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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 μg/mL and 2.37 μg/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-chlorotrityl)-1*H*-imidazole] [20,21] and metronidazole (Flagyl® [2-(2-methyl-5-nitro-imidazol-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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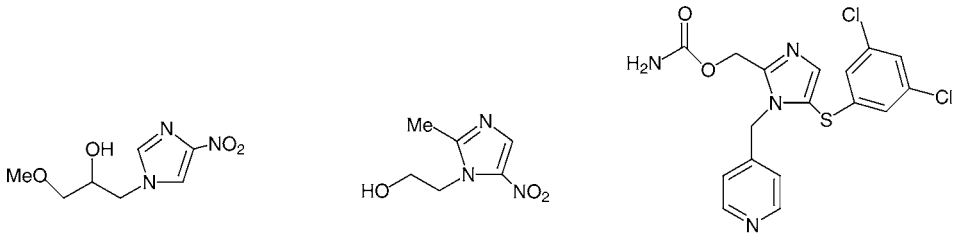

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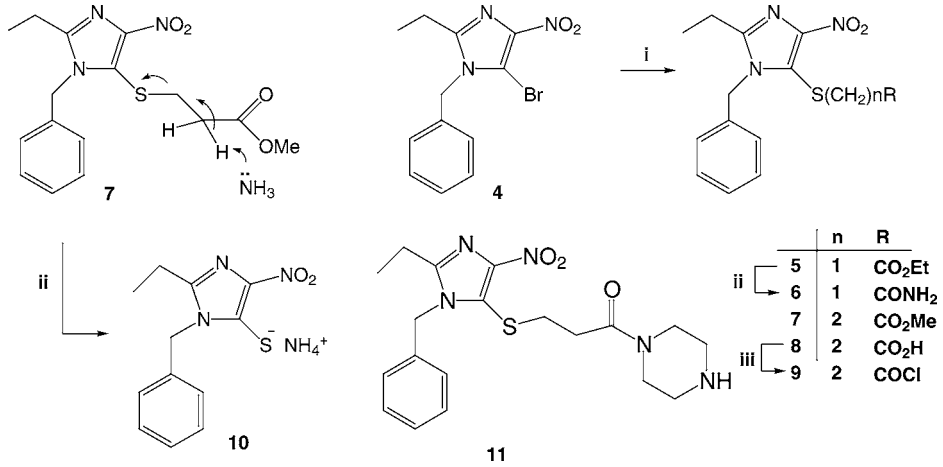
high-yielding routes leading to interesting imidazole derivatives bearing various alkylsulfanyl or alkylamino groups via nucleophilic substitution of the halogen by nitrogen or sulfur nucleophiles. We report here the synthesis of new 5-alkylsulfanyl and 5-(4′-arylsulfonyl)piperazinyl-4-nitroimidazole 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 C_5–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. S*C*H_2



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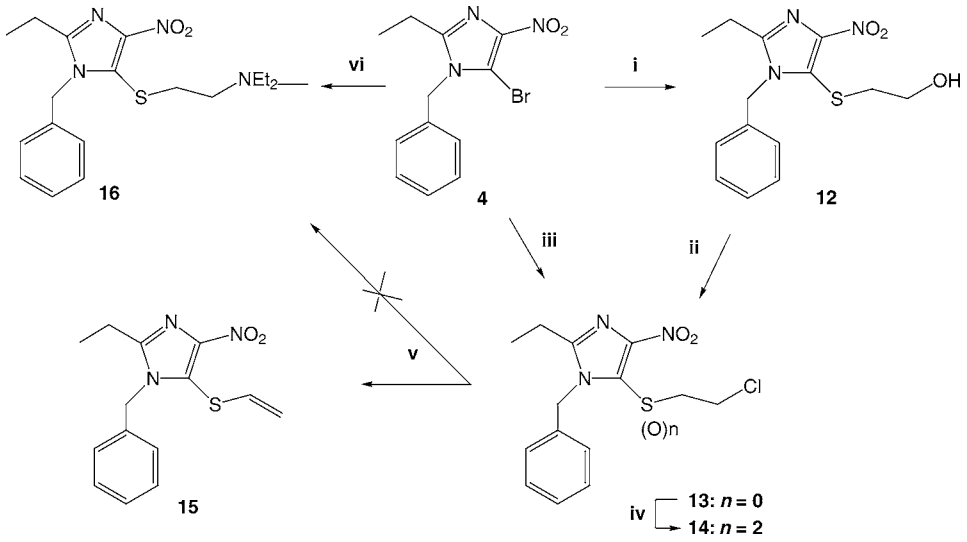
SCHEME 1 Reagents and conditions: (i) $R(CH_2)_nSH$, K_2CO_3, i-PrOH, 60–70°C; 4h; (ii) NH_3/MeOH, 23°C, 10 h; (iii) $SOCl_2$, $CHCl_3$, 23°C, 18 h.



