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Original research paper

Nitroimidazoles. V. Synthesis and anti-HIV evaluation of new 5-substituted piperazinyl-4-nitroimidazole derivatives

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A series of 2-alkylthio-1-[4-(1-benzyl-2-ethyl-4-nitro-1*H*--imidazol-5-yl)-piperazin-1-yl]ethanones (**3–9**) and alkyl-[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin--1-yl)ketones (**11–20**) as well as the indole analogue **22** were synthesized from 4-nitro-5-piperazinyl imidazole derivative **1**, with the aim to develop newly non-nucleoside reverse transcriptase inhibitors (NNRTIs). The newly synthesized compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. Compound **4** showed inhibition of HIV-1 (EC_{50} 0.45 μg mL^{-1}) and HIV-2 (0.50 μg mL^{-1}), while **11** showed inhibition of HIV-1 (EC_{50} 2.48 μg mL^{-1}, SI = 4).

Keywords: anti-HIV activity, 4-nitroimidazoles, NNRTIs, piperazine

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Substituted imidazoles are known as chemotherapeutic agents, such as Dacarbazine® (DTIC) [5-(3,3-dimethyl-1-triazeno)imidazol-4-carboxamide] (1). Temozolomide, the lymphoma malignant melanoma agent and misonidazole (2), the inhibitor of *de novo* purine synthesis. Clotrinazole [1-(2-chlorotrityl)-1*H*-imidazole] (3, 4) and metronidazole [2-(2-methyl-5-nitro-imidazol-1-yl)ethanol] (5) are clinically used as potent fungicides and antiprotozoal agents (especially for treatment of *Trichomonas vaginalis*, *Entamoeba histolytica* and *Gardia lamblia*). Capravirine (S-1153) [5-(3,5-dichlorophenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1*H*-imidazol-2-ylmethyl carbamate] is an imidazole analogue with high anti-HIV inhibitory activity (6) (Fig. 1).

Some compounds of nitroimidazoles are reported as potent and selective histamine H-3 receptor agonists (7, 8), mitogen-activated protein (MAP) kinases inhibitors (9), nitric-

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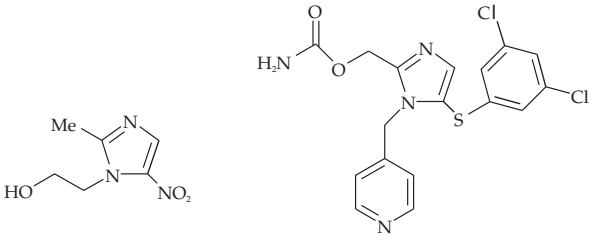


Metronidazole Capravirine (S-1153)

Fig. 1. Structural formulae of some imidazole drugs

-oxide synthase inhibitors (10) and antibacterial agents (11). Furthermore, 5-nitro-substituted-haloimidazoles, an interesting class of such compounds, showed important biological activity as potential radiosensitizers (12). Other imidazole derivatives having 5-alkylsulfanyl residues exhibited remarkable antitumor activity (13). The facile replacement of halogen in these compounds prompted many laboratories (14–16) to develop a new high-yielding method leading to interesting imidazole compounds bearing various alkylsulfanyl or alkylamino groups *via* nucleophilic substitution of the halogen by N or S nucleophiles.

Based on these pharmacological activities, and in continuation of our work on 4-nitroimidazoles (17–20), we report here the synthesis of new 5-substituted piperazinyl-4--nitroimidazole derivatives and the evaluation of their anti-HIV activity.

EXPERIMENTAL

Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (Büchi Labortechnik AG, Switzerland). Microanalytical data were obtained with a Vario, Elemental apparatus (Shimadzu, Japan). NMR spectra were recorded on 300 and 600 MHz (^{1}H) and on 62.9 MHz (^{13}C) spectrometers (Bruker, Germany) with TMS as internal standard and on the δ scale in ppm. Heteronuclear assignments were verified by the ^{1}H-^{13}C HMBC experiment. Mass spectra were recorded at 70 eV on EI and FAB mass spectra were measured on a MAT 8200 spectrometer (Finnigana MAT, USA) using 3-nitrobenzyl alcohol (NBOH) or glycerol as matrices. Some molecular ions were detected by doping the sample with Na^+ ion.

Physico-chemical and spectral data for the synthesized compounds are given in Tables I and II. Synthetic routes are presented in Schemes 1–3.

Syntheses

*1-[4-(1-Benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]-2-chloromethylene ketone (***2***)*

To a solution of **1** (20) (315 mg, 1.0 mmol) in CH_2Cl_2 (15 mL) containing triethylamine (110 mg, 1.0 mmol), 2-chloroacetyl chloride (112 mg, 1.0 mmol) was added and stirred at room temperature for 3 h. The solution was evaporated to dryness and the residue was recrystallized from EtOH to give 2.

