Preparation of a Clinically Investigated Ras Farnesyl Transferase Inhibitor

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The synthesis of *ras* farnesyl-protein transferase inhibitor **1** is described on a multi-kilogram scale. Retrosynthetic analysis reveals chloromethylimidazole **2** and a piperazinone **3** as viable precursors. The 1,5-disubstituted imidazole system was regioselectively assembled *via* an improved Marckwald imidazole synthesis. A new imidazole dethionation procedure has been developed to convert the Marckwald mercaptoimidazole product to the desired imidazole. This methodology was found to be tolerant of a variety of functional groups providing good to excellent yields of 1,5-disubstituted imidazoles. A new Mitsunobu cyclization strategy was developed to prepare the arylpiperazinone fragment **3**.

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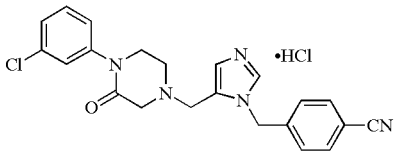
Introduction.

Mutant *ras* proteins, the products of *ras* oncogenes, are involved in a significant proportion of human cancers [1]. The enzyme farnesyl-protein transferase (FPTase) catalyzes the farnesylation of the *ras* protein thereby activating it; thus, FPTase inhibitors are currently the object of intense interest as novel and improved anticancer agents [2]. Piperazinone **1** has been identified as an effective FPTase inhibitor and has been found to be efficacious in animal models with a relatively high therapeutic index [3]. Phase I and phase II clinical studies of **1** in cancer patients have been completed [3c].



1

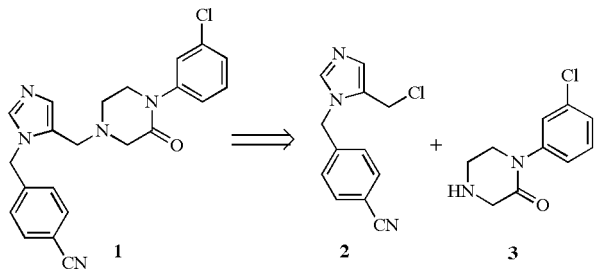
Figure 1

Results and Discussion.

Retrosynthetic analysis of **1** can lead to an alkylation of piperazinone **3** with an electrophilic halomethylimidazole such as **2** (Scheme 1). The original preparation of **1** employed the same bond disconnection *via* a reductive amination of the imidazole-5-carboxaldehyde with **3**; thus, both routes require a 1,5-disubstituted imidazole and a 1-arylpiperazin-2-one [4].

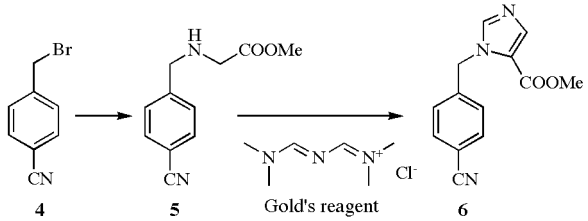
Originally this 1,5-substitution was achieved by selective trityl and acetyl protection of commercially available 5-hydroxymethylimidazole at the 3- and hydroxyl positions respectively followed by alkylation of the remaining 1-position and subsequent deprotection [4]. The starting material 5-hydroxymethylimidazole is expensive and difficult to obtain in large (>100 g) quantities [5]. Since large quantities of **1** would be needed for safety assessment and clinical studies, we sought a more financially and atom economical route.

Scheme 1



1 **2** **3**

Scheme 2

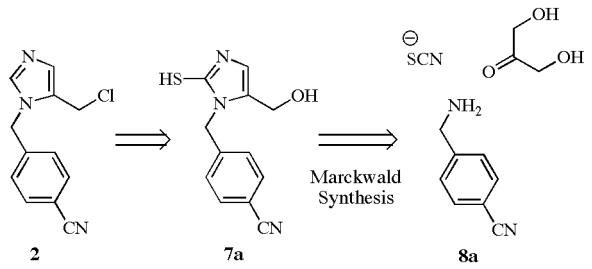


4 **5** **6**

Many methods for the preparation of imidazoles are known [6], but the convenient regioselective preparation of 1,5-substituted imidazoles can be more challenging. 1,5-Substituted imidazoles can be accessed by reaction of Gold's reagent with an *N*-substituted glycine ester [7]. In Scheme 2 alkylation of glycine ethyl ester with commercially available 4-(bromomethyl)benzonitrile (**4**) gave **5**

which upon treatment with Gold's reagent in the presence of sodium methoxide gave imidazole **6**, albeit in 28% yield.

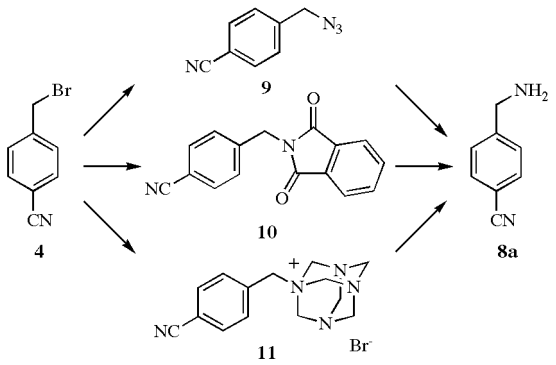
Scheme 3



The Marckwald imidazole synthesis (Scheme 3) provides 1,5-substituted imidazoles *via* a three component coupling of an amine and a hydroxyketone with thiocyanate [8]. Furthermore, the use of dihydroxyacetone as a starting material would provide the 1,5-substituted imidazole with the desired oxidation state at the 5 substituent [9]. The benzylic amine **8a** can be obtained from **4** in several ways (Scheme 4). The two classical approaches to primary amines from the corresponding halide *via* the azide **9** and the phthalimide **10** successfully provided **8a** [10]. A route free from the dangers associated with the treacherous nature of azides and the toxicity of hydrazine required for the deprotection of phthalimide **10** [11] was desired. Another classical but less exploited approach to benzylic amines *via* the Delépine reaction [12] was examined. In this reaction inexpensive hexamethylenetetramine (HMTA) serves as the nitrogen surrogate. Benzylic bromide **4** readily reacted with HMTA in ethanol to form the quaternary ammonium salt **11** which, by treatment with anhydrous alcoholic hydrogen chloride (HCl), provided a mixture of crystalline halide salts of **8a** and ammonia. Subsequent free basing, extraction of **8a** into an organic solvent and treatment with HCl provided **8a** as its pure crystalline HCl salt [13]. The use of phosphoric acid (H_3PO_4) for the deprotection was found to simplify the isolation of **8a** as its less soluble pure phosphoric acid salt. In the optimized procedure treatment of the crude ethanolic reaction mixture from the formation of **11** with H_3PO_4 and propionic acid was followed by filtration of the crystallized salt mixture. Washing of these salts with water to remove the soluble phosphate salts provided the relatively insoluble **8a**•H_3PO_4 salt in 88% yield from **4** [14].

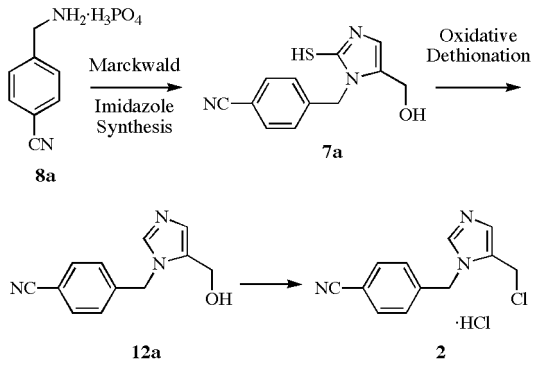
The Marckwald synthesis of mercaptoimidazole **7a** (Scheme 5) in *n*-butanol proceeded smoothly employing the literature protocol [9]. Unfortunately, filtration of **7a** from the reaction mixture proved to be very difficult. A screen of solvents and conditions revealed acetonitrile to

Scheme 4



be ideal [15]. The optimized procedure employed acetonitrile containing 5-10% water as the solvent in the presence of 2-3 equivalents of acetic or propionic acid. The generality of this improved procedure is demonstrated for several substituted benzyl mercaptoimidazoles in Table 1. Interestingly, the bicyclic byproduct **X** (Figure 2) was isolated from the reaction mixture in the preparation of **7b** from **8b**. We postulate a mechanism in which the final elimination follows an alternative path B resulting in an exocyclic olefin which is trapped by excess thiocyanate followed by cyclization to **X**. Compound **X** was rigorously characterized using 1-D and 2-D nmr studies. Nuclear Overhauser Effect (NOE) experiments were used to establish the *cis* relationship of the ring junction (strong NOE between the $-CH_3$ and the methyne CH). ^1H-^{13}C and ^1H-^{15}N Heteronuclear Multiple Bond Correlation (HMBC) experiments show all the expected correlation for the proposed structure (Figure 3).

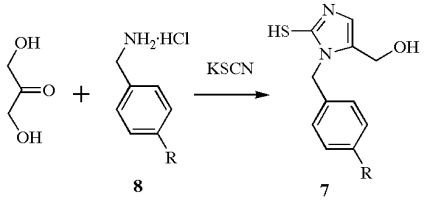
Scheme 5



The replacement of the thiol with hydrogen has been accomplished by use of concentrated nitric acid [9b,d]. However, this procedure proved to be rather hazardous at scales above several grams due to an unpredictable induction

Table 1

Mercaptoimidazole Synthesis



8 **7**

R	Amine	Mercaptoimidazole product	Yield, Conditions A[a]	Yield, Conditions B[b]
CN	**8a**	**7a**	90	78
H	**8b**	**7b**	97	97[c]
OMe	**8c**	**7c**	92	87
Br	**8d**	**7d**	90	83
NO_2	**8e**	**7e**	92	75[d]

[a] Reaction performed in 49:1 acetonitrile-water, see experimental section for details; [b] Conditions in **B** similar to those in **A** except reaction was performed in *n*-butanol.; [c] See reference 9a; [d] See reference 9b.

