# Synthesis of Imidazoles as Novel Emivirine and S-DABO Analogues



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5-Alkyl-4-benzyl-1,3-dihydroimidazol-2-ones (**3a-d**) and 5-alkyl-4-benzyl-1,3-dihydroimidazole-2-thiones (**7a-d**) were prepared *via* Dakin West reaction on *DL*-phenylalanine with the appropriate aliphatic acid anhydrides followed by hydrolysis and reaction with potassium cyanate or potassium thiocyanate. Compounds **3a-d** were alkylated with ethoxymethyl chloride to give the alkylated imidazoles **5a-d** which were considered analogues of Emivirine with deletion of carbonyl group at the 4-position. Alkylation of **7a-d** afforded the corresponding S-alkylated derivatives **8a-p** which in a similar way were considered analogues of S-DABO. However all the imidazole derivatives were devoid of activity against HIV.

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1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) [1] showed low activity against HIV-1 but when the hydroxy group was removed from the acyclic sugar, the activity was increased 21 fold [2]. The activity was further increased 55 fold when the methyl group at the 5-position was replaced by an isopropyl group [3]. After replacement of sulfur with a methylene group, the compound 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (Emivirine or MKC-442) [4] was chosen as a candidate for the clinical trials on AIDS patients.

The dihydroalkoxybenzyloxopyrimidines (DABO) and their thio analogues (S-DABO) [5-7] are closely related to the HEPT derivatives. 6-Benzyl-4-oxopyrimidines were synthesized as dihydrofolate reductase inhibitors and because of their structural similarities with HEPT, they were also tested against HIV and some were found active.

In the present report, we are interested in studying the importance of the carbonyl group at the 4-position in Emivirine and S-DABO analogues, for their activity against HIV. This is done by deletion of the carbonyl group at the 4-position (Figure 1).

1,3-Dihydroimidazol-2-ones and 1,3-dihydroimidazole-2-thiones have been prepared by reaction of cyanate and thiocyanate salts, respectively, with α-aminoaldehydes [8-10] or α-aminoketones [11-13]. The unstable α-aminoaldehydes have been prepared by reduction of α-amino acids by sodium amalgam. However, the yield of 1,3-dihydroimidazol-2-ones by the reaction of cyanate salts with freshly reduced α-aminoacid was low and furthermore, the method is expensive because of the amounts of sodium amalgam used. Also, there is a risk of poluting the environment. α-Aminoketones have been prepared by the reaction of α-haloketones with the potassium salt of phathalimide followed by hydrolysis in acidic medium

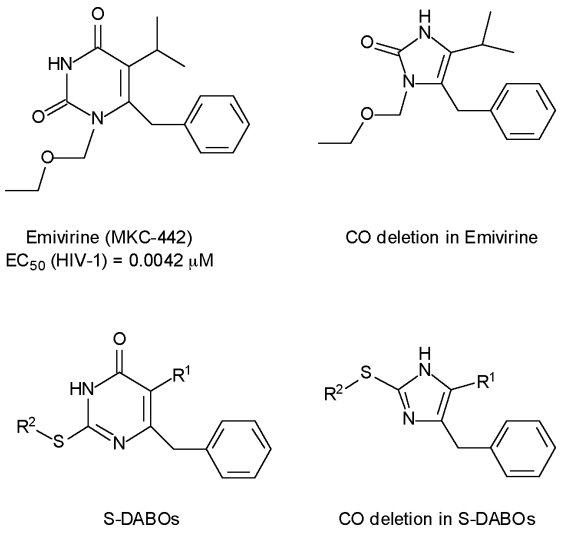



Figure 1. Carbonyl group deletion in Emivirine and S-DABO.

[12]. However, we have chosen the Dakin-West reaction [14,15] to prepare *N*-(1-benzyl-3-methyl-2-oxobutyl)-isobutyramide **1d** by refluxing *DL*-phenylalanine with isobutyric anhydride in the presence of pyridine to induce the acylation of the chiral CH group and subsequent decarboxylation in the same manner as described for **1a-c** by Cleland and Niemann [16]. For the hydrolysis of **1d**, there was used the procedure already described by Dakin and West [15] for **1a**, Sheppard *et al.* [17] for **1b** and Cheng *et al*. [18] for **1c** , in which α-acylaminoketones **1a-d** were hydrolysed by 6 *M* HCl to afford α-aminoketone hydrochlorides **2a-d**.

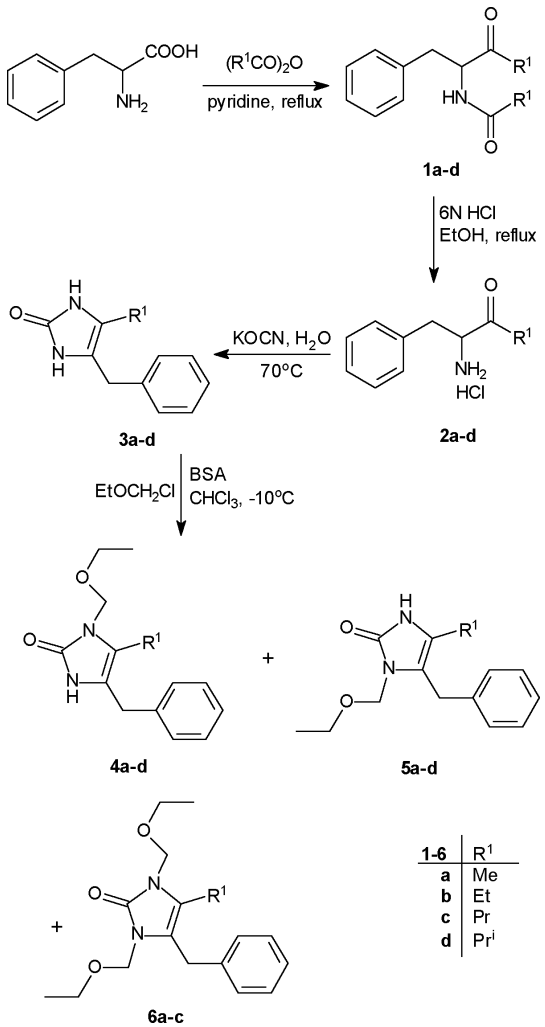
α-Aminoketone hydrochlorides **2a-d** were heated with potassium cyanate to give 4-benzyl-5-alkyl-1,3-

dihyroimidazol-2-ones **3a-d**. Compound **3a** has previously been prepared by two other methods [19,20], either by reduction of the benzoyl group of 5-benzoyl-4-methyl-1,3-dihydroimidazol-2-one with $H_2$/Pt in acetic acid [19] or by reaction of urea with 4-benzyl-3-methylisoxazol-5-ylamine [20].

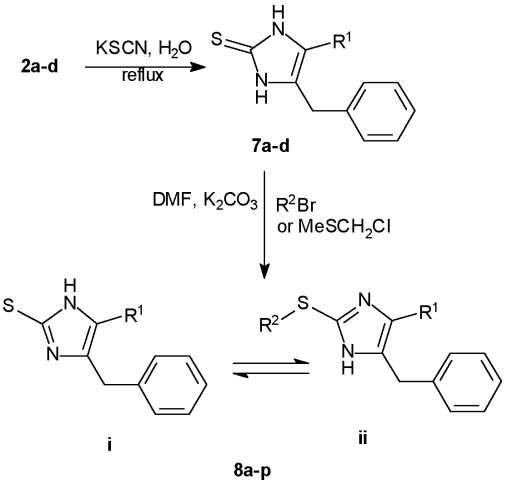
Compounds **3a-d** were silylated by the action of *N,O*-bis-(trimethylsilyl)acetamide (BSA) and followed by alkylation with ethoxymethyl chloride to afford monoalkylated products at $N^1$ **4a-d** and $N^3$ **5a-d** (Emivirine analogues with deletion of CO at the 4-position) and $N^1$,$N^3$-dialkylated products **6a-d** (Scheme 1). The assignment of structures of **4a-d** and **5a-d** was confirmed by NOE. Irradiation of C$H_2$Ph in compounds **4b** and **4d**, respectively, did not show NOE of the $CH_2$-N resonance but the same irradiation in compounds **5b** and **5d** showed 2.3% and 1.6% NOE, respectively, of the $CH_2$-N resonance. Also, on irradiation of the $CH_2$-N resonance in compounds **4b** and **4d**, NOE was not observed at the C$H_2$Ph resonance, whereas the C$H_2$Ph resonance showed 1.9% and 1.3% NOE, respectively, when the $CH_2$-N resonance in compounds **5b** and **5d**, respectively, was irradiated.