SCHEME 2 Reagents and conditions: (i) $OH(CH_2)_2SH$, KOH, ^iPrOH, 60–80°C; (ii) $SOCl_2$, $CHCl_3$, 23°C, 18 h; (iii) $Cl(CH_2)_2SH$, KOH, ^iPrOH, 60–80°C; 4 h; (iv) mCPBA, 1N NaOH, CH_2Cl_2, 23°C, 6 h; (v) $NHEt_2$, DMF, 80–90°C, 4 h; (vi) $HS(CH_2)_2NEt_2$, KOH, ^iPrOH, 60–80°C, 4 h.

of **5, 6, 8,** and **11** resonated between δ_C 31.2 and δ_C 37.2.

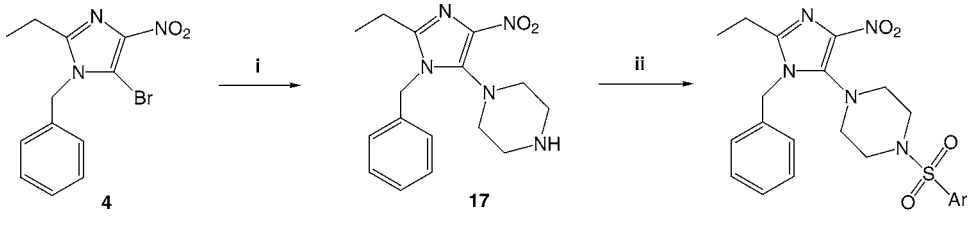
Other models of alkylsulfanyl groups at C-5 of the imidazole backbone are prepared. Thus, treatment of **4** with 2-mercaptoethanol in the presence of KOH afforded **12** (65%). Chlorination of **12** by treatment with $SOCl_2$ afforded **13** at low yield (30%). Oxidation of **13** with mCPBA in the 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 ^iPrOH and KOH furnished **16** in 55% yield (Scheme 2).

The assignment of protons and carbons of the imidazole ring was deduced in comparison to compounds **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



	R
18	*p*-Me-Ph
19	*p*-Cl-Ph
20	*p*-NO_2-Ph
21	*p*-NHAc-Ph

SCHEME 3 Reagents and conditions: (i) piperazine, DMF, 70–80°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. Compounds **9** and **13** showed EC_{50} of 4.04 μg/mL (CC_{50} of 57.9 ± 7.8 μg/mL) and 2.37 μg/mL (CC_{50} 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

[a]Anti-HIV-1 activity measured with strain III_B.
[b]Anti-HIV-2 activity measured with strain ROD.
[c]Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and HIV-2-induced cytopathogenic effect.
[d]Compound concentration that reduces the viability of mock-infected MT-4 cells by 50%.
[e]SI: Selectivity index (CC_{50}/EC_{50}).

data were obtained with a Vario, Elementar apparatus (Shimadzu, Japan). NMR spectra were recorded on 300 and 600 MHz (^{1}H) 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 ^{1}H-^{13}C HMBC experiment. Mass spectra were recorded on 70 eV EI and FAB MAT 8200 spectrometers (Finnigana MAT), using 3-nitrobenzyl alcohol (NBOH) or glycerol as matrixes. 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-mecaptoacetate (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. ^{1}H NMR (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 (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 $C_{16}H_{19}N_3O_4S$ (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 $(M + H)^+$.

*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. ^{1}H NMR (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 (DMSO-d_6): δ 170.1 (*C*ONH$_2$); 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 $C_{14}H_{16}N_4O_3S$ (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 $(M + H)^+$.

*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 ^{1}H- 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. ^{1}H 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 (SCH$_2CH_2$CO$_2$H); 31.2 (SCH_2CH$_2$CO$_2$H); 21.3 (CH_2CH$_3$); 11.6 (CH$_2CH_3$). Anal. Calcd for $C_{15}H_{17}N_3O_4S$ (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 $(M + Na)^+$.

*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. ^{1}H NMR (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 (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 $C_{12}H_{16}N_4O_2S$. (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 $(M - NH_4^+)^+$.

