

Nitroimidazoles, Part 4: Synthesis and Anti-HIV Activity of New 5-alkylsulfanyl and 5-(4'-arylsulfonyl)piperazinyl-4-nitroimidazole Derivatives

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ABSTRACT: The development of new HIV nonnucleoside reverse transcriptase inhibitors (NNRTIs) offers the possibility of generating structures of increased potency. On this basis, a series of 5-alkylsulfanyl and 5-(4'-arylsulfonyl)piperazine derivatives of 1-phenyl-2-alkyl-4-nitroimidazoles **5–21** was synthesized with the aim to develop new NNRTIs. The new synthesized compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. Compounds **9** and **13**, with an alkylsulfanyl group at C-5 of the 4-nitroimidazole backbone, showed inhibition of HIV-1 with EC_{50} 4.04 μ g/mL and 2.37 μ g/mL, and therapeutic indexes (SI) of 17 and 13, respectively. © 2007 Wiley Periodicals, Inc. *Heteroatom Chem* 18:333–340, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20301

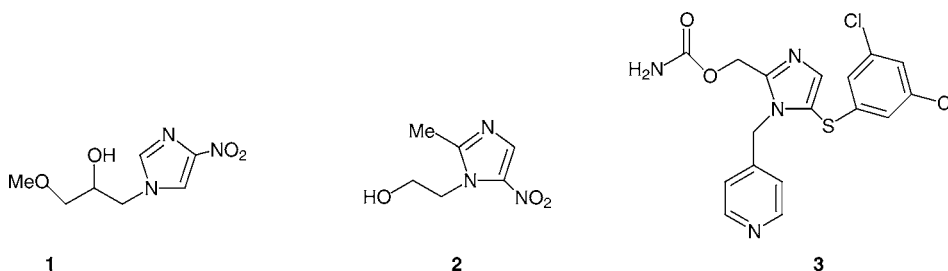
INTRODUCTION

Nitro-substituted imidazoles have important applications, particularly as antibacterial agents

and in cancer chemotherapy [1–4]. Dacarbazine[®] (DTIC) [5] and misonidazole [1-methoxy-3-(4-nitroimidazol-1-yl)propan-2-ol, **1**] [6] are approved drugs for inhibition of de novo purine synthesis in addition to the potent anticancer activity. Some compounds of nitroimidazoles are reported as potent whereas selective histamine H-3 receptor agonists [7–9], mitogen-activated protein (MAP) kinases inhibitors [10–15], nitric-oxide synthase inhibitors [16], and anti-inflammatory agents [17]. 5-Nitro-substituted-haloimidazoles, the interesting class of such compounds, showed an important biological activity as potential radiosensitizers [18].

Other imidazole derivatives having 5-alkylsulfanyl residues exhibited remarkable antitumor activity [19]. Clotrinazole [1-(2-chlorotriptyl)-1H-imidazole] [20,21] and metronidazole (Flagyl[®]) [2-(2-methyl-5-nitroimidazol-1-yl)ethanol, **2**] [22] are considered as potent fungicides and antiprotozoal agents especially for treatment of *Trichomonas vaginalis*, *Entamoeba histolytica*, and *Gardia lamblia*. Capravirine S-1153 **3** [23] is reported as a new imidazole analogue with a high anti-HIV inhibitory activity. Many laboratories [24–32] have engaged in the development of new

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high-yielding routes leading to interesting imidazole derivatives bearing various alkylsulfanyl or alkylamino groups via nucleophilic substitution of the halogen by nitrogen or sulfur nucleophiles. We report here the synthesis of new 5-alkylsulfanyl and 5-(4'-arylsulfonyl)piperazinyl-4-nitroimidazole derivatives with evaluation of their anti-HIV activity.