4-Benzyl-5-alkyl-1,3-dihydroimidazole-2-thiones (**7a-d**) were obtained by refluxing compounds **2a-d** with potassium thiocyanate in water. Compounds **7a,b** have previously been prepared by Sonn [21] and Bullerwell and Lawson [22] by the same synthetic procedure. Compounds **7a-d** were alkylated by appropriate alkylating reagents to afford the S-alkylated 1,3-dihydroimidazole-2-thiones **8a-p** which are considered as S-DABO analogues with carbonyl group deletion at the 4-position (Scheme 2). $^1$H-nmr spectra of some of these compounds **8m-p** did not show fine splitting of the peaks, which appeared as broad singlets, even for aromatic protons. This is explained by an equilibrium between the two tautomeric forms **i** and **ii**. For the same reason, C-4 and C-5 in all the compounds **8a-p** were never observed in the $^{13}$Cnmr spectra whereas, C-2 and the methylene carbon atom in the benzyl group showed significant broadening of the peaks.

Scheme 1




Scheme 2




| 8 | $R^1$ | $R^2$ | 8 | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| **a** | Me | $MeSCH_2$ | **i** | Me | $Bu^s$ |
| **b** | Et | $MeSCH_2$ | **j** | Et | $Bu^s$ |
| **c** | Pr | $MeSCH_2$ | **k** | Pr | $Bu^s$ |
| **d** | $Pr^i$ | $MeSCH_2$ | **l** | $Pr^i$ | $Bu^s$ |
| **e** | Me | $Pr^i$ | **m** | Me | Bn |
| **f** | Et | $Pr^i$ | **n** | Et | Bn |
| **g** | Pr | $Pr^i$ | **o** | Pr | Bn |
| **h** | $Pr^i$ | $Pr^i$ | **p** | $Pr^i$ | Bn |

The test for activity against HIV-1 was performed in MT4 cell cultures infected with either wild type HIV-1 (strain IIIB) or non nucleoside reverse transcriptase inhibitors (NNRTI) resistant HIV-1 (strain N119) that harboured a substitution of cysteine for the tyrosine at position 181 in the reverse transcriptase enzyme (Cys181Tyr mutant strain). The compounds **4-6** including Emivirine analogues and **8** (S-DABO analogues) are inactive at 100 μM or inactive at subtoxic concentrations.

In conclusion, the effect of activity against HIV has been studied on deletion of the carbonyl group at the 4-position for both of Emivirine and S-DABO analogues by synthesizing the corresponding imidazole analogues. It was found that deletion of the carbonyl group leads to complete loss of the activity against HIV.

## EXPERIMENTALS

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrophotometer at 300 MHz for $^1$H and 75.5 MHz for $^{13}$C with TMS as an internal standard. EI mass spectra were recorded on a Finnigan MAT SSQ 710. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck. Microanalyses were caried out at Atlantic Microlab, Inc., Norcross, Georgia, USA.

*N*-(1-Benzyl-3-methyl-2-oxobutyl)-isobutyramide (**1d**).

A mixture of *DL*-phenylalanine (6.6 g, 40 mmoles), anhydrous pyridine (34 ml, 400 mmoles) and isobutyric anhydride (66.5 ml, 40 mmoles) was heated in an oil bath at 150° for 12 hours until carbon dioxide was no longer evolved. After that, excess of pyridine, acid anhydride and the acid formed were removed under reduced pressure, the residue obtained was treated with an aqueous saturated solution of sodium bicarbonate (10 ml) to remove the acidic components and then extracted with ether (3 × 50 ml). After removal of solvent from the dried ether extract, the residue was treated with petroleum ether (60–80°) (50 ml) and left at 5° overnight. The solid product formed was isolated by filtration, washed with petroleum ether (60–80°), dried and recrystallized from xylene/petroleum ether (60–80°) to give *N*-(1-benzyl-3-methyl-2-oxo-butyl)isobutyramide (**1d**) as pale yellow crystals. Yield 1.88 g (18%); mp 90–92°; $^1$H-nmr ($CDCl_3$): δ 1.01 (d, 3H, $CH_3$, *J* = 6.6 Hz), 1.02 (d, 3H, $CH_3$, *J* = 6.3 Hz) 1.07 (d, 3H, $CH_3$, *J* = 6.6 Hz), 1.10 (d, 3H, $CH_3$, *J* = 6.6 Hz), 2.33 (hept., 1H, CHCO, *J* = 6.9 Hz), 2.66 (hept., 1H, CHCO, *J* = 6.6 Hz), 2.90 (dd, 1H, *H*CH-CH, *J* = 6.0, 13.8 Hz), 3.04 (dd, 1H, HC*H*-CH, *J* = 6.9, 13.8 Hz), 5.05 (q, 1H, $PhCH_2CHNH$, *J* = 7.3 Hz), 6.13 (1H, d, NH, *J* = 6.8 Hz), 7.29–7.09 (m, 5H, Ph); $^{13}$C-nmr ($CDCl_3$): δ 16.95 ($CH_3)_2$, 18.87 ($CH_3)_2$, 35.35 (*C*HCONH), 37.66 (*C*HCOCH), 38.61 ($CH_2$), 56.42 (CHNH), 126.91, 128.43, 129.19, 135.94 ($C_{arom}$), 176.25 (CO-amide), 212.66 (CO-ketone); EI ms: *m/z* 261 ($M^+$).

*Anal.* Calcd. for $C_{16}H_{23}NO_2$ (261.36): C, 73.53; H, 8.87; N, 5.36. Found: C, 73.38; H, 8.77; N, 5.39.

2-Amino-4-methyl-1-phenylpentan-3-one Hydrochloride (**2d**).

A solution of **1d** (5.2 g, 20 mmoles) in 6 *M* hydrochloric acid (110 ml) and ethanol (60 ml) was refluxed for 10 hours, the solvents were removed under reduced pressure. The residue was left overnight, dissolved in ethanol (20 ml) and the hydrochloride of 2-amino-4-methyl-1-phenylpentan-3-one (**2d**) was pecipitated by the addition of ether (100 ml), the solid so formed was isolated by filtration and washed with ether (50 ml). White crystals. Yield 3.5 g (77%); mp 140–142°; $^1$H-nmr (DMSO-$d_6$): δ 0.83 (d, 3H, C*H*$_3$CH, *J* = 6.3 Hz), 1.02 (d, 3H, C*H*$_3$CH, *J* = 6.9 Hz), 2.59 (hept., 1H, $(CH_3)_2$C*H*, *J* = 6.9 Hz), 3.08 (dd, 1H, *H*CH-CH, *J* = 7.5, 14.1 Hz), 3.25 (dd, 1H, HC*H*-CH, *J* = 6.0, 14.1 Hz) 4.54 (brs, 1H, CH-N), 7.37–7.26 (m, 5H, Ph), 8.65 (brs, 3H, $NH_3^+$); $^{13}$C-nmr (DMSO-$d_6$): δ 16.41 ((*C*H$_3)_2$C), 35.59 ($(CH_3)_2$*C*H), 37.78 ($CH_2$), 56.60 (CH-N), 127.20, 128.57, 129.41, 134.79 ($C_{arom}$), 209.81 (CO); EI ms: *m/z* 227 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{18}ClNO\bullet1.0H_2O$ (245.75): C, 58.65; H, 8.20; N, 5.70. Found: C, 59.55; H, 7.88; N, 5.98.

General Procedure for Preparation of 4-Benzyl-5-alkyl-1,3-dihydroimidazol-2-ones (**3b-d**).

To a hot solution of potassium cyanate (0.65 g, 8 mmoles) in water (20 ml), **2b-d** (8 mmoles) was added. The mixture was heated at 70° for 1 hour, cooled to room temp., the solid product formed was isolated by filtration and recrystallized from ethanol/water to give compounds **3b-d**.

