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Synthesis of Novel 1-, 1,4- and 1,7-Substituted 2-Mercapto- and 2-Methylmercapto- Benzimidazoles: Acyclic Analogues of the HIV-1 RT Inhibitor, TIBO.

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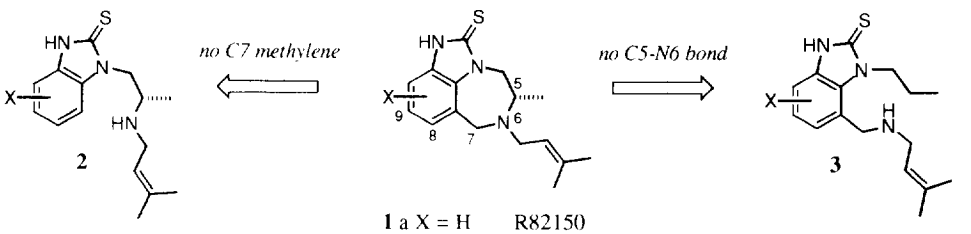
Abstract: Synthetic approaches towards acyclic analogues of the HIV-1 RT inhibitor TIBO ring system, lacking either the diazepine C7 methylene, C5-N6 bond or the N1-N6 two-carbon bridge, are reported, utilizing ring opening reactions of 2-methylaziridines. A number of isomeric 2-methylmercaptobenzimidazole analogues have also been prepared, and the regiochemistry of 2-methylmercaptobenzimidazole alkylations is discussed, as a convenient route to 1,2,7-trifunctionalized benzimidazoles.

The search for agents for therapy of human immunodeficiency virus (HIV) infection and AIDS has involved extensive random screening programs, coupled with an increasingly detailed knowledge of biology of the virus. Currently, clinically approved therapeutics for treatment of HIV infection and AIDS are the nucleoside analogues AZT, ddC, ddI and d4T.[1] All these agents undergo intracellular phosphorylation and then act as mimics of the deoxynucleotide substrates of the HIV Reverse Transcriptase (RT) enzyme, involved in the essential reverse transcription stage of the HIV life cycle. A number of other nucleoside analogues, including carbocyclic and acyclic analogues, have been evaluated as potential HIV RT inhibitors, but as yet none have been approved for clinical use. The toxicity of current drugs and the development of resistant viral strains necessitate a continued pursuit of new anti-HIV agents. The search continues for compounds targeting RT as well as several other stages of the viral life cycle (e.g. HIV protease, early stages of the viral life cycle, such as virus-cell binding, viral entry to the cell and viral uncoating, and HIV integrase). Future therapy is likely to involve combinations of agents which are not cross-resistant, which may produce non-viable viral strains, and which may interfere at different stages of viral reproduction. A number of structurally diverse natural product leads showing promising anti-HIV activity have been identified, notable amongst these being the cramescidins,[2a] macrolactins,[2b] concurvone,[2c] suksdorfins,[2d] macrocarpals,[2e] calanolides[2f] and terpestacins.[2g] Though some of these are RT inhibitors, alternative sites of action are proposed or have been confirmed for other compounds.

Reverse Transcriptase, however, continues to be an important target for potential therapeutic intervention and drug design, with increasing detailed knowledge and understanding of the subtleties of this enzyme's function. Screening of *non-natural* products has yielded a number of anti-HIV agents, all specific for HIV-1, and all inhibitors of RT. The TIBO (4,5,6,7-tetrahydro-5-methylimidazo-[4,5,1-*jk*][1,4]benzodiazepino-2(1*H*)-thione) compounds, **1**, first reported in 1990,[3] attracted much attention as potent RT inhibitors with much lower toxicity than nucleoside antiviral analogues such as AZT. Several related families of non-nucleoside heteroaromatic compounds also proved to be potent inhibitors of HIV-1 RT, notably certain 2-pyridinones,[4] bis-heteroarylpiperazines,[5] HEPT (1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine)[6] and derivatives,[7] and another group of benzodiazepine derivatives, nevirapine and analogues.[8] Nevirapines and TIBOs were shown to inhibit HIV-RT at a non-substrate, allosteric site.[9] Modified analogues of nevirapine,[10a-d] HEPT,[10e] 2-pyridinone,[10f] bis-heteroarylpiperazine and tricyclic TIBO

systems[11] continue to be reported, but examples of a significant number of new structural classes of other non-nucleoside HIV-1 RT inhibitors (NNRTIs) have now been described.[12] Despite the apparent lack of any structural analogies amongst these classes of NNRTIs, a common RT binding site now appears to be universal amongst these agents. Several mechanisms of action have been proposed, though the relative importance of these is as yet unresolved.[13] An X-ray structure of nevirapine bound to HIV-1 RT[14] was reported in 1992, and very recently, X-ray structures of a range of NNRTIs bound to RT have been reported,[15] assisting significant advances in understanding the basis of non-nucleoside RT inhibition. NNRTIs are able to adopt a 'butterfly'-type conformation allowing them to fit one common binding pocket on RT, and structural studies have detailed the binding interactions involved. Clinical evaluations of NNRTIs have indicated that, like anti-HIV nucleoside analogues, development of resistant HIV-1 strains is problematic.[16] However, the mutations leading to this resistance have in most cases been determined. The development of resistance to NNRTIs offers two primary opportunities for potential therapeutic advantage. The use of combination therapy with agents which are non-cross resistant provides one avenue, and some clinical trials show promise on this front. Alternatively, certain NNRTIs have been shown to produce mutant RT which possesses much lower activity than wild-type RT. For example, a Gly190Glu mutation induced by 3,3-dialkyl-3,4-dihydroquinoxalin-2(1H)-thiones produced an RT mutant with only 3% of wild type activity.[17] The design of agents that effect 'suicidal mutation' of RT would thus add a new avenue of potential therapeutic application of NNRTIs.

The activity of TIBO compounds and the subsequently reported structural details of TIBO and nevirapine, prompted us to undertake a program aimed at the synthesis of novel, acyclic analogues of the TIBO ring system, lacking the benzodiazepine ring, i.e. analogues of general structure, **2**, possessing a 1-(2'-aminopropyl) substituent on a 2-mercaptobenzimidazole nucleus, or analogues of type **3** with the C5-N6 bond absent. At that time, no antiviral testing had been reported for mimics not possessing all three rings, though recently, Townsend *et al*[18] reported the synthesis and modest anti-HIV activity of some 1-(2-aminopropyl)-mercaptobenzimidazoles (analogous to **2**, X=H). Our objectives were several fold, including that the synthesis be applicable also to elaboration to the complete TIBO ring system (e.g. from **2**), and to other substituted and isomeric analogues related to both **2** *and* **3**.

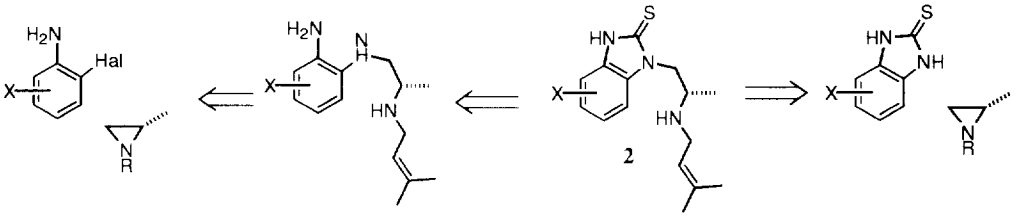


1 a X = H R82150
b X = 8-Cl R86183
c X = 9-Cl R82913

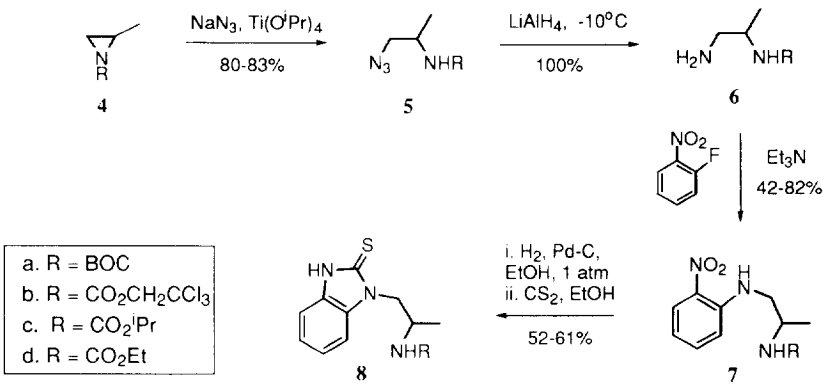
In this paper, we detail routes to acyclic analogues of **2** and **3**, some regioisomeric analogues,[19] and also discuss the regiochemical outcome of 2-methylmercaptobenzimidazole alkylations, leading to a convenient route to several multifunctionalized benzimidazole derivatives. We envisaged that the 2-aminopropyl substituent of **2**, and analogues thereof, could be introduced using simple 2-substituted aziridine precursors. Two approaches were considered from such aziridines: firstly, regiospecific azide aziridine opening, reduction of the azide and then introduction of the 2-aminopropyl unit *via* nucleophilic aromatic substitution, or secondly, *via* regiospecific aziridine opening by a thioimidazolone equivalent [see general retrosynthesis of Scheme 1]. These general strategies was attractive for several reasons. The regioselective ring opening of N-protected-2-substituted (2-alkyl or carboxylate group) aziridines with heteroatom nucleophiles (S, O or N) has extensive precedent. An enantioselective synthesis of **2** would then just employ enantiopure aziridines. Aziridine-2-carboxylic acid methyl ester and

