**Supplementary Information**

**Materials and Methods**

***Synthesis of HAT inhibitors****-* 2-Bromo-3-methylthiophene, diphenyl disulphide, 2,2'-dithio(bis)benzothiazole, 2,2'- and 4,4'-dithiodipyridine (Aldrithiols)were purchased from the Aldrich Chemical Company.

**3,3-Dibromo-2-methylacrylaldehyde (3a)**

To pyruvic aldehyde dimethylacetal **2a** (5.13 mL, 42.3 mmol) and triphenylphosphine (20.2 g, 77.0 mmol) suspended in trifluoromethylbenzene (20 mL) was added dropwise a solution (pre-filtered through basic alumina) of carbon tetrabromide (12.8 g, 38.5 mmol) in trifluoromethylbenzene (80 mL). The mixture was heated at 100 oC for 3 h, cooled and filtered to remove triphenylphosphine oxide. The solvent was removed and the crude product was purified by chromatography (silica; elution with 25% dichloromethane in petrol) to afford **2a** as a pale yellow oil (2.23 g, 24 %). 1H NMR (CDCl3, 300 MHz) δ 1.86 (s, 3H, CH3), 9.89 (s, 1H, CHO); 13C NMR (CDCl3, 75 MHz) δ 17.3, 113.6, 140.5, 189.6.

**4-Methyl-5-thiocyanatoisothiazole (4)**

To 3,3-dibromo-2-methylacrylaldehyde (1.45 g, 6.36 mmol) in dimethylformamide (10 mL) was added ammonium thiocyanate (0.97 g, 12.7 mmol). The resulting solution was heated at 70 oC for 2 h, cooled, diluted with brine and extracted with diethyl ether. The ethereal extract was washed with water, dried (MgSO4) and concentrated to give an orange liquid. Chromatography (silica; elution with 12% dichloromethane in petrol) gave compound **4**, which was further purified by recrystallisation: yellow crystals (0.59 g, 60 %) from ethyl acetate-petrol. 1H NMR (CDCl3, 300 MHz) δ 2.42 (s, 3H, CH3), 8.41 (s, 1H, isothiazole CH); 13C NMR (CDCl3, 75 MHz) δ 12.0, 108.0, 138.2, 140.8, 160.2; HRMS (EI+) calculated for C5H4N2S2: 155.9816; found: 155.9814.

**1,2-Bis(4-methylisothiazol-5-yl)disulfane ( 5)**

Aqueous ammonia (ca. 40 M, 5 mL) was added to a stirred solution of **4** (0.45 g, 2.88 mmol) in dioxane (5 mL) and water (2.5 mL) and the mixture was heated at 90 oC for 1 h. The solution was cooled to room temperature and the solvent was removed *in vacuo*. The red residue was partitioned between water and dichloromethane (DCM). The organic layer was dried (MgSO4), filtered and concentrated *in vacuo*. Chromatography (silica; elution with 6% ethyl acetate in petrol) gave compound **5** (0.14 g, 37 %) as a yellow oil. IR 2925, 2855, 2362, 2338, 1725, 1449, 1366, 1282, 1224, 1122, 992, 881, 788, 664 cm-1; 1H NMR (CDCl3, 300 MHz) δ 2.19 (s, 6H, 2 × CH3), 8.30 (s, 2H, 2 × isothiazole CH); 13C NMR (CDCl3, 75 MHz) δ 11.7 (2 × CH3), 138.2 (2 × CH3*C*), 153.7 (C-S-S-C), 159.8 (2 × CH=N); HRMS (EI+) calculated for C8H8N2S4: 259.9570; found: 259.9568.