4-Benzyl-5-ethyl-1,3-dihydroimidazol-2-one (**3b**).

The compound was obtained as white crystals. Yield 1.2 g (75%); mp 208–210°; $^1$H-nmr (DMSO-$d_6$): δ 1.03 (t, 3H, C*H*$_3$CH$_2$, *J* = 7.2 Hz), 2.29 (q, 2H, C*H*$_2$CH$_3$, *J* = 7.3 Hz), 3.54 (s, 2H, C*H*$_2$Ph), 7.15–7.29 (m, 5H, Ph), 9.57 (s, 1H, NH), 9.66 (s, 1H, NH); $^{13}$C nmr (DMSO-$d_6$): δ 13.89 ($CH_3$), 16.70 (*C*H$_2$CH$_3$), 29.38 (*C*H$_2$Ph), 114.13 (C-4), 118.56 (C-5), 125.94, 128.02, 128.23, 139.71 ($C_{arom}$), 154.32 (CO); EI ms: *m/z* 202 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{14}N_2O$ (202.25): C, 71.26; H, 6.98; N, 13.85. Found: C, 71.09; H, 6.93; N, 13.70.

4-Benzyl-5-propyl-1,3-dihydroimidazol-2-one (**3c**).

The compound was obtained as white crystals. Yield 1.6 g (92%); mp 146–148°; $^1$H-nmr (DMSO-$d_6$): δ 0.84 (t, 3H, *J* = 7.2 Hz, C*H*$_3$CH$_2$), 1.48 (sext., 2H, $CH_3$C*H*$_2$CH$_2$, *J* = 6.9 Hz), 2.27 (t, 2H, $CH_3CH_2$C*H*$_2$, *J* = 7.2 Hz), 3.57 (s, 2H, C*H*$_2$Ph), 7.21–7.32 (m, 5H, Ph), 9.61 (s, 1H, NH), 9.66 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 13.38 ($CH_3$), 21.76 (*C*H$_2$CH$_3$), 25.26 (*C*H$_2$CH$_2$CH$_3$), 29.41 (*C*H$_2$Ph), 114.94 (C-4), 117.04 (C-5), 125.96, 128.07, 128.22, 139.66 ($C_{arom}$), 154.33 (CO); EI ms: *m/z* 216 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{16}N_2O$ (216.28): C, 72.19; H, 7.46; N, 12.95. Found: C, 71.95; H, 7.34; N, 12.92.

4-Benzyl-5-isopropyl-1,3-dihydroimidazol-2-one (**3d**).

The compound was obtained as white crystals. Yield 1.0 g (58%); mp 123–125°; $^1$H-nmr (DMSO-$d_6$): δ 1.09 (d, 3H, (C*H*$_3)_2$CH, *J* = 6.9 Hz), 2.85 (hept., 1H, $(CH_3)_2$C*H*, *J* = 6.9 Hz), 3.57 (s, 2H, $CH_2$Ph), 7.16–7.31 (m, 5H, Ph), 9.60 (s, 1H, NH), 9.81 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 21.93 ((*C*H$_3)_2$CH), 23.45 ($(CH_3)_2$*C*H), 29.41($CH_2$Ph), 112.93 (C-4), 122.70 (C-5), 125.94, 127.98, 128.23, 139.76 ($C_{arom}$), 154.49 (C-2); EI ms: *m/z* 216 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{16}N_2O\bullet0.5H_2O$ (225.29): C, 69.31; H, 7.16; N, 12.43. Found: C, 68.95; H, 7.34; N, 12.48.

General Procedure for Preparation of Compounds 4**a-d, 5a-d** and **6a-c**.

To **3a-d** (5 mmoles) in chloroform (20 ml) under nitrogen atmosphere, was added *N*,*O*-bis-(trimethylsilyl)acetamide (2.7 ml, 11 mmoles). The mixture was stirred at room temp. for 0.5 hour for complete silylation, then cooled to –10°. Ethoxymethyl chloride (0.46 ml, 5 mmoles) was added dropwise and the mixture was stirred until the dialkylated product started to appear (tlc, high r.f. value). After *ca*. 0.5–1 hour, the reaction was quenched at –10° by addition of a saturated solution of sodium carbonate (10 ml), the mixture was filtered, the two layers were separated and the aqueous phase was further extracted with chloroform (20 ml). The chloroform phases were dried with

sodium sulfate and the solvent was removed under reduced pressure. The residual products were chromatographed on a column of silica gel with methanol:chloroform (1:25, v/v) to afford compounds **4a-d**, **5a-d** and **6a-c**.

4-Benzyl-1-ethoxymethyl-5-methyl-1,3-dihydroimidazol-2-one (**4a**).

The compound was obtained as yellow oil. Yield 74 mg (6%); $^1$H-nmr (DMSO-$d_6$): δ 1.08 (t, 3H, C$H_3$CH$_2$, *J* = 6.9 Hz), 2.02 (s, 3H, CH$_3$), 3.41 (q, 2H, CH$_3$C$H_2$, *J* = 7.2 Hz), 3.59 (s, 2H, C$H_2$Ph), 4.88 (s, 2H, NCH$_2$O), 7.18–7.31 (m, 5H, Ph), 9.85 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 7.75 (CH$_3$), 14.82 (*C*H$_3$CH$_2$), 29.29 (*C*H$_2$Ph), 62.75 (CH$_3$*C*H$_2$), 69.33 (NCH$_2$O), 113.78 (C-4), 115.01 (C-5), 126.06, 128.03, 128.29, 139.23 (C$_{arom}$), 153.56 (C-2); HiResMALDI *m/z* 269.1249 (M$^+$+ Na. $C_{14}H_{18}N_2NaO_2$) requires 269.1261.

4-Benzyl-1-ethoxymethyl-5-ethyl-1,3-dihydroimidazol-2-one (**4b**).

The compound was obtained as yellow crystals. Yield 104 mg (8%); mp 53–55°; $^1$H-nmr (DMSO-$d_6$): δ 1.04 (t, 3H, CH$_3$, *J* = 7.2 Hz), 1.07 (t, 3H, CH$_3$, *J* = 7.2 Hz), 2.44 (q, 2H, CH$_3$C$H_2$, *J* = 7.2 Hz), 3.40 (q, 2H, CH$_3$C$H_2$O, *J* = 7.2 Hz), 3.61 (s, 2H, C$H_2$Ph), 4.89 (s, 2H, NCH$_2$O), 7.19–7.29 (m, 5H, Ph), 9.87 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 14.46 (*C*H$_3$CH$_2$), 14.80 (CH$_3$*C*H$_2$), 15.52 (*C*H$_3$CH$_2$), 29.31 (*C*H$_2$Ph), 62.70 (CH$_3$*C*H$_2$O), 69.27 (NCH$_2$O), 114.76 (C-4), 119.68 (C-5), 126.06, 128.01, 128.28, 139.18 (C$_{arom}$), 153.65 (C-2); HiResMALDI *m/z* 283.1415 (M$^+$+ Na. $C_{15}H_{20}N_2NaO_2$) requires 283.1417.

4-Benzyl-1-ethoxymethyl-5-propyl-1,3-dihydroimidazol-2-one (**4c**).

The compound was obtained as white crystals. Yield 68 mg (5%); mp 106–108°; $^1$H-nmr (DMSO-$d_6$): δ 0.87 (t, 3H, C$H_3$CH$_2$CH$_2$, *J* = 7.2 Hz), 1.09 (t, 3H, C$H_3$CH$_2$O, *J* = 6.9 Hz), 1.48 (sext., 2H, CH$_3$C$H_2$CH$_2$, *J* = 7.2 Hz), 2.41 (t, 2H, CH$_3$CH$_2$C$H_2$, *J* = 7.1 Hz), 3.45 (q, 2H, CH$_3$C$H_2$O, *J* = 6.9 Hz), 3.64 (s, 2H, C$H_2$Ph), 4.91 (s, 2H, NCH$_2$O), 7.22–7.31 (m, 5H, Ph), 9.92 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 13.51 (*C*H$_3$CH$_2$CH$_2$), 14.81 (*C*H$_3$CH$_2$O), 22.33 (CH$_3$*C*H$_2$CH$_2$), 24.15 (CH$_3$CH$_2$*C*H$_2$), 29.39 (*C*H$_2$Ph), 62.72 (CH$_3$*C*H$_2$O), 69.31 (NCH$_2$O), 115.42 (C-4), 118.07 (C-5), 126.06, 128.04, 128.25, 139.11 (C$_{arom}$), 153.71 (C-2); HiResMALDI *m/z* 297.1563 (M$^+$+ Na. $C_{16}N_{22}N_2NaO_2$) requires 297.1574.