derivatives are readily prepared homochiral from L-serine,[20a] while convenient resolution procedures have been reported for racemic 2-alkyl aziridines,[20b] including 2-methyl aziridine employed in this work. Aziridine-2-carboxylic acid methyl ester was envisaged as potentially providing routes to substituted methyl groups on the 1-(2'-aminopropyl) side chain (e.g. hydroxymethyl). A number of practical asymmetric aziridine syntheses are also now available.[20c] Aziridine ring opening chemistry thus promised a potentially short and general route to a range of 1-(2'-aminopropyl) substituted mercaptobenzimidazoles, structurally related to the TIBO ring system.

Scheme 1: Strategies for synthesis of **2**

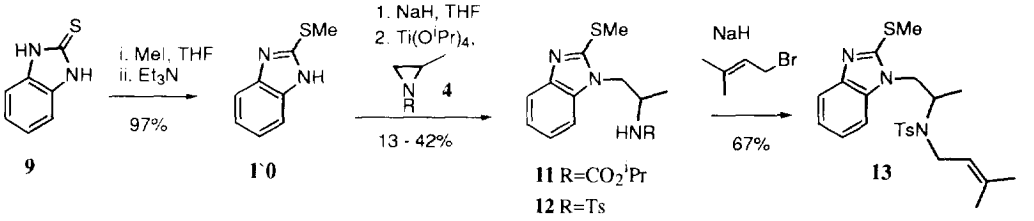


The conversion of N-protected-2-substituted aziridines to functionalized 1,2-diamino intermediates was first investigated, proceeding *via* ring opening with azide nucleophile. The carbamate protected 2-methylaziridines, **4a** and **4b**, were ring opened in consistently good yields with NaN_3 using $Ti(O^iPr)_4$ as Lewis acid promoter. The trichloroethyl carbamate, **4b** (and also the ethylcarbamate analogue **4d**) were concomitantly cleanly trans-acylated to the isopropylcarbamate, **5c**. The azides, **5a** and **5c**, were then selectively reduced in quantitative yields by $LiAlH_4$ at -10°C, providing the desired 2-isopropylcarbamate protected 1,2-diaminopropanes, **6a** and **6c**, in quantitative yields. Nucleophilic aromatic substitution of 2-fluoronitrobenzene by **6a** and **6c** afforded very good yields of the bright orange coloured nitroaniline derivatives, **7**. Hydrogenation followed by ring closure with CS_2 provided the 2-mercaptobenzimidazoles, **8**, as crystalline solids. This provides a short (5 steps from aziridine **4**) and efficient route to the simplest acyclic TIBO analogue, **2**, differing only in the nature of the side chain nitrogen substituent. Unfortunately, removal or either the BOC or the isopropylcarbamate protecting groups was impracticably complicated due to accompanying decomposition.



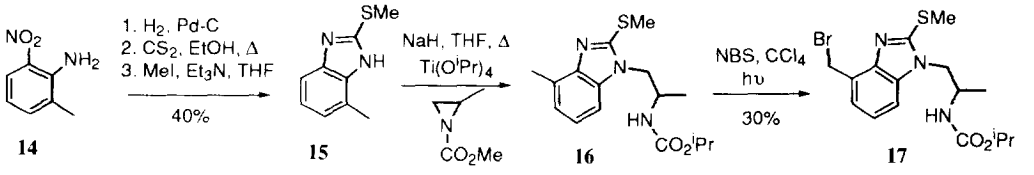
An alternative to the convergent approach above would be Lewis acid-promoted regioselective opening of N-activated 2-methyl aziridines directly by 2-mercaptobenzimidazole, or an equivalent.[21] Since 2-mercaptobenzimidazole alkylates selectively on sulfur and not on nitrogen, direct ring opening of the aziridine with 2-mercaptobenzimidazole is precluded. The 2-methylmercaptobenzimidazole functionality serves to protect the S-

nucleophile, allowing N-alkylation, and the S-methyl group is ultimately removable under acidic conditions. Ring opening of 2-methylaziridine derivatives with the anion of 2-methylmercaptobenzimidazole (derived by methylation of 2-mercaptobenzimidazole) would directly provide the target acyclic TIBO analogue **2** functionality in one step. There are few reports of N-heteroaromatics as nucleophiles for ring opening of aziridines.[22] A range of 2-methylaziridine derivatives, N-protected with BOC, FMOC, CBZ, 3,5-dinitrobenzoyl, tosyl, trityl, or ethylcarbamate were evaluated in ring opening reactions by the anion of **10**. Several Lewis acids, specifically TMSOTf, $ZnCl_2$, HBF_4, $BF_3.OEt_2$, $MgBr_2.OEt_2$ and $Ti(O^iPr)_4$, were also examined, but only $Ti(O^iPr)_4$, in combination with the sodium salt of **10**, led to isolation of the desired products, **11** and **12**, and only tosyl and carbamate functionality appeared routinely suitable for this reaction. Yields were poor to modest, with the N-tosyl aziridine, **4** [R=Ts] providing the better yield. The N-tosyl compound, **12**, was alkylated in good yield with 3,3-dimethylallyl bromide to afford **13**, a close analogue of the target benzimidazole, **2**. Disappointingly, deprotection of **13** proved low yielding.



Evaluation of these compounds for inhibition of HIV-1 infectivity, showed **12** and **13** to both be modest inhibitors, with EC_{50}s of 20 and 4μM respectively.[19] Both compounds were, however, also considerably cytotoxic, with TC_{50} values of 100 and 8μM respectively, with selectivity indices therefore of only 5 and 2. These EC_{50}s are comparable to those reported for analogues of **2** with a 2-mercaptobenzimidazole ring. We thus decided to also prepare other 2-methylmercapto derivatives and further aryl ring substituted analogues.

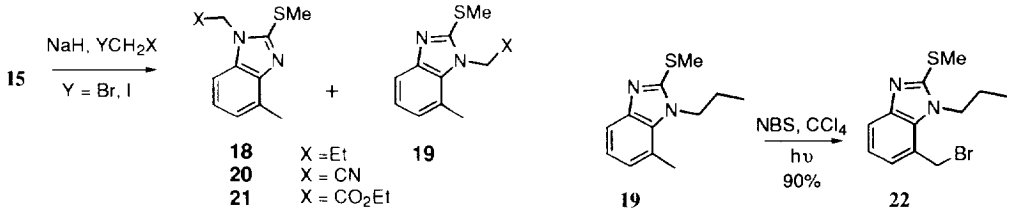
We also envisaged that an aziridine ring opening approach could provide compounds analogous to **2**, *possessing* a C7 methyl but *lacking* the N6-C7 bond. Such acyclic analogues would also allow for an intramolecular N-alkylation approach for conversion to analogues of **1** (an alternative to possible Pictet-Spengler-like conversion of **2** to analogues of **1**) *via* the bromomethyl derivative. This would require that the anion generated from the 7-methyl-2-methylmercaptobenzimidazole, **15**, react analogously to **10**, and that the *N*-regioselectivity (N1 *versus* N3) of this reaction be favourable. Furthermore, analogous methods using N-alkylation by a propyl group would lead towards the acyclic TIBO analogues, **3**. The synthesis of **15** by reduction, CS_2 ring closure and methylation, afforded a single regioisomeric product, which, by NMR analogy to subsequently unambiguously prepared N-alkylated regioisomers (below) was indicated to be the 7-methyl compound, **15**. The sodium salt of this benzimidazole (generated using NaH) reacted with N-ethylcarbamate-2-methylaziridine under titanium isopropoxide catalysis to afford a single N-(2-aminopropyl) derivative.



This was identified as the regioisomer **16**, indicating that alkylation proceeded at N3, and no N1 alkylation was observed. Though the yield of this reaction was poor, this was typical of all aziridine ring opening reactions using

the heterocyclic nucleophiles described here, and from NMR and TLC analysis of the crude product, it was clear that the other regioisomeric product was not present. With **16** available by this route, the bromomethyl derivative, **17**, was also prepared as a novel compound for antiviral testing, and as a precursor to further derivatizations.