**5-Thiocyanatoisothiazole (6) and 1,2-Bis(isothiazol-5-yl)disulfane (NU9056, 7)**

3,3-Dibromoacrylaldehyde **3b** was prepared from 2,2-dimethoxyethanal **2b** in the manner described above for **3a**. A mixture of **3b** (0.35 g, 1.63 mmol) and ammonium thiocyanate (0.25 g, 3.26 mmol) in dry dimethylformamide (3 mL) was stirred for 2.5 h at 70 °C and allowed to cool to room temperature. Ethyl acetate (50 mL) was added and the mixture was washed (3×) with brine. The organic phase was dried (MgSO4) and concentrated *in vacuo*. Chromatography (silica gel; 30% dichloromethane in petrol followed by 5% methanol in dichloromethane) gave:

**6**, yellow solid (94 mg), mp 43 °C. IR (in CDCl3) 2960, 2925, 1714, 1621, 1386, 1269, 1220, 1057, 1149, 996, 907, 663 cm-1; 1H NMR (300 MHz, CDCl3)  7.20 (d, 1H, *J* 1.5 Hz, CH=CS), 8.36 (d, 1H, *J* 1.5 Hz, CH=N). 13C NMR (75 MHz, CDCl3) 126.4 (*C*H=CS), 158.3 (CH=N), 160.8 (CH=*C*S); HRMS (EI+) calculated for C3H2NS2 [M – CN]+ 115.9629; found: 115.9629.

**7**, yellow oil (68 mg). IR (in CDCl3) 2965, 2932, 2164, 1714, 1559, 1388, 1257, 1227, 1107, 1059, 1007, 820, 725, 664 cm-1; 1H NMR (300 MHz, CDCl3) 7.40 (d, 2H, *J* 1.7 Hz, 2 × CH=CS), 8.46 (d, 2H, *J* 1.7 Hz, 2 × CH=N); 13C NMR (75 MHz, CDCl3)  107.8 (2 × SCN), 129.1 (2 × *C*H=CS), 145.2 (2 × CH=*C*S), 158.5 (2 × CH=N); HRMS (EI+) calculated for C6H4N2S4: 231.9252; found, 231.9255.

**4-Methylisothiazole** **(11)**

Ammonium thiocyanate (3.37 g, 44 mmol) was added to a stirred solution of a mixture of (*E*)- and (*Z*)-3-bromo-2-methylacrylaldehyde **10** (prepared from methacrolein **8** *via* **9**: cf. ref. 40) (2.2 g, 15 mmol) in dimethylformamide (10 mL). The mixture was heated at 70 oC for 16 h, cooled to room temperature, diluted with brine, and extracted with diethyl ether. The combined organic extracts were washed with water (4 × 10 mL), dried (MgSO4) and concentrated *in vacuo*. Chromatography (silica; elution with 50 % DCM in petrol) gave compound **11** as a pale yellow oil (0.56 g, 38 %). IR (in CDCl3) 3092, 2961, 2926, 2872, 1451, 1363, 1332, 1229, 964, 883, 853, 781 cm-1; 1H NMR (CDCl3, 300 MHz) δ 2.35 (s, 3H, CH3), 8.19 (s, 1H, CH=N), 8.27 (s, 1H, CHS); 13C NMR (CDCl3, 75 MHz) δ 11.59 (CH3), 133.9 (CH3*C*), 143.1 (=CHS), 158.5 (CH=N); HRMS (EI+) calculated for C4H5NS 99.0143; found 99.0147.

**4-Methyl-5-bromoisothiazole (1)**

To a solution of **11** (0.25 g, 2.5 mmol) in THF (10 mL) cooled to -78 oC was added n-butyl lithium (2.5 M in hexanes, 1.1 mL, 2.7 mmol). After stirring for 15 min, bromine (0.14 mL, 2.8 mmol) was added and the mixture was allowed to warm slowly to room temperature. Aqueous NH4Cl was added and the mixture was extracted with diethyl ether, dried (MgSO4) and concentrated *in vacuo*. Chromatography (silica; elution with 25 % DCM in petrol) gave compound **1** as a yellow oil (0.043 g, 10 %). IR (in CDCl3) 3032, 2960, 2927, 2867, 1537, 1449, 1365, 1323, 1225, 1096, 1036, 941, 880, 780 cm-1; 1H NMR (CDCl3, 300 MHz) δ 2.25 (s, 3H, CH3), 8.20 (s, 1H, CH=N); 13C NMR (CDCl3, 75 MHz) δ 12.1 (CH3), 133.2 (CH3*C*), 135.2 (=CBr-S), 159.1 (*CH=N*); HRMS (EI+) calculated for C4H479BrNS: 176.9248; found: 176.9249.