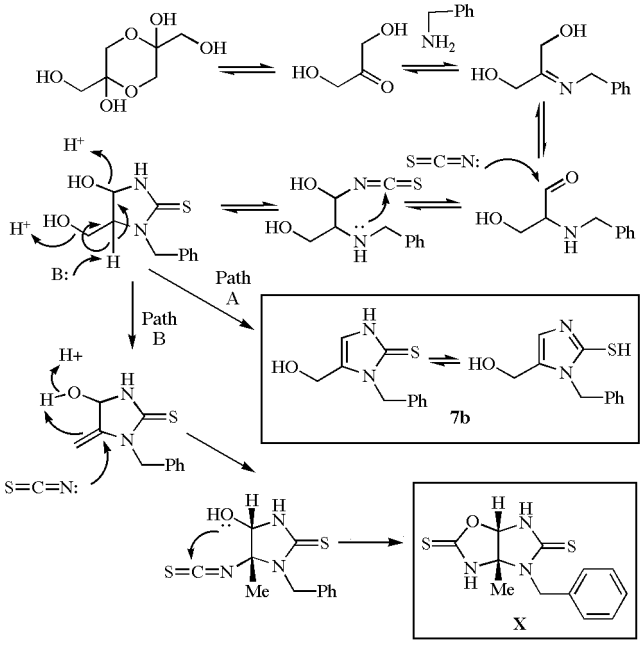


Figure 2

period, followed by a sudden exothermic reaction accompanied by the release of large volumes of nitrogen oxide gases. The addition of nitrite salts to the mixture eliminated the induction period [8c,d,9a] and we found that the reaction could also be performed by the addition of sodium nitrite to a suspension of **7a** in acetic acid [16]. Although both of these procedures eliminated the induction period, the release of large volumes of nitrogen oxide gases still rendered the

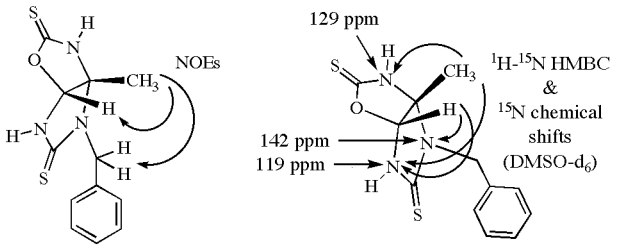
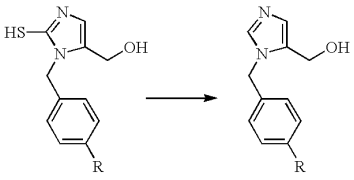


Figure 3

reaction difficult to control and undesirable from an environmental and safety standpoint. The oxidation of mercaptoimidazoles with excess iron(III) salts [9c,e] and the reduction with Raney nickel [9d,g] are known, but the necessity of large excesses of these environmentally unfriendly reagents to complete the reaction was undesirable. Further study revealed hydrogen peroxide (H_2O_2) to be the ideal oxidant since no hazardous byproducts are produced. This new protocol involves the controlled addition of 30% hydrogen peroxide to an aqueous acetic acid suspension of **7a** followed by basification and filtration of the precipitated product [17]. This improved mild dethionation protocol was demonstrated on a series of substituted benzylmercaptoimidazoles (Table 2) [18].

Table 2

Dethionation of Mercaptoimidazoles



7 **12**

R	Mercaptoimidazole	Dethionated product	Yield, Conditions A[a]	Yield, Conditions B[b]
CN	**7a**	**12a**	84	75
H	**7b**[c]	**12b**[c]	90	65
OMe	**7c**	**12c**	81	20
Br	**7d**	**12d**	92	74
NO_2	**7e**[d]	**12e**[d]	93	79

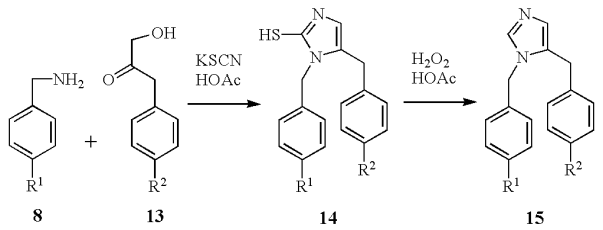
[a] Dethionation performed with H_2O_2 in aqueous acetic acid, see experimental section for details; [b] Dethionation perfor med with sodium nitrite in aqueous acetic acid, see experimental section for details; [c] See reference 9a; [d] See reference 9b.

The improved imidazole synthesis and dethionation was applied to the rapid preparation of several more complex imidazoles with structure **15** [2,3] from benzylic hydroxyketones **13a-c** [19]. Table 3 illustrates the general and regioselective preparation of these 1,5-disubstituted imidazoles in

good yield. Nmr studies have shown the thiono-form to be the predominant form [20].

Table 3

1,5 Disubstituted Imidazole Synthesis

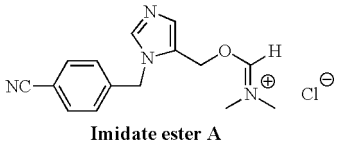


8 **13** **14** **15**

R^1	R^2	Hydroxy ketone	Amine	Mercaptoimidazole (% yield)[a]	Dethionated Imidazole (% yield)[b]
CN	H	**13a**	**8a**	**14a** (65)	**15a** (83)
H	CN	**13b**	**8b**	**14b** (66)	**15b** (91)
F	H	**13a**	**8f**	**14c** (69)	**15c** (80)
F	CN	**13b**	**8f**	**14d** (85)	**15d** (76)
CN	F	**13c**	**8a**	**14e** (57)	**15e** (74)

[a] Isolated after crystallization directly from the reaction mixture by basification with aqueous ammonium hydroxide, see experimental section for details; [b] Isolated after flash chromatography and crystallization, see experimental section for details.

With the appropriately 1,5-disubstituted imidazole **12a** in hand, activation to the electrophilic **2** would provide the imidazole coupling-partner. Chloromethylimidazoles have been prepared from the corresponding hydroxymethylimidazoles by treatment with excess thionyl chloride [21,9f,8a] or phosphorus pentachloride [9h]. Treatment of **12a** with excess thionyl chloride afforded **2** in 72% yield. Performing the reaction in *N*,*N*-dimethylformamide (DMF) with 2 equivalents thionyl chloride followed by precipitation with ethyl acetate (EtOAc) gave 77-83% yield of **2** as its HCl salt. After a screen of conditions and activating reagents, a 94% yield of **2** was obtained by treatment of **12a** with Vilsmeier reagent obtained from oxalyl chloride and DMF in acetonitrile. A closer examination of this reaction revealed imidate ester **A** (Figure 4) to be formed as an intermediate, which then converts to **2** [22].

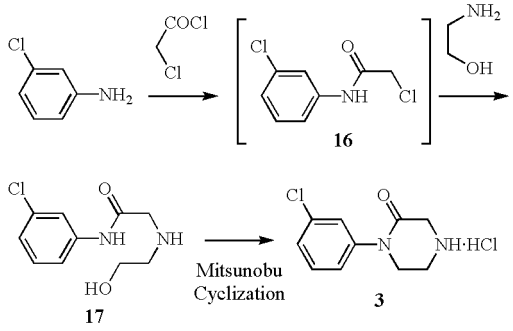


Imidate ester A

Figure 4

With a convenient route to large quantities of **2** in place [23] attention was focused on preparation of coupling partner **3**. The original five step route to piperazinone **3** involved a high temperature condensation of 3-chloroaniline•HCl salt with oxazolidone to give the *N*-arylethylenediamine [24] followed by Boc-protection, acylation of the aniline nitrogen with chloroacetyl chloride, cyclization with base and Boc-deprotection. A retrosynthetic analysis revealed that the piperazinone could be more efficiently derived from 3-chloroaniline, chloroacetyl chloride and ethanolamine without the need for a protection/deprotection sequence [25]. Thus, a one-pot synthesis of hydroxyamide **17** was developed. The acylation of 3-chloroaniline with chloroacetyl chloride under Schotten-Baumann conditions in isopropyl acetate/aqueous potassium bicarbonate provided a quantitative yield of chloroacetamide **16** (Scheme 6). Removal of the aqueous layer, followed by treatment of the isopropyl acetate layer containing **16** with ethanolamine at 60 °C provided hydroxyamide **17** in 83% overall yield from 3-chloroaniline. The cyclodehydration of hydroxyamide **17** was studied under a series of Mitsunobu conditions from which tributylphosphine and diisopropylazodicarboxylate (DIAD) in EtOAc emerged as the preferred combination. The piperazinone was directly isolated from the reaction mixture by the addition of ethanolic HCl which crystallized **3** as its HCl salt in 77% isolated yield, thus obviating the need for the typical chromatographic removal of the Mitsunobu by-products.

Scheme 6



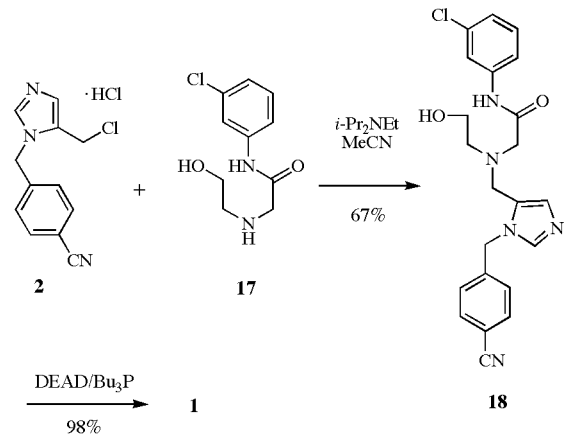
16 **17** **3**

Alkylation of piperazinone **3** with chloride **2** was examined under a variety of conditions [26]. Alkylation of **3** with **2** in acetonitrile in the presence of diisopropylethylamine (*i*-Pr_2NEt) at 0 °C in acetonitrile afforded **1** in 83% yield [27]. An alternate route to **1** was realized in Scheme 7 by first coupling hydroxyamide **17** with chloromethylimidazole salt **2** to give penultimate intermediate **18** in 67% yield. Mitsunobu cyclodehydration of **18** with tributylphosphine and diethylazodicarboxylate in tetrahydrofuran provided a 98% yield of **1**.

Conclusion.

During the process of identifying and demonstrating a practical preparation of *ras* FPTase inhibitor **1**, the classical Marckwald imidazole synthesis has been exploited and improved so that large quantities of 1,5-disubstituted mercaptoimidazoles can be prepared. A safer and more convenient new dethionation procedure for the preparation

Scheme 7



of 1,5-disubstituted imidazoles has also been discovered. This chemistry has been demonstrated on several imidazole systems and was found to be tolerant of a variety of functional groups providing good to excellent yields. Alkylation of the desired chloromethylimidazole **2** with piperazinone **3** prepared *via* a novel application of the Mitsunobu reaction, affords FPTase inhibitor **1**. The inhibitor **1** has also been prepared *via* a Mitsunobu cyclization protocol of hydroxyamide intermediate **18** in high yield.

EXPERIMENTAL

General.

Reagents were used as received unless otherwise stated and glassware was not specially dried prior to use. Reactions were performed under an atmosphere of nitrogen and temperatures were recorded internally by thermocouple probe. A% refers to hplc area%. Analytical TLC was performed using Merck Kieselgel G60 F254 precoated plates (0.25 mm) followed by visualization with UV light (254 nm), staining with iodine vapor, staining with a solution of 14% ammonium molybdate and 0.5% ceric sulfate in 10% aqueous sulfuric acid then heat or staining with a solution of 0.085% bismuth subnitrate ($BiONO_3$) and 2% potassium iodide in 3:1 water–acetic acid (Dragendorff's reagent). Flash column chromatography was performed using silica gel (Merck, 70-230 mesh ASTM). Melting points were obtained with a Barnstead/Thermolyne MEL-TEMP® apparatus and are uncorrected. ^1H and ^{13}C nmr chemical shifts are reported in ppm; coupling constants are reported in Hz. ^1H and ^{13}C nmr spectra were recorded on Bruker AM and AMX systems. Elemental analyses were obtained from Quantitative Technologies Inc, Whitehouse, NJ. Solvent ratios are reported by volume. Solka-Floc® [9004-34-6] is a powdered cellulose filter aid obtained from Fiber Sales & Development, Dupont.