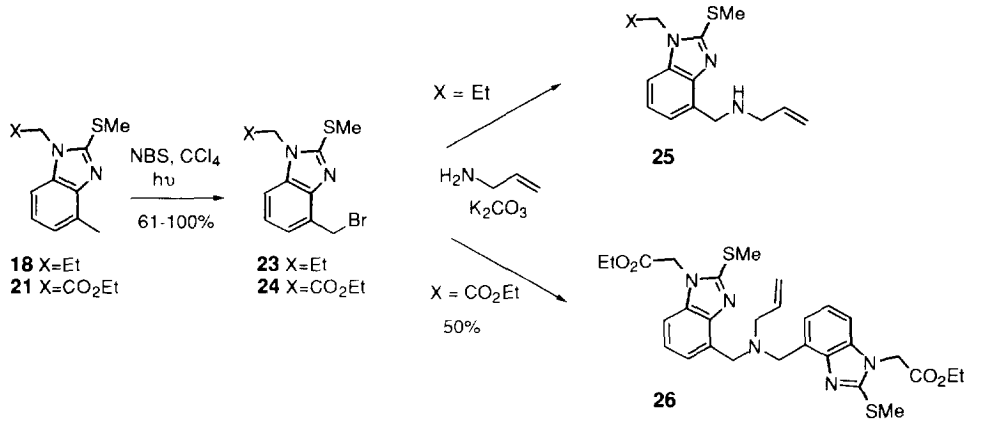
The anion generated from 2-methylmercaptobenzimidazole is an ambident nucleophile, with potential reactivity at both N1 and N3. In such unsymmetrically substituted benzimidazoles, the relative nucleophilicity of N1 and N3 could be influenced by the electronic nature of the aryl ring substituent, but the regiochemistry would be anticipated to then be dependent on the relative importance of these electronic effects and the steric effects of the aryl substituent. The regiochemical outcome of N-alkylations of benzimidazoles has been the subject of considerable previous work, and recent reports.[23] In the case of 4-methylbenzimidazole, electrostatic and thermodynamic factors alone are predicted to show little N1 versus N3 selectivity, however, *ab initio*[24] and experimental studies[23] generally concur with predominant N3 alkylation due to *steric* contributions. The ratio of products is a function of the nature of the electrophile, consequent from differences in the structure of the transition state involved. In such model benzimidazoles it is noteworthy that replacing the 4-methyl substitutent on the aryl ring with electronically very different groups can in fact direct alkylation to favour the *more* sterically congested alkylation product. We turned to examining other N-alkylations of **15**, with three purposes: as a route potentially towards acyclic TIBO analogues of type **3** (*via* bromomethylation of the 4-Me analogue and subsequent reaction with appropriate amine nucleophiles), as a route to regioisomeric analogues of **3**, and also to provide further insight into the regiochemistry of N-alkylation of this benzimidazole derivative. Alkylation of the anion of **15** with propyl iodide and with activated haloalkanes such as iodoacetonitrile and ethyl bromoacetate provided varying yields of N-alkylated compounds. Alkylation of the sodium salt of **15** with propyl iodide led to a 3.7:1 ratio of N3 to N1 alkylation products **18** and **19** respectively. With other activated halides (iodoacetonitrile and ethyl bromoacetate), N3 alkylation was the only observed outcome, affording **20** and **21**. The product ratios of these alkylations of **15** is broadly consistent with the results for 4-methylbenzimidazole itself. Specifically, an increasingly 'tight' S_N2 transition state[25] would be anticipated on moving from alkyl iodides to activated electrophiles such as ethyl bromoacetate, which would be predicted to result in increasing transition state steric effects leading to enhancement of the N3 selectivity (the 2-SMe group may have some effect on increasing the steric hindrance for N1 attack by activated electrophiles, relative to the parent heterocycle).



The *minor* regioisomer, **19**, obtained from alkylation of the sodium salt of **15** with propyl iodide directs towards the initial target functionality of TIBO analogue **3**. However, while bromination of the 4-methyl analogue of **19** proceeded in excellent yield, attempts to react this with allylamine led only to recovery of starting material.

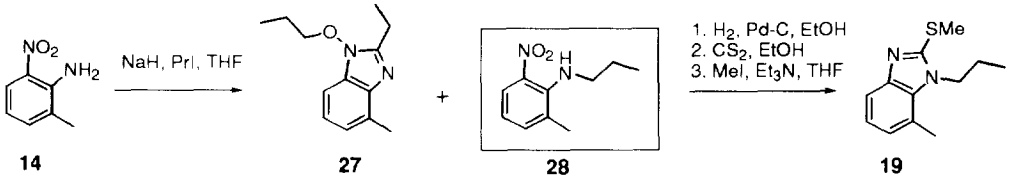
Though the major isomer, **18**, does not direct towards the target substitutions of **3**, the regioisomeric nature of **18** warranted further elaboration for antiviral testing. Thus, **18** and the ester analogue, **21**, were each brominated with NBS, affording the bromomethyl compounds, **23** and **24**. Reaction of these benzylic bromides with allylamine was then examined. In the N-propyl case the N-monoalkylated derivative, **25** [X=Et], was obtained in modest yield (along with some unreacted starting material), but in the case of **24**, the major product obtained in 50% yield was consistent with the dimeric compound, **26** (along with ~15% of the monoalkylated analogue, **25** [$X=CO_2Et$]). Evidence for this structure was provided by the very similar proton NMR to compound **25**, but which showed the

allyl alkene signals integrating to half the values expected (relative to aromatic and ester signals) for a N-monoalkylated product. Mass spectroscopic evidence supported the dimeric structure of **26**.



Evaluation of **18**, **23** and **25** [X=Et] for inhibition of HIV-1 infectivity, showed that while the compounds bearing 7-methyl or 7-bromomethyl substitution had reasonable EC_{50}s of 4 and 8μM, and selectivity indices of 10 and 25 respectively,[19] the analogue, **25** [X=Et], bearing an N-allyl function (more analogous to the acyclic TIBO analogue **3**) was a much poorer HIV-1 inhibitor (EC_{50}>40μM) showing no selectivity for virus over host toxicity.

To unambiguously establish the regiochemistry of N-alkylation of **15**, we attempted N-alkylation of 2-methyl-6-nitroaniline, **14**, which on subsequent reduction of the nitro group and S-methylation could lead only to 7-methyl-2-methylmercapto-1-propylbenzimidazole, **19**. However, the alkylation reaction led instead to a novel N-alkylation-cyclization-O-alkylation cascade reaction affording 2-ethyl-4-methyl-1-propyloxybenzimidazole, **27**, as the major product.[26] Fortunately, the initially desired N-isopropyl-2-methyl-6-nitroaniline, **28**, was obtained as a minor product, and was taken on to the regioisomerically pure, structurally unambiguous, 7-methyl-2-methylmercapto-1-propylbenzimidazole, **19**. ^1H and ^{13}C NMR spectroscopy showed this product to be identical to the *minor* regioisomer obtained from N-alkylation of 4-methyl-2-methylmercaptobenzimidazole, **15**. The two isomeric compounds showed particularly characteristic differences in the aromatic region of the ^1H NMR spectrum, with the 4-methyl isomer, **18**, showing a narrow range multiplet for all aryl protons [7.15-7.05, (m, 3H)] and the 7-methyl isomer, **19**, showing three well-separated signals [7.51 (d, *J*=8.0Hz, 1H), 7.05 (t, *J*=7.8Hz, 1H), 6.87 (d, *J*=7.3Hz)]. A similar aromatic pattern was evident for all the other 4-methyl compounds, **20**, **21**, and substituted analogues derived from **18** or **21**. *This distinct NMR difference thus functions as a useful and general indicator of the regioisomeric outcome of 4-methyl-2-methylmercaptobenzimidazole alkylations.*



In summary, starting from 2-methylaziridine and simple aromatic precursors (2-methylmercaptobenzimidazoles and 2-fluoronitrobenzene), short syntheses of compounds **8**, **11-13**, and **16**, designed as simplified analogues of the HIV-1 RT inhibitor TIBO, but lacking the benzodiazepine ring, have been developed, *via* regiocontrolled aziridine ring opening with azide and benzimidazole nucleophiles. The regiochemical outcome of alkylations of 4-methyl-2-methylmercaptobenzimidazole has been determined for several electrophiles, and this regiochemistry has

been proven by unambiguous synthesis. A number of novel 2-methylmercaptobenzimidazoles substituted on the benzene ring and at an imidazole nitrogen have been prepared, including the bis-heteroaromatic allylamine, **26**. Compounds **24** and **26** possess 'bidirectional' functionality for which several applications can be envisaged. Several of the compounds described inhibit HIV-1 infectivity in the 4-20μM range, but all are also significantly cytotoxic and the highest selectivity index is a modest 25.