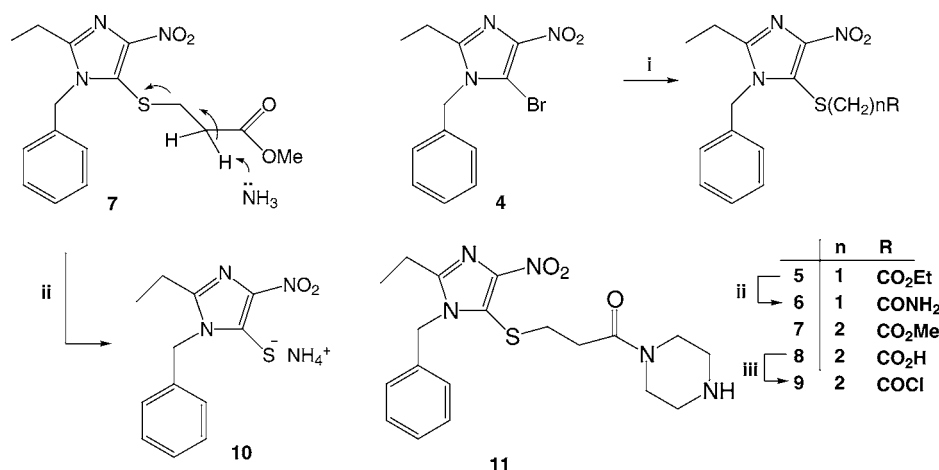
RESULTS AND DISCUSSION

Chemistry

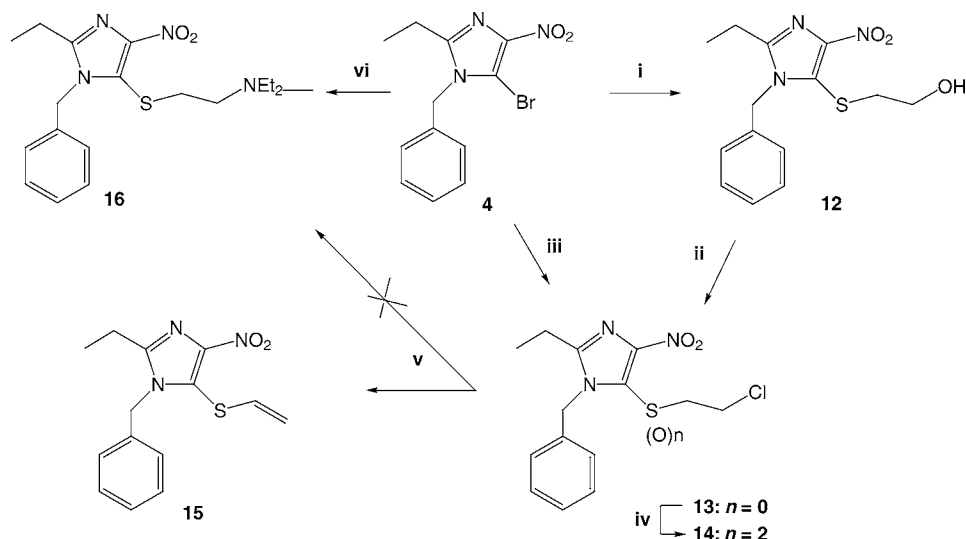
Recently, we have prepared some new 5-alkylamino and 5-alkylsulfanyl derivatives of imidazoles [33] via the nucleophilic displacements of the bromine group activated by an adjacent nitro group. Our efforts are continued in preparation of such compounds carrying various potential groups and might lead to biological active candidates. Benzyl-5-bromo-2-ethyl-4-nitro-1*H*-imidazole **4** has been selected for the synthesis of our targets by treatment with different alkylsulfanyl nucleophiles such as ethyl 2-mercaptoacetate and 3-mercaptopropanoic acid in the presence of K_2CO_3 in hot *i*-PrOH to give, after purification, **5** and **8** in 83% and 60% yield, respectively. Treatment of **5** with 16% $NH_3/MeOH$ at

23°C afforded the amide **6** (90%), whereas a similar treatment of **7**, prepared previously in our laboratory [33] with $NH_3/MeOH$, gave the thioammonium salt **10** as a result of the β -elimination of the ethyl ester group at C5–S group. When the acid **8** was treated with $SOCl_2$ at 23°C, the acyl chloride **9** was obtained, which, in turn, was used directly without purification in the next step by treating it with the piperazine in the presence of Et_3N to give **11** (71%) (Scheme 1).

The structures of the newly synthesized products **5–11** were confirmed by the 1H , ^{13}C NMR, and mass spectra. In the 1H NMR spectra, the phenyl and ethyl protons showed rather similar patterns, whereas the singlets in the region δ_H 5.49–5.31 were attributed to the methylene of benzyl group. The SCH_2 protons of **5** and **6** appeared as singlets at δ_H 3.74 and 3.60, respectively, whereas the same protons of **8** and **11** appeared as triplets at δ_H 3.15 and 3.19 ($J = 6.8$ and 6.6 Hz), respectively. The triplet at δ_H 2.69 represent the methylene protons adjacent piperazine of **11**, whereas the two broad singlets at δ_H 3.36 and 2.82 represent the piperazine protons. In the ^{13}C NMR spectra of **5–11**, C-2 resonated between δ_C 146.6 and δ_C 152, whereas C-4 appeared between δ_C 134.9 and δ_C 138.4. The resonances between δ_C 129.8 and δ_C 23.3 represent C-5 and the phenyl carbon atoms. SCH_2



SCHEME 1 Reagents and conditions: (i) $R(CH_2)_nSH$, K_2CO_3 , *i*-PrOH, 60–70°C, 4h; (ii) $NH_3/MeOH$, 23°C, 10 h; (iii) $SOCl_2$, $CHCl_3$, 23°C, 18 h.



SCHEME 2 Reagents and conditions: (i) $\text{OH}(\text{CH}_2)_2\text{SH}$, KOH , $^i\text{PrOH}$, $60\text{--}80^\circ\text{C}$; (ii) SOCl_2 , CHCl_3 , 23°C , 18 h; (iii) $\text{Cl}(\text{CH}_2)_2\text{SH}$, KOH , $^i\text{PrOH}$, $60\text{--}80^\circ\text{C}$; 4 h; (iv) mCPBA , 1N NaOH , CH_2Cl_2 , 23°C , 6 h; (v) NHET_2 , DMF , $80\text{--}90^\circ\text{C}$, 4 h; (vi) $\text{HS}(\text{CH}_2)_2\text{NEt}_2$, KOH , $^i\text{PrOH}$, $60\text{--}80^\circ\text{C}$, 4 h.

of **5**, **6**, **8**, and **11** resonated between δ_{C} 31.2 and δ_{C} 37.2.

Other models of alkylsulfanyl groups at C-5 of the imidazole backbone are prepared. Thus, treatment of **4** with 2-mercaptoethanol in the presence of KOH afforded **12** (65%). Chlorination of **12** by treatment with SOCl_2 afforded **13** at low yield (30%). Oxidation of **13** with mCPBA in the presence of base furnished, after purification, the sulfone **14** (71%).