Methyl *N*-(4-Cyanobenzyl)glycinate (**5**).

A mixture of 4-(bromomethyl)benzonitrile (19.6 g, 100 mmol), glycine methyl ester hydrochloride (25.1 g, 200 mmol), potassium carbonate (55.3 g, 400 mmol), tetrabutylammonium hydrogen sulfate (339 mg, 1.00 mmol), tetrahydrofuran (100 mL) and water (7.2 mL) was stirred for 1 h at 40 °C. The mixture was partitioned between EtOAc (100 mL) and water (100 mL) at 40 °C. The organic phase was washed with brine (40 mL), dried over sodium sulfate and evaporated to an oil. The residue was purified by flash column chromatography (silica, 4:1 *t*-butyl methyl ether (MTBE)-hexane) to provide **5** (19.8 g, 97%). Hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 30% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 1.69 min. **5**: mp = 198-200 °C; ^1H nmr (250 MHz, deuteriochloroform): δ 7.58 (d, *J* = 8.5, 2H), 7.43 (d, *J* = 8.5, 2H), 3.83 (s, 2H), 3.69 (s, 3H), 3.38 (s, 2H), 1.96 (br s, 1H); ^{13}C nmr (62.9 MHz, deuteriochloroform): δ 172.7, 145.2, 132.2, 128.7, 118.9, 110.9, 52.6, 51.9, 49.8.

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.75; H, 5.81; N, 13.65.

Methyl 1-(4-Cyanobenzyl)-1*H*-imidazole-5-carboxylate (**6**).

A solution of 25% sodium methoxide in methanol (3.53 mL, 15.0 mmol) was added to a solution of **5** (1.02 g, 5.00 mmol) and diethyl oxalate (590 mg, 5.00 mmol) in tetrahydrofuran (12 mL) at 20 °C. Gold's reagent (1.06 g, 6.5 mmol) was added to the mixture to give an orange suspension, which was stirred for 18 h at 50 °C. The mixture was diluted with brine (10 mL) and *n*-propanol (1 mL). The organic layer was separated and the aqueous phase was extracted with tetrahydrofuran (10 mL). The combined organic phases were dried over potassium carbonate and evaporated to dryness. The residue was purified by flash column chromatography (silica, 19:1 MTBE-methanol) to provide **6** (335 mg, 28%). Hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 20% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 5.8 min. **6**: mp = 154-155 °C; ^1H nmr (400 MHz, deuteriochloroform): δ 7.80 (s, 1H), 7.71 (s, 1H), 7.63 (d, *J* = 8.2, 2H), 7.622 (d, *J* = 8.2, 2H), 5.58 (s, 2H), 3.80 (s, 3H); ^{13}C nmr (62.9 MHz, deuteriochloroform): δ 160.6, 142.4, 141.7, 138.4, 132.7, 127.5, 122.4, 118.3, 112.2, 51.7, 49.5.

Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.57; H, 4.51; N, 17.33.

4-(Azidomethyl)benzonitrile (**9**).

A mixture of **4** (19.6 g, 100 mmol), sodium azide (7.15 g, 110 mmol), *n*-tetrabutylammonium hydrogen sulfate (170 mg, 0.50 mmol), lithium iodide (134 mg, 1.00 mmol) and 95% ethanol (40 mL) was stirred at 80 °C for 1 h. The mixture was evaporated to an oil and the residue was dissolved in MTBE (50 mL). The resulting suspension was filtered through a plug of silica (5 g) washing the plug with MTBE (30 mL). The combined filtrates were evaporated to provide 15.8 g of **9** (quantitative). Hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 40% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 9.6 min. **9:** R_f = 0.32 (3:1 hexane-MTBE); ^1H nmr (250 MHz, deuteriochloroform): δ 7.67 (d, *J* = 8.2, 2H), 7.44 (d, *J* = 8.2, 2H), 4.45 (s, 2H); ^{13}C nmr (62.9 MHz, deuteriochloroform): δ 140.9, 132.7, 128.6, 118.5, 112.2, 54.1.

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.42. Found: C, 60.47; H, 3.78; N, 35.56.

4-[(1,3-Dioxo-2*H*-isoindol-2-yl)methyl]benzonitrile (**10**).

Potassium phthalimide (194 g, 1.05 mol), 4-(bromomethyl)-benzonitrile (**4**) (196 g, 1.00 mol), tetrabutylammonium iodide

(369 mg, 1.00 mmol) and DMF (400 g) were charged at 25 °C into a 3 neck 1 L flask. The mixture was maintained at 60 °C for 30 min. The mixture was diluted with water (400 mL) to precipitate the product **10** and the slurry aged for an hour at 35 °C, followed by dilution with additional water (800 mL) and aging for an hour at 10 °C. The slurry was filtered and the cake was washed with water (400 mL), 0.1 *M* aqueous HCl in 10% aq. methanol (300 mL), 10% aq. methanol (300 mL), 0.1 *M* ammonium hydroxide in 10% aq. methanol (300 mL) and finally 10% aq. methanol (300 mL). The crystals were dried under an N_2 stream to a constant weight to afford 262 g of crude phthalimide **10** (quantitative yield). Hplc conditions: S-5 micron B-03-5 YMC basic 4.6 x 250 mm column, isocratic elution with 42:58 acetonitrile-0.025% aqueous H_3PO_4 over 10 min then gradient elution to 62:38 acetonitrile-0.025% aqueous H_3PO_4 over 5 min, 1.0 mL/min flow and detection at 220 nm; hplc retention times: **4** = 12.5 min, **10** = 13.6 min. **10**: mp = 178-180 °C; ^{1}H nmr (400 MHz, d_6-DMSO): δ 7.85 (m, 4H), 7.76 (d, *J* = 8.2, 2H), 7.48 (d, *J* = 8.2, 2H), 4.82 (s, 2H); ^{13}C nmr (100 MHz, d_6-DMSO): δ 168.2, 142.7, 135.1, 133.0, 132.1, 128.7, 123.8, 119.1, 110.7, 41.1.

Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 72.94; H, 3.98; N, 10.55.

1-(4-Cyanobenzyl)-3,5,7-triaza-1-azoniatricyclo[3.3.1.1^{3,7}]-decane bromide (**11**).

A mixture of **4** (392 g, 2.00 mol) and HMTA (286 g, 2.04 mol) was dissolved in ethanol (1 L) in a 3 L 3 neck flask and the mixture was heated to 78-80 °C for 30 min. A mild exotherm set in within the first 5 min with a very gentle reflux, which subsided after 5 min and hplc analysis indicated the reaction was complete (>95% conversion). The mixture was allowed to cool to 65 °C over 30 min, and MTBE (1750 mL) was gradually added over 1 h during which time the temperature fell to 40 °C. The mixture was cooled to –3 °C over 30 min and aged at –3 to –5 °C for 30 min. The mixture was filtered and the crystalline solid was washed with 4:1 MTBE-ethanol (1 L), then with MTBE (3 x 1 L). The solid was dried under a N_2 stream for 16 h to afford 653 g of **11** (97% yield). Hplc conditions: S-5 micron B-03-5 YMC basic 4.6 x 250 mm column, isocratic elution with 42:58 acetonitrile-0.025% aqueous H_3PO_4 over 10 min then gradient elution to 62:38 acetonitrile-0.025% aqueous H_3PO_4 over 5 min, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 3.3 min. **11**: mp = 159-169 °C (dec); ^{1}H nmr (250 MHz, d_6-DMSO): δ 8.00 (d, *J* = 8.1, 2H), 7.74 (d, *J* = 8.1, 2H), 5.19 (s, 6H), 4.59 (d, *J* = 12.5, 3H), 4.44 (d, *J* = 12.5, 3H), 3.30 (s, 2H); ^{13}C nmr (62.9 MHz, d_6-DMSO): δ 133.5, 132.9, 131.2, 118.4, 112.9, 77.7, 69.7, 58.0.

Anal. Calcd for $C_{14}H_{18}BrN_5$: C, 50.01; H, 5.40; Br, 23.76; N, 20.83. Found: C, 49.68; H, 5.62; Br, 23.68; N, 20.56.

4-(Aminomethyl)benzonitrile (**8a**) *via* Azide **9**.

A solution of triphenylphosphine (26.2 g, 100 mmol) in tetrahydrofuran (25 mL) was gradually added to a solution of **9** (15.8 g, 100 mmol) over 20 min at reflux (exothermic, gas evolution). Hplc analysis indicated complete consumption of **9** (>98%) after 30 min at 50 °C. Water (10 mL), 50 wt% aqueous sodium hydroxide (NaOH, 8.0 g) and 95% ethanol (15 mL) were added to give a homogeneous mixture, which was aged at 60-65 °C for 40 min. Hplc analysis indicated complete consumption of the phosphazine intermediate (>98%). The mixture was cooled to 20 °C and acidified to pH = 7 with 5 *M* aqueous NaOH (20 mL) and evaporated. The residue was stirred with 2 *M* aqueous HCl (60 mL), MTBE (300 mL) and dichloromethane (20 mL) and partitioned. The aqueous phase was washed with MTBE (60 L). The organic phase was back extracted with water (25 mL). The aqueous back extract was washed with the MTBE (60 mL) used to wash the first aqueous extract. The two aqueous phases were combined, basified with 50 wt% aqueous NaOH (12 g) and extracted with dichloromethane (2 x 30 mL). The combined organic extracts were dried over potassium carbonate and evaporated to give 12.6 g of **8a** (95%) as an oil. Hplc conditions: S-5 micron B-03-5 YMC basic 4.6 x 250 mm column, isocratic elution with 42:58 acetonitrile-0.025% aqueous H_3PO_4 over 10 min then gradient elution to 62:38 acetonitrile-0.025% aqueous H_3PO_4 over 5 min, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 5.3 min. **8a** (as free base): ^{1}H nmr (250 MHz, deuteriochloroform): δ 7.58 (d, *J* = 8.2, 2H), 7.41 (d, *J* = 8.2, 2H), 3.92 (s, 2H), 1.45 (s, 2H); ^{13}C nmr (62.9 MHz, deuteriochloroform): δ 148.5, 132.3, 127.7, 119.0, 110.5, 46.0.

4-(Aminomethyl)benzonitrile HCl Salt (**8a•HCl**) *via* Phthalimide **10**.