Since functionalized benzimidazoles are a common structural feature of many biologically active compounds, we hope that the straightforward synthesis of multifunctional benzimidazole derivatives described herein may facilitate syntheses of novel biologically active derivatives.

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Experimental section.[27]

Nuclear magnetic resonance spectra (^1H, ^{13}C) were recorded using Bruker AC-200 (UMIST), Bruker AC-250 (Aston University) and Bruker AC-300 (UMIST) instruments. Resonances are reported in ppm (δ) downfield of tetramethylsilane. All NMR spectra were recorded in $CDCl_3$ unless otherwise indicated. Infrared spectra were obtained using a Perkin Elmer 1605 FTIR instrument. Mass spectra were obtained on VG 70/70 Hybrid [low resolution], or Kratos MS-50 [FAB] spectrometers (Michael Barber Centre for Mass Spectrometry, UMIST) or a Kratos Concept 1H spectrometer [high resolution] (University of Manchester). Melting points were recorded on a Gallenkamp melting point apparatus. THF was distilled from sodium benzophenone ketyl, dichloromethane from phosphorus pentoxide, triethylamine from potassium hydroxide and acetonitrile from calcium hydride. Column chromatography employed Prolabo Silica Gel 60 (70-230 Mesh), and thin-layer chromatography used Merck 60 F_{254} silica gel, aluminium-backed plates, visualized by UV irradiation (254nm) and/or dipping in an acidic *p*-anisaldehyde solution and charring.

***N*-BOC-2-methylaziridine (4a).** 2-Methylaziridine (1.05 g, 18.5 mmol) was dissolved in dry dichloromethane (50 mL), and triethylamine (5.6 g, 55.4 mmol) was added. The solution was cooled to 0°C under argon, and a solution of BOC anhydride (4.03 g, 18.5 mmol) in dichloromethane was slowly added. The reaction was stirred at 0°C for three hours and at room temperature for one hour, and was then filtered through silica, washed with sodium carbonate solution, and the product extracted with dichloromethane. The organic phase was evaporated to leave a pale yellow liquid (2.90 g, 100%): ^1H NMR (250 MHz) δ 2.24 (m, 1H), 2.05 (d, *J*=5.8Hz, 1H), 1.69 (d, *J*=3.7Hz, 1H), 1.27 (s, 9H), 1.08 (d, *J*=5.5Hz, 3H). ^{13}C NMR (62.5 MHz) δ 162.0, 80.4, 33.1, 32.0, 27.5, 17.0. IR ν_{max} cm^{-1} 2980, 2955, 1720, 1460, 1410, 1370, 1310, 1225, 1160, 1065. Elemental analysis for $C_8H_{15}NO_2$ requires C 61.1, H 9.6, N 8.9, found C 60.8, H 9.3, N 9.0.

***N*-Ethoxycarbonyl-2-methylaziridine (4d).** 2-Methylaziridine (500 mg, 8.77 mmol) was dissolved in dry dichloromethane (5 mL) and cooled to 0°C. Triethylamine (2.66g, 3.66 mmol) was added, followed by dropwise addition of ethyl chloroformate (951mg, 8.77 mmol, 0.84 mL) under argon. The reaction was stirred at 0°C for three hours and at room temperature for two hours, and then the triethylammonium hydrochloride that had formed was removed by filtration and the filtrate washed with aqueous sodium carbonate solution. The organic layer was evaporated to leave the desired product as a pale yellow liquid (795 mg, 70%): ^1H NMR (200 MHz) δ 3.39 (q, *J*=7.1Hz, 2H), 2.33 (m, 1H), 2.15 (d, *J*=5.9Hz, 1H), 1.78 (d, *J*=3.7Hz, 1H), 1.20-1.10 (m, 6H). ^{13}C NMR

(62.5 MHz) δ 163.5, 62.1, 33.5, 32.3, 17.2, 14.1. IR ν_{max} cm^{-1} 2980, 1713. Elemental analysis for $C_6H_{11}NO_2$ requires C 55.8, H 8.5, N 10.9, found C 55.5, H 8.8, N 10.8. MS (FAB, MH^+) *m/z* 130.
Other 2-methylaziridine derivatives were prepared analogously.

1-Azido-2-butylcarbamatoaminopropane (5a). To *N*-BOC-2-methylaziridine (100 mg, 0.64 mmol) dissolved in dry DMF (10 mL), was added sodium azide (163 mg, 1.72 mmol) and titanium (IV) isopropoxide (723 mg, 1.72 mmol, 0.76 mL). The reaction was heated at 60°C for 24 hours and then quenched with water, the precipitate filtered off, and the filtrate extracted with ethyl acetate. The crude product was obtained as a brown oil, and was chromatographed using hexane-ethyl acetate (3:1), as eluent to give a colourless oil (52.1 mg, 41%): ^1H NMR (250 MHz) δ 4.65 (br s, 1H), 3.90-3.75 (m, 1H), 3.45-3.20 (m, 2H), 1.39 (s, 9H), 1.10 (d, *J*=7.5Hz, 3H). ^{13}C NMR (62.5 MHz) δ 155.4, 79.9, 58.0, 36.3, 28.6, 18.5. IR ν_{max} cm^{-1} 3437, 2980, 2104, 1711, 1674, 1503, 1387, 1167.

1-Azido-2-isopropylcarbamatopropane (5c). To *N*-trichloroethoxycarbonyl-2-methylaziridine, **4b** (250 mg, 1.07 mmol) dissolved in DMF (20 mL) was added sodium azide (209.7 mg, 3.22 mmol) and titanium (IV) isopropoxide (916.9 mg, 3.22 mmol, 0.96 mL). The reaction was heated under argon at 70°C for eight hours and stirred overnight at room temperature. Water was added to quench the reaction and the precipitate was filtered off. The filtrate was extracted with ethyl acetate (3 x 50 mL) and the organic fractions were combined, dried and evaporated. The crude product was purified by filtering through a pad of silica and the pure product was obtained as a yellow oil (130 mg, 44%): ^1H NMR (200 MHz) δ 4.94-4.76 (m, 1H), 4.12-4.07 (m, 1H), 3.97-3.80 (m, 1H), 3.44-3.27 (m, 2H), 1.25-1.15 (m, 9H). ^{13}C NMR (75 MHz) δ 156.3, 76.1, 57.5, 55.6, 18.1, 16.6. IR ν_{max} cm^{-1} 3325, 2990, 2105, 1690, 1530, 1205, 1110. Elemental analysis for $C_7H_{14}N_4O_2$ requires C 45.2, H 7.5, N 30.1, found C 45.5, H 7.8, N 29.8. MS (CI, MH^+) *m/z* 187.

1-Amino-2-butylcarbamatopropane (6a). The azide **5a** (618 mg, 3.09 mmol) was dissolved in THF (15 mL) and cooled to -10°C under argon. Lithium aluminium hydride (117.4 mg, 3.09 mmol) was added and the solution stirred at -10°C until TLC showed no azide remaining (4-7 hours). The reaction was quenched with saturated sodium chloride solution and the product extracted with dichloromethane. The solvent was dried and evaporated to leave a yellow oil (458.9 mg, 85%). IR showed loss of azide and the product was used immediately without further purification: ^1H NMR (250 MHz) δ 4.67 (br s, 1H), 3.60-3.55 (m, 1H), 2.70 (dd, *J*=4.8, 13.0Hz, 1H), 2.57 (dd, *J*=6.0, 13.0Hz, 1H), 1.69 (br s, 2H), 1.39 (s, 9H), 1.06 (d, *J*=6.8Hz, 3H). IR ν_{max} cm^{-1} 3435, 2980, 2934, 1732, 1502, 1373, 1246, 1170, 1046.

1-Amino-2-isopropylcarbamatopropane (6c). Prepared analogously to **6a**, starting from **5c**. The crude product showed loss of azide by IR, and was used without further purification or characterization (analogously to use of **6a**) to prepare **7c**. (below)

N-(2'-Butylcarbamatopropyl)-2-nitroaniline (7a). The diamine **6a** (55 mg, 0.32 mmol) was dissolved in acetonitrile (10 mL). To this solution was added triethylamine (63.9 mg, 0.63 mmol) and 1-fluoro-2-nitrobenzene (45.2 mg, 0.32 mmol) and the solution was heated at reflux for 36 hours. The solvents were then removed and the product isolated by flash silica chromatography using hexane-ethyl acetate (5:1), as eluent (39.2 mg, 42%): ^1H NMR (250 MHz) δ 8.23 (br s, 1H), 8.13 (d, *J*=8.6Hz, 1H), 7.41 (t, *J*=7.1Hz, 1H), 6.98 (d, *J*=8.5Hz, 1H), 6.63 (t, *J*=8.4Hz, 1H), 4.53 (br s, 1H), 4.00-3.85 (m, 1H), 3.40-3.20 (m, 2H), 1.41 (s, 9H), 1.23 (d, *J*=6.7Hz, 3H). ^{13}C

NMR (62.5 MHz) δ 155.7 145.8, 136.6, 132.2, 127.2, 115.8, 114.3, 81.2, 48.6, 45.8, 28.7, 18.9. HRMS for $C_{14}H_{21}N_3O_2$ requires 296.1610, found 296.1610.