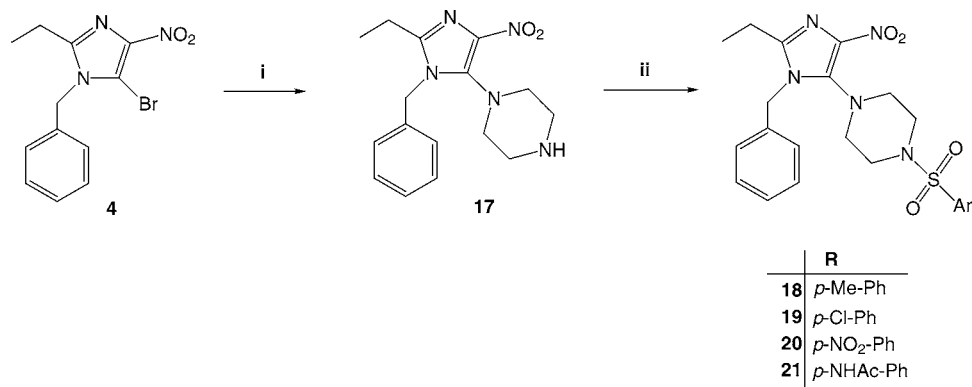
Our attempt to prepare **16** from the chloro compound **13** by treatment with diethyl amine was unsuccessful, and instead, compound **15** was obtained (76%) as a result of dehydrochlorination of **13**. Alternatively, treatment of **4** with 2-(diethylamino)ethanethiol hydrochloride in hot $^i\text{PrOH}$ and KOH furnished **16** in 55% yield (Scheme 2).

The assignment of protons and carbons of the imidazole ring was deduced in comparison to com-

pounds **5–11** and the previously reported data of **7** [33]. The structural assignment of **15** follows from the mass spectrum and the ^1H and ^{13}C NMR spectra. Irradiation at δ_{H} 6.18 produced an 18% NOE on the signals at δ_{H} 5.33 and 5.14 assigned to SCH olefinic proton.

Replacement of the bromo residue of **4** by piperazine in hot DMF furnished **17** (72%). When **17** was treated with the arylsulfonyl chlorides in the presence of Et_3N , the sulfonate derivatives **18–21** were obtained in 53, 43, 49, and 43% yields, respectively (Scheme 3).

The structures of **17–21** were assigned on the basis of the ^1H , ^{13}C NMR, and mass spectra. The ^1H NMR spectra demonstrated broad singlets, triplets, or multiplets in the region between δ_{H} 2.89 and 3.58, attributed to the piperazine protons. The ^{13}C NMR spectra supported the proposed structures because the carbons of the imidazole ring were deduced by



SCHEME 3 Reagents and conditions: (i) piperazine, DMF , $70\text{--}80^\circ\text{C}$, 6 h; (ii) ArSO_2Cl , Et_3N , CH_2Cl_2 , 23°C , 4 h.

comparison with those of **5–11** and the structurally proven 5-alkylamino imidazole derivatives [33].

In Vitro Anti-HIV Activity

Compounds **5–21** were evaluated for their in vitro anti-HIV-1 activity by using the III_B strain for HIV-1 and the ROD strain for the HIV-2, and monitored by the inhibition of the virus-induced cytopathic effect in the human T-lymphocyte (MT-4) cells. The results are summarized in Table 1, in which the data for efavirenz [34] and capravirine [35] were included for comparison purposes. Compound **9** and **13** were found to be the only two compounds from the series inhibiting HIV-1 replication in cell culture. Com-

pounds **9** and **13** showed EC₅₀ of 4.04 µg/mL (CC₅₀ of 57.9 ± 7.8 µg/mL) and 2.37 µg/mL (CC₅₀ of 2.85 ± 0.4 µg/mL), and resulting in selectivity index of 17 and 13, respectively.

On the basis of the chemical structure and the fact that compounds **9** and **13** inhibits HIV-1, but not HIV-2 replication, these molecule can be proposed to act as an NNRTI.

EXPERIMENTAL

General

Melting points were measured on a Büchi melting point apparatus B-545 (BÜCHI Labortechnik AG, Switzerland) and are uncorrected. Microanalytical

TABLE 1 In Vitro Anti-HIV-1^a and HIV-2^b of Some New Nitroimidazoles

	Virus strain	EC ₅₀ (µg/mL) ^c	CC ₅₀ (µg/mL) ^d	SI ^e
5	III _B	>44.3	48.2 ± 4.8	<1
	ROD	>53.6	48.2 ± 4.8	<1
6	III _B	>12.4	13.0 ± 0.6	<1
	ROD	>13.4	13.0 ± 0.6	<1
7	III _B	>11.8	12.4 ± 0.5	<1
	ROD	>12.6	12.4 ± 0.5	<1
8	III _B	>64.5	64.5 ± 5.3	<1
	III _B	>64.5	64.5 ± 5.3	<1
9	III _B	4.04	57.9 ± 7.8	17
	ROD	>57.9	57.9 ± 7.8	<1
10	III _B	>0.39	0.41 ± 0.1	<1
	ROD	>0.37	0.41 ± 0.1	<1
11	III _B	>42.8	46.2 ± 3.1	<1
	ROD	>48.7	46.2 ± 3.1	<1
12	III _B	>0.44	0.46	<1
	ROD	>0.48	0.46	<1
13	III _B	2.37	2.85 ± 0.4	13
	ROD	>2.95	2.85 ± 0.4	<1
14	III _B	>4.43	6.1 ± 3.4	<1
	ROD	>3.79	6.1 ± 3.4	<1
15	III _B	>0.39	0.41 ± 0.1	<1
	ROD	>0.37	0.41 ± 0.1	<1
16	III _B	>34.4	46.8 ± 18.5	<1
	ROD	>37.9	46.8 ± 18.5	<1
17	III _B	>36.0	>or = 36.0	<1
	ROD	>21.4	>or = 36.0	<1
18	III _B	>68.5	80.8 ± 26.3	<1
	ROD	>62.9	80.8 ± 26.3	<1
19	III _B	>91.2	90.0 ± 7.2	<1
	ROD	>82.3	90.0 ± 7.2	<1
20	III _B	>68.5	80.8 ± 26.3	<1
	ROD	>62.9	80.8 ± 26.3	<1
21	III _B	>91.2	90.0 ± 7.22	<1
		82.3	90.0 ± 7.22	<1
Efavirenz [34]	III _B	0.003	40	13,333
Capravirine [35]	III _B	0.0014	11	7,857