Hydrazine monohydrate (100 g, 2.00 mol) was added over 40 min to a mixture of 4-cyanobenzyl phthalimide (**10**) (262 g, 1.00 mol) and ethanol (3.5 L) in a 5 L 3 neck flask, equipped with a mechanical stirrer, a nitrogen inlet adapter with a bubbler, and a thermocouple probe allowing the temperature to rise from 20 to 40 °C. The mixture was stirred for 1 h and hplc analysis indicated the reaction was complete by hplc analysis (>95% conversion). The thick slurry of the phthalhydrazide was filtered using ethanol (2 L) to wash the filter cake and the filtrate was concentrated under vacuum to an oily residue. The residue was dissolved in dichloromethane (500 mL) and 50% NaOH (200 g, 2.5 mol) was added to the mixture. The reaction mixture was transferred to a separatory funnel and dichloromethane (300 mL) was added. The combined aqueous phases were separated and extracted with dichloromethane (2 x 400 mL). The organic phase was dried over potassium carbonate (25 g) and filtered through a mixture of (potassium carbonate 20 g) and Solka-Floc® (20 g), using dichloromethane (300 mL) to wash the filter plug. The filtrate was concentrated under vacuum to afford the crude amine as an oil. A solution of HCl (72.9 g, 2.0 mol) in ethanol (275 g) was added over 90 min to a solution of the crude amine in ethanol (500 mL) in a 5 L 3 neck flask with mechanical stirring allowing the temperature to rise from 25 °C to 62 °C. EtOAc (2100 mL) was added over 90 min, during which the temperature was allowed to fall from 60 to 30 °C. The mixture was cooled to –5 °C over an hour and aged for an hour. The precipitate was filtered and washed with 9:1 EtOAc-ethanol (500 mL), then with EtOAc (2 x 500 mL). The HCl salt of **8a** was dried under a N_2 stream for 60 h to afford 152 g (90%). **8a•HCl**: mp = 290-294 °C; ^{1}H nmr (250 MHz, d_6-DMSO): δ 8.84 (br s, 3H), 7.87 (d, *J* = 8.3, 2H), 7.72 (d, *J* = 8.3, 2H), 4.10 (q, *J* = 5.7, 2H); ^{1}H nmr (250 MHz, D_2O): δ 7.86 (d, *J* = 8.1, 2H), 7.66 (d, *J* = 8.1, 2H), 4.34 (s, 2H); ^{13}C nmr (62.9 MHz, d_6-DMSO): δ 139.7, 132.4, 129.9, 118.6, 111.0, 41.6; ^{13}C nmr (62.9 MHz, D_2O): δ 138.8, 134.1, 130.4, 120.1, 112.6, 43.5.

Anal. Calcd for $C_8H_9ClN_2$: C, 56.89; H, 5.38; N, 16.61. Found: C, 57.06; H, 5.21; N, 16.47.

4-(Aminomethyl)benzonitrile Phosphate Salt (**8a•H_3PO_4**) *via* Hexamethylenetetramine Salt **11**.

A slurry of HMTA (715 g, 5.10 mol) in ethanol (2.5 L) was added gradually (in 10 equal portions) over 30-60 min to a stirred

slurry of **4** (980 g, 5.00 mol) in ethanol (3.5 L) maintained at 48-53 °C in a 22 L 4 neck flask equipped with a mechanical stirrer, thermocouple probe, condenser with nitrogen inlet and a large powder funnel. The transfer of HMTA to the reaction mixture was completed with the use of ethanol (1.0 L). The reaction mixture was heated up to 68-73 °C and aged at 68-73 °C for 90 min. Hplc analysis of the reaction mixture indicated complete consumption of **4** (<0.5 A%). The mixture was cooled to 55 °C and propionic acid (4.00 kg) was added. Concentrated phosphoric acid (2.11 kg, 18.4 mol) was gradually added over 5-10 min maintaining the reaction mixture below 65 °C. The mixture was aged at 65-70 °C for 30 min. Hplc analysis of the reaction mixture indicated complete reaction (<1.0 A% HMTA salt **11** remaining). The mixture was gradually cooled to 20-25 °C over 1 h and aged at 20-25 °C for 1 h. The reaction slurry was filtered. The filter cake was washed with ethanol (4 x 2.5 L), water (5 x 1.5 L) and acetonitrile (2 x 1.0 L). The solid was dried to provide 1.01 kg of **8a** as phosphate salt (88% yield from **4**) of 99.9 hplc A%, 98-100 hplc wt% phosphate salt. Hplc conditions: Waters Spherisorb S5 OD/CN 150 x 4.6 mm column, gradient elution over 15 min with 5/95 → 75/25 acetonitrile/aqueous 0.05 *M* ammonium dihydrogen phosphate ($NH_4H_2PO_4$), 1.5 mL/min flow at 25 °C with detection at 230 nm; hplc retention times: **4** = 10.8 min, **11** = 4.1 min, **8a** = 2.6 min. **8a•H_3PO_4**: mp = 147-155 °C (dec).

Anal. Calcd for $C_8H_{11}N_2O_4P$: C, 41.72; H, 4.82; N, 12.17. Found: C, 41.68; H, 4.75; N, 12.20.

4-{[5-(Hydroxymethyl)-2-mercapto-1*H*-imidazol-1-yl]methyl}-benzonitrile (**7a**).

A mixture of acetonitrile/water (93:7, v/v, 5.0 L) was charged to a 22 L round bottom flask equipped with mechanical stirrer and reflux condenser. Phosphate salt **8a** (125 g, 5.02 mol), potassium thiocyanate (604 g, 6.22 mmol), dihydroxyacetone dimer (561 g, 6.22 mmol as monomer), and propionic acid (1.00 L, 13.5 mol) were added respectively. Acetonitrile/water 93:7 (2.5 L) was used to rinse down the sides of the flask. The colorless slurry was heated to 60 °C, aged for 30 minutes, and seeded with **7a** (10 g). The mixture was aged an additional 1.5 hours at 60 °C. The reaction was further heated to 70 °C for an additional 2 h. The mixture was cooled to room temperature and aged overnight. The solids were isolated *via* vacuum filtration to give a light tan solid and black mother liquors. The solids were washed with acetonitrile (4 x 2.5 L) and water (3 x 5.0 L) and dried to give 100 g of **7a** (98.2 hplc wt%, 81.5% yield). Hplc conditions: Waters Spherisorb S5 OD/CN 150 x 4.6 mm column, gradient elution over 15 min with 5/95 → 75/25 acetonitrile/aqueous 0.05 *M* $NH_4H_2PO_4$, 1.5 mL/min flow at 25 °C with detection at 230 nm; hplc retention time = 5.4 min. **7a**: mp = 160-162 °C; ^{1}H nmr (250 MHz, d_6-DMSO): δ 12.27 (s, 1H), 7.79 (d, *J* = 8.1, 2H), 7.36 (d, *J* = 8.1, 2H), 6.91 (s, 1H), 5.38 (s, 2H), 5.25 (t, *J* = 5.1, 1H), 4.16 (d, *J* = 5.1, 2H); ^{13}C nmr (62.9 MHz, d_6-DMSO): δ 162.7, 142.9, 132.4, 130.2, 127.7, 118.8, 113.1, 110.0, 53.2, 46.3.

Anal. Calcd for $C_{12}H_{11}N_3OS$: C, 58.76; H, 4.52; N, 17.13. Found: C, 58.69; H, 4.48; N, 16.91.

General Procedure for Preparation of Mercaptoimidazoles **7a – 7e** in Table 1.

A mixture of the appropriate benzylamine hydrochloride **8a**-**8e** (50.0 mmol), dihydroxyacetone dimer (4.95 g, 55.0 mmol as monomer), potassium thiocyanate (7.29 g, 75.0 mmol), acetic acid (6.01g, 100 mmol), acetonitrile (49 mL) and water (1.0 mL) were stirred for 18 h at 55 °C. The mixture was cooled to 20 °C and filtered. The filter cake was washed with acetonitrile (50 mL), water (100 mL) and EtOAc (50 mL). The solid was dried under a stream of nitrogen to provide mercaptoimidazoles **7a**-**7e**.

4-{[5-(Hydroxymethyl)-2-mercapto-1*H*-imidazol-1-yl]methyl}-benzonitrile (**7a**).

This compound was obtained in 90% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 20% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 1.9 min.

(1-Benzyl-2-mercapto-1*H*-imidazol-5-yl)methanol (**7b**).

This compound was obtained in 97% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 20% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 7.9 min. **7b**: mp = 203-206 °C (lit 195-200 °C) [9a]; ^{13}C nmr (100 MHz, d_6-DMSO) δ 162.9, 137.6, 130.8, 128.9, 127.7, 127.3, 113.3, 53.7, 46.8. (For isolation of byproduct **X** from mother liquor see below)

Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.98; H, 5.49; N, 12.72; S, 14.55. Found: C, 59.86; H, 5.39; N, 12.66; S, 14.64.

[2-Mercapto-1-(4-methoxybenzyl)-1*H*-imidazol-5-yl]methanol (**7c**).

This compound was obtained in 92% yield; hplc conditions: ACE 3 C18 4.6 x 150 column, isocratic elution with 20% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 9.0 min. **7c**: mp = 217-220 °C; ^{1}H nmr (400 MHz, d_6-DMSO): δ 12.24 (s, 1H), 7.18 (d, *J* = 8.7, 2H), 6.84 (d, *J* = 8.7, 2H), 6.77 (s, 1H), 5.21 (s, 2H), 4.70 (br s, 1H), 4.12 (s, 2H), 3.68 (s, 3H); ^{13}C nmr (100 MHz, d_6-DMSO): δ 162.8, 159.0, 130.8, 129.6, 128.9, 114.3, 113.3, 55.6, 53.8, 46.4.

Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; S, 12.81. Found: C, 57.25; H, 5.47; N, 11.20; S, 12.78.

[1-(4-Bromobenzyl)-2-mercapto-1*H*-imidazol-5-yl]methanol (**7d**).

This compound was obtained in 90% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 30% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 7.7 min. **7d**: mp = 229-231 °C; ^{1}H nmr (400 MHz, d_6-DMSO): δ 12.27 (s, 1H), 7.47 (d, *J* = 8.4, 2H), 7.15 (d, *J* = 8.4, 2H), 6.83 (s, 1H), 5.24 (s, 2H), 4.75 (br s, 1H), 4.12 (s, 2H); ^{13}C nmr (100 MHz, d_6-DMSO): δ 163.1, 137.0, 131.8, 130.3, 129.7, 120.8, 113.5, 53.7, 46.4.

Anal. Calcd for $C_{11}H_{11}BrN_2OS$: C, 44.16; H, 3.71; Br, 26.71; N, 9.36; S, 10.72. Found: C, 43.90; H, 3.64; Br, 26.91; N, 9.06; S, 10.56.