4-Benzyl-1-ethoxymethyl-5-isopropyl-1,3-dihydroimidazol-2-one (**4d**).

The compound was obtained as yellow oil. Yield 96 mg (7%); $^1$H-nmr (DMSO-$d_6$): δ 1.07 (t, 3H, C$H_3$CH$_2$O, *J* = 6.9 Hz), 1.16 (d, 3H, (C$H_3$)$_2$CH, *J* = 6.9 Hz), 2.93 (hept., 1H, (CH$_3$)$_2$C*H*, *J* = 7.2 Hz), 3.41 (q, 2H, CH$_3$C$H_2$O, *J* = 7.0 Hz), 3.66 (s, 2H, C$H_2$Ph), 4.93 (s, 2H, NCH$_2$O), 7.10–7.30 (m, 5H, Ph), 9.85 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 14.84 (*C*H$_3$CH$_2$O), 21.88 ((*C*H$_3$)$_2$CH), 23.85 ((CH$_3$)$_2$*C*H), 29.83 (*C*H$_2$Ph), 62.55 (CH$_3$*C*H$_2$O), 69.46 (NCH$_2$O), 114.05 (C-5), 123.24 (C-4), 126.03, 127.86, 128.26, 139.23 (C$_{arom}$), 153.56 (C-2); HiResMALDI *m/z* 297.1572 (M$^+$+ Na. $C_{16}N_{22}N_2NaO_2$) requires 297.1574.

4-Benzyl-3-ethoxymethyl-5-methyl-1,3-dihydroimidazol-2-one (**5a**).

The compound was obtained as white crystals. Yield 246 mg (20%); mp 116–118°; $^1$H-nmr (DMSO-$d_6$): δ 0.97 (t, 3H, CH$_3$, *J* = 6.9 Hz), 1.94 (s, 3H, CH$_3$), 3.31 (q, 2H, CH$_3$C$H_2$O), 3.75 (s, 2H, C$H_2$Ph), 4.67 (s, 2H, NCH$_2$O), 7.12–7.31 (m, 5H, Ph), 9.93 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 8.95 (CH$_3$), 14.64 (CH$_3$), 27.99 (*C*H$_2$Ph), 62.52 (CH$_3$C$H_2$O), 69.25 (NCH$_2$O), 113.89 (C-5), 115.30 (C-4), 126.12, 127.79, 128.34, 138.95 (C$_{arom}$), 153.53 (C-2); EI ms: *m/z* 246 (M$^+$).

*Anal.* Calcd. for $C_{14}H_{18}N_2O_2$•0.25$H_2O$ (250.82): C, 67.04; H, 7.43; N, 11.17. Found: C, 67.21; H, 7.34; N, 10.96.

4-Benzyl-3-ethoxymethyl-5-ethyl-1,3-dihydroimidazol-2-one (**5b**).

The compound was obtained as white crystals. Yield 234 mg (18%); mp 91–93°; $^1$H-nmr (DMSO-$d_6$): δ 0.97 (t, 3H, CH$_3$, *J* = 6.9 Hz), 1.07 (t, 3H, CH$_3$, *J* = 7.5 Hz), 2.33 (q, 2H, CH$_3$C$H_2$, *J* = 7.2 Hz), 3.29 (q, 2H, CH$_3$C$H_2$O, *J* = 7.2 Hz), 3.76 (s, 2H, C$H_2$Ph), 4.66 (s, 2H, NCH$_2$O), 7.12–7.31 (m, 5H, Ph), 10.00 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 13.66 (*C*H$_3$CH$_2$), 14.64 (*C*H$_3$CH$_2$O), 16.72 (CH$_3$*C*H$_2$), 27.94 (*C*H$_2$Ph), 62.55 (CH$_3$*C*H$_2$O), 69.25 (NCH$_2$O), 114.44 (C-4), 119.85 (C-5), 126.12, 127.73, 128.34, 138.98 (C$_{arom}$), 153.68 (C-2); EI ms: *m/z* 260 (M$^+$).

*Anal.* Calcd. for $C_{15}H_{20}N_2O_2$ (260.33): C, 69.20 ; H, 7.74; N, 10.76. Found: C, 68.79; H, 7.70;N, 10.41.

4-Benzyl-3-ethoxymethyl-5-propyl-1,3-dihydroimidazol-2-one (**5c**).

The compound was obtained as white crystals. Yield 137 mg (10%); mp 116–118°; $^1$H-nmr (DMSO-$d_6$): δ 0.91 (t, C$H_3$CH$_2$O3H, *J* = 7.2 Hz), 1.05 (t, 3H, C$H_3$CH$_2$CH$_2$, *J* = 6.9 Hz), 1.56 (sext., 2H, CH$_3$C$H_2$CH$_2$, *J* = 7.2 Hz), 2.35 (t, 2H, CH$_3$CH$_2$C$H_2$, *J* = 7.2 Hz), 3.38 (q, 2H, CH$_3$C$H_2$O, *J* = 6.9 Hz), 3.84 (s, 2H, C$H_2$Ph), 4.73 (s, 2H, NCH$_2$O), 7.20–7.38 (m, 5H, Ph), 10.05 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 13.34 (*C*H$_3$CH$_2$CH$_2$), 14.65 (*C*H$_3$CH$_2$O), 21.56 (CH$_3$*C*H$_2$CH$_2$), 25.23 (CH$_3$CH$_2$*C*H$_2$), 27.98 (*C*H$_2$Ph), 62.53 (CH$_3$*C*H$_2$O), 69.28 (NCH$_2$O), 115.18 (C-4), 118.34 (C-5), 126.12, 127.74, 128.32, 138.95 (C$_{arom}$), 153.68 (C-2); EI ms: *m/z* 274 (M$^+$).

*Anal.* Calcd. for $C_{16}H_{22}N_2O_2$•0.25$H_2O$ (278.87): C, 68.91; H, 8.13; N, 10.05. Found: C, 68.68; H, 7.85; N, 9.85.

4-Benzyl-3-ethoxymethyl-5-isopropyl-1,3-dihydroimidazol-2-one (**5d**).

The compound was obtained as white crystals. Yield 164 mg (6%); mp 118–120°; $^1$H-nmr (DMSO-$d_6$): δ 1.00 (t, 3H, C$H_3$CH$_2$O, *J* = 6.9 Hz), 1.14 (d, 3H, (C$H_3$)$_2$CH, *J* = 6.9 Hz), 2.88 (hept., 1H, (CH$_3$)$_2$C*H*, *J* = 6.9 Hz), 3.34 (q, 2H, CH$_3$C$H_2$O, *J* = 6.9 Hz), 3.81 (s, 2H, C$H_2$Ph), 4.69 (s, 2H, NCH$_2$O), 7.14–7.34 (m, 5H, Ph), 10.11 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 14.63 (*C*H$_3$CH$_2$O), 21.71 ((*C*H$_3$)$_2$CH), 23.42 ((CH$_3$)$_2$*C*H), 27.93 (*C*H$_2$Ph), 62.58 (CH$_3$*C*H$_2$O), 69.25 (NCH$_2$O), 113.19 (C-4), 123.9 (C-5), 126.09, 127.66, 128.34, 139.03 (C$_{arom}$), 153.83 (CO); EI ms: *m/z* 274 (M$^+$).

*Anal.* Calcd. for $C_{16}H_{22}N_2O_2$•0.5$H_2O$ (283.37): C, 67.82; H, 8.18; N, 9.89. Found: C, 67.58; H, 7.82; N, 9.87.

4-Benzyl-1,3-bis(ethoxymethyl)-5-methyl-1,3-dihydroimidazol-2-one (**6a**).