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. ^{1}H NMR ($CDCl_3$): δ 7.37–7.26 (m, 3H, Ph-H); 7.01–6.97

(m, 2H, Ph-H); 5.40 (s, 2H, PhCH_2); 3.36 (br s., 4H, piperazine); 3.19 (t, 2H, $J = 6.6$ Hz, SCH_2CH_2); 2.82 (br s., 4H, piperazine); 2.69 (t, 2H, $J = 6.6$ Hz, SCH_2CH_2); 2.59 (q, 2H, $J = 6.7$ Hz, CH_2CH_3); 1.27 (t, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): 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 (CH_2Ph); 45.6 (piperazine); 34.8 (SCH_2CH_2CO); 31.3 (SCH_2CH_2CO); 21.2 (CH_2CH_3); 11.8 (CH_2CH_3). Anal. Calcd for $C_{19}H_{25}N_5O_3S$. (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. ^{1}H NMR ($CDCl_3$): δ 7.38–7.29 (m, 3H, Ph-H); 7.07–6.98 (m, 2H, Ph-H); 5.41 (s, 2H, PhCH_2); 3.65 (t, 2H, $J = 5.6$ Hz, CH_2OH); 3.00 (t, 2H, $J = 5.6$ Hz, SCH_2); 2.64 (q, 2H, $J = 7.5$ Hz, CH_2CH_3); 1.21 (t, 3H, CH_2CH_3). Anal. Calcd for $C_{14}H_{17}N_3O_3S$ (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**—$SOCl_2$ (1.19 g, 10.08 mmol) was added stepwise to a solution of **12** (1.55 g, 5.04 mmol) in $CHCl_3$ (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. ^{1}H NMR ($CDCl_3$): δ 7.39–7.26 (m, 3H, Ph-H); 6.99–6.96 (m, 2H, Ph-H); 5.39 (s, 2H, PhCH_2); 3.50 (t, 2H, $J = 6.9$ Hz, CH_2Cl); 3.22 (t, 2H, $J = 6.9$ Hz, SCH_2); 2.68 (q, 2H, $J = 7.4$ Hz, CH_2CH_3); 1.28 (t, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$). 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 (CH_2Ph); 42.6 (CH_2Cl); 38.4 (SCH_2); 21.3 (CH_2CH_3); 11.3 (CH_2CH_3). Anal. Calcd for $C_{14}H_{16}ClN_3O_2S$ (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 CH_2Cl_2 (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 (Na_2SO_4), filtered, and evaporated to dryness, and the residue was recrystallized from EtOH to give **14** (0.25 g, 71%), mp 135–136°C dec. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40–7.34 (m, 3H, Ph-H); 7.07 (m, 2H, Ph-H); 5.59 (s, 2H, PhCH_2); 3.78–3.75 (m, 2H, CH_2Cl); 3.34–3.31 (m, 2H, SCH_2); 2.76 (q, 2H, $J = 7.4$ Hz, CH_2CH_3); 1.36 (t, 3H, CH_2CH_3). ^{13}C NMR (HMQC, $CDCl_3$). δ 153.7 (C-2); 135.3, 129.128.5, 128.3, 126.2 (Ph-*C*); 47.9 (CH_2Ph); 55.6 (SO_2CH_2); 47.9 (CH_2Ph); 36.2 (SCH_2); 20.4 (CH_2CH_3); 11.3 (CH_2CH_3). Anal. Calcd for $C_{14}H_{16}ClN_3O_4S$ (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***).* Et_2NH (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 $CHCl_3$ (2×15 mL) and water (15 mL), and the combined organic extracts was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was poured onto SiO_2 column (5.0 g), using CH_3Cl-MeOH (95–5%) as eluent to give **15** (0.22 g, 76%); mp 58–61°C dec. ^{1}H NMR ($CDCl_3$): 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=CH_2); 5.33 (dd, 1H, $J = 9.4$ Hz, 16.5 Hz; SCH=CH_2); 5.14 (d, 1H, $J = 16.5$ Hz, SCH=CH_2); 5.30 (s, 2H, CH_2Ph); 2.66 (q, 2H, $J = 7.5$ Hz, CH_2CH_3); 1.25 (t, 2H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): 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 (S*CH*=CH_2); 116.5 (SCH=*C*H_2); 47.7 (CH_2Ph); 21.2 (CH_2CH_3); 11.1 (CH_2CH_3). Anal. Calcd for $C_{14}H_{15}N_3O_2S$ (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. ^{1}H 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, CH_2Ph); 3.02 (t, 2H, $J = 5.7$ Hz, SCH_2CH_2); 2.67 (t, 2H, $J = 5.7$ Hz, SCH_2CH_2); 2.60 (q, 2H, $J = 7.2$ Hz, CH_2CH_3); 2.46 (q, 4H, $J = 7.4$ Hz, $2 \times NCH_2CH_3$); 