[2-Mercapto-1-(4-nitrobenzyl)-1*H*-imidazol-5-yl]methanol (**7e**).

This compound was obtained in 92% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 20% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 9.9 min. **7e**: mp = 216-217 °C (lit 214-215 °C) [9b]; ^{13}C nmr (100 MHz, d_6-DMSO): δ 163.2, 147.1, 145.4, 130.7, 128.4, 124.0, 113.6, 53.6, 46.6.

Anal. Calcd for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.84; S, 12.09. Found: C, 49.60; H, 4.17; N, 15.76; S, 11.80.

Isolation of Byproduct 4-Benzyl-3a-methyltetrahydro-2*H*-imidazo[4,5-*d*][1,3]oxazole-2,5(3*H*)-dithione (**X**) from Formation of **7b** in 49:1 Acetonitrile-water.

The mother liquor obtained from the reaction mixture employing benzylamine·HCl (50 mmol) was partitioned between water (60 mL) and $CHCl_3$ (12 mL). The organic phase was evaporated and the residue was purified by flash column chromatography (silica, 4:1 MTBE-hexane) to provide **X** (390 mg, 2.8%). Hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 30% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 7.3 min. **X**: mp = 211-213 °C; ^{1}H nmr (400 MHz, d_6-acetone): δ 8.23 (br s, 1H), 8.18 (br s, 1H), 7.41 (m, 2H), 7.30-7.19 (m, 3H), 5.87 (d, *J* = 1.3, 1H), 4.98 (d, *J* = 16.2, 1H), 4.82 (d, *J* = 16.2, 1H), 1.58 (s, 3H); ^{13}C nmr (100 MHz, d_6-acetone): δ 182.1, 169.7, 138.4, 128.2, 127.2, 127.0, 83.4, 68.5, 45.3, 22.7.

Anal. Calcd for $C_{12}H_{13}N_3OS_2$: C, 51.59; H, 4.69; N, 15.04; S, 22.95. Found: C, 51.87; H, 4.52; N, 14.68; S, 22.88.

4-{[5-(Hydroxymethyl)-1*H*-imidazol-1-yl]methyl}benzonitrile (**12a**).

A 100 L glass reactor equipped with internal cooling/heating coils and mechanical stirrer was charged with water (26 L), mercaptoimidazole **7a** (6.37 kg, 26.0 mol) and acetic acid (12.0 L) to form a pale pink slurry. Hydrogen peroxide (30% aq, 8.70 kg, 80.6 mol) was added slowly over 2 h maintaining a temperature of 35-45 °C. *Caution: exothermic* [17]. The temperature was lowered to 25 °C and the resulting homogeneous yellow solution aged for 1 h. Hplc analysis indicated complete reaction (<1 A% **7a** remaining). The solution was cooled to 10 °C and quenched by addition of 20% aqueous sodium sulfite (2.0 L) over 30 min maintaining the temperature <15 °C. The solution was filtered through a bed of Darco G-60 carbon (1 kg) over a bed of Solka-Floc® (1 kg). The bed was washed with of 10% aqueous acetic acid (10 L). The combined filtrates were cooled to 5 °C and 25% aqueous ammonia (16.6 kg, 292 mol) was added over a 1 h, maintaining the temperature below 25 °C, to a pH of 9.3. The slurry was aged 1 h at 5 °C. The solids were isolated *via* vacuum filtration. The cake was washed with a solution composed of 1.25% aqueous ammonium hydroxide (20 L) and ethyl acetate (16 L). The cake was dried to provide 4.98 kg of **7a** (90%). Hplc conditions: Waters Spherisorb S5 OD/CN 150 x 4.6 mm column, gradient elution over 15 min with 5/95 → 75/25 acetonitrile/aqueous 0.05M $NH_4H_2PO_4$, 1.5 mL/min flow at 25 °C with detection at 230 nm; hplc retention time = 4.7 min. **12a**: mp = 165-167 °C; ^{1}H nmr (250 MHz, CD_3OD): δ 7.76 (s, 1H), 7.70 (d, *J* = 7.0, 2H), 7.32 (d, *J* = 7.0, 2H), 6.98 (s, 1H), 5.41 (s, 2H), 4.43 (s, 2H); ^{1}H nmr (400 MHz, d_6-DMSO): δ 7.78 (d, *J* = 8.4, 2H), 7.69 (s, 1H), 7.27 (d, *J* = 8.4, 2H), 6.83 (s, 1H), 5.32 (s, 2H), 5.12 (br s, 1H), 4.28 (s, 2H); ^{13}C nmr (100 MHz, d_6-DMSO): δ 143.9, 139.2, 133.1, 132.2, 128.3, 128.1, 119.1, 110.8, 53.2, 47.7.

Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.37; H, 5.07; N, 19.55.

General Procedure for Preparation of Imidazoles **12a-e** in Table 2.

Method A.

A solution of 30% aqueous hydrogen peroxide (3.74 g, 33.0 mmol) was gradually added over 30 min to a suspension of the appropriate mercaptoimidazole **7a-e** (10.0 mmol) in acetic acid (5.0 mL) and water (1.0 mL) while maintaining the temperature at 35-45 °C. *Caution: exothermic* [17]. The now homogeneous mixture was stirred for 30 min at 40 °C and then cooled to 20 °C. The mixture was quenched by addition of 10% aqueous sodium sulfite (1 mL) at 25 °C. The mixture was treated with Darco G60 carbon (0.1 g) for 30 min at 20 °C and filtered through a plug of Solka-Floc®. The filtrates were basified to pH = 9.0 with 25% aqueous ammonia (10 mL) at 20 °C. The resulting slurry was stirred for 30 min and filtered. The solid was washed with water (30 mL) and 2:1 water-methanol (15 mL). The solid was dried under a stream of nitrogen to provide hydroxymethylimidazoles **12a-e**.

Method B.

A solution of sodium nitrite (552 mg, 8.00 mmol) in water (0.6 mL) was added to a suspension of the appropriate mercaptoimidazole **7a-e** (2.00 mmol) in acetic acid (10 mL) over 20 min at 20-30 °C. *Caution: nitrogen oxides evolved* [16]. Ice (10 g) was added and the mixture was basified with concentrated aqueous ammonia at 20-30 °C. The resulting slurry was stirred for 30 min and filtered. The solid was washed with water (30 mL) and 2:1 water-methanol (15 mL). The solid was dried under a stream of nitrogen to provide hydroxymethylimidazoles **12a-e**.

4-{[5-(Hydroxymethyl)-1*H*-imidazol-1-yl]methyl}benzonitrile (**12a**).

This compound was obtained by Method A in 84% yield and by Method B in 75% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with a 20% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 1.9 min.

(1-Benzyl-1*H*-imidazol-5-yl)methanol (**12b**).

This compound was obtained by Method A in 90% yield and by Method B in 65% yield; hplc conditions: ACE 3 C18 4.6 x 150 column, isocratic elution with a 30% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 1.69 min. **12b**: mp = 137-141 °C (lit 131-138 °C) [9a]; ^{13}C nmr (100 MHz, d_6-DMSO): δ 138.9, 138.0, 132.1, 129.1, 128.0, 127.9, 127.5, 53.3, 48.0.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.97; H, 6.48; N, 14.79.

[1-(4-Methoxybenzyl)-1*H*-imidazol-5-yl] methanol (**12c**).

This compound was obtained by Method A in 81% yield and by Method B in 20% yield; hplc conditions: ACE 3 C18 4.6 x 150 column, isocratic elution with a 30% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 1.75 min. **12c**: mp = 114-116 °C; ^{1}H nmr (400 MHz, d_6-DMSO): δ 7.61 (d, *J* = 0.8, 1H), 7.12 (d, *J* = 8.7, 2H), 6.87 (d, *J* = 8.7, 2H), 6.78 (d, *J* = 0.8, 1H), 5.11 (s, 2H), 5.09 (br s, 1H), 4.31 (s, 2H), 3.69 (s, 3H); ^{13}C nmr (100 MHz, d_6-DMSO): δ 159.3, 138.7, 132.1, 129.9, 129.1, 127.8, 114.5, 55.6, 53.3, 47.6.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.65; H, 6.33; N, 12.75.

[1-(4-Bromobenzyl)-1*H*-imidazol-5-yl]methanol (**12d**).

This compound was obtained by Method A in 92% yield and by Method B in 74% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with a 20% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220

nm; hplc retention time = 5.0 min. **12d**: mp = 125-126 °C; ^{1}H nmr (400 MHz, *d*6-DMSO): δ 7.69 (d, *J* = 0.8, 1H), 7.53 (d, *J* = 8.4, 2H), 7.12 (d, *J* = 8.4, 2H), 6.83 (d, *J* = 0.8, 1H), 5.21 (s, 2H), 5.14 (br s, 1H), 4.32 (s, 2H); ^{13}C nmr (100 MHz, *d*6-DMSO): δ 138.9, 137.5, 132.1, 132.0, 129.7, 128.0, 121.1, 53.2, 47.3.

Anal. Calcd for $C_{11}H_{11}BrN_2O$: C, 49.46; H, 4.15; Br, 29.91; N, 10.49. Found: C, 49.30; H, 3.99; Br, 29.67; N, 10.48.

[1-(4-Nitrobenzyl)-1*H*-imidazol-5-yl]methanol (**12e**).

This compound was obtained by Method A in 93% yield and by Method B in 79% yield: ACE 3 C18 4.6 x 150 mm column, isocratic elution with a 20% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 2.6 min. **12e**: mp = 207-210 °C (lit 203-206 °C) [9b]; ^{13}C nmr (100 MHz, *d*6-DMSO): δ 147.4, 145.9, 139.2, 132.2, 128.5, 128.2, 124.2, 53.2, 47.5.

Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.49; H, 4.66; N, 17.80.

General Procedure for Preparation of Mercaptoimidazoles **14a** – **14e** in Table 3.

A mixture of the appropriate benzylamine **8** (8.00 mmol), hydroxyketone **13a-c** (9.60 mmol), potassium thiocyanate (1.17 g, 12.0 mmol), acetic acid (1.44 g, 24.0 mmol), acetonitrile (8.0 mL) and water (0.16 mL, 8.8 mmol) were stirred for 18 h at 55-60 °C. The mixture was cooled to 20 °C and filtered. The filter cake was washed with acetonitrile (16 mL), water (32 mL) and 3:1 water-methanol (16 mL). The solid was dried under a stream of nitrogen to provide mercaptoimidazoles **14a**-**14e**.

4-[(5-Benzyl-2-mercapto-1*H*-imidazol-1-yl)methyl]benzonitrile (**14a**).