Table I. Physical data of the newly prepared compounds

Compd. No.	Yield (%)	M.p. (°C)	Mol. formula (M_r)	Found/calcd. (%)		
				C	H	N
2	50	152–153	$C_{18}H_{22}ClN_5O_3$ (391.85)	54.95 55.17	5.57 5.66	17.69 17.87
3	62	60–63	$C_{24}H_{27}N_5O_3S$ (465.57)	61.75 61.92	5.77 5.85	14.87 15.04
4	58	69–72	$C_{24}H_{26}ClN_5O_3S$ (500.01)	57.44 57.65	5.16 5.24	13.85 14.01
5	51	oil	$C_{25}H_{29}N_5O_4S$	–	–	–
6	65	111–113	$C_{25}H_{29}N_5O_3S$ (479.59)	62.38 62.61	5.98 6.09	14.45 14.60
7	61	oil	$C_{25}H_{28}ClN_5O_3S$	–	–	–
8	64	76–79	$C_{28}H_{29}N_5O_3S$ (515.20)	64.93 65.22	5.58 5.67	13.34 13.58
9	72	133–136	$C_{23}H_{31}N_5O_5S$ (489.59)	56.18 56.42	6.29 6.38	13.98 14.30
10	76	122–126	$C_{28}H_{29}N_5O_5S$ (547.63)	61.19 61.41	5.29 5.34	12.55 12.79
11	78	141–143	$C_{18}H_{23}N_5O_3$ (357.41)	60.25 60.49	6.32 6.49	19.32 19.59
12	81	121–123	$C_{23}H_{24}ClN_5O_3$ (453.92)	60.59 60.86	5.21 5.33	15.21 15.43
13	72	110.115	$C_{23}H_{24}FN_5O_3$ (437.47)	62.97 63.15	5.43 5.53	15.86 16.01
14	73	150–152 dec.	$C_{23}H_{24}N_6O_5$ (464.47)	59.23 59.48	5.11 5.21	17.84 18.09
15	79	183–184	$C_{24}H_{27}N_5O_4$ (449.50)	63.94 64.13	5.96 6.05	15.32 15.58
16	40	219–223	$C_{23}H_{23}Cl_2N_5O_3$ (488.37)	56.35 56.57	4.62 4.75	14.15 14.34
17	53	125–128	$C_{21}H_{23}N_5O_3S$ (425.50)	59.01 59.28	5.32 5.45	16.19 16.46
18	69	73–75	$C_{21}H_{27}N_5O_5$ (429.47)	58.53 58.73	6.21 6.34	16.11 16.31
19	91	oil	$C_{20}H_{26}N_6O_4$	–	–	–
20	74	semi-solid	$C_{30}H_{30}N_6O_4$ (538.60)	66.68 66.90	5.47 5.61	15.38 15.60
22	56	oil	$C_{27}H_{30}N_6O_3$	–	–	–