^aAnti-HIV-1 activity measured with strain III_B.

^bAnti-HIV-2 activity measured with strain ROD.

^cCompound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and HIV-2-induced cytopathogenic effect.

^dCompound concentration that reduces the viability of mock-infected MT-4 cells by 50%.

^eSI: Selectivity index (CC₅₀/EC₅₀).

data were obtained with a Vario, Elementar apparatus (Shimadzu, Japan). NMR spectra were recorded on 300 and 600 MHz (^1H) and at 150.91 MHz (^{13}C) spectrometers (Bruker, Germany) with TMS as internal standard and on δ scale in ppm. Heteronuclear assignments were verified by ^1H - ^{13}C HMBC experiment. Mass spectra were recorded on 70 eV EI and FAB MAT 8200 spectrometers (Finnigan MAT), using 3-nitrobenzyl alcohol (NBOH) or glycerol as matrices. Some molecular ions were detected by doping the sample with Na^+ ion.

Ethyl 2-(1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-ylthio)acetate (5). A suspension of ethyl 2-mercaptoacetate (1.44 g, 12.0 mmol) and K_2CO_3 (2.45 g, 25.0 mmol) was stirred in dry i-PrOH (40 mL) under argon at 23°C . To this suspension, **4** (3.10 g, 10 mmol) was added slowly and was stirred at 60 – 70°C for 4 h. The mixture was poured into ice water, and the precipitate was filtered off and recrystallized from EtOH to give **5** (2.78 g, 83%); mp 80 – 81°C . ^1H NMR ($\text{DMSO}-d_6$): δ 7.36–7.32 (m, 3H, Ph-H); 7.00–6.96 (m, 2H, Ph-H); 5.49 (s, 2H, CH_2Ph); 4.09 (q, 2H, $J = 7.1$ Hz, OCH_2CH_3); 3.74 (s, 2H, SCH_2); 2.68 (q, 2H, $J = 7.2$ Hz, CH_2CH_3); 1.28 (t, 3H, OCH_2CH_3); 1.22 (t, 2H, CH_2CH_3). ^{13}C NMR ($\text{DMSO}-d_6$): δ 168.7 (C=O); 150.6 (C-2); 135.1 (C-4); 129.4, 129.1, 128.9, 128.2, 127.1, 126.0, 123.3 (C-5, Ph-C); 61.9 (OCH_2CH_3); 47.9 (CH_2Ph); 37.2 (SCH_2); 21.2 (CH_2CH_3); 13.9 (OCH_2CH_3); 11.2 (CH_2CH_3). Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$ (349.4): C, 55.00; H, 5.48; N, 12.03. Found: C, 54.72; H, 5.31; N, 11.84. m/z (FAB): 350 ($\text{M} + \text{H}$) $^+$.

2-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-ylthio)acetamide (6). A solution of **5** (0.50 g, 1.43 mmol) in 16% NH_3/MeOH (20 mL) was stirred at 23°C for 10 h. The solution was evaporated to dryness, and the residue was recrystallized from EtOH to give **6** (90%), as orange crystals, mp 175 – 178°C dec. ^1H NMR ($\text{DMSO}-d_6$): δ 7.53 (m, 1H, Ph-H); 7.34 (m, 2H, Ph-H); 7.09–7.02 (m, 2H, Ph-H); 5.49 (s, 2H, CH_2Ph); 3.60 (s, 2H, SCH_2); 2.63 (q, 2H, $J = 7.2$ Hz, CH_2CH_3); 1.10 (t, 3H, CH_2CH_3). ^{13}C NMR ($\text{DMSO}-d_6$): δ 170.1 (CONH_2); 151.1 (C-2); 136.6 (C-4); 129.8, 128.6, 126.9, 125.5 (C-5, Ph-C); 48.0 (CH_2Ph); 40.0 (SCH_2); 21.2 (CH_2CH_3); 11.5 (CH_2CH_3). Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$ (320.4): C, 52.49; H, 5.03; N, 17.49. Found: C, 52.17; H, 4.96; N, 17.27; m/z (FAB): 321 ($\text{M} + \text{H}$) $^+$.

Methyl 3-(1-benzyl-2-ethyl-4-nitro-3H-imidazole-5-ylsulfanyl)propanoate (7). This compound was prepared according to reference [33]. Compound **4** (1.55 g, 5.0 mmol) and methyl 3-mercapto-

propanoate (0.30 g, 2.50 mmol). Yield: 1.43 g, 82%; mp 94 – 95°C (from EtOH). MS: m/z (EI) 349 (M) $^+$. The ^1H - and ^{13}C NMR spectra were identical to the authentic sample prepared previously.