N-(2'-Isopropylcarbamatopropyl)-2-nitroaniline (7c). The diamine **6c** (446mg, 1.59 mmol), 1-fluoro-2-nitroaniline (224.2 mg, 1.59 mmol, 0.16 mL) and triethylamine (321.2 mg, 3.18 mmol, 0.44 mL) were dissolved in acetonitrile (15 mL) and refluxed for 26 hours. The solvent was then removed and the crude product purified on a flash silica column using hexane-ethyl acetate (5:1) as eluent. The product was obtained as an orange solid (364.8 mg, 82%): ^{1}H NMR (200 MHz): δ 8.24 (br s, 1H), 8.13 (dd, *J*=1.5, 8.6Hz, 1H), 7.42 (dt, *J*=1.3, 8.5Hz, 1H), 7.02 (br d, *J*=8.5Hz, 1H), 6.63 (dt, *J*=1.1, 7.0Hz, 1H), 4.90 (septet, *J*=6.2Hz, 1H), 4.72 (d, *J*=7.5Hz, 1H), 4.07-3.93 (m, 1H), 3.50-3.35 (m, 1H), 3.35-3.25 (m, 1H, 1.23 (m, 9H). ^{13}C NMR (75 MHz) δ 156.0, 145.2, 136.3, 132.0, 126.9, 115.5, 114.0, 68.4, 48.2, 45.8, 22.2, 18.6. IR ν_{max} cm^{-1} 3360, 3320, 2980, 1690 1630, 1570, 1540, 1520, 1420, 1360, 1260, 1160, 1110. HRMS requires 281.1377, found 281.1378. mp 98-100°C.

1-(2'-Butylcarbamatopropyl)-2-mercaptobenzimidazole (8a). Nitroamine **7a** (248 mg, 0.84 mmol) was dissolved in ethanol (50 mL) and palladium on activated carbon catalyst (50 mg) was added. Hydrogen was bubbled through the suspension until TLC showed that reaction was complete. The catalyst was removed by filtration through a Celite® pad, and the solvent removed to leave the crude diamine which was used immediately without further purification. The crude product (ca 0.84 mmol) was dissolved in ethanol (20 mL) and carbon disulphide (127.8 mg, 1.68 mmol) was added. The solution was warmed at 40°C under argon for 48 hours. The solvent and unreacted carbon disulphide were removed and the crude product was purified by flash chromatography eluting with hexane-ethyl acetate (2:1) to give the pure product (130 mg, 50% over two steps): ^{1}H NMR (250 MHz, DMSO) δ 12.75 (br s, 1H), 7.47 (d, *J*=6.4Hz, 1H), 7.20-7.15 (m, 3H), 6.85 (d, *J*=8.3Hz, 1H), 4.32-4.27 (m, 1H), 4.05-3.90 (m, 2H), 1.15-1.05 (m, 12H). ^{13}C NMR (62.5 MHz) δ 168.9, 155.2, 133.7, 131.1, 123.1, 122.4, 110.3, 109.9, 77.9, 48.9, 45.4, 28.4, 15.9. HRMS required for $C_{15}H_{22}N_3O_2S$ 308.1433, found 308.1433.

1-(2'-Isopropylcarbamatopropyl)-2-mercaptobenzimidazole (8c). The aromatic nitroamine **7c** (171.7 mg, 0.46 mmol) was dissolved in ethanol (15 mL) and palladium on activated carbon catalyst (35 mg) was added. Hydrogen was bubbled through the suspension until TLC showed that reaction was complete and then the catalyst was removed by filtration through a pad of Celite®, washing through with a further 15 mL of ethanol. The solution of diamine in ethanol was immediately placed under an argon atmosphere and carbon disulphide (70 mg, 0.92 mmol, 0.06 mL) was added *via* syringe. The reaction was stirred at 40°C for 44 hours and then the solvent and excess carbon disulphide removed *in vacuo* to leave a brown solid which was purified on a flash silica column using hexane-ethyl acetate (2:1), as eluent. The product was obtained as a colorless solid (93.3 mg, 53% for two steps): ^{1}H NMR (200 MHz, DMSO) δ 12.73 (br s, 1H), 7.45 (d, *J*=5.0Hz, 1H), 7.20-7.10 (m, 4H), 4.49-3.99 (m, 4H), 1.12 (d, *J*=6.3Hz, 3H), 1.06 (d, *J*=6.0Hz, 3H), 0.83 (d, *J*=6.2Hz, 3H). ^{13}C NMR (75 MHz) δ 172.4, 159.1, 137.1, 134.5, 126.5, 125.9, 113.6, 113.4, 70.4, 52.3, 49.3, 25.7, 25.6, 22.0. IR ν_{max} cm^{-1} 3355, 2975, 1681, 1531, 1465, 1251, 1112, 1057. HRMS (MH$^+$) for $C_{14}H_{20}N_3O_2S$ requires 294.1278, found 294.1278. mp 59-60°C.

1-(2'-Isopropylcarbamatopropyl)-2-methylmercaptobenzimidazole (11). 2-Methylmercapto-benzimidazole (250.2 mg, 1.52 mmol) was dissolved in dry THF (15 mL) and sodium hydride (70.5 mg, 3.04 mmol) was added. The solution was heated at 70°C under argon for 20 minutes, and then a mixture of N-ethoxycarbonyl-2-methylaziridine (196.0 mg, 1.51 mmol), and titanium (IV) isopropoxide (1.73 g, 1.80 mL, 6.07 mmol) in THF (2 mL) was added slowly. The reaction was heated at 80°C for 45 minutes and then stirred overnight at room temperature. The reaction was quenched with water, the precipitate was removed by filtration, and the filtrate

extracted with dichloromethane to give the crude product as an oil. The product was purified on a silica column to give a pale yellow oil (60.5 mg, 13%), together with unreacted starting material (47.7 mg). Compound **11**: ^{1}H NMR (250 MHz) δ 7.66-7.61 (m, 1H), 7.25-7.15 (m, 3H), 4.74 (br s, 1H), 4.30-3.95 (m, 4H), 2.75 (s, 3H), 1.20-1.15 (m, 9H). ^{13}C NMR (62.5 MHz) δ 155.7, 153.0, 143.3, 136.5, 121.9, 121.8, 117.9, 109.1, 60.9, 48.7, 46.6, 21.9, 18.2, 14.4. IR ν_{max} cm^{-1} 3435, 3057, 2983, 1731, 1246. HRMS for $C_{15}H_{22}N_3O_2S$ (MH^+) requires 308.1428, found 308.1425.

1-(2'-Tosylaminopropyl)-2-methylmercaptobenzimidazole (12). 2-Methylmercaptobenzimidazole hydroiodide (53 mg, 0.18 mmol) was suspended in dry THF (20 mL), NaH (30.2 mg, 1.25 mmol) was added, and the reaction heated at 75°C for 15 minutes. A mixture of N-tosyl-2-methylaziridine (36 mg, 0.18 mmol), and titanium (IV) isopropoxide (194.4 mg, 0.66 mmol, 0.2 mL) was added slowly and heating was continued for 45 minutes. The mixture was then stirred at room temperature for three hours and quenched by addition of water. The solid was removed by filtration, and the filtrate extracted with dichloromethane, the organic extracts dried ($MgSO_4$), filtered and evaporated. Purification by flash silica chromatography eluting with hexane-ethyl acetate (2:1) gave the product as a colourless oil (27.2 mg, 42%): ^{1}H NMR (200 MHz) δ 7.60-7.55 (m, 1H), 7.49 (d, J=8.3Hz, 2H), 7.20-7.10 (m, 3H), 7.06 (d, J=8.1Hz, 2H), 5.21 (d, J=7.7Hz, 1H), 4.09 (dd, J=7.5, 14.9Hz, 1H), 3.97 (dd, J=6.5, 14.9Hz, 1H), 3.77 (sept, J=6.9Hz, 1H), 2.73 (s, 3H), 2.32 (s, 3H), 1.15 (d, J=6.6Hz, 3H). ^{13}C NMR (62.5 MHz) δ 152.4, 143.3, 143.2, 136.3, 135.9, 129.4, 126.3, 121.9, 121.7, 118.1, 108.5, 49.2, 49.0, 21.4, 19.8, 14.8. IR ν_{max} cm^{-1} 3290, 2929, 1652, 1541, 1496, 1456, 1338, 1158, 1090. HRMS for $C_{18}H_{22}N_3O_2S_2$ (MH^+) requires 376.1153, found 376.1148.