This compound was obtained in 65% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 40% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 10.0 min. **14a**: mp = 247-250 °C; ^{1}H nmr (400 MHz, *d*6-DMSO): δ 12.26 (s, 1H), 7.64 (d, *J* = 8.0, 2H), 7.22 (m, 5H), 7.07 (d, *J* = 8.0, 2H), 6.69 (s, 1H), 5.16 (s, 2H), 3.80 (s, 2H); ^{13}C nmr (100 MHz, *d*6-DMSO): δ 163.0, 143.4, 137.0, 132.8, 129.8, 128.8, 128.6, 127.5, 127.0, 119.2, 113.6, 109.9, 46.9, 30.7.

Anal. Calcd for $C_{18}H_{15}N_3S$: C, 70.79; H, 4.95; N, 13.76; S, 10.50. Found: C, 70.50; H, 4.87; N, 13.88; S, 10.38.

4-[(1-Benzyl-2-mercapto-1*H*-imidazol-1-yl)methyl]benzonitrile (**14b**).

This compound was obtained in 66% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 40% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 9.4 min. **14b**: mp = 236-239 °C; ^{1}H nmr (400 MHz, *d*6-DMSO): δ 12.27 (s, 1H), 7.69 (d, *J* = 8.5, 2H), 7.18 (m, 5H), 7.05 (d, *J* = 8.5, 2H), 6.68 (s, 1H), 5.24 (s, 2H), 3.70 (s, 2H); ^{13}C nmr (100 MHz, *d*6-DMSO): δ 162.9, 142.8, 137.2, 132.7, 129.7, 128.9, 128.8, 127.9, 127.0, 119.2, 113.3, 110.3, 46.6, 30.6.

Anal. Calcd for $C_{18}H_{15}N_3S$: C, 70.79; H, 4.95; N, 13.76; S, 10.50. Found: C, 70.54; H, 4.78; N, 13.85; S, 10.21.

5-Benzyl-1-(4-fluorobenzyl)-1*H*-imidazole-2-thiol (**14c**).

This compound was obtained in 69% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 40% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 18.1 min. **14c**: mp = 210-212 °C; ^{1}H nmr (400 MHz, *d*6-DMSO): δ 12.17 (s, 1H), 7.19 (m, 5H), 7.06 (m, 4H), 6.56 (s, 1H), 5.10 (s, 2H), 3.65 (s, 2H); ^{13}C nmr (100 MHz, *d*6-DMSO): δ 162.8, 161.8 (d, *J* = 243, *aryl*-*C*F), 137.3, 133.4 (d, *J* = 3.1, *aryl*-*C*-*para*-F), 129.8, 129.3 (d, *J* = 8.2, *aryl*-*C*-*meta*-F), 129.0, 128.8, 127.1, 115.7 (d, *J* = 21.3, *aryl*-*C*-*ortho*-F), 113.2, 46.2, 30.8.

Anal. Calcd for $C_{17}H_{15}FN_2S$: C, 68.43; H, 5.07; F, 6.37; N, 9.39; S, 10.75. Found: C, 68.05; H, 4.81; F, 6.37; N, 9.39; S, 10.84.

4-{[1-(4-Fluorobenzyl)-2-mercapto-1*H*-imidazol-5-yl]methyl}-benzonitrile (**14d**).

This compound was obtained in 85% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 40% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 10.0 min. **14d**: mp = 234-236 °C; ^{1}H nmr (400 MHz, *d*6-DMSO): δ 12.24 (s, 1H), 7.59 (d, *J* = 8.3, 2H), 7.18 (d, *J* = 8.3, 2H), 7.07 (m, 2H), 6.98 (m, 2H), 6.80 (d, *J* = 2.4, 1H), 5.12 (s, 2H), 3.81 (s, 2H); ^{13}C nmr (100 MHz, *d*6-DMSO): δ 163.0, 161.8 (d, *J* = 243, *aryl*-*C*F), 143.0, 133.2 (d, *J* = 2.8, *aryl*-*C*-*para*-F), 132.7, 129.9, 129.3 (d, *J* = 8.2, *aryl*-*C*-*meta*-F), 128.5, 119.2, 115.5 (d, *J* = 21.4, *aryl*-*C*-*ortho*-F), 113.8, 109.9, 46.3, 30.7.

Anal. Calcd for $C_{18}H_{14}FN_3S$: C, 66.85; H, 4.36; F, 5.87; N, 12.99; S, 9,92. Found: C, 66.54; H, 4.18; F, 6.13; N, 13.10; S, 9.81.

4-{[5-(4-Fluorobenzyl)-2-mercapto-1*H*-imidazol-1-yl]methyl}-benzonitrile (**14e**).

This compound was obtained in 57% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 40% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 10.4 min. **14e**: mp = 246-252 °C; ^{1}H nmr (400 MHz, *d*6-DMSO): δ 12.27 (s, 1H), 7.63 (d, *J* = 8.1, 2H), 7.13 (d, *J* = 8.1, 2H), 7.02 (m, 2H), 6.92 (m, 2H), 6.67 (s, 1H), 5.22 (s, 2H), 3.68 (s, 2H); ^{13}C nmr (100 MHz, *d*6-DMSO): δ 163.1, 161.4 (d, *J* = 243, *aryl*-*C*F), 142.7, 133.3 (d, *J* = 2.8, *aryl*-*C*-*para*-F), 132.7, 130.7 (d, *J* = 8.1, *aryl*-*C*-*meta*-F), 129.8, 127.9, 119.2, 115.6 (d, *J* = 21.3, *aryl*-*C*-*ortho*-F), 113.3, 110.2, 46.7, 29.8.

Anal. Calcd for $C_{18}H_{14}FN_3S$: C, 66.85; H, 4.36; F, 5.87; N, 12.99; S, 9,92. Found: C, 66.55; H, 4.23; F, 6.18; N, 12.99; S, 9.68.

General Procedure for Preparation of Imidazoles **15a** – **15e** in Table 3.

A solution of 30% aqueous hydrogen peroxide (1.93 g, 17.0 mmol) was gradually added over 30 min to a suspension of the appropriate mercaptoimidazole **14a-e** (5.00 mmol) in acetic acid (4.0 mL) and water (0.80 mL) while maintaining the temperature at 35-65 °C. *Caution exothermic* [17]. The now homogeneous mixture was stirred for 30 min at 40 °C and then cooled to 20 °C. The mixture was quenched by addition of 10% aqueous sodium sulfite (1 mL) at 25 °C. The mixture was basified to pH = 9.0 with 25% aqueous ammonia (8 mL) at 20 °C and extracted with chloroform (2 x 5 mL). The combined organic extracts were washed with 0.5 *M* aqueous NaOH (10 mL) and dried (magnesium sulfate). The solid was washed with water (30 mL) and 2:1 water-methanol (15 mL). The organic phase was evaporated and the residue was purified by flash column chromatography (silica,

1:1 MTBE-EtOAc then EtOAc) to provide **15a-e**. The chromatographed material was recrystallized from EtOAc-hexanes to provide the pure imidazoles **15a-e**.

4-[(5-Benzyl-1*H*-imidazol-1-yl)methyl]benzonitrile (**15a**).

This compound was obtained in 83% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 30% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 5.1 min. **15a**: mp = 130-132 °C; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.55 (m, 2H), 7.50 (m, 1H), 7.21 (m, 3H), 6.99 (m, 5H), 4.96 (s, 2H), 3.7 (s, 2H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 141.7, 138.3, 137.5, 132.7, 130.2, 129.3, 128.7, 128.3, 127.1, 126.9, 118.3, 112.0, 48.1, 30.3.

Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37. Found: C, 78.70; H, 5.48; N, 15.11.

4-[(1-Benzyl-1*H*-imidazol-5-yl)methyl]benzonitrile (**15b**).

This compound was obtained in 91% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 30% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 4.9 min. **15b**: mp = 122-124 °C; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.53 (s, 1H), 7.51 (d, *J* = 8.2, 2H), 7.28 (m, 3H), 7.14 (d, *J* = 8.2, 2H), 6.92 (m, 2H), 6.88 (s, 1H), 4.90 (s, 2H), 3.83 (s, 2H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 143.5, 138.7, 135.8, 132.4, 129.4, 129.2, 129.1, 128.8, 128.2, 126.6, 118.7, 110.7, 48.8, 30.5.

Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37. Found:. C, 78.84; H, 5.44; N, 15.27

5-Benzyl-1-(4-fluorobenzyl-1*H*-imidazole (**15c**).

This compound was obtained in 80% yield; hplc conditions: ACE 3 C18 4.6 x 150 mm column, isocratic elution with 30% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 8.7 min. **15c**: mp = 61-63 °C; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.47 (s, 1H), 7.24 (m, 3H), 7.07 (m, 2H), 6.99 (m, 2H), 6.92 (m, 3H), 4.85 (s, 2H), 3.78 (s, 2H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 162.4 (d, *J* = 247, *aryl-C*F), 138.2, 137.8, 132.0 (d, *J* = 3.2, *aryl-C-para*-F), 130.2, 129.0, 128.7, 128.5 (d, *J* = 8.4, *aryl-C-meta*-F), 128.4, 126.8, 115.9 (d, *J* = 21.7, *aryl-C-ortho*-F), 48.0, 30.4.

Anal. Calcd for $C_{17}H_{15}FN_2$: C, 76.67; H, 5.68; F, 7.13; N, 10.52. Found: C, 76.46; H, 5.75; F, 6.96; N, 10.47.

4-{[1-(4-Fluorobenzyl)-1*H*-imidazol-5-yl]methyl}benzonitrile (**15d**).

This compound was obtained in 76% yield; hplc conditions: ACE 3 C18 4.6 x 150 column, isocratic elution with 30% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 5.2 min. **15d**: mp = 105-107 °C; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.53 (d, *J* = 8.3, 2H), 7.52 (m, 1H), 7.15 (d, *J* = 8.3, 2H), 6.97 (m, 2H), 6.90 (m, 3H), 4.87 (s, 2H), 3.82 (s, 2H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 162.5 (d, *J* = 248, *aryl-C*F), 143.4, 138.6, 132.5, 131.5 (d, *J* = 3.2, *aryl-C-para*-F), 129.5, 129.2, 128.7, 128.4 (d, *J* = 8.1, *aryl-C-meta*-F), 118.6, 116.0 (d, *J* = 21.7, *aryl-C-ortho*-F), 110.8, 48.1, 30.5.

Anal. Calcd for $C_{18}H_{14}FN_3$: C, 74.21; H, 4.84; F, 6.52; N, 14.42. Found: C, 73.99; H, 4.69; F, 6.63; N, 14.35.

4-{[5-(4-Fluorobenzyl)-1*H*-imidazol-1-yl]methyl}benzonitrile (**15e**).