3-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-ylthio)propanoic acid (8). To a solution of **4** (3.10 g, 10.0 mmol) in i-PrOH (50 mL) was added 3-mercapto-propanoic acid (1.06 g, 10.0 mmol) and KOH (0.56 g, 10.0 mmol) and stirred at 60 – 70°C for 4 h. After cooling, the solution was neutralized with 1N HCl to give **8** (2.0 g, 60%) as a powder; mp 167 – 170°C dec. ^1H NMR (CDCl_3): δ 10.8 (s, 1H, CO_2H); 7.35–7.26 (m, 3H, Ph-H); 6.99–6.95 (m, 2H, Ph-H); 5.35 (s, 2H, PhCH_2); 3.15 (t, 2H, $J = 6.8$ Hz, SCH_2CH_2); 2.66 (t, 2H, $J = 6.8$ Hz, SCH_2CH_2); 2.58 (q, 2H, $J = 6.8$ Hz, CH_2CH_3); 1.26 (t, 3H, CH_2CH_3). ^{13}C NMR (CDCl_3): δ 174.8 (CO_2H); 150.7 (C-2); 134.9 (C-4); 129.3, 129.2, 128.4, 126.0, 125.7 (C-5, Ph-C); 48.6 (CH_2Ph); 34.1 ($\text{SCH}_2\text{CH}_2\text{CO}_2\text{H}$); 31.2 ($\text{SCH}_2\text{CH}_2\text{CO}_2\text{H}$); 21.3 (CH_2CH_3); 11.6 (CH_2CH_3). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$ (335.38): C, 53.72; H, 5.11; N, 12.53. Found: C, 53.43; H, 5.00; N, 12.31; m/z (FAB): 358 ($\text{M} + \text{Na}$) $^+$.

Ammonium 1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-thiolate (10). A solution of **7** (1.67 g, 4.78 mmol) in 16% NH_3/MeOH (20 mL) was stirred at 23°C for 5 h. The solution was evaporated to dryness, and the residue was recrystallized from EtOH to give **10** (1.20 g, 90%), mp 170 – 171°C . ^1H NMR ($\text{DMSO}-d_6$): δ 7.30–7.15 (m, 5H, Ph-H); 5.31 (s, 2H, CH_2Ph); 2.36 (q, 2H, $J = 7.5$ Hz, CH_2CH_3); 1.01 (t, 3H, CH_2CH_3). ^{13}C NMR ($\text{DMSO}-d_6$): δ 146.6 (C-2); 138.4 (C-4); 128.6, 127.2, 127.0 (C-5, Ph-C); 45.1 (CH_2Ph); 21.0 (CH_2CH_3); 11.2 (CH_2CH_3). Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$ (280.35): C, 51.41; H, 5.75; N, 19.98. Found: C, 51.22; H, 5.41; N, 19.84. m/z (FAB): 262 ($\text{M} - \text{NH}_4^+$) $^+$.

3-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-ylthio)-1-(piperazin-1-yl)propan-1-one (11). SOCl_2 (0.36 g, 3.0 mmol) was added stepwise to a solution of **8** (0.50 g, 1.50 mmol) in CHCl_3 (10 mL), and the reaction mixture was stirred at 23°C for 18 h. The solution was evaporated to dryness, and the residue was washed with ether (3×30 mL) to give a crude **9** (0.34 g, 65%). This product was used directly for the next step by dissolving in CH_2Cl_2 (15 mL), followed by the addition of piperazine (0.15 g, 1.70 mmol) and Et_3N (1.0 mL), and the reaction mixture was stirred at 23°C for 18 h. The mixture was evaporated to dryness, and the residue was recrystallized from EtOH to give **11** (0.27 g, 71%), mp 149 – 152°C . ^1H NMR (CDCl_3): δ 7.37–7.26 (m, 3H, Ph-H); 7.01–6.97

(m, 2H, Ph-H); 5.40 (s, 2H, PhCH₂); 3.36 (br s., 4H, piperazine); 3.19 (t, 2H, *J* = 6.6 Hz, SCH₂CH₂); 2.82 (br s., 4H, piperazine); 2.69 (t, 2H, *J* = 6.6 Hz, SCH₂CH₂); 2.59 (q, 2H, *J* = 6.7 Hz, CH₂CH₃); 1.27 (t, 3H, CH₂CH₃). ¹³C NMR (CDCl₃): δ 171.6 (CO-piperazine); 152.1 (C-2); 135.2 (C-4); 129.6, 129.7, 128.9, 126.3, 125.9 (C-5, Ph-C); 49.5 (piperazine); 48.4 (CH₂Ph); 45.6 (piperazine); 34.8 (SCH₂CH₂CO); 31.3 (SCH₂CH₂CO); 21.2 (CH₂CH₃); 11.8 (CH₂CH₃). Anal. Calcd for C₁₉H₂₅N₅O₃S. (403.50): C, 56.56; H, 6.25; N, 17.36. Found: C, 56.32; H, 6.12; N, 17.16. *m/z* (FAB): 404 (M + H)⁺.