The compound was obtained as yellow oil. Yield 152 mg (10%); $^1$H-nmr (DMSO-$d_6$): δ 0.97 (t, 3H, C$H_3$CH$_2$O, *J* = 7.2 Hz), 1.09 (t, 3H, C$H_3$CH$_2$O), 2.07 (s, 3H, CH$_3$), 3.32 (q, 2H, CH$_3$C$H_2$O, *J* = 6.9 Hz), 3.45 (q, 2H, CH$_3$C$H_2$O, *J* = 6.9 Hz), 3.82

(s, 2H, C$H_2$Ph), 4.75 (s, 2H, NC$H_2$O), 4.99 (s, 2H, NC$H_2$O), 7.13–7.32 (m, 5H, Ph); $^{13}$C-nmr (DMSO-$d_6$): δ 7.73 (C$H_3$), 14.57 (*C*$H_3$CH$_2$O), 14.77 (*C*$H_3$CH$_2$O), 27.78 (*C*$H_2$Ph), 62.71 (CH$_3$*C*H$_2$O), 62.95 (CH$_3$*C*H$_2$O), 69.63 (N*C*H$_2$O), 69.76 (NCH$_2$O), 115.48 (C-5), 115.68 (C-4), 126.21, 127.72, 128.38, 138.58 (C$_{arom}$), 153.32 (C-2); EI ms: *m/z* 304 (M$^+$).

*Anal.* Calcd. for $C_{17}H_{24}N_2O_3$•0.5$H_2O$ (313.40). C, 65.15; H, 8.04; N, 8.93. Found: C, 64.76; H, 7.67; N, 8.85.

4-Benzyl-1,3-bis(ethoxymethyl)-5-ethyl-1,3-dihydroimidazol-2-one (**6b**).

The compound was obtained as yellow oil. Yield 318 mg (20%); $^1$H-nmr (DMSO-$d_6$): δ 0.98 (t, 3H, C*H*$_3$CH$_2$O, *J* = 7.2 Hz), 1.06 (t, 3H, C*H*$_3$CH$_2$O, *J* = 7.2 Hz), 1.10 (t, 3H, C*H*$_3$CH$_2$, *J* = 7.2 Hz), 2.48 (q, 2H, CH$_3$C*H*$_2$, *J* = 7.5 Hz), 3.33 (q, 2H, CH$_3$C*H*$_2$O, *J* = 7.2 Hz), 3.47 (q, 2H, CH$_3$C*H*$_2$O, *J* = 6.9 Hz), 3.84 (s, 2H, C*H*$_2$Ph), 4.74 (s, 2H, NCH$_2$O), 5.01 (s, 2H, NCH$_2$O), 7.14–7.32 (m, 5H, Ph); $^{13}$C-nmr (DMSO-$d_6$): δ 14.22 (*C*H$_3$CH$_2$), 14.57 (*C*H$_3$CH$_2$O), 14.76 (*C*H$_3$CH$_2$O), 15.45 (CH$_3$*C*H$_2$), 27.78 (*C*H$_2$Ph), 62.77 (CH$_3$*C*H$_2$O), 62.93 (CH$_3$*C*H$_2$O), 69.66 (N*C*H$_2$O), 69.73 (NCH$_2$O), 115.34 (C-4), 121.25 (C-5), 126.21, 127.65, 128.37, 138.48 (C$_{arom}$), 153.46 (C-2); EI ms: *m/z* 318 (M$^+$).

*Anal.* Calcd. for $C_{18}H_{26}N_2O_3$•0.5$H_2O$ (327.43). C, 66.03; H, 8.31; N, 8.56. Found: C, 66.28; H, 8.02; N, 8.42.

4-Benzyl-1,3-bis(ethoxymethyl)-5-propyl-1,3-dihydroimidazol-2-one (**6c**).

The compound was obtained as yellow oil. Yield 162 mg (10%); $^1$H-nmr (DMSO-$d_6$): δ 0.85 (t, 3H, C*H*$_3$CH$_2$O, *J* = 7.2 Hz), 0.98 (t, 3H, C*H*$_3$CH$_2$O, *J* = 6.6 Hz), 1.09 (t, 3H, C*H*$_3$CH$_2$CH$_2$, *J* = 6.6 Hz), 1.48 (sext., 2H, CH$_3$C*H*$_2$CH$_2$, *J* = 7.2 Hz), 2.42 (t, 2H, CH$_3$CH$_2$C*H*$_2$) , *J* = 7.2 Hz, 3.32 (q, 2H, CH$_3$C*H*$_2$O, *J* = 7.2 Hz), 3.46 (q, 2H, CH$_3$C*H*$_2$O, *J* = 6.6 Hz), 3.84 (s, 2H, C*H*$_2$Ph), 4.73 (s, 2H, NCH$_2$O), 4.99 (s, 2H, NCH$_2$O), 7.14–7.32 (m, 5H, Ph); $^{13}$C-nmr (DMSO-$d_6$): δ 13.47 (*C*H$_3$CH$_2$CH$_2$), 14.59 (*C*H$_3$CH$_2$O), 14.78 (*C*H$_3$CH$_2$O), 22.22 (CH$_3$*C*H$_2$CH$_2$), 24.01 (CH$_3$CH$_2$*C*H$_2$), 27.89 (*C*H$_2$Ph), 62.75 (CH$_3$*C*H$_2$O), 62.94 (CH$_3$*C*H$_2$O), 69.69 (N*C*H$_2$O), 69.76 (NCH$_2$O), 115.97 (C-4), 119.68 (C-5), 126.22, 127.65, 128.36, 138.42 (C$_{arom}$), 153.504 (C-2); EI ms: *m/z* 332 (M$^+$).

*Anal.* Calcd. for $C_{19}H_{28}N_2O_3$•0.6$H_2O$ (343.25): Calc. C, 66.42; H, 8.50; N, 8.15. Found: C, 66.18; H, 8.18; N, 8.03.

General Procedure for Preparation of 4-Benzyl-5-alkyl-1,3-dihydroimidazole-2-thione (**7c,d**).

A mixture of **2c,d** (6.5 mmoles) and potassium thiocyanate (0.62 g, 6.5 mmoles) in water (20 ml) was refluxed for 3 hours. The reaction mixture was cooled and the solid product was isolated by filtration and recrystallized from ethanol/water to give compounds **7c,d**.

4-Benzyl-5-propyl-1,3-dihydroimidazole-2-thione (**7c**).

The compound was obtained as white crystals. Yield 920 mg (61%); mp 230–232°; $^1$H-nmr (DMSO-$d_6$): δ 0.79 (t, 3H, C*H*$_3$CH$_2$CH$_2$, *J* = 7.2 Hz), 1.46 (sext., 2H, CH$_3$C*H*$_2$CH$_2$, *J* = 7.2 Hz), 2.30 (t, 2H, CH$_3$CH$_2$C*H*, *J* = 7.2 Hz ), 3.67 (s, 2H, C*H*$_2$Ph), 7.16–7.31 (m, 5H, Ph), 11.69 (s, 1H, NH), 11.71 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 13.27 (CH$_3$), 21.85 (CH$_3$CH$_2$CH$_2$), 24.81 (CH$_3$CH$_2$*C*H$_2$), 28.91 (*C*H$_2$Ph), 122.80 (C-4), 124.60 (C-5), 126.15, 128.09, 128.28, 139.03 (C$_{arom}$), 158.92 (C-2); EI ms: *m/z* 232 (M$^+$).

*Anal.* Calcd. for $C_{13}H_{16}N_2S$ (232.34): C, 67.20; H, 6.94; N, 12.06. Found: C, 67.21; H, 6.97; N, 12.06.

4-Benzyl-5-isopropyl-1,3-dihydroimidazole-2-thione (**7d**).

The compound was obtained as white crystals. Yield 900 mg (60%); mp 263–265°; $^1$H-nmr (DMSO-$d_6$): δ 1.13 (d, 3H, (C*H*$_3$)$_2$CH, *J* = 6.9 Hz), 2.94 (hept., 1H, (CH$_3$)$_2$C*H*, *J* = 6.6 Hz), 3.70 (s, 2H, CH$_2$), 7.20–7.34 (m, 5H, Ph), 11.71 (s, 1H, NH), 11.77 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 21.78 ((*C*H$_3$)$_2$CH), 23.43 ((CH$_3$)$_2$*C*H ), 28.95 (CH$_2$), 121.07 (C-4), 130.29 (C-5), 126.18, 128.03, 128.36, 139.22 (C$_{arom}$), 159.08 (C-2); EI ms: *m/z* 232 (M$^+$).

