated in *vacuo*. The crude was then diluted with water (40 mL) and extracted with ethyl acetate (3x20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure using rotary evaporator. The crude was purified through column chromatography (silica gel, 5-100 percent DCM in hexanes), to provide 5-vinylisothiazole as a dark yellow oil. 0.36 g, 66% ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm)[S5] = 8.65 (s, 1H), 7.76 (s, 1H), 6.84 (dd, J = 17.3, 10.8 Hz, 1H), 5.59 (d, J = 17.3 Hz, 1H), 5.31 (d, J = 10.8 Hz, 1H).



F5;[S6] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 9.10 (s, 1H), 8.8 (s, 2H), 6.70-6.63 (m, 1H), 5.96-5.91 (d, J = 18 Hz, 1H), 5.53-5.50 (d, J = 11.2 Hz, 1H).

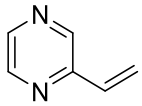


N5;[S5] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 7.87 (d, J= 3.0 Hz, 1H), 7.22 (d, J= 3.0 Hz, 1H), 6.93 (dd, J= 11.0, 17.5 Hz, 1H), 6.04 (d, J= 17.5 Hz, 1H), 5.54 (d, J= 11.0 Hz, 1H).

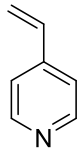


R5;[S3] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 7.76 (d, J= 2.8 Hz, 1H), 7.20 (d, J= 2.8 Hz, 1H), 6.90 (dd, J= 10.8, 18 Hz, 1H), 6.0 (d, J= 18 Hz, 1H), 5.55 (d, J= 10.8 Hz, 1H).

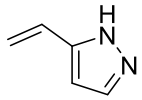
Compounds **C5**, **G5**, **K5**, and **L5** where synthesized using following procedure



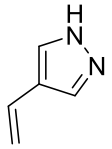
Example **G5**; hydrogenation experiments were carried out in a 50 mL (or 20 mL) stainless steel autoclaves provided with a manometer, a thermostat, a magnetic stirrer, and a gas inlet/outlet system. The Lindlar's catalyst (0.1 g) and 2-ethynylpyrazine (0.8 g, 7.69 mmol,) were placed in the autoclave along with 0.1 M amount of ethyl acetate. under a nitrogen atmosphere. The autoclave was closed, flushed with hydrogen (1 bar) three times, and thereafter pressurized with the synthesis gas hydrogen and stirred at room temperature for 20 min. After the reaction was finished, the residual gases were depressurized. The product mixture was investigated by GC analysis then purified through column chromatography (silica gel, 5-100 percent ethyl acetate in hexanes) to provide 2-vinylpyrazine as a colorless liquid. 0.33 g, 40% ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm)[S7] = 8.45 (d, J= 1.2 Hz, 1H), 8.37 (dd, J= 2.5, 1.2 Hz), 8.29-8.27 (m, 1H), 6.68 (dd, J= 17.2, 11 Hz, 1H), 6.22 (d, J= 17.2 Hz, 1H), 5.47 (d, J= 11 Hz, 1H,).



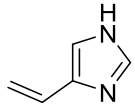
C5;[S8] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 8.55 (dd, J= 4.6, 1.0 Hz, 2H), 7.32 –7.15 (m, 2H), 6.63 (dd, J= 17.6, 10.8 Hz, 1H), 5.94 (d, J= 17.6 Hz, 1H), 5.46 (d, J= 10.8 Hz, 1H).



K5;[S5] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 7.52 (d, J = 1.6 Hz, 1H), 6.71 (dd, J = 17.8, 11.1 Hz, 1H), 6.41 (d, J = 1.6 Hz, 1H), 5.72 (d, J = 17.8 Hz, 1H), 5.33 (d, J = 11.1 Hz, 1H).



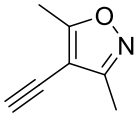
L5;[S9] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 7.64 (s, 2H), 6.58 (dd, J = 17.7, 11.0 Hz, 1H), 5.51 (d, J = 17.7 Hz, 1H), 5.12 (d, J = 11.0 Hz, 1H).