2-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-ylthio)-ethanol (12). This compound was prepared from **4** (0.93 g, 3.0 mmol) and 2-mercaptoethanol (0.24 g, 3.0 mmol) by following the same procedure as for **5**. Yield: 0.60 g (65%); oil. ¹H NMR (CDCl₃): δ 7.38–7.29 (m, 3H, Ph-H); 7.07–6.98 (m, 2H, Ph-H); 5.41 (s, 2H, PhCH₂); 3.65 (t, 2H, *J* = 5.6 Hz, CH₂OH); 3.00 (t, 2H, *J* = 5.6 Hz, SCH₂); 2.64 (q, 2H, *J* = 7.5 Hz, CH₂CH₃); 1.21 (t, 3H, CH₂CH₃). Anal. Calcd for C₁₄H₁₇N₃O₃S (307.37): C, 54.71; H, 5.57; N, 13.67. Found: C, 54.52; H, 5.39; N, 13.38; *m/z* (FAB): 330 (M + Na)⁺.

1-Benzyl-5-(2-chloroethylthio)-2-ethyl-4-nitro-1H-imidazole (13). **Method a**—SOCl₂ (1.19 g, 10.08 mmol) was added stepwise to a solution of **12** (1.55 g, 5.04 mmol) in CHCl₃ (20 mL) and the reaction mixture was stirred at 23°C for 18 h. The solution was evaporated to dryness and the residue was washed with ether (3 × 30 mL) and the residue was recrystallized from EtOH to give **13** (0.47 g, 30%), as a light yellow crystal, mp 146–147°C dec. ¹H NMR (CDCl₃): δ 7.39–7.26 (m, 3H, Ph-H); 6.99–6.96 (m, 2H, Ph-H); 5.39 (s, 2H, PhCH₂); 3.50 (t, 2H, *J* = 6.9 Hz, CH₂Cl); 3.22 (t, 2H, *J* = 6.9 Hz, SCH₂); 2.68 (q, 2H, *J* = 7.4 Hz, CH₂CH₃); 1.28 (t, 3H, CH₂CH₃). ¹³C NMR (CDCl₃): δ 150.8 (C-2); 134.9 (C-4); 129.5, 129.3, 128.4, 126.0, 123.5 (C-5, Ph-C); 47.9 (CH₂Ph); 42.6 (CH₂Cl); 38.4 (SCH₂); 21.3 (CH₂CH₃); 11.3 (CH₂CH₃). Anal. Calcd for C₁₄H₁₆ClN₃O₂S (325.81): C, 51.61; H, 4.95; N, 12.90. Found: C, 51.29; H, 4.78; N, 12.70; *m/z* (FAB): 325/327 (M + H)⁺.

Method b—This compound was prepared from **4** (1.0 g, 3.22 mmol) and 2-chloroethanethiol (0.29 g, 3.0 mmol) by following the same procedure as for **5**. Yield: 0.30 g (29%); mp, mixed mp, and the NMR spectra were identical to the authentic sample prepared in Method a.

1-Benzyl-5-(2-chloroethylsulphonyl)-2-ethyl-4-nitro-1H-imidazole (14). A solution of **13** (0.35 g,

1.07 mmol) in CH₂Cl₂ (15 mL) was stirred with mCPBA (0.47 g, 2.15 mmol) for 6 h at 23°C. The solution was partitioned with water (15 mL), the organic layer was dried (Na₂SO₄), filtered, and evaporated to dryness, and the residue was recrystallized from EtOH to give **14** (0.25 g, 71%), mp 135–136°C dec. ¹H NMR (600 MHz, CDCl₃): δ 7.40–7.34 (m, 3H, Ph-H); 7.07 (m, 2H, Ph-H); 5.59 (s, 2H, PhCH₂); 3.78–3.75 (m, 2H, CH₂Cl); 3.34–3.31 (m, 2H, SCH₂); 2.76 (q, 2H, *J* = 7.4 Hz, CH₂CH₃); 1.36 (t, 3H, CH₂CH₃). ¹³C NMR (HMQC, CDCl₃): δ 153.7 (C-2); 135.3, 129.128.5, 128.3, 126.2 (Ph-C); 47.9 (CH₂Ph); 55.6 (SO₂CH₂); 47.9 (CH₂Ph); 36.2 (SCH₂); 20.4 (CH₂CH₃); 11.3 (CH₂CH₃). Anal. Calcd for C₁₄H₁₆ClN₃O₄S (357.81): C, 46.99; H, 4.51; N, 11.74. Found: C, 46.72; H, 4.36; N, 11.52; *m/z* (FAB): 357/359 (M + H)⁺.

1-Benzyl-2-ethyl-4-nitro-5-(vinylthio)-1H-imidazole (15). Et₂NH (73 mg, 1.0 mmol) was added to a solution of **13** (330 mg, 1.0 mmol) in DMF (10 mL) containing NaH (30 mg, 1.25 mmol). The solution was stirred at 80–90°C for 4 h and evaporated to dryness. The residue was partitioned between CHCl₃ (2 × 15 mL) and water (15 mL), and the combined organic extracts was dried (Na₂SO₄), filtered, and evaporated to dryness. The residue was poured onto SiO₂ column (5.0 g), using CH₃Cl-MeOH (95–5%) as eluent to give **15** (0.22 g, 76%); mp 58–61°C dec. ¹H NMR (CDCl₃): δ 7.40–7.30 (m, 3H, Ph-H); 7.02–6.99 (m, 2H, Ph-H); 6.18 (dd, 1H, *J* = 9.4 Hz, 16.5 Hz, SCH=CH₂); 5.33 (dd, 1H, *J* = 9.4 Hz, 16.5 Hz, SCH=CH₂); 5.14 (d, 1H, *J* = 16.5 Hz, SCH=CH₂); 5.30 (s, 2H, CH₂Ph); 2.66 (q, 2H, *J* = 7.5 Hz, CH₂CH₃); 1.25 (t, 2H, CH₂CH₃). ¹³C NMR (CDCl₃): δ 150.9 (C-2); 134.5 (C-4); 129.3, 129.1, 128.3, 128.2, 127.1, 125.1 (C-5, Ph-C); 120.7 (SCH=CH₂); 116.5 (SCH=CH₂); 47.7 (CH₂Ph); 21.2 (CH₂CH₃); 11.1 (CH₂CH₃). Anal. Calcd for C₁₄H₁₅N₃O₂S (289.35): C, 58.11; H, 5.23; N, 14.52. Found: C, 57.94; H, 5.14; N, 14.31; *m/z* (FAB): 290 (M + H)⁺.