*Anal.* Calcd. for $C_{13}H_{16}N_2S$•0.25$H_2O$ (236.85): C, 65.92; H, 7.02; N, 11.83. Found: C, 65.79; H, 6.70; N, 11.65.

General Procedure for Preparation of 4-Benzyl-5-alkyl-2-methylsulfanylmethylsulfanyl-1*H*-imidazole (**8a-d**).

A mixture of **7a-d** (2 mmoles), chloromethyl methyl sulfide (0.168 ml, 2 mmoles) and potassium carbonate (0.276 g, 1 mmole) in dimethylformaide (10 ml) was stirred for 10 hours at room temp. The reaction mixture was treated with ice/cold water (50 ml). The solid product formed was isolated by filtration and washed with petroleum ether (60–80°) (20 ml) to give compounds **8a-d**.

4-Benzyl-5-methyl-2-methylsulfanylmethylsulfanyl-1*H*-imidazole (**8a**).

The compound was obtained as white crystals. Yield 216 mg (41%); mp 130–132°; $^1$H-nmr (CDCl$_3$): δ 2.14 (s, 3H, CH$_3$S), 2.16 (s, 3H, CH$_3$), 3.87 (s, 2H, C*H*$_2$Ph), 3.93 (s, 2H, SCH$_2$S), 7.15–7.26 (m, 5H, Ph); $^{13}$C-nmr (CDCl$_3$): δ 11.07 (br, CH$_3$), 15.07 (CH$_3$S), 31.93 (br, *C*H$_2$Ph),. 41.49 (SCH$_2$S), 126.17, 128.33, 128.44, 135.61 (C$_{arom}$); EI ms: *m/z* 264 (M$^+$).

*Anal.* Calcd. for $C_{13}H_{16}N_2S_2$•0.5$H_2O$ (273.42): C, 57.11; H, 6.27; N, 10.25. Found: C, 57.46; H, 5.89; N, 10.03.

4-Benzyl-5-ethyl-2-methylsulfanylmethylsulfanyl-1*H*-imidazole (**8b**).

The compound was obtained as white crystals. Yield 268 mg (54%); mp 113–115°; $^1$H-nmr (CDCl$_3$): δ 1.08 (t, 3H, C*H*$_3$CH$_2$, *J* = 7.5 Hz), 2.06 (s, 3H, CH$_3$S), 2.47 (q, 2H, CH$_3$C*H*$_2$, *J* = 7.5 Hz), 3.82 (s, 2H, SCH$_2$S), 3.86 (s, 2H, C*H*$_2$Ph), 7.07–7.18 (m, 5H, Ph); $^{13}$C-nmr (CDCl$_3$): δ 14.31 (*C*H$_3$CH$_2$), 15.07 (CH$_3$S), 18.92 (br, CH$_3$*C*H$_2$), 31.18 (br, *C*H$_2$Ph), 41.49 (SCH$_2$S), 126.13, 128.41, 135.70 (C$_{arom}$), 139.76 (br, C-2); EI ms: *m/z* 278 (M$^+$).

*Anal.* Calcd. for $C_{14}H_{18}N_2S_2$•0.5$H_2O$ (287.45): C, 58.50; H, 6.66; N, 9.75. Found: C, 58.75; H, 6.64; N, 9.35.

4-Benzyl-5-propyl-2-methylsulfanylmethylsulfanyl-1*H*-imidazole (**8c**).

The compound was obtained as white crystals. Yield 340 mg (58%); mp 71–73°; $^1$H-nmr (CDCl$_3$): δ 0.89 (t, 3H, C*H*$_3$CH$_2$CH$_2$, *J* = 7.2 Hz), 1.58 (sext., 2H, CH$_3$C*H*$_2$CH$_2$, *J* = 7.5 Hz), 2.14 (s, 3H, CH$_3$S), 2.49 (t, 2H, CH$_3$CH$_2$C*H*$_2$, *J* = 7.5 Hz), 3.89 (s, 2H, SCH$_2$S), 3.94 (s, 2H, C*H*$_2$Ph), 7.16–7.29 (m, 5H, Ph); $^{13}$C-nmr (CDCl$_3$): δ 13.79 (*C*H$_3$CH$_2$CH$_2$), 15.07 (CH$_3$S), 23.04 (CH$_3$*C*H$_2$CH$_2$), 27.57 (br, CH$_3$CH$_2$*C*H$_2$), 31.91 (br, *C*H$_2$Ph), 41.53 (SCH$_2$S), 126.13, 128.34, 128.39, 135.72 (C$_{arom}$), 139.63 (br, C-2); EI ms: *m/z* 292 (M$^+$).

*Anal.* Calcd. for $C_{15}H_{20}N_2S_2$•0.25$H_2O$ (296.97): C, 60.67; H, 6.96; N, 9.43. Found: C, 60.92; H, 6.70; N, 9.46.

4-Benzyl-5-isopropyl-2-methylsulfanylmethylsulfanyl-1*H*-imidazole (**8d**).

The compound was obtained as white crystals. Yield 300 mg (51%); mp 111–113°; $^1$H-nmr ($CDCl_3$): δ 1.22 (d, 3H, $(CH_3)_2CH$, *J* = 6.9 Hz), 2.14 (s, 3H, $CH_3S$), 2.98 (hept., 1H, $(CH_3)_2CH$, *J* = 6.9 Hz), 3.92 (s, 2H, $SCH_2S$), 3.95 (s, 2H, $CH_2Ph$), 7.15–7.29 (m, 5H, Ph); $^{13}$C-nmr ($CDCl_3$): δ 15.08 ($CH_3S$), 22.68 ($(CH_3)_2CH$), 25.37 (br, $(CH_3)_2CH$), 31.92 (br, $CH_2Ph$), 41.53 ($SCH_2S$), 126.10, 128.29, 128.38, 135.60 ($C_{arom}$), 139.70 (br, C-2); EI ms: *m/z* 292 ($M^+$).

General Procedure for Preparation of 4-Benzyl-5-alkyl-2-alkylsulfanyl-1*H*-imidazole (**8e-l**).

A mixture of **8a-d** (1 mmole), isopropyl bromide or *sec*-butyl bromide (1 mmole) and potassium carbonate (0.138 g, 1 mmole) in dimethylformamide (5 ml) was stirred for 20 hours at room temp. The reaction mixture was treated with ice/cold water (100 ml). The solid product formed was isolated by filtration, dried and recrystallized from petroleum ether (60–80°) to give compounds **8e-l**.

4-Benzyl-2-isopropylsulfanyl-5-methyl-1*H*-imidazole (**8e**).

The compound was obtained as white crystals. Yield 120 mg (48%); mp 126–128°; $^1$H-nmr (DMSO-$d_6$): δ 1.19 (d, 3H, $(CH_3)_2CHS$, *J* = 6.6 Hz), 2.07 (s, 3H, $CH_3$), 3.34 (hept., 1H, $(CH_3)_2CHS$, *J* = 6.6 Hz), 3.76 (s, 2H, $CH_2$), 7.15–7.27 (m, 5H, Ph), 11.95 (brs, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 10.43 (br, $CH_3$), 23.15 ($(CH_3)_2CH$), 31.34 (br, $CH_2$), 38.71 ($(CH_3)_2CH$), 125.62, 128.06, 128.11, 134.45 ($C_{arom}$), 140.00 (br, C-2); EI ms: *m/z* 246 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{18}N_2S\bullet0.25H_2O$ (250.88): C, 67.03; H, 7.43; N, 11.17. Found: C, 66.73; H, 7.21; N, 11.14.

4-Benzyl-2-isopropylsulfanyl-5-ethyl-1*H*-imidazole (**8f**).