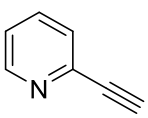
Example **L5**; In a three-necked round bottom flask equipped with addition funnel, oil trap, magnetic stirring bar and argon atmosphere, 4-bromo-1H-imidazole (0.5 g, 3.4 mmol, 1 eq) was dissolved in 25 mL of anhydrous THF. The solution was cooled to 0°C and then a suspension of NaH 60% in mineral oil (0.15 g 3.74 mmol, 1.1 eq) was added very slowly and allowed to effervesce, and reach room temperature over the course of an hour. Then p-toluenesulfonyl chloride (0.65 g, 3.4 mmol, 1 eq) was dissolved in 10 mL of anhydrous THF and added dropwise. The resulting mixture was stirred overnight at rt. The crude mixture was concentrated in *vacuo* to remove the THF before being diluted with water (40 mL) and extracted with ethyl acetate (3x20 mL). The organic layer was washed with brine, and concentrated under reduced pressure using rotary evaporator. To remove impurities, the solid compound was transferred to a Buchner funnel and washed with a hot 1:1 water:methanol solution. The vinylation reaction was achieved *via* the Stille coupling procedure already described. The deprotection procedure was as follows. The 1-tosyl-4-vinyl-1H-imidazole compound was dissolved in DMF (5 mL). Lithium hydroxide assuming 100 % conversions (0.33g, 8.0 mmol, 4 eq) was added followed by thioglycolic acid (200 µL, 2.4 mmol, 1.2 eq). The resulting solution was stirred at ambient temperature and the reaction progress monitored by LC-MS. Once reaction was complete after 5 h, the solution was diluted with ethyl acetate (10 mL) and water (10 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3x5 mL) and the combined organic solutions washed with saturated aqueous sodium carbonate (3x10 mL) then dried, filtered and evaporated to leave a pure 4-vinyl-1H-imidazole as a pale yellow oil. 33 mg, 10% ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm)[S10] = 12.40 (br s, 1 H) 7.60 (s, 1H), 7.26 (s, 1H), 6.62 (dd, J = 17.5 Hz, 11.3 Hz, 1H), 5.66 (d, J = 17.5 Hz, 1H), 5.11 (d, J = 11.3 Hz, 1H).

General procedure for the ehtynylation reactions

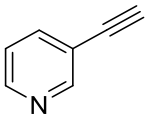
Compounds **A6**, **B6**, **C6**, **D6**, **F6**, **G6**, **N6**, **P6**, **Q6**, and **R6** where synthesized using following procedure



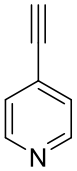
Example **P6**; To a solution of 4-iodo-3,5-dimethylisoxazole (0.5 g, 2.24 mmol, 1 eq), $Pd(PPh_3)_4$ (0.2 g, 0.18 mmol), CuI (40 mg, 0.22 mmol), and purged trimethylamine (15 ml) was added trimethylsilylacetylene (447 µL, 3.14 mmol, 1.4 eq) with syringe under argon. After the reaction mixture was stirred at 110 ^{0}C in a microwave reactor for 80 minutes, it was diluted with ethyl acetate (30 mL) and filtered through a pad of celite. The filtrate was diluted with H_2O, and extracted several times with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was dissolved in methanol (30 mL), followed by adding KOH (140 mg, 2.47 mmol). The reaction mixture was stirred at room temperature overnight, and concentrated in *vacuo*. The residue was diluted with H_2O, and extracted several times with ethyl acetate. The combined organic phases were washed with brine and dried over $MgSO_4$. Filtration and removal of the solvent gave a crude oil that was subjected to column chromatography (silica gel, 5-100 percent ethyl acetate in hexanes) to give the title product **P6** as a light brown crystalline solid. 212 mg, 78% ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm)[S11] = 2.30 (s, 3H), 2.46 (s, 3H), 3.20 (s, 1H).



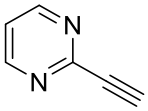
A6;[S12] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 8.60 (d, J= 4.9Hz, 1H), 7.64-7.69 (m, 1H), 7.49 (d, J= 7.8Hz, 1H), 7.25-7.29 (m, 1H), 3.16 (s, 1H).



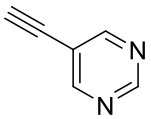
B6;[S13] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 8.72 (s, 1H), 8.56 (d, J= 4.9 Hz, 1H), 7.77 (d, J= 7.9 Hz, 1H), 7.26 (m, 1H), 3.21 (s, 1H).



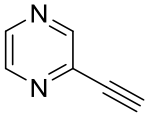
C6;[S14] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 8.56 (d, J= 4.6 Hz, 2H), 7.32 (d, J= 4.6 Hz, 2H), 3.28 (s, 1H).



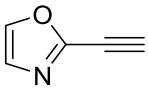
D6;[S15] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 8.67 (m, 2H), 7.24 (t, J=5.0 Hz, 1H), 3.10 (s, 1H).



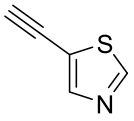
F6;[S16] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 9.12 -9.19 (s, 1H), 8.74 -8.85 (s, 2H), 3.39 -3.41 (s, 1H).



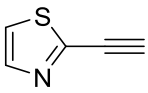
G6;[S17] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 8.71 (s, 1H), 8.56 (d, 1H), 8.52 (d, 1H), 3.35 (s, 1H).



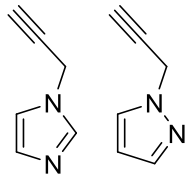
N6;[S18] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 7.87 (d, J= 3.0 Hz, 1H), 7.22 (d, J= 3.0 Hz, 1H), 3.50 (s, 1H).



Q6;[S19] ^{1}H NMR (CDCl3, 500 MHz) δH(ppm) = 8.72 (s, 1H), 8.05 (s, 1H), 3.46 (s, 1H).