This compound was obtained in 74% yield; hplc conditions: ACE 3 C18 4.6 x 150 column, isocratic elution with 30% acetonitrile in 0.1% aqueous H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm; hplc retention time = 5.5 min. **15e**: mp = 109-111 °C; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.57 (d, *J* = 8.2, 2H), 7.51 (s, 1H), 6.99 (d, *J* = 8.2, 2H), 6.97 (m, 2H), 6.92 (m, 3H), 4.96 (s, 2H), 3.71 (s, 2H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 161.7 (d, *J* = 246, *aryl-C*F), 141.5, 138.4, 133.0 (d, *J* = 3.2, *aryl-C-para*-F), 132.7, 130.0, 129.7 (d, *J* = 7.9, *aryl-C-meta*-F), 129.2, 127.0, 118.2, 115.5 (d, *J* = 21.7, *aryl-C-ortho*-F), 112.0, 48.0, 29.5.

Anal. Calcd for $C_{18}H_{14}FN_3$: C, 74.21; H, 4.84; F, 6.52; N, 14.42. Found: C, 74.06; H, 4.77; F, 6.59; N, 14.38.

4-{[5-(Chloromethyl)-1*H*-imidazol-1-yl]methyl}benzonitrile Hydrochloride Salt (**2•HCl**).

Oxalyl chloride (101 mL, 1.15 mol) was added over 30 min to a mixture of DMF (178 mL, 2.30 mol) and acetonitrile (2.56 L) in a 5 L 3 neck round bottom flask maintained below 10 °C to give a white slurry containing the Vilsmeier reagent. The slurry of Vilsmeier reagent was transferred over 15 min to a slurry of **12a** (213 g, 1.00 mol) and acetonitrile (1.7 L) in a 12 L round bottom flask, using acetonitrile (1.1 L) to complete the transfer and maintaining the temperature below 6 °C. The mixture was warmed to 25 °C and aged for 3 h. The reaction was determined to be complete when ≤ 0.5 mole% **12a** remained by ^{1}H nmr [28]. The slurry was then cooled to 0 °C and aged 60 min. The solid was isolated *via* vacuum filtration, washed with ice-cold acetonitrile (1.5 L) and dried *in vacuo* yielding 268 g of **2•HCl** as a light tan solid (94.2 hplc wt% purity, 94% yield, product contained 0.77 wt% **12a**, 1.28 wt% DMF and 1.57 wt% acetonitrile by ^{1}H nmr). **2•HCl**: mp = 199-207 °C (dec); ^{1}H nmr (250 MHz, d_6-DMSO): δ 9.44 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.89 (s, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 5.70 (s, 2H), 4.93 (s, 2H), 4.2 (very br s, 1 H). ^{13}C nmr (75.5 MHz DMSO-d_6): δ 139.7, 137.7, 132.7, 130.1, 128.8, 120.7, 118.4, 111.2, 48.9, 33.1.

Anal. Calcd for $C_{12}H_{11}Cl_2N_3$: C, 53.75; H, 4.13; Cl, 26.44; N, 15.67. Found C, 53.39; H, 4.18; Cl, 26.08; N, 15.61.

N^1-(3-Chlorophenyl)-N^2-(2-hydroxyethyl)glycinamide (**17**).

Chloroacetyl chloride (4.8 kg, 42.2 mol) was added over 1 h to a stirred biphasic mixture of 3-chloroaniline (3.99 kg, 31.3 mol) in isopropyl acetate (37.1 L) and potassium bicarbonate (6.25 kg, 42.2 mol) in water (25 L) maintained <10 °C. The aqueous layer was removed and the organic phase containing chloroacetamide **16** was treated with ethanolamine (7.5 L). The mixture was heated to 56-62 °C for 1 h. Water (11 L) and isopropyl acetate (3 L) were added and the mixture was brought to 55 °C. The organic phase was separated and cooled to 5 °C over 1 h. The crystallized solid was collected by filtration, washed with isopropyl acetate (2 x 5 L) and dried to constant weight *in vacuo* to provide 5.95 kg **17** (83%, >99.5 hplc A%). Hplc conditions: Advantage Basic 250 x4.6 mm column, isocratic elution with 30:70 acetonitrile-0.01 *M* aqueous $NH_4H_2PO_4$ over 6 min then gradient elution to 80:20 acetonitrile-0.01 *M* aqueous $NH_4H_2PO_4$ over 7 min, 1.0 mL/min flow at 25 °C with detection at 230 nm; hplc retention times: 3-chloroaniline = 12.2 min, chloroacetamide **16** = 13.2 min, hydroxyamide **17** = 6.0 min. **17**: mp = 104-105 °C; ^{1}H nmr (400 MHz, d_6-DMSO): δ 10.10 (br s, 1H), 7.85 (br t, *J* = 2.0, 1H), 7.52 (d, *J* = 8.0, 1H), 7.33 (t, *J* = 8.0, 1H), 7.10 (d, *J* = 2.0, 1H), 4.5-4.8 (br s, 1H), 3.47 (t, *J* = 5.0, 2H), 3.30 (s, 2H), 2.60 (t, *J* =

5.0, 2H); ^{13}C nmr (75 MHz, d_6-DMSO): δ 170.9, 140.1, 133.0, 130.3, 122.8, 118.5, 117.5, 60.3, 52.7, 51.5.

Anal. Calcd for $C_{10}H_{13}ClN_2O_2$: C, 52.52; H, 5.73; N, 12.25; Cl, 15.50. Found: C, 52.41; H, 5.50; N, 12.15; Cl, 15.53.

1-(3-Chlorophenyl)piperazine-2-one HCl Salt (**3•HCl**).

DIAD (1.02 kg, 5.4 mol) was added over 1.5 h to a mixture of tributylphosphine (1.1 kg, 5.4 mol) and EtOAc (2.7 L) maintained <0 °C and the mixture was aged at 0 °C for 30 min. The resulting solution was added over 1.5 h to a solution of **17** (0.905 kg, 3.97 mol) in EtOAc (5.6 L) maintained <5 °C and the mixture was warmed to 20 °C over 1 h. The mixture was warmed to 40 °C and 3.8 *M* anhydrous ethanolic HCl (1.04 L, 3.95 mol) was added over 2 h. The resulting slurry was cooled to 0 °C over 1.5 h and aged at 0 °C for 1 h. The crystalline HCl salt was filtered, washed with EtOAc (3 x 1 L) at 5 °C and dried to constant weight *in vacuo* to afford 760 g of piperazinone salt **3•HCl** (77%, 99.0 hplc wt%). Hplc conditions: Advantage Basic 250 x 4.6 mm column, isocratic elution with 30:70 acetonitrile-0.01 *M* aqueous $NH_4H_2PO_4$ over 6 min then gradient elution to 80:20 acetonitrile-0.01 *M* aqueous $NH_4H_2PO_4$ over 7 min, 1.0 mL/min flow at 25 °C with detection at 230 nm; hplc retention time = 5.2 min. **3•HCl**: mp = 232-235 °C; ^{1}H nmr (300 MHz, d_6-DMSO): δ 10.24 (br s, 2H), 7.50-7.30 (m, 4H), 3.92 (t, *J* = 5.5, 2H), 3.84 (s, 2H), 3.51 (t, *J* = 5.5, 2H); ^{13}C nmr (75 MHz, d_6-DMSO): δ 162.1, 142.6, 132.9, 130.7, 127.0, 126.1, 124.5, 46.1, 44.9, 39.8.

Anal. Calcd for $C_{10}H_{12}Cl_2N_2O$: C, 48.60; H, 4.89; N, 11.34; Cl, 28.69. Found: C, 48.60; H, 4.67; N, 11.33; Cl, 28.55.

N^1-(3-Chlorophenyl)-N^2-{[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]methyl}N^2-(2-hydroxyethyl)glycinamide (**18**).

i-Pr_2NEt (4.4 ml; 25.1 mmol) was added over 2 minutes to a slurry of hydroxyamide **17** (2.6 g; 11.4 mmol) and imdiazole **2** (3.66 g; 13.6 mmol) in acetonitrile (29 ml) maintained at 0 °C. The solution was aged at 0 °C for 23 h and warmed to 23 °C. Water (100 ml) was added dropwise over 30 min to crystallize the product. The slurry was cooled to 5 °C and aged for 1 h before filtering. The cake was washed with water (2 ? 10 ml) and dried *in vacuo* at 40 °C for 16 h to provide 3.2 g of **18** (67%). **18**: mp = 131-133 °C; ^{13}C nmr (75 MHz, deuteriochloroform): δ 169.5, 141.8, 139.2, 139.1, 134.3, 132.8, 130.4, 129.9, 127.7, 126.9, 124.1, 119.3, 118.2, 117.5, 112.0, 58.5, 58.0, 57.5, 47.9, 47.7.

Anal. Calcd for $C_{22}H_{22}ClN_5O_2$: C, 62.34; H, 5.23; N, 16.52. Found: C, 62.32, H, 5.10, N, 16.35.

4[(5-{[4-(3-Chlorophenyl)-3-oxopiperazin-1-yl]methyl}-1*H*-imidazol-1-yl)methyl]benzonitrile (**1**) Free Base from Intermediate **18**.

Tributylphosphine (0.94 ml; 3.8 mmol) and diethylazodicarboxylate (0.60 ml; 3.8 mmol) were added to a slurry of hydroxyamide **18** (1.0 g; 2.4 mmol) in tetrahydrofuran (6 ml) at 23 °C. The reaction mixture was stirred at 23 °C for 1 h. Quantitative hplc analysis of the crude homogeneous reaction mixture indicated 0.94 g of **1** was present (98% yield).

4[(5-{[4-(3-Chlorophenyl)-3-oxopiperazin-1-yl]methyl}-1*H*-imidazol-1-yl)methyl]benzonitrile Free Base Monohydrate (**1•H_2O**) by alkylation of **3** with **2**.

A 100 mL flask was charged with acetonitrile (27 mL), **3•HCl** (4.11 g, 16.5 mmol), *i*-Pr_2NEt (9.30 mL, 52.9 mmol) and **2•HCl** (5.00 g, 17.2 mmol) respectively at 0-3 °C to give a homogenous mixture. The solution was stirred at 0 °C for 39 h [29]. Water (10 mL) and *i*-Pr_2NEt (0.63 mL) were added to the mixture, whereupon any crystalline **1** dissolved [30]. The homogenous solution was aged at 0 °C for 30 min and heated to 35 °C. Water (41 mL) was added over 5 min, and the resulting solution was aged for 5-10 min at 35 °C. The solution was seeded with crystalline **1•H_2O** (10 mg), and aged 60 min at 35 °C. Additional water (38 mL) was added over 30 min and the mixture was aged for 30 min at 35 °C. The mixture was cooled to +4 °C over 2 h, and aged at +4 °C for 30-60 min. The crystals were collected by filtration and washed with 1:5 acetonitrile/H_2O at 5 °C (25 mL) and 1:9 acetonitrile/H_2O at 5 °C (2 ? 30 mL). The crystalline solid was dried *in vacuo* at 23 °C, yielding 5.80 g (99.4 hplc A% purity, 82.9% yield) of **1•H_2O**: mp = 90-92 °C; ^{13}C nmr (100 MHz, deuteriochloroform): δ 166.3, 142.7, 142.2, 139.5, 134.6, 132.8, 130.9, 130.3, 127.3, 127.2, 126.4, 126.1, 123.9, 118.2, 112.1, 57.8, 50.7, 49.8, 48.9, 48.4.