The compound was obtained as white crystals 104 mg (40%); mp 94–96°; $^1$H-nmr (DMSO-$d_6$): δ 1.04 (t, 3H, $CH_3CH_2$, *J* = 7.2 Hz), 1.23 (d, 3H, $(CH_3)_2CH$, *J* = 6.6 Hz), 2.44 (q, 2H, $CH_3CH_2$, *J* = 6.9 Hz), 3.34 (hept., 1H, $(CH_3)_2CH$, *J* = 6.3 Hz), 3.77 (s, 2H, $CH_2Ph$), 7.14–7.24 (m, 5H, Ph), 11.92 (s, 1H, NH); $^{13}$C nmr (DMSO-$d_6$): δ 14.46 ($CH_3CH_2$), 18.09 (br, $CH_3CH_2$), 23.14 ($(CH_3)_2CH$), 31.25 (br, $CH_2Ph$), 38.69 ($(CH_3)_2CH$), 125.60, 128.03, 128.08, 134.68 ($C_{arom}$), 145.54 (br, C-2); EI ms: *m/z* 260 ($M^+$).

*Anal.* Calcd. for $C_{15}H_{20}N_2S$ (260.39): C, 69.19; H, 7.74; N, 10.76. Found: C, 68.76; H, 7.66; N, 10.71.

4-Benzyl-2-isopropylsulfanyl-5-propyl-1*H*-imidazole (**8g**).

The compound was obtained as white crystals. Yield 104 mg 3(8%); mp 112–114°; $^1$H-nmr (DMSO-$d_6$): δ 0.79 (t, 3H, $CH_3CH_2CH_2$, *J* = 7.2 Hz), 1.19 (d, 3H, $(CH_3)_2CH$, *J* = 6.9 Hz), 1.47 (sext., 2H, $CH_3CH_2CH_2$, *J* = 7.5 Hz), 2.41 (t, 2H, $CH_3CH_2CH_2$, *J* = 7.2 Hz), 3.35 (hept., 1H, $(CH_3)_2CH$, *J* = 6.6 Hz), 3.78 (s, 2H, $CH_2Ph$), 7.11–7.27 (m, 5H, Ph), 11.94 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 13.43 ($CH_3CH_2CH_2$), 22.56 ($CH_3CH_2CH_2$), 23.10 ($(CH_3)_2CH$), 26.57 (br, $CH_3CH_2CH_2$), 31.34 (br, $CH_2Ph$), 38.71 ($(CH_3)_2CH$), 125.59, 128.04, 128.05, 134.65 ($C_{arom}$), 140.70 (br, C-2); EI ms: *m/z* 274 ($M^+$).

*Anal.* Calcd. for $C_{16}H_{22}N_2S$ (274.42): C, 70.03; H, 8.08; N, 10.21. Found: C, 69.98; H, 8.09; N, 10.16.

4-Benzyl-2-isopropylsulfanyl-5-isopropyl-1*H*-imidazole (**8h**).

The compound was obtained as white crystals. Yield 68 mg (25%); mp 121–123°; $^1$H-nmr (DMSO-$d_6$): δ 1.10 (d, 3H, $(CH_3)_2CH$, *J* =6.9 Hz), 1.20 (d, 3H, $(CH_3)_2CHS$, *J* = 6.9 Hz), 2.92 (hept., 1H, $(CH_3)_2CH$, *J* = 6.9 Hz), 3.36 (hept., 1H, $(CH_3)_2CHS$, *J* = 6.6 Hz), 3.79 (s, 2H, $CH_2$), 7.13–7.27 (m, 5H, Ph), 11.94 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 22.66 ($(CH_3)_2CH$), 23.12 ($(CH_3)_2CHS$), 24.60 (br, *C*H), 31.41 (br, $CH_2$), 38.75 (CH-S), 125.60, 128.00, 128.09, 134.77 ($C_{arom}$), 140.84 (br, C-2); EI ms: *m/z* 274 ($M^+$).

*Anal.* Calcd. for $C_{16}H_{22}N_2S\bullet0.25H_2O$ (278.94): C, 68.90; H, 8.13; N, 10.04. Found: C, 69.21; H, 7.90; N, 9.92.

4-Benzyl-2-*sec*-butylsulfanyl-5-methyl-1*H*-imidazole (**8i**).

The compound was obtained as white crystals. Yield 110 mg (42%); mp 88–90°; $^1$H-nmr (DMSO-$d_6$): δ 0.95 (t, 3H, $CH_3CH_2$, *J* = 7.2 Hz), 1.18 (d, 3H, $CH_3CH$, *J* = 6.9 Hz), 1.41–1.57 (m, 2H, $CH_3CH_2CH$), 2.06 (s, 3H, $CH_3$), 3.15 (hext, 1H, $CH_3CHCH_2$, *J* = 6.9 Hz), 3.76 (s, 2H, $CH_2Ph$), 7.12–7.27 (m, 5H, Ph), 11.92 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 11.12 ($CH_3CH_2CH$ and br, $CH_3$ at C-5), 20.67 ($CH_3CH$), 29.13 ($CH_3CH_2CH$), 31.59 (br, $CH_2Ph$), 45.17 (CH-S), 125.60, 128.05, 128.08, 134.28 ($C_{arom}$), 140.58 (br, C-2); EI ms: *m/z* 260 ($M^+$).

*Anal.* Calcd. for $C_{15}H_{20}N_2S$ (260.40): C, 69.19; H, 7.74; N, 10.76. Found: C, 68.77; H, 7.72; N, 10.66.

4-Benzyl-2-*sec*-butylsulfanyl-5-ethyl-1*H*-imidazole (**8j**).

The compound was obtained as white crystals. Yield 82 mg (30%) mp 100–102°; $^1$H-nmr (DMSO-$d_6$): δ 0.92 (t, 3H, $CH_3CH_2CH$, *J* = 7.2 Hz), 1.04 (t, 3H, $CH_3CH_2$, *J* = 7.2 Hz), 1.18 (d, 3H, $CH_3CH$, *J* = 6.6 Hz), 1.41–1.59 (m, 2H, $CH_3CH_2CH$), 2.39 (q, 2H, $CH_3CH_2$, *J* = 6.9 Hz), 3.17 (sext., 1H, $CH_3CHCH_2$, *J* = 6.6 Hz), 3.37 (s, 2H, $CH_2Ph$), 7.16–7.26 (m, 5H, Ph), 11.88 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 11.10 ($CH_3CH_2CH$), 14.41 ($CH_3CH_2$ ), 17.05 (br, $CH_3CH_2$), 20.64 ($CH_3CH$), 29.13 ($CH_3CH_2CH$), 32.51 (br, $CH_2Ph$), 45.16 (CH-S), 125.39, 128.12, 128.23, 134.43 ($C_{arom}$), 141 (br, C-2); EI ms: *m/z* 274 ($M^+$).

*Anal.* Calcd. for $C_{16}H_{22}N_2S$ (274.43): C, 70.03; H, 8.08; N, 10.21. Found: C, 69.60; H, 8.13; N, 10.12.

4-Benzyl-2-*sec*-butylsulfanyl-5-propyl-1*H*-imidazole (**8k**).

The compound was obtained as white crystals. Yield 75 mg (26%); mp 96–98°; $^1$H-nmr (DMSO-$d_6$): δ 0.83 (t, 3H, $CH_3CH_2CH_2$, *J* = 6.9 Hz), 0.97 (t, 3H, $CH_3CH_2CH$, *J* = 7.2 Hz), 1.23 (d, 3H, $CH_3CH$, *J* = 6.9 Hz), 1.48–1.63 (m, 4H, $CH_3CH_2CH_2$ and $CH_3CH_2CH$), 2.47 (t, 2H, $CH_3CH_2CH_2$, *J* = 7.2 Hz), 3.22 (sext., 1H, $CH_3CHCH_2$, *J* = 6.6 Hz), 3.79 ($CH_2Ph$), 7.23–7.27 (m, 5H, Ph), 11.91 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 11.12 ($CH_3CH_2CH$), 13.32 ($CH_3CH_2CH_2$), 20.64 ($CH_3CH$), 22.53 ($CH_3CH_2CH_2$), 25.55 (br, $CH_3CH_2CH_2$), 29.14 ($CH_3CH_2CH$), 32.51 (br, $CH_2Ph$), 45.18 (CH-S), 125.38, 127.89, 128.16, 134.39 ($C_{arom}$), 141.28 (br, C-2); EI ms: *m/z* 288 ($M^+$).