Table II. Mass, ^{1}H NMR and ^{13}C NMR data of the newly prepared compounds

Compd.	Mass (*m*/z)	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
2	391/393 $(M+H)^+$	7.42–7.28 (m, 3H, ArH), 7.07–6.99 (m, 2H, Ar), 5.17 (s, 2H, CH_2Ph), 4.12 (s, 2H, CH_2Cl), 3.42 (br s., 8H, piperazine), 2.76 (q, 2H, *J* = 7.4 Hz, **CH_2**CH_3), 1.30 (t, 3H, CH_2**CH_3**)	165.1 (C=O); 145.2 (C-2); 139.8 (C-4); 137.9 (C-5); 135.4, 129.2, 128.2, 125.6 (Ar), 48.7, 46.3 (4C, piperazine), 42.3 (CH_2Cl), 40.7 (**CH_2**Ph), 21.0 (**CH_2**CH_3), 11.3 (CH_2**CH_3**)
3	466 $(M+H)^+$	7.47–7.23 (m, 8H, ArH), 6.97 (m, 2H, Ar), 5.14 (s, 2H, **CH_2**Ph), 3.72 (s, 2H, **CH_2**SPh), 3.49 (br s., 8H, piperazine), 2.64 (q, 2H, *J* = 7.6 Hz, **CH_2**CH_3), 1.30 (t, 3H, CH_2**CH_3**)	167.2 (C=O), 145.2 (C-2), 138.1 (C-4), 135.5 (C-5), 134.5, 130.8, 129.3, 129.2, 128.4, 127.4, 125.6 (Ar), 49.1, 46.7 (4C, piperazine), 40.7 (**CH_2**Ph), 36.7 (**CH_2**SPh), 21.2 (**CH_2**CH_3), 11.4 (CH_2**CH_3**)
4	500/502 $(M+H)^+$	7.42–7.27 (m, 7H, ArH), 6.98 (m, 2H, Ar), 5.14 (s, 2H, **CH_2**Ph), 3.70 (s, 2H, **CH_2**SPh), 3.51 (br s., 8H, piperazine), 2.63 (q, 2H, *J* = 7.5 Hz, **CH_2**CH_3), 1.31 (t, 3H, CH_2**CH_3**)	166.8 (C=O), 145.2 (C-2), 137.0 (C-4), 135.5 (C-5), 132.2, 131.8, 129.3, 128.4, 125.4 (Ar), 49.1, 46.7 (4C, piperazine); 40.7 (CH_2Ph); 36.7 (**CH_2**SPh); 21.2 (**CH_2**CH_3), 11.4 (CH_2**CH_3**)
5	496 $(M+H)^+$	7.48–7.27 (m, 5H, ArH), 7.32 (d, 2H, *J* = 9.0 Hz, *p*-OMe-Ar**H**), 6.99 (d, 2H, *J* = 9.0 Hz, *p*-OMe-Ar**H**), 3.75 (s, 3H, *p*-OMe-Ar-**H**), 5.14 (s, 2H, **CH_2**Ph), 3.79 (s, 2H, **CH_2**SPh), 3.60 (br s., 8H, piperazine), 2.65 (q, 2H, *J* = 7.4 Hz, **CH_2**CH_3), 1.30 (t, 3H, CH_2**CH_3**)	167.4 (C=O), 145.2 (C-2), 135.5 (C-4), 134.7 (C-5), 134.4, 129.3, 128.3, 125.7 (Ar), 55.3 (OMe), 49.0, 46.6 (4C, piperazine), 42.1 (**CH_2**Ph), 38.1 (**CH_2**SPh), 21.2 (**CH_2**CH_3), 11.3 (CH_2**CH_3**)
6	480 $(M+H)^+$	7.37–7.23 (m, 8H, ArH), 6.98 (m, 2H, Ar), 5.14 (s, 2H, CH_2Ph), 3.80 (s, 2H, **CH_2**SCH_2Ph), 3.41 (br s., 8H, piperazine), 3.20 (s, 2H, CH_2S**CH_2**Ph), 2.62 (q, 2H, *J* = 7.4 Hz, **CH_2**CH_3), 1.30 (t, 3H, CH_2**CH_3**)	167.6 (C=O), 145.1 (C-2), 139.9 (C-4), 138.0 (C-5), 135.4, 129.2, 129.1, 128.4, 128.2, 127.1, 125.7 (Ar), 49.0, 46.2 (4C, piperazine), 42.0 (**CH_2**Ph), 36.2 (**CH_2**SCH_2Ph), 32.3 (CH_2S**CH_2**Ph), 21.0 (**CH_2**CH_3), 11.3 (CH_2**CH_3**)
7	514/516 $(M+H)^+$	7.38–7.26 (m, 7H, ArH), 6.98 (m, 2H, ArH), 5.15 (s, 2H, **CH_2**Ph), 3.77 (s, 2H, CH_2S**CH_2**Ph), 3.49 (br s., 8H, piperazine), 3.18 (s, 2H, **CH_2**SCH_2Ph), 2.64 (q, 2H, *J* = 7.4 Hz, **CH_2**CH_3), 1.30 (t, 3H, CH_2**CH_3**)	167.4 (C=O), 145.1 (C-2), 138.0 (C-4), 136.0 (C-5), 135.4, 133.0, 130.5, 129.2, 128.6, 128.3, 125.7 (Ar), 49.0, 46.3 (4C, piperazine), 42.0 (**CH_2**Ph), 35.4 (**CH_2**SCH_2Ph), 32.1 (CH_2S**CH_2**Ph), 21.1 (**CH_2**CH_3), 11.3 (CH_2**CH_3**)
8	515 $(M+H)^+$	7.94–7.76 (m, 4H, ArH), 7.53–7.26 (m, 6H, Ar), 6.98 (m, 2H, Ar), 5.12 (s, 2H, **CH_2**Ph), 3.84 (s, 2H, **CH_2**S--Naph.), 3.45 (br s., 8H, piperazine), 2.63 (q, 2H, *J* = 7.5 Hz, **CH_2**CH_3), 1.30 (t, 3H, CH_2**CH_3**)	167.0 (C=O), 145.1 (C-2), 139.9 (C-4), 138.0 (C-5), 135.4, 133.7, 132.3, 131.7, 129.3, 129.2, 128.7, 128.3, 128.1, 127.8, 127.6, 127.3, 126.7, 126.2, 125.7 (Ar), 49.0, 46.3 (4C, piperazine), 42.2 (**CH_2**Ph), 36.6 (**CH_2**S-naph.), 21.1 (**CH_2**CH_3), 11.3 (CH_2**CH_3**)