1.29 (t, 3H, CH_2CH_3); 0.95 (t, 6H, $2 \times NCH_2CH_3$). ^{13}C 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 (NCH_2CH_2S); 47.7 (CH_2Ph); 46.7 (2 × NCH_2CH_3); 34.2 (NCH_2CH_2S); 21.2 (C_2-CH_2CH_3); 11.3 (C_2-CH_2CH_3, 2xNCH_2CH_3). Anal. Calcd for $C_{18}H_{26}N_4O_2S$ (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. ^{1}H 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, CH_2Ph); 3.02, 2.89 (2 × br s., 8H, piperazine); 2.56 (q, 2H, $J = 7.8$ Hz, CH_2CH_3); 1.09 (t, 3H, CH_2CH_3). ^{13}C 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 (CH_2Ph); 20.9 (CH_2CH_3); 11.3 (CH_2CH_3). Anal. Calcd for $C_{16}H_{21}N_5O_2$ (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 CH_2Cl_2 (20 mL) containing Et_3N (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 $CHCl_3$ (3 × 20 mL) and water (20 mL). The combined organic layer was dried (Na_2SO_4), 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. ^{1}H NMR ($CDCl_3$): δ 7.53 (d, 2H, $J = 8.6$ Hz, $ArSO_2$—*H*); 7.28 (d, 2H, $J = 8.6$ Hz, $ArSO_2$—*H*); 7.27–721 (m, 3H, Ph-H); 6.81–6.72 (m, 2H, Ph-H), 4.94 (s, 2H, CH_2Ph); 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, CH_2CH_3); 2.37 (s, 3H, Ar-*Me*); 1.19 (t, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 160.6 (C-2); 145.2 ($ArSO_2$-*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 (CH_2Ph); 21.0 (CH_2CH_3); 11.3 (CH_2CH_3). Anal. Calcd for $C_{23}H_{27}N_5O_4S$ (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. ^{1}H NMR ($CDCl_3$): δ 7.60 (d, 2H, $J = 8.5$ Hz, $ArSO_2$—*H*); 7.47 (d, 2H, $J = 8.5$ Hz, $ArSO_2$—*H*); 7.22 (m, 3H, Ph-H); 6.83–6.78 (m, 2H, Ph-H), 4.94 (s, 2H, CH_2Ph); 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, CH_2CH_3); 1.18 (t, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 160.6 (C-2); 145.6 ($ArSO_2$—*C*); 139.6 (C-4); 138.8, 137.8 ($ArSO_2$—*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 (CH_2Ph); 20.8 (CH_2CH_3); 11.4 (CH_2CH_3). Anal. Calcd for $C_{22}H_{24}ClN_5O_4S$ (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-nitrobenezenesulfonylpiperazine (***20***).* From 4-nitrobenzenesulfonyl chloride (0.22 g). Yield: 0.25 g (49%); mp 246–247°C dec. ^{1}H NMR ($CDCl_3$): δ 8.41 (d, 2H, $J = 8.8$ Hz, $ArSO_2$—*H*); 7.94 (d, 2H, $J = 8.8$ Hz, $ArSO_2$—*H*); 7.31–7.27 (m, 3H, Ph-H); 6.88–6.82 (m, 2H, Ph-H), 5.00 (s, 2H, CH_2Ph); 3.52 (br s., 8H, piperazine); 2.57 (q, 2H, $J = 7.6$ Hz, CH_2CH_3); 1.25 (t, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 150.3 (C-2); 145.3 ($ArSO_2$—*C*-NO_2); 142.6 (C-4); 139.9 ($ArSO_2$—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 (CH_2Ph); 21.1 (CH_2CH_3); 11.2 (CH_2CH_3). Anal. Calcd for $C_{22}H_{24}N_6O_6S$ (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. ^{1}H NMR ($CDCl_3$): 9.12 (s, 1H, NH), δ 7.77 (d, 2H, $J = 8.7$ Hz, $ArSO_2$—*H*); 7.51 (d, 2H, $J = 8.7$ Hz, $ArSO_2$—*H*); 7.21–7.17 (m, 3H, Ph-H); 6.79–6.75 (m, 2H, Ph-H), 4.97–4.93 (m, 2H, CH_2Ph); 3.00 (br s., 8H, piperazine); 2.53 (q, 2H, $J = 7.5$ Hz, CH_2CH_3); 1.14 (t, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 169.7 ($NHCO_2Me$); 145.8 (C-2); 143.2 ($ArSO_2$—*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 (CH_2Ph); 24.5 ($NHCO_2Me$); 20.8 (CH_2CH_3); 11.2 (CH_2CH_3). Anal. Calcd for $C_{24}H_{28}N_6O_5S$ (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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