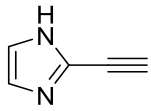
R6;[S20] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 7.85 (1 H, d), 7.39 (1 H, d), 3.48 (s, 1H).



Both **I6** and **M6** were synthesized using the following procedure

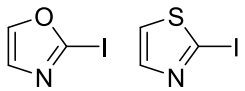
Example **I6**; A suspension of NaH 60% in mineral oil (2.6 g, 66 mmol, 1.5 eq) was added to a DMF solution (0.2 M), containing the imidazole (3 g, 44 mmol, 1 eq) at 0 ^{0}C and stirred for 5 h. Then propargyl bromide 80% solution in toluene (7.8 mL, 70 mmol, 1.6 eq) was added. The resulting mixture was vigorously stirred at room temperature for 15 h. Then filtered through a pad of celite and washed with DMF. As much DMF as possible was removed *via* rotary evaporation before the mixture was diluted with H_2O, and extracted several times with ethyl acetate. The combined organic phases were washed with brine and dried over $MgSO_4$. Filtration and removal of the solvent gave a crude oil that was subjected to column chromatography (silica gel, 5-100 percent ethyl acetate in hexanes) to give the title product **I6** as a light brown oil. 3.36 g, 72% ^{1}H NMR (dimethylsulfoxide-d6, 500 MHz) δH(ppm)[S21] δ= 7.69 (s, 1H), 7.19 (s, 1H), 6.95 (s, 1H), 4.89 (d, J= 2.6 Hz, 2H), 3.46-3.44 (t, J= 2.6 Hz, 1H) ppm.

M6;[S22] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 7.47-7.44 (m, 2H), 6.21 (t, J= 2.1 Hz, 1H), 4.79 (d, J= 2.5 Hz, 2H), 2.42 (t, J= 2.5 Hz, 1H) ppm.



Example **H6**; In a three-necked round bottom flask equipped with addition funnel, oil trap, magnetic stirring bar and argon atmosphere, 2-bromo-1H-imidazole (0.5 g, 3.4 mmol, 1 eq) was dissolved in 25 mL of anhydrous THF. The solution was cooled to 0 °C and then a suspension of NaH 60% in mineral oil (0.15 g 3.74 mmol, 1.1 eq) was added very slowly and allowed to effervesce, and reach room temperature over the course of 1 h. Then p-toluenesulfonyl chloride (0.65 g, 3.4 mmol, 1 eq) was dissolved in 10 mL of anhydrous THF and added dropwise. The resulting mixture was stirred overnight at rt. The crude mixture was concentrated in vacuo to remove the THF before being diluted with water (40 mL) and extracted with ethyl acetate (3x20 mL). The organic layer washed with brine, and concentrated under reduced pressure using rotary evaporator. To remove impurities, the solid compound was transferred to a Buchner funnel and washed with a hot 1:1 water:methanol solution. The ethylation reaction was achieved *via* the sonagashira coupling procedure already described. The deprotection procedure was as follows. The 1-tosyl-4-vinyl-1H-imidazole compound was dissolved in DMF (5 mL). Lithium hydroxide assuming 100 % conversions (4 eq) was added followed by thioglycolic acid (1.2 eq). The resulting solution was stirred at ambient temperature and the reaction progress monitored by LCMS. Once reaction was complete after 5 h, the solution was diluted with ethyl acetate (10 mL) and water (10 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3x5 mL) and the combined organic solutions washed with saturated aqueous sodium carbonate (3x10 mL) then dried, filtered and evaporated to leave a pure 2-ethynyl-1H-imidazole as a brown oil. 20 mg, 6.4% ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm)[S23] = 10.53 (br s, 1H), 7.12 (s, 2H) 3.48 (s, 1H).

General procedures for halogenation reactions



Both **N3** and **R3** were synthesized using the following procedure

Example **N3**; To a solution of oxazole (0.66 mL, 10.0 mmol) in dry THF (20 mL) at -78°C was added n-BuLi (4.40 mL of a 2.5M solution in hexanes, 5.50 mmol), dropwise over 3 min. The mixture was stirred 30 min and a solution of anhydrous $ZnBr_2$ (10.6 mL of a 1.13M solution in THF, 12 mmol) was added, dropwise over 3 min. The mixture was warmed to RT and I_2 (2.80 g, 5.5 mmol) was added in one portion. The mixture was stirred for 30 min, quenched with satd. $Na_2S_2O_3$, diluted with Et_2O and poured into 10 wt % citric acid solution. The biphasic mixture was stirred vigorously until clean EPO phase separation occurred, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and carefully concentrated in *vacuo* (45°C water bath temp., 100 mbar vacuum). The residue was filtered through a short pad of silica gel (CH_2Cl_2 eluent), affording 0.5 g of the title compound 2-Iodo-1,3-oxazole as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm)[S24] = 7.77 (d, J = 0.7 Hz, 1H), 7.11 (d, J = 0.7 Hz, 1H).

R3;[S25] ^{1}H NMR ($CDCl_3$, 500 MHz) δH(ppm) = 7.62 (d, 1H), 7.32 (d, 1H).

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