1-[2'-(N-Tosyl-N-(3-methylbut-2-ene))-propyl]-1-methylmercaptobenzimidazole (13). Product **12** (59.8 mg, 0.16 mmol) was dissolved in THF (5 mL) and warmed to 40°C under argon. Sodium hydride (7.7 mg, 0.32 mmol) was added and the suspension warmed to 70°C. 3,3-Dimethylallyl bromide (44.7 mg, 0.03 mmol, 0.03 mL) was then added and the reaction was refluxed for 2 hours until TLC showed disappearance of starting material. The reaction was quenched by addition of saturated sodium chloride solution and extracted with dichloromethane. The organic extracts were dried ($MgSO_4$), filtered and evaporated, and the product was purified on a flash silica column using hexane-ethyl acetate (1:1) as eluent to afford a colourless oil (47.2 mg, 67%): ^{1}H NMR (200 MHz) δ 7.70-7.60 (m, 3H), 7.43-7.19 (m, 5H), 5.20 (dd, J=5.8, 6.9Hz, 1H), 4.35-4.15 (m, 3H), 4.00 (dd, J=5.7, 15.5Hz, 1H), 3.79 (dd, J=8.0, 15.5Hz, 1H), 2.77 (s, 3H), 2.39 (s, 3H), 1.75 (s, 3H), 1.73 (s, 3H), 1.12 (d, J=7.1Hz, 3H). ^{13}C NMR (75 MHz) δ 153.0, 143.6, 143.4, 137.9, 136.2, 135.9, 129.8, 127.2, 122.5, 122.3, 121.6, 118.3, 109.4, 53.2, 49.2, 42.7, 26.1, 21.8, 18.0, 16.2, 15.1. IR ν_{max} cm^{-1} 3382, 3054, 2930, 1597, 1442, 1378, 1341, 1247, 1154, 1090. HRMS for $C_{23}H_{30}N_3O_2S_2$ (MH^+) requires 444.1779, found 444.1777.

7-Methyl-2-methylmercaptobenzimidazole (15). 2-Methyl-6-nitroaniline (5.2 g, 34.2 mmol) was dissolved in ethanol (125 mL) and palladium (10%) on activated carbon catalyst (1.0 g) was added. Hydrogen was passed through the suspension until TLC indicated consumption of starting material. The catalyst was removed by filtration through a pad of Celite®, which was washed with a further 125 mL of ethanol. The crude filtrate was used directly. The 250 mL solution of diamine in ethanol was warmed to 40°C under argon and carbon disulphide (34.2 mmol, 2.05 mL) was added. The reaction was stirred at this temperature for 44 hours and then the solvent and excess carbon disulphide were removed to leave a dark brown solid. The crude solid was washed with chloroform, the insoluble product was collected by filtration and washed with chloroform to give the pure product, 7-methyl-2-mercaptobenzimidazole, as a yellow powder (2.4 g, 43% over two steps): ^{1}H NMR (250 MHz, DMSO) δ 12.53 (br s, 2H), 7.05-6.90 (m, 3H), 2.37 (s, 3H). ^{13}C NMR (62.5 MHz, DMSO) δ 168.9, 132.1, 131.6, 123.3, 122.5,

119.8, 107.1, 18.1. IR ν_{max} cm^{-1} 3440, 1635, 1523, 1382, 1157, 613. Elemental analysis for $C_8H_8N_2S$ calculated C 58.5, H 4.9, N 17.1, S 19.5, found C 58.5, H 4.9, N 16.5, S 20.0. MS (FAB, MH^+) *m/z* 165. mp 310°C (decomposed).

7-Methyl-2-mercaptobenzimidazole (2.4 g, 14.6 mmol) was dissolved in THF (120 mL) and warmed to 40°C under argon. Iodomethane (2.28 g, 16.1 mmol, 1.0 mL) was added *via* syringe and the reaction was stirred for 24 hours at 40°C. The excess iodomethane was removed and excess triethylamine was added to give the free base. Water and ethyl acetate were added and the organic layer was removed. The aqueous layer was extracted twice more with ethyl acetate and then the organic layers were combined, dried and evaporated to leave a brown solid which showed no significant impurities by NMR (2.60 g, 100%): ^1H NMR (250 MHz) δ 9.67 (br s, 1H), 7.35 (d, *J*=7.9Hz, 1H), 7.07 (t, *J*=7.5Hz, 1H), 6.97 (d, *J*=7.3Hz, 1H), 2.72 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (62.5 MHz) δ 151.0, 139.5, 138.2, 123.5, 122.8, 122.1, 111.9, 17.1, 15.0. IR ν_{max} cm^{-1} 3070, 2975, 1617, 1534, 1507, 1451, 1350, 1274, 1028. HRMS for $C_9H_{10}N_2S$ requires 178.0565, found 178.0567. mp 120-124°C.

1-(2'-Isopropylcarbamatopropyl)-4-methyl-2-methylmercaptobenzimidazole (16). 7-Methyl-2-methylmercaptobenzimidazole (60 mg, 0.34 mmol) was dissolved in dry THF (5 mL) and sodium hydride (15.5 mg, 0.67 mmol). The suspension was warmed to 60°C under argon, and then a mixture of N-ethoxycarbonyl-2-methylaziridine (43.5 mg, 0.34 mmol) and titanium (IV) isopropoxide (383.1 mg, 1.35 mmol, 0.40 mL) in THF (3 mL) was added *via* syringe. Heating was continued until TLC showed no aziridine (ca. 8 hrs) and then the reaction was quenched with water and the precipitate removed by filtration. The filtrate was extracted with ethyl acetate (3 x 50mL) and the organic fractions were combined, dried and evaporated *in vacuo* to leave a brown oil which was found to be a mixture of products by TLC. Preparative TLC using hexane-ethyl acetate (2:1) as eluent was used to separate the products, and the least polar was the desired product, **16** (19.4 mg, 19%): ^1H NMR (200 MHz) δ 7.10-6.95 (m, 3H), 4.95-4.85 (m, 1H), 4.60 (br s, 1H), 4.30-3.97 (m, 3H), 2.80 (s, 3H), 2.63 (s, 3H), 1.45-1.15 (m, 9H). ^{13}C NMR (62.5 MHz) δ 155.4, 151.8, 142.7, 136.2, 128.2, 122.3, 121.9, 106.7, 68.3, 48.7, 46.6, 21.9, 18.3, 16.4, 15.2. IR ν_{max} cm^{-1} 3331, 2976, 2930, 1686, 1537, 1453, 1372, 1263, 1111, 1058. HRMS for $C_{16}H_{24}N_3O_2S$ requires 322.1589, found 322.1580.

4-bromomethyl-1-(2'-Isopropylcarbamatopropyl)-2-methylmercaptobenzimidazole (17). Compound **16** (31 mg, 0.10 mmol) was dissolved in dry carbon tetrachloride (2mL) and N-bromosuccinimide (18 mg, 0.10 mmol) was added. The reaction was heated with a 250W infra-red heating lamp for three hours and then the insoluble succinimide was removed by filtration, washing the precipitate with a little carbon tetrachloride. Removal of the solvent afforded the crude product which was purified on a flash silica column using hexane-ethyl acetate (2:1) as eluent to afford **17** (11.7 mg, 30%): ^1H NMR (250 MHz) δ 7.36-7.14 (m, 3H), 4.96 (s, 2H), 4.95-4.80 (m, 1H), 4.56 (br s, 1H), 4.18-3.95 (m, 3H), 2.81 (s, 3H), 1.25-1.15 (m, 9H). ^{13}C NMR (62.5 MHz) δ 155.4 153.5, 141.8, 136.9, 127.1, 122.7, 121.9, 109.5, 68.4, 48.9, 46.6, 28.8, 21.9, 18.3, 15.1. IR ν_{max} cm^{-1} 3434, 1629, 1429, 1355, 752. HRMS for $C_{16}H_{23}N_3O_2S^{79}Br$ requires 400.0696, found 400.0685.