Table II. continued

Compd.	Mass (*m*/z)	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
9	490 $(M+H)^+$	7.35 (m, 3H, ArH), 7.01 (m, 2H, Ar), 5.15 (s, 2H, **CH$_2$**Ph), 4.19 (q, 2H, *J* = 7.5 Hz, O**CH$_2$**CH$_3$), 3.48 (s, 2H, CH$_2$S**CH$_2$**CO$_2$Et), 3.45 (br s., 8H, piperazine), 3.38 (s, 2H, **CH$_2$**SCH$_2$CO$_2$Et), 2.63 (q, 2H, *J* = 7.5 Hz, **CH$_2$**CH$_3$), 1.31 (t, 3H, CH$_2$**CH$_3$**), 1.26 (t, 3H, OCH$_2$**CH$_3$**)	169.8, 167.0 (C=O), 155.4 (C-2), 145.1 (C-4), 139.9 (C-5), 138.0, 135.4, 129.2, 128.2, 125.7 (Ar), 61.4 (O**CH$_2$**CH$_3$), 49.1, 46.2 (4C, piperazine), 45.8 (CH$_2$S**CH$_2$**CO$_2$Et), 42.0 (**CH$_2$**Ph), 33.6 (**CH$_2$**SCH$_2$CO$_2$Et), 21.0 (**CH$_2$**CH$_3$), 14.0 (OCH$_2$**CH$_3$**), 11.3 (CH$_2$**CH$_3$**)
10	548 $(M+H)^+$	8.26–7.72 (m, 10H, ArH), 7.00 (m, 2H, Ar), 5.16 (s, 2H, **CH$_2$**Ph), 4.36 (s, 2H, **CH$_2$**SO$_2$-naph.), 3.53 (br s., 8H, piperazine), 2.64 (q, 2H, *J* = 7.6 Hz, **CH$_2$**CH$_3$), 1.25 (t, 3H, CH$_2$**CH$_3$**)	167.0 (C=O), 145.1 (C-2), 139.9 (C-4), 138.0 (C-5), 135.4, 133.7, 132.3, 131.7, 129.3, 129.2, 128.7, 128.3, 128.1, 127.8, 127.6, 127.3, 126.7, 126.2, 125.7 (Ar), 49.0, 46.3 (4C, piperazine), 42.2 (**CH$_2$**Ph), 36.6 (**CH$_2$**S-naph.), 21.1 (**CH$_2$**CH$_3$), 11.3 (CH$_2$**CH$_3$**)
11	358 $(M+H)^+$	7.41-7.28 (m, 3H, ArH), 6.98 (m, 2H, Ar), 5.15 (s, 2H, **CH$_2$**Ph), 3.02 (br s., 8H, piperazine), 2.63 (q, 2H, *J* = 7.5 Hz, **CH**$_2$CH$_3$), 2.05 (s, 3H, COCH$_3$), 1.30 (t, 3H, CH$_2$**CH$_3$**)	169.0 (C=O), 145.1 (C-2), 138.1 (C-4), 135.5 (C-5), 129.2, 128.3, 126.1, 125.7 (Ar), 49.0, 46.3 (4C, piperazine), 41.6 (**CH$_2$**Ph), 21.2 (CO**Me**), 21.0 (**CH$_2$**CH$_3$), 11.3 (CH$_2$**CH$_3$**)
12	453/455 $(M+H)^+$	8.05 (d, 2H, *J* = 8.0 Hz, *p*-Cl-Ar**H**), 7.43–7.27 (m, 4H, ArH + *p*-Cl-Ar**H**), 6.97 (m, 2H, ArH), 5.15 (s, 2H, **CH$_2$**Ph), 3.55 (br s., 8H, piperazine), 2.67 (q, 2H, *J* = 7.5 Hz, **CH$_2$**CH$_3$), 1.31 (t, 3H, CH$_2$**CH$_3$**)	169.5 (C=O), 145.2 (C-2); 140.0 (C-4), 138.0 (C-5), 136.3, 135.4, 133.5, 129.3, 128.9, 128.7, 128.6, 128.3, 125.7 (Ar), 49.1, 46.3 (4C, piperazine), 41.7 (**CH$_2$**Ph), 21.1 (**CH$_2$**CH$_3$), 11.3 (CH$_2$**CH$_3$**)