*Anal.* Calcd. for $C_{17}H_{24}N_2S$ (288.46): C, 70.79; H, 8.39; N, 9.71. Found: C, 70.77; H, 8.31; N, 9.74.

4-Benzyl-2-*sec*-butylsulfanyl-5-isopropyl-1*H*-imidazole (**8l**).

The compound was obtained as white crystals. Yield 81 mg (28%); mp 125–127°; $^1$H-nmr (DMSO-$d_6$): δ 0.92 (t, 3H, $CH_3CH_2CH$, *J* = 7.2 Hz), 1.09 (d, 3H, $(CH_3)_2CH$, *J* = 6.6 Hz), 1.18 (d, 3H, $CH_3CH$-S, *J* = 6.9 Hz), 1.42–1.58 (m, 2H, $CH_3CH_2CH$), 2.95 (hept., 1H, $(CH_3)_2CH$, *J* = 7.2 Hz), 3.19 (sext., 1H, $CH_3CHCH_2$, *J* =

6.6 Hz), 3.75 (s, 2H, C$H_2$Ph), 7.16–7.26 (m, 5H, Ph), 11.82 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 11.10 ($CH_3CH_2CH_2$), 20.62 ($CH_3CHCH_2$), 22.43 (($CH_3$)$_2$CH), 24.05 (br, ($CH_3$)$_2$CH), 29.15 ($CH_3CH_2CH$), 32.63 (br, $CH_2$Ph), 45.12 (CH-S), 125.36, 128.07, 128.21, 134.98 ($C_{arom}$), 141.43 (br, C-2); EI ms: *m/z* 288 ($M^+$).

*Anal.* Calcd. for $C_{17}H_{24}N_2S$•0.25$H_2O$ (292.96): C, 69.70; H, 8.43; N, 9.56. Found: C, 69.62; H, 8.16; N, 9.57.

General Procedure for Preparation of 4-Benzyl-5-alkyl-2-benzylsulfanyl-1*H*-imidazole **(8m-p)**.

A mixture of 7a-d (1 mmole), benzyl bromide (0.12 ml, 1 mmole) and potassium carbonate (0.138 g, 1 mmoles) in dimethylformamide (5 ml) was stirred for 10 hours at room temp. The reaction mixture was treated with ice/cold water (100 ml) and left to stand at room temperature for 3 hours. The solid product was isolated by filtration and recrystallized from acetone/water to give compounds **8m-p**.

4-Benzyl-2-benzylsulfanyl-5-methyl-1*H*-imidazole (**8m**).

The compound was obtained as white crystals. Yield 76 mg (26%); mp 105–107°; $^1$H-nmr (DMSO-$d_6$): δ 2.07 (s, 3H, $CH_3$), 3.76 (s, 2H, C$H_2$Ph ), 4.16 (s, 2H, S-C$H_2$Ph), 7.20 (brs, 10H, 2Ph), 11.88 (brs, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 10.37 (br, $CH_3$), 31.30 (br, $CH_2$Ph), 37.81 (S-$CH_2$Ph), 125.62, 126.91, 128.09, 128.19, 128.61, 135.16, 138.03 ($C_{arom}$), 140.55 (br, C-2); EI ms: *m/z* 294 ($M^+$).

*Anal.* Calcd. for $C_{18}H_{18}N_2S$•0.5$H_2O$ (303.43): C, 71.25; H, 6.31; N, 9.22. Found: C, 71.34; H, 5.99; N, 9.19.

4-Benzyl-2-benzylsulfanyl-5-ethyl-1*H*-imidazole (**8n**).

The compound was obtained as white crystals. Yield 98 mg (32%); mp 138–140°; $^1$H-nmr (DMSO-$d_6$): δ 1.04 (brs, 3H, C$H_3$CH$_2$), 2.44 (brs, 2H, CH$_3$C$H_2$), 3.75 (s, 2H, C$H_2$Ph), 4.16 (s, 2H, S-C$H_2$Ph), 7.22 (brs, 10H, 2Ph), 11.83 (brs, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 14.53 ($CH_3CH_2$), 17.06 (br, $CH_3CH_2$), 32.54 (br, $CH_2$Ph), 37.80 (S-$CH_2$Ph), 125.44, 125.83, 126.89, 128.16, 128.65, 138.07 ($C_{arom}$); EI ms: *m/z* 308 ($M^+$); HiResMALDI *m/z* 331.1238 ($M^+$+ Na. $C_{19}H_{20}N_2NaS$) requires 331.1244.

4-Benzyl-2-benzylsulfanyl-5-propyl-1*H*-imidazole (**8o**).

The compound was obtained as white crystals. Yield 216 mg (67%); mp 98–100°; $^1$H-nmr (DMSO-$d_6$): δ 0.78 (t, 3H, C$H_3$CH$_2$CH$_2$, *J* = 7.5 Hz), 1.41–1.50 (m, 2H, CH$_3$C$H_2$CH$_2$), 2.39 (t, 2H, CH$_3$CH$_2$C$H_2$, *J* = 7.5 Hz), 3.74 (s, 2H, C$H_2$Ph), 4.16 (s, 2H, S-C$H_2$Ph), 7.11–7.29 (m, 10H, 2Ph), 11.81 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 13.33 ($CH_3CH_2CH_2$), 22.54 (br, $CH_3CH_2CH_2$), 25.57 (br, $CH_3CH_2CH_2$), 28.30 (br, Ph$CH_2$), 37.84 (S-$CH_2$Ph), 125.4, 126.87, 127.90, 128.10, 128.24, 128.64, 135.17, 135.44 ($C_{arom}$), 141.26 (br, C-2); EI ms: *m/z* 322 ($M^+$).

*Anal.* Calcd. for $C_{20}H_{22}N_2S$ (322.46): C, 74.49; H, 6.88; N, 8.69. Found: C, 74.39; H, 6.81; N, 8.61.

4-Benzyl-2-benzylsulfanyl-5-isopropyl-1*H*-imidazole (**8p**).

The compound was obtained as white crystals. Yield 190 mg (59%); mp 123–125°; $^1$H-nmr (DMSO-$d_6$): δ 1.09 (d, 3H, ($CH_3$)$_2$CH, *J* = 6.6 Hz), 2.92 (hept., 1H, ($CH_3$)$_2$C*H*, *J* = 6.0 Hz), 3.78 (s, 2H, C$H_2$Ph), 4.16 (s, S-C$H_2$Ph), 7.12–7.26 (m, 10H, 2Ph), 11.77 (s, 1H, NH); $^{13}$C-nmr (DMSO-$d_6$): δ 22.71 (($CH_3$)$_2$CH), 24.56 (br, ($CH_3$)$_2$CH), 31.59 (br, $CH_2$Ph), 37.84 (S-$CH_2$Ph), 125.58, 126.87, 128.04 128.12, 128.68, 135.27, 138.01 ($C_{arom}$), 140.81 (br, C-2); EI ms: *m/z* 322 ($M^+$).

*Anal*. Calcd. for $C_{20}H_{22}N_2S$•0.25$H_2O$ (326.98): Calc. C, 73.47; H, 6.94; N, 8.57. Found: C, 73.26; H, 6.75; N, 8.44.

The HIV-1 strains HTLV-IIIB [23] and the NNRTI resistant strain N119 [24] were propagated in H9 cells [25] at 37°, 5% $CO_2$ using RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS) and antibiotics (growth medium). Culture supernatant was filtered (0.45 nm), aliquotted, and stored at –80° until use. Both HIV-1 strains were obtained from NIH AIDS Research and Reference Program.

Compounds were examined for possible antiviral activity against both strains of HIV-1 using MT4 cells as target cells. MT4 cells were incubated with virus (0.005 MOI) and growth medium containing the test dilutions of compound for six days in parallel with virus-infected and uninfected control cultures without compound added. Expression of HIV in the cultures was indirectly quantified using the MTT assay [26]. Compounds mediating less than 30% reduction of HIV expression were considered without biological activity. Compounds were tested in parallel for cytotoxic effect in uninfected MT4 cultures containing the test dilutions of compound as described above. A 30% inhibition of cell growth relative to control cultures was considered significant.

The 50% inhibitory concentration ($IC_{50}$) and the 50% cytotoxic concentration ($CC_{50}$) were determined by interpolation from the plots of percent inhibition versus concentration of compound.

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