Anal. Calcd for $C_{22}H_{20}ClN_5O{\cdot}H_2O$: C, 62.34; H, 5.23; N, 16.52; Cl: 8.36. Found: C, 62.24; H, 5.23; N, 16.33; Cl: 8.38.

4[(5-{[4-(3-Chlorophenyl)-3-oxopiperazin-1-yl]methyl}-1*H*-imidazol-1-yl)methyl]benzonitrile•HCl Salt (**1•HCl**).

A 50 L flask was charged with isopropanol (14.4 L) and 1.13 *M* aqueous HCl (2.45 L) then **1•H_2O** (1.20 kg, 2.83 mol) was added to the stirred mixture over 2 min at 15-17 °C. Titration analysis of the homogenous mixture indicated 75 mmoles (2.6 mol%) free base **1** remained in solution. Based upon this determination, additional 1.13 *M* aqueous HCl (50 mL, 56 mmol) was added. Darco G-60 carbon (300 g) was added to the solution, the mixture was heated to 50 °C for 2 h and was allowed to cool to 22 °C gradually over 18 h. The mixture was filtered through a pad of Solka-Floc® (800 g) and the pad was washed with 86:14 IPA/H_2O (3 x 2 L). The colorless filtrate was transferred through a Whatman Polycap 75 TF, PTFE/polypropylene 0.45 μm filter into a 72 L round bottom flask and concentrated at 30 °C and 26-29 in Hg pressure with the gradual simultaneous addition of isopropanol (36 L). The mixture was concentrated to a final volume of 8 L, Karl Fischer analysis indicated 0.35% water remaining in the mixture. The mixture cooled to 0 °C and aged for 90 min. The crystalline solid was collected by filtration, washed with isopropanol (5 L) at 5 °C and dried *in vacuo* to provide 1.14 kg (91%) of **1•HCl**. Hplc conditions: Eclipse XDB-C18 3.5 x 75 mm column, gradient elution over 7 min with 10:90 → 70:30 acetonitrile/10 mM pH 6.33 aqueous phosphate buffer, 2 mL/min flow at 22 °C with detection at 210 nm; hplc retention time = 4.65 min. **1•HCl:** ^{13}C nmr (62.9 MHz, D_2O): δ 169.4, 142.3, 141.8, 138.0, 135.0, 133.7, 131.7, 130.6, 128.9, 128.0, 126.9, 125.3, 121.0, 119.8, 111.5, 55.9, 51.0, 50.3, 49.1, 48.6.

Anal. Calcd for $C_{22}H_{20}ClN_5O$•HCl: C, 59.74; H, 4.79; N, 15.83; Cl: 16.03. Found: C, 59.55; H, 4.45; N, 15.78; Cl: 15.94.

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[11] The filtration of the phthalazine byproduct from the reaction mixture resulting from the deprotection of **10** with hydrazine was very slow and required prolonged washing of the filter cake to recover all of **8a**. Attempted phthalimide deprotection with borohydride followed by acid catalyzed hydrolysis resulted in complex mixtures. [a] F. Dasgupta and P. J. Garegg, *J. Carbohydrate Chem.*, **7**, 701 (1988); [b] J. O. Osby, M. G. Martin and B. Ganem, *Tetrahedron Lett.*, **25**, 2093 (1984); Cleavage of the phthalimide from **10** with methylamine or aqueous NaOH gave complex mixtures; [c] M. S. Motawia, J. Wengel, A. E.-S. Abdel-Megid and E. B. Pedersen, *Synthesis*, 384 (1989).

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[13] This isolation protocol was required because the crude salt mixture gave complex mixtures upon attempted conversion to the 1,5-disubstituted imidazole. It was found that the presence of small quantities of HMTA, paraformaldehyde and related impurities in the crude mixture of **8a** and ammonium salts were very detrimental to the subsequent conversion to the imidazole. The separation of **8a** free base from the mixture *via* aqueous base extractions and conversion to the corresponding HCl salt removed the formaldehyde related impurities, thus allowing smooth conversion to the desired imidazole. Interestingly, the presence of ammonium salts (NH_4Cl, NH_4Br, $NH_4H_2PO_4$) did not affect the yield or purity of the imidazole formation.

[14] The solubility of **8a**•H_3PO_4 is much greater in water than in dilute aqueous solutions of ammonium phosphate. Therefore, care should be exercised during the washing of the filter cake with water, and it is recommended to use 1-2% aqueous $NH_4H_2PO_4$ rather than pure water to

wash the filter cake. Solubility of **8a**•H_3PO_4 at 20 °C: 11 g/L in water, 3.5 g/L in 0.13% $NH_4H_2PO_4$, 0.7 g/L in 0.50% $NH_4H_2PO_4$, 0.3 g/L in 3.0% $NH_4H_2PO_4$.

[15] Several solvents were examined as mediums for the Marckwald reaction to prepare **7a**. The use of water, methanol, ethanol, isopropanol and acetic acid as solvents for the preparation of **7a** resulted in lower yields. The amounts of acetic acid and water employed in the Marckwald reaction were found to have a considerable effect on the yield.

[16] A copious quantity of a colorless gas is evolved during the addition of sodium nitrite (presumably nitric oxide), which is converted to brown nitrogen dioxide gas upon contact with air.

[17] It is important to maintain a temperature above 35 °C during the addition of peroxide to avoid the buildup of peroxide in the reaction mixture. The peroxide reacts more slowly with the mercaptoimidazole below 35 °C allowing peroxide to build up during the addition leading to a less controlled reaction later. No reaction takes place in the absence of acetic acid or in more dilute aqueous solutions of acid.

[18] The rate of reaction of the mercaptoimidazoles with H_2O_2 dramatically depends on the nature of the R substituent. The dethionation is much faster and exothermic when R is electron donating *i.e.*, R = OMe than when R is electron deficient *i.e.*, R = NO_2.

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[20] Nmr studies for several of these compounds in d_6-DMSO solution have shown the proton to reside predominantly on the nitrogen rather than on the sulfur. ^{1}H-^{15}N HMQC 2-D nmr experiments, which provide one-bond correlation data for NH groups, show conclusively that the hydrogen resides on the nitrogen and not on sulfur for compounds **14c** and **14d** in d_6-DMSO.

[21]M. M. Paz, J. F. Correa, M. I. Cabeza, and F. J. Sardina, *Tetrahedron Lett.*, **37**, 9259 (1996).

[22] The imidate ester **A** was observed to be formed rapidly at –20 °C (React-IR) and is not converted to **2** until the mixture is heated to –5 °C. Conducting the reaction in pure DMF (5 mL/g **12a**) renders **A** completely soluble at –10 °C. Upon warming, **A** is converted to **2**, which crystallizes from solution.

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[26] In general, hydroxylic solvents (*i.e*., ethanol, isopropanol) slow the rate of alkylation and increase the levels of byproducts formed. Dipolar aprotic solvents (DMF, DMSO, tetrahydrofuran and acetonitrile) give good conversions. Several acid scavengers (potassium carbonate, cesium carbonate, triethylamine and *i*-Pr_2NEt) were examined with *i*-Pr_2NEt providing the cleanest conversions to **1**. Excess **2** can alkylate the remaining imidazole nitrogen in **1** giving the quaternary ammonium salt as a byproduct. Addition of triethylborane or boron trifluoride ether complex to coordinate and protect the imidazole nitrogen of **2** prior to the alkylation suppressed the formation of the quaternary ammonium salt; however, the hplc assay yield of **1** dropped to 76% (Et_3B). Activation of **12a** as its acetate, pivaloate, phenyl and 4-nitrophenyl derivatives followed by reaction with **3** began forming product **1** only at temperatures above 120 °C. Similarly reaction of **2** with 1,4-diazabicyclo[2.2.2]octane and 4-dimethylaminopyridine to form the corresponding quaternary salt derivatives *in situ* followed by reaction with **3** gave **1** only at elevated temperatures.

[27] D. Askin, J. A. Cowen, P. E. Maligres, J. C. McWilliams, and J. A. McCauley, PCT International Patent 0001691 (2000); *Chem. Abstr*., **132**, 93336w (2000).

[28] ^{1}H nmr analysis consists of dissolving an aliquot (0.1 – 0.3 mL) of the reaction mixture in d_6-DMSO and comparing the integration of the ^{13}C satellites of chloromethylene protons signal at 4.65 ppm with the hydroxymethylene protons signal integral at 4.4 ppm. Hplc analysis of a reaction mixture aliquot quenched with DABCO (1,4-diazabicyclo[2.2.2]octane) indicated ≥99.5% conversion to **2**. DABCO reacts with **2** forming a quaternary ammonium salt DABCO adduct. Hplc conditions: Zorbax Eclipse XDB-C18 4.6 ? 75 mm column, gradient elution over 7 min with 10/90 → 70/30 acetonitrile/ 0.01 *M* aqueous phosphate buffer (pH = 6.3), 2.0 mL/min flow at 40 °C with detection at 210 nm. Hplc retention times: DABCO-**2** adduct = 0.7 min, **12a** = 1.8 min.

[29] Progress of the reaction was monitored by quantitative hplc analysis, analyzing for the mg/mL of remaining **2**. The analysis distinguishes **2** from **12a** by comparing a sample quenched with DABCO versus a sample quenched with an aqueous phosphate buffer (pH = 6.33). The reaction usually proceeds so that ≤ 4-6% **2** remains unreacted after 24 h, but requires much longer (typically 38-45 h) so that ≤ 2% **2** remains. The reaction can be crystallized at 24 h, with only a slight decrease in assay/isolated yields (2-4%). Hplc conditions: Eclipse-XDB 0.46 ? 7.5 cm column, gradient elution over 10 min with 10:90 → 80:20 acetonitrile/10 mM aqueous phosphate buffer (pH = 6.33), 2.0 mL/min flow at 25 °C with detection at 210 nm. Retention times: DABCO-chloromethylimidazole adduct = 0.9 min, **2** = 2.0 min, **3** = 2.6 min, Quaternary ammonium salt (double alkylation product in ref 25) = 4.8 min, **1** = 5.2 min.

[30] The purpose of the water is to hydrolyze any remaining **2** prior to heating. If **2** isn't hydrolyzed, some will react with **1** to give the undesired quaternary ammonium salt. The addition of 0.2 equivalents of *i*-Pr_2NEt prior to crystallization has been found to reduce the amount of a trace phenolic impurity in the final crystalline product. The formation of a solid is often observed during the course of the reaction. This precipitate is crystalline **1** in its anhydrous form.