7-Methyl-2-methylmercapto-1-propylbenzimidazole (19) and 4-methyl-2-methylmercapto-1-propyl benzimidazole (18) [By alkylation of 7-methyl-2-methylmercaptobenzimidazole]. 7-Methyl-2-methylmercaptobenzimidazole (165 mg, 0.93 mmol) was dissolved in dry THF (10 mL). Sodium hydride (42.6 mg, 1.85 mmol) was added and the suspension was warmed to 60°C under argon. 1-Iodopropane (157.6 mg, 0.93 mmol, 0.09 mL) was added and heating continued for one hour before stirring overnight at room temperature. The reaction was quenched with saturated sodium chloride solution and the products extracted into dichloromethane, dried

and evaporated. Two regioisomers were formed which were separated by flash silica chromatography using hexane-ethyl acetate (4:1) as eluent. The less polar major product was 4-methyl-2-methylmercapto-1-propylbenzimidazole, (**18**), which was obtained as a yellow oil (143.7 mg, 70%): ^{1}H NMR (250 MHz) δ 7.15-7.05 (m, 3H), 4.03 (t, *J*=7.1Hz, 2H), 2.83 (s, 3H), 2.71 (s, 3H), 1.85 (apparent sextet, *J*=7.4Hz, 2H), 0.97 (t, *J*=7.4Hz, 3H). ^{13}C NMR (62.5 MHz) δ 151.6, 142.8, 136.0, 128.2, 122.0, 121.5, 106.2, 45.5, 22.7, 16.5, 14.9, 11.4. IR ν_{max} cm^{-1} 2980, 2960, 1600, 1460, 1455, 1440, 1380, 1350, 1245. Elemental analysis for $C_{12}H_{16}N_2S$ calculated C 65.5, H 7.3, N 12.7, S 14.5, found C 65.3, H 7.6, N 13.0, S 14.3. MS (FAB, MH$^+$) *m/z* 221.

The more polar product was 7-methyl-2-methylmercapto-1-propylbenzimidazole, (**19**) and was obtained as a yellow oil (38.2 mg, 19%): ^{1}H NMR (250 MHz) δ 7.51 (d, *J*=8.0Hz, 1H), 7.05 (t, *J*=7.8Hz, 1H), 6.87 (d, *J*=7.3Hz, 1H), 4.10 (t, *J*=7.8Hz, 2H), 2.75 (s, 3H), 2.58 (s, 3H), 1.77 (sextet, *J*=7.5 Hz, 2H), 0.96 (t, *J*=7.4Hz, 3H). ^{13}C NMR (62.5 MHz) δ 153.1, 143.9, 134.6, 124.4, 121.5, 119.7, 116.1, 46.7, 24.6, 18.2, 14.6, 10.9. IR ν_{max} cm^{-1} 3422, 2966, 2877, 1594, 1444, 1372, 1350, 1272, 1211, 1116, 1072. HRMS (MH$^+$) for $C_{12}H_{17}N_2S$ requires 221.1112, found 221.1108.

7-Methyl-2-methylmercapto-1-propylbenzimidazole (19) [Unambiguous synthesis from N-propyl-2-methyl-6-nitroaniline]. N-Propyl-2-methyl-6-nitroaniline, **28** (188.3 mg, 0.97 mmol) was dissolved in ethanol (15 mL). 10% Palladium on activated carbon (35 mg) was added and hydrogen passed through the reaction until TLC indicated no nitro compound remaining (ca. 3 hours). The catalyst was removed by filtration through Celite® and the crude filtrate was used directly. The ethanolic solution of the diamine was warmed to 40°C and carbon disulphide (147.4 mg, 1.94 mmol, 0.12 mL) added. The solution was stirred at this temperature for 48 hours, after which time solvent and excess carbon disulphide was removed to give 7-methyl-2-methylmercapto-1-propylbenzimidazole. The overall yield was low (10% for two steps) which was used without purification. The crude product (20.2 mg, 0.10 mmol) was dissolved in THF (5 mL) and iodomethane (28.4 mg, 0.20 mmol, 0.01 mL) was added. The reaction was warmed at 40°C under argon for 48 hours, after which time the excess iodomethane was removed. Triethylamine (0.03 mL) was added to give the free base and the triethylammonium iodide by-product removed by filtration. The crude product was purified on a flash silica column using hexane-ethyl acetate (4:1) as eluent, affording **19**. ^{1}H and ^{13}C NMR corresponded to 7-methyl-2-methylmercapto-1-propylbenzimidazole, **19**, the minor product from the reaction of 7-methyl-2-methylmercaptobenzimidazole with 1-iodopropane: ^{1}H NMR (250 MHz) δ 7.51 (d, *J*=8.0Hz, 1H), 7.06 (t, *J*=7.6Hz, 1H), 6.89 (d, *J*=7.3Hz, 1H), 4.17 (d, *J* =7.9Hz, 2H), 2.77 (s, 3H), 2.64 (s, 3H), 1.79 (apparent sextet, *J*=7.7Hz, 2H), 1.00 (t, *J*=7.4Hz, 3H). ^{13}C NMR (62.5 MHz) δ 153.1, 143.9, 134.6, 124.5, 121.5, 119.7, 116.2, 46.8, 24.7, 18.3, 14.6, 10.9.

1-Cyanomethyl-4-methyl-2-methylmercaptobenzimidazole (20). 7-Methyl-2-methylmercapto-benzimidazole (50 mg, 0.28 mmol) was dissolved in dry THF (5 mL), sodium hydride (12.9 mg, 0.56 mmol) was added and the suspension warmed to 60°C under argon. Iodoacetonitrile (46.8 mg, 0.28 mmol, 0.02 mL) was added and the resulting brown suspension was heated for one hour and then stirred at room temperature for four hours. The suspension was filtered through a pad of silica and the filtrate partitioned between dichloromethane and water. The organic phase was dried, and evaporated and the crude product purified on a flash silica column using hexane-ethyl acetate (2:1) as eluent. The product was obtained as a cream solid (22.9 mg, 38%): ^{1}H NMR (250 MHz) δ 7.25-7.05 (m, 3H), 4.96 (s, 2H), 2.81 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (62.5 MHz) δ 150.6, 142.6, 134.7, 129.2, 123.6, 122.9, 113.1, 105.7, 31.5, 16.4 , 15.6. IR ν_{max} cm^{-1} 2960, 2930, 2250, 1730, 1605, 1500, 1455, 1360, 1155, 910. HRMS for $C_{11}H_{11}N_3S$ (MH$^+$) requires 218.0754, found 218.0756. mp 78-81°C.

1-Carboethoxymethyl-4-methyl-2-methylmercaptobenzimidazole (21). 7-Methyl-2-methylmercaptobenzimidazole (156 mg, 0.88 mmol) was dissolved in dry THF (10 mL). Sodium hydride (40.3 mg, 1.75 mmol) was added and the suspension warmed to 60°C under argon. Ethyl bromoacetate (146.9 mg, 0.88 mmol, 0.10 mL) was added and heating was continued for one hour. The reaction was then stirred overnight at room temperature before being quenched with saturated sodium chloride solution and extracted with dichloromethane. The product was purified on a flash silica column using hexane:ethyl acetate (2:1) as the eluent, and obtained as a brown oil (169.2 mg, 86%): ^{1}H NMR (250 MHz) δ 7.25-6.95 (m, 3H), 4.78 (s, 2H), 4.18 (q, *J*=7.1Hz, 2H), 2.76 (s, 3H), 2.64 (s, 3H), 1.23 (t, *J*=7.1Hz, 3H). ^{13}C NMR (62.5 MHz) δ 167.1, 151.6, 142.6, 135.8, 128.6, 122.7, 122.2, 105.8, 61.9, 45.1, 16.4, 15.5, 14.0. IR ν_{max} cm^{-1} 3461, 2979, 2931, 1751, 1452, 1365, 1205. Elemental analysis for $C_{13}H_{16}N_2O_2S$ calculated C 59.1, H 6.1, N 10.6, S 12.1, found C 58.8, H 5.8, N 10.9, S 12.5. MS (FAB, MH$^+$) *m/z* 265.

7-Bromomethyl-2-methylmercapto-1-propylbenzimidazole (22). 7-Methyl-2-methylmercapto-1-propylbenzimidazole (45.3 mg, 0.20 mmol) was dissolved in dry carbon tetrachloride (2.5 mL), and N-bromosuccinimide (40.1 mg, 0.23 mmol) was added. The suspension was refluxed for 6.5 hours while being irradiated with a 250W lamp. The insoluble material was then removed by filtration and the solvent evaporated to give **22** as a light brown solid (54.1 mg, 90%): ^{1}H NMR (200 MHz) δ 7.66 (dd, *J*=3.0, 6.2Hz, 1H), 7.20-7.10 (m, 2H), 4.76 (s, 2H), 4.32 (t, *J*=7.9Hz, 2H), 2.80 (s, 3H), 1.88 (sextet, *J*=7.7Hz, 2H), 1.04 (t, *J*=7.4Hz, 3H). ^{13}C NMR (75 MHz) δ 154.4, 144.2, 133.2, 125.2, 122.0, 120.3, 119.7, 47.3, 30.5, 24.7, 14.9, 11.0. IR ν_{max} cm^{-1} 2980, 2960, 1710, 1455, 1420, 1345, 1275, 1170, 1125, 795, 760. HRMS for $C_{12}H_{16}N_2S^{79}Br$ requires 299.0219, found 229.0220.