2-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-ylthio)-N,N-diethylamine (16). This compound was prepared from **4** (0.47 g, 1.5 mmol) and 2-(diethylamino)ethanethiol hydrochloride (0.25 g, 1.5 mmol) by following the same procedure as for **5**. Yield 0.30 g (55%); oil. ¹H NMR (DMSO-*d*₆): δ 7.36–7.33 (m, 3H, Ph-H); 7.00–6.97 (m, 2H, Ph-H); 5.40 (s, 2H, CH₂Ph); 3.02 (t, 2H, *J* = 5.7 Hz, SCH₂CH₂); 2.67 (t, 2H, *J* = 5.7 Hz, SCH₂CH₂); 2.60 (q, 2H, *J* = 7.2 Hz, CH₂CH₃); 2.46 (q, 4H, *J* = 7.4 Hz, 2 × NCH₂CH₃); 1.29 (t, 3H, CH₂CH₃); 0.95 (t, 6H, 2 × NCH₂CH₃). ¹³C NMR (DMSO-*d*₆): δ 150.0 (C-2); 135.1 (C-4); 129.1,

128.1, 125.9 (C-5, Ph-C); 51.7 (NCH₂CH₂S); 47.7 (CH₂Ph); 46.7 (2 × NCH₂CH₃); 34.2 (NCH₂CH₂S); 21.2 (C₂-CH₂CH₃); 11.3 (C₂-CH₂CH₃, 2xNCH₂CH₃). Anal. Calcd for C₁₈H₂₆N₄O₂S (362.5): C, 59.64; H, 7.23; N, 15.46. Found: C, 59.44; H, 7.09; N, 15.23; *m/z* (FAB): 363 (M + H)⁺.

1-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-piperazine (17). Piperazine (1.03 g, 12.0 mmol) was added to a stirred solution of **4** (3.10 g, 10 mmol) in DMF (25 mL) and heated at 70–80°C for 6 h. The solution was evaporated to dryness, and the residue was recrystallized from EtOH to give **17** (3.41 g, 72%); mp 228–231°C dec. ¹H NMR (DMSO-*d*₆): δ 10.6 (s, 1H, NH); 7.38–7.27 (m, 3H, Ph-H); 7.15–7.08 (m, 2H, Ph-H); 5.25–5.21 (m, 2H, CH₂Ph); 3.02, 2.89 (2 × br s., 8H, piperazine); 2.56 (q, 2H, *J* = 7.8 Hz, CH₂CH₃); 1.09 (t, 3H, CH₂CH₃). ¹³C NMR (DMSO-*d*₆): δ 145.8 (C-2); 139.4 (C-4); 137.0 (C-5); 129.6, 128.3, 127.0 (Ph-C); 46.6, 43.8 (piperazine-C); 41.0 (CH₂Ph); 20.9 (CH₂CH₃); 11.3 (CH₂CH₃). Anal. Calcd for C₁₆H₂₁N₅O₂ (315.37): C, 60.94; H, 6.71; N, 22.21. Found: C, 60.79; H, 6.59; N, 21.97; *m/z* (FAB): 316 (M + H)⁺.

General Preparation of 4-Arylsulfonyl-1-(benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-piperazines (18–21). Arylsulfonyl chloride (1.0 mmol) was added to a solution of **17** (0.32 g, 1.0 mmol) in CH₂Cl₂ (20 mL) containing Et₃N (0.10 g, 1.0 mmol) and stirred at 23°C for 4 h. Few drops of water were added, and the solution was stirred for 1 h, and then partitioned between CHCl₃ (3 × 20 mL) and water (20 mL). The combined organic layer was dried (Na₂SO₄), filtered, and evaporated to dryness. The residue was coevaporated with EtOH (3 × 20 mL) and then recrystallized from EtOH to give the desired sulfonate derivatives.