***Baculovirus production of His-Tip60***- Wild-type Tip60-His baculovirus was generated in insect cells using the Bac-to-Bac expression system (Invitrogen) according to the manufacturer’s protocol. N-terminal His-tagged wild-type Tip60 was produced by infection of insect cells. Cell lysates were harvested in lysis buffer (50 mM NaH2PO4, 300 mM NaCl, 10 mM imidazole, pH 8) and applied to Ni-NTA superflow (Qiagen) columns. The columns were washed (50 mM NaH2PO4, 300 mM NaCl, 20 mM imidazole, pH 8) and Tip60-His was eluted in elution buffer (50 mM NaH2PO4, 300 mM NaCl, 250 mM imidazole, pH 8). The activity of the protein was confirmed using *in vitro* histone acetylation assays.

***Purification of recombinant HAT enzymes (GST-tagged)****-* Expression constructs, pGEX-p300 and pGEX-PCAF, obtained from Dr Andrew Bannister (Cambridge Cancer Centre, UK), were transformed into XA90 *Escherichia coli* cells. A single colony was selected and grown to an OD 0.5 IPTG (1 mM) induction was carried out for 4 hours then cell pellets were collected, lysed, and sonicated. Supernatants were then passed through glutathione Sepharose 4B (GE Healthcare) and purified protein was eluted with 50 mM Tris-HCl, 10 mM reduced glutathione, pH 8. Eluted fractions were tested for enzymatic activity by HAT assay. Active fractions were combined and used to assess inhibitor efficacy.

**Supplementary Results**

***Chemical Synthesis***

Few practical syntheses of isothiazoles have been reported [[1-6](#_ENREF_1)]. In one method, 4-arylisothiazoles were obtained by treatment of aryl-substituted β-chloroacroleins with ammonium thiocyanate (33). In a similar manner, we have prepared isothiazoles (**4** and **6**) by the reaction of 3,3-dibromoacroleins (**3a** and **3b**, respectively) with ammonium thiocyanate. Thus, treatment of 1,1-dimethoxypropanone **2a** with triphenylphosphine-carbon tetrabromide [Corey-Fuchs reaction [[7](#_ENREF_7)]] gave 3,3-dibromo-2-methylacrylaldehyde dimethyl acetal**,** whichwas converted into 3,3-dibromo-2-methylacrylaldehyde **3a** during chromatography on silica (Scheme 1a). Reaction of **3a** with ammonium thiocyanate gave 4-methyl-5-thiocyanatoisothiazole **4**, which arises by double displacement of bromides with thiocyanate, combination of the resulting aldehyde with ammonia and cyclization (Scheme 1a) [[8-10](#_ENREF_8)]. Treatment of aldehyde **3b**, prepared in an analogous manner to **3a**, with ammonium thiocyanate gave a mixture of compounds from which 5-thiocyanatoisothiazole **6** and1,2-bis(isothiazol-5-yl)disulfane **7** were separated. The disulfide 1,2-bis(4-methylisothiazol-5-yl)disulfane **5** (hereinafter called NU9056) was not observed in the reaction of **3a** with ammonium thiocyanate, but was obtained on heating **4** with aqueous ammonia.

Efforts to convert **4** into bromide **1** by displacement of the thiocyanato group failed either using molecular bromine or tetrabutylammonium bromide. However, lithiation of compound **11** [[11](#_ENREF_11)] and quenching of the intermediate carbanion with bromine afforded the desired 4-methyl-5-bromoisothiazole **1**. The synthesis of isothiazole **11** was closely based on literature protocols (Scheme 1b). A sequence of dibromination of the double bond, protection of the aldehyde and elimination of hydrogen bromide was used to convert methacrolein **8** into a mixture of geometrical isomers of bromo-diethylacetal **9** [[12](#_ENREF_12)]. Hydrolysis of the acetals to aldehydes **10** was followed by treatment with ammonium thiocyanate in dimethylformamide, which gave isothiazole **11** [[13](#_ENREF_13)].

**Supplementary References**

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