4-Bromomethyl-2-methylmercapto-1-propylbenzimidazole (23). 4-Methyl-2-methylmercapto-1-propylbenzimidazole (250 mg, 1.13 mmol) was dissolved in dry carbon tetrachloride (10 mL), N-bromosuccinimide (222.5 mg, 1.25 mmol) was added and the reaction was heated with a 250W infra-red lamp for three hours. The insoluble material was filtered off and the solvent removed to leave the crude product which was purified on a flash silica column using hexane-ethyl acetate (4:1) as eluent. The product was obtained as colourless crystalline plates (337 mg, 100%): ^{1}H NMR (200 MHz) δ 7.24-7.11 (m, 3H), 5.01 (s, 2H), 3.96 (t, *J*=7.2Hz, 2H), 2.82 (s, 3H), 1.80 (apparent sextet, *J*=7.2Hz, 2H), 0.95 (t, *J*=7.4Hz, 3H). ^{13}C NMR (75 MHz) δ 153.2, 142.0, 136.6, 127.0, 122.4, 121.6, 108.9, 45.7, 29.1, 22.6, 14.8, 11.4. IR ν_{max} cm^{-1} 3420, 2980, 1465, 1420, 1370, 1355, 1200. HRMS for $C_{12}H_{16}N_2S^{79}Br$ requires 299.0219, found 299.0210. mp 82-84°C.

4-Bromomethyl-1-carboethoxymethyl-2-methylmercaptobenzimidazole (24): 1-Carboethoxymethyl-4-methyl-2-methylmercaptobenzimidazole (78 mg, 0.30 mmol) was dissolved in dry carbon tetrachloride (5 mL). N-Bromosuccinimide (53.4 mg, 0.30 mmol) was added and the reaction was heated with a 250W infra-red lamp for three hours. The solid was removed by filtration, the solvent evaporated and the product purified on a flash silica column using hexane-ethyl acetate (3:1) as eluent. The product was obtained as colourless crystals (62.4 mg, 61%): ^{1}H NMR (250 MHz) δ 7.27 (d, *J*=6.4Hz, 1H), 7.20-7.05 (m, 2H), 4.97 (s, 2H), 4.76 (s, 2H), 4.20 (q, *J*=7.1Hz, 2H), 2.79 (s, 3H), 1.25 (t, *J*=7.1Hz, 3H). ^{13}C NMR (62.5 MHz) δ 166.9, 153.4, 141.5, 136.4, 127.4, 123.1, 122.3, 108.5, 62.0, 45.1, 28.8, 15.3, 14.0. IR ν_{max} cm^{-1} 2990, 2970, 1745, 1610, 1445, 1370, 1210, 1020. Elemental analysis for $C_{13}H_{15}N_2O_2SBr$ calculated C 45.6, H 4.4, N 8.2, S 9.4, found C 45.3, H 5.3, N 7.3, S 7.7. HRMS for $C_{13}H_{16}N_2O_2S^{81}Br$ requires 345.0096. Found 345.0072. mp 96-98°C.

4-(N-Allylaminomethyl)-2-methylmercapto-1-propylbenzimidazole (25). 4-Bromomethyl-2-methylmercapto-1-propylbenzimidazole (150 mg, 0.50 mmol) was dissolved in dry acetonitrile (2 mL) and added slowly to a suspension of allylamine (85.5 mg, 1.50 mmol, 0.11 mL) and potassium carbonate (245.5 mg, 2.50 mmol) in acetonitrile (5 mL). The reaction was stirred at 40°C for 40 hours and then insoluble material was filtered off and the solvent evaporated. The product was purified by neutral alumina chromatography, eluting with hexane-ethyl acetate (2:1) to ethyl acetate-methanol (10:1) to provide **25** as a pale yellow oil (5.3 mg, 25%): ^{1}H NMR (200 MHz) δ 7.15-7.05 (m, 3H), 6.00-5.95 (m, 1H), 5.13 (m, 2H), 4.18 (s, 2H), 4.01 (t, *J*=7.3Hz, 2H), 3.30 (d, *J*=5.9Hz, 2H), 2.75 (s, 3H), 1.85-1.75 (m, 2H), 0.94 (t, *J*=7.4Hz, 3H). ^{13}C NMR (75 MHz) δ 152.1, 142.1, 136.2, 128.9, 126.9, 121.4, 121.0, 116.2, 107.6, 51.2, 49.5, 45.6, 22.6, 14.8, 11.3. IR ν_{max} cm^{-1} 3389, 2964, 2782, 1715, 1651, 1601, 1427, 1383, 1245, 1130. HRMS for $C_{15}H_{22}N_3S$ requires 276.1534, found 276.1534.

Bis-N,N-(1-carboethoxymethyl-4-methylene-2-methylmercaptobenzimidazole) (26). Compound **24**, (60.0 mg, 0.17 mmol) was dissolved in dry acetonitrile (5 mL) and potassium carbonate (47.0 mg, 0.34 mmol) was added and the reaction stirred for fifteen minutes. Allylamine (9.7 mg, 0.17 mmol) was added and the reaction was stirred at 40°C for 28 hours. After filtration and removal of solvents, the crude product was purified by neutral alumina chromatography using an elution gradient of hexane-ethyl acetate (2:1) to dichloromethane-methanol (20:1) affording a yellow oil (25 mg, 50 %): ^{1}H NMR (250 MHz) δ 7.60 (d, *J*=7.4Hz, 2H), 7.24 (dd, *J*=4.7, 7.6Hz, 2H), 7.04 (d, *J*=7.8Hz, 2H), 6.20-6.05 (m, 1H), 5.35-5.15 (m, 2H), 4.78 (s, 4H), 4.29 (s, 4H), 4.18 (q, *J*=7.1Hz, 4H), 3.34 (d, *J*=6.2Hz, 2H), 2.75 (s, 6H), 1.23 (t, *J*=7.1Hz, 6H). ^{13}C NMR (62.5 MHz) δ 167.0, 152.1, 142.6, 136.0, 122.4, 122.3 (3C), 119.5, 106.9, 61.9, 56.7, 52.0, 45.1, 15.4, 14.0. IR ν_{max} cm^{-1} 2979, 2935, 1753, 1452, 1371, 917. HRMS for $C_{29}H_{36}N_5O_4S_2$ requires 582.2212, found: 582.2210.

N-Propyl-2-methyl-6-nitroaniline (28). 2-Methyl-6-nitroaniline (5 g, 32.9 mg) was dissolved in THF (150 mL) and potassium *tert*-butoxide (4.06 g, 36.2 mmol) was added and the resulting red suspension heated to reflux. 1-Iodopropane (5.59 g, 32.9 mmol, 3.21 mL) was added in one portion and the reaction was refluxed overnight and then quenched with saturated sodium chloride solution and extracted with dichloromethane. The main product was 2-ethyl-4-methyl-1-propyloxybenzimidazole, **27**, which was separated from the desired product by flash silica chromatography using hexane-ethyl acetate (5:1) as eluent.[26] Compound **28** was obtained as an orange solid (88.3 mg, 3%): ^{1}H NMR (250 MHz) δ 7.85 (d, *J*=8.4Hz, 1H), 7.21 (d, *J*=7.1Hz, 1H), 6.97 (br s, 1H), 6.67 (dd, *J*=7.6, 8.2Hz, 1H), 3.17 (t, *J*=7.0Hz, 2H), 2.33 (s, 3H), 1.52 (apparent sextet, *J*=7.2Hz, 2H), 0.97 (t, *J*=7.5Hz, 3H). ^{13}C NMR (62.5 MHz) δ 145.7, 138.2, 137.7, 129.9, 124.1, 118.1, 49.9, 24.1, 20.6, 11.2. IR ν_{max} cm^{-1} 3409, 2964, 1604, 1531, 1492, 1332, 1263. HRMS for $C_{10}H_{15}N_2O_2$ requires 195.1134, found 195.1128.

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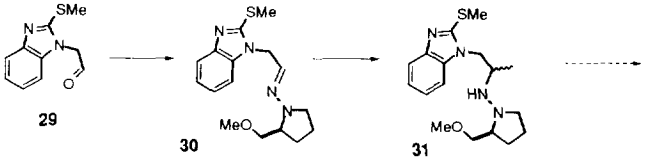

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