1-(Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-4-toluenesulfonylpiperazine (18). From 4-toluenesulfonyl chloride (0.19 g). Yield: 0.25 g (53%); mp 181–83°C. ¹H NMR (CDCl₃): δ 7.53 (d, 2H, *J* = 8.6 Hz, ArSO₂-H); 7.28 (d, 2H, *J* = 8.6 Hz, ArSO₂-H); 7.27–7.21 (m, 3H, Ph-H); 6.81–6.72 (m, 2H, Ph-H); 4.94 (s, 2H, CH₂Ph); 3.56 (t, 2H, *J* = 5.5 Hz, piperazine); 3.40 (t, 2H, *J* = 5.5 Hz, piperazine); 2.98–2.89 (m, 4H, piperazine); 2.58 (q, 2H, *J* = 7.6 Hz, CH₂CH₃); 2.37 (s, 3H, Ar-Me); 1.19 (t, 3H, CH₂CH₃). ¹³C NMR (CDCl₃): δ 160.6 (C-2); 145.2 (ArSO₂-C-Me); 143.9 (C-4); 135.4, 129.8, 129.7, 129.1, 128.2, 127.7, 127.6, 126.1, 125.7 (C-5, Ar-C); 48.6, 46.0 (piperazine-C); 39.3 (CH₂Ph); 21.0 (CH₂CH₃); 11.3 (CH₂CH₃). Anal. Calcd for C₂₃H₂₇N₅O₄S (469.56): C, 58.83; H, 5.80; N, 14.91. Found: C, 58.63; H, 5.68; N, 14.70; *m/z* (FAB): 470 (M + H)⁺.

1-(Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-4-chlorobenzenesulfonylpiperazine (19). From 4-chlorobenzenesulfonyl chloride (0.19 g). Yield: 0.21 g (43%); mp 191–193°C. ¹H NMR (CDCl₃): δ 7.60 (d, 2H, *J* = 8.5 Hz, ArSO₂-H); 7.47 (d, 2H, *J* = 8.5 Hz, ArSO₂-H); 7.22 (m, 3H, Ph-H); 6.83–6.78 (m, 2H, Ph-H); 4.94 (s, 2H, CH₂Ph); 3.58 (t, 2H, *J* = 5.7 Hz, piperazine); 3.42 (t, 2H, *J* = 5.7 Hz, piperazine); 3.01–2.92 (m, 4H, piperazine); 2.56 (q, 2H, *J* = 7.5 Hz, CH₂CH₃); 1.18 (t, 3H, CH₂CH₃). ¹³C NMR (CDCl₃): δ 160.6 (C-2); 145.6 (ArSO₂-C); 139.6 (C-4); 138.8, 137.8 (ArSO₂-C); 135.0, 134.6, 129.5, 129.1, 129.2, 129.1, 128.3, 125.7 (C-5, Ar-C); 48.5, 46.0 (piperazine-C); 39.3 (CH₂Ph); 20.8 (CH₂CH₃); 11.4 (CH₂CH₃). Anal. Calcd for C₂₂H₂₄ClN₅O₄S (489.98): C, 53.93; H, 4.94; N, 14.29. Found: C, 53.72; H, 4.89; N, 13.96; *m/z* (FAB): 490/492 (M + H)⁺.

1-(Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-4-nitrobenzenesulfonylpiperazine (20). From 4-nitrobenzenesulfonyl chloride (0.22 g). Yield: 0.25 g (49%); mp 246–247°C dec. ¹H NMR (CDCl₃): δ 8.41 (d, 2H, *J* = 8.8 Hz, ArSO₂-H); 7.94 (d, 2H, *J* = 8.8 Hz, ArSO₂-H); 7.31–7.27 (m, 3H, Ph-H); 6.88–6.82 (m, 2H, Ph-H); 5.00 (s, 2H, CH₂Ph); 3.52 (br s., 8H, piperazine); 2.57 (q, 2H, *J* = 7.6 Hz, CH₂CH₃); 1.25 (t, 3H, CH₂CH₃). ¹³C NMR (CDCl₃): δ 150.3 (C-2); 145.3 (ArSO₂-C-NO₂); 142.6 (C-4); 139.9 (ArSO₂-C_a); 137.5, 135.2, 129.2, 128.8, 128.3, 125.5, 124.4 (C-5, Ar-C); 48.5, 46.2 (piperazine-C); 46.1 (CH₂Ph); 21.1 (CH₂CH₃); 11.2 (CH₂CH₃). Anal. Calcd for C₂₂H₂₄N₆O₆S (500.53): C, 52.79; H, 4.83; N, 16.79. Found: C, 52.57; H, 4.77; N, 16.57; *m/z* (FAB): 501 (M + H)⁺.

4-Acetamidobenzenesulfonyl-1-(benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)piperazine (21). From 4-acetamidobenzenesulfonyl chloride (0.22 g). Yield: 0.22 g (43%); mp 136–139°C. ¹H NMR (CDCl₃): 9.12 (s, 1H, NH), δ 7.77 (d, 2H, *J* = 8.7 Hz, ArSO₂-H); 7.51 (d, 2H, *J* = 8.7 Hz, ArSO₂-H); 7.21–7.17 (m, 3H, Ph-H); 6.79–6.75 (m, 2H, Ph-H); 4.97–4.93 (m, 2H, CH₂Ph); 3.00 (br s., 8H, piperazine); 2.53 (q, 2H, *J* = 7.5 Hz, CH₂CH₃); 1.14 (t, 3H, CH₂CH₃). ¹³C NMR (CDCl₃): δ 169.7 (NHCO₂Me); 145.8 (C-2); 143.2 (ArSO₂-C-NHAc); 138.6 (C-4); 138.3, 134.8, 129.4, 129.1, 128.6, 128.3, 125.6, 119.6 (C-5, Ar-C); 48.4, 46.5 (piperazine-C); 46.0 (CH₂Ph); 24.5 (NHCO₂Me); 20.8 (CH₂CH₃); 11.2 (CH₂CH₃). Anal. Calcd for C₂₄H₂₈N₆O₅S (512.58): C, 56.24; H, 5.51; N, 16.40. Found: C, 56.06; H, 5.44; N, 16.20; *m/z* (FAB): 513 (M + H)⁺.

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