13	460/462 $(M+Na)^+$	8.11 (dd, 2H, *J* = 8.0 Hz, 2.5 Hz, *p*-F-Ar**H**), 7.45–7.28 (m, 5H, Ar**H** + *p*-F-Ar**H**).), 6.98 (m, 2H, ArH), 5.16 (s, 2H, **CH$_2$**Ph), 3.58 (br s., 8H, piperazine), 2.64 (q, 2H, *J* = 7.5 Hz, **CH$_2$**CH$_3$), 1.31 (t, 3H, CH$_2$**CH$_3$**)	169.8 (C=O), 163.5 (Ar-*p*-**C**-F, d, $J_{C,F}$ = 245.0 Hz), 145.2 (C-2), 138.1 (C-4), 135.5 (C-5), 135.4, 129.6, 129.3, 128.3 (Ar-*o*-**C**-F, d, $J_{C,F}$ = 9.0 Hz), 125.7 (Ar); 115.7 (Ar-*m*-**C**-F, d, $J_{C,F}$ = 23.0 Hz); 49.1, 46.3 (4C, piperazine), 40.1 (**CH$_2$**Ph), 21.1 (**CH$_2$**CH$_3$), 11.4 (CH$_2$**CH$_3$**)
14	465 $(M+H)^+$	8.26 (d, 2H, *J* = 7.0 Hz, NO$_2$-ArH), 7.57 (d, 2H, *J* = 7.0 Hz, NO$_2$-ArH), 7.40–7.24 (m, 3H, ArH), 6.97 (m, 2H, ArH), 5.16 (s, 2H, **CH$_2$**Ph), 3.49 (br s., 8H, piperazine), 2.64 (q, 2H, *J* = 7.6 Hz, **CH$_2$**CH$_3$), 1.30 (t, 3H, CH$_2$**CH$_3$**)	168.2 (C=O), 148.5 (Ar-**C**-NO$_2$), 145.3 (C-4), 141.5 (Ar), 137.8 (C-5), 135.4, 129.3, 128.4, 128.17, 125.6, 124.9, 123.9 (Ar), 49.0, 46.3 (4C, piperazine), 41.6 (**CH$_2$**Ph), 21.1 (**CH$_2$**CH$_3$), 11.3 (CH$_2$**CH$_3$**)
15	450 $(M+H)^+$	7.39–7.23 (m, 5H, ArH + *p*-OMe--Ar**H**), 6.97 (m, 4H, Ar**H** + *p*-OMe--Ar**H**), 5.16 (s, 2H, **CH$_2$**Ph), 3.85 (s, 3H, OMe), 3.21 (br s., 8H, piperazine), 2.63 (q, 2H, *J* = 7.6 Hz, **CH$_2$**CH$_3$), 1.29 (t, 3H, CH$_2$**CH$_3$**)	167.8 (C=O), 155.2 (Ar-**C**-OMe), 145.0 (C-2), 139.8 (C-4), 135.4 (C-5), 130.7, 130.5, 129.1, 128.1, 128.0, 127.9, 125.3, 120.9, 110.9 (Ar), 55.4 (OMe), 49.0, 46.2 (4C, piperazine), 41.8 (**CH$_2$**Ph), 21.0 (**CH$_2$**CH$_3$), 11.2 (CH$_2$**CH$_3$**)

Table II. continued

Compd.	Mass (*m/z*)	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
16	488/490 $(M+H)^+$	7.41–7.27 (m, 6H, ArH), 6.98 (m, 2H, ArH), 5.16 (s, 2H, **CH_2**Ph), 3.45 (br s., 8H, piperazine), 2.62 (q, 2H, *J* = 7.5 Hz, **CH_2**CH_3), 1.30 (t, 3H, CH_2**CH_3**)	166.1 (C=O), 145.2 (C-2), 140.0 (C-4), 138.8 (C-5), 137.8, 135.7, 1354, 133.8, 131.2, 129.8, 128.8, 128.3, 127.7, 126.0, 125.7 (Ar), 49.2, 46.3 (4C, piperazine), 41.9 (**CH_2**Ph), 21.1 (**CH_2**CH_3), 11.3 (CH_2**CH_3**)
17	426 $(M+H)^+$	7.51–6.99 (m, 8H, Ar**H** + thiophene-**H**), 5.17 (s, 2H, **CH_2**Ph), 3.75 (br s., 8H, piperazine), 2.66 (q, 2H, *J* = 7.6 Hz, **CH_2**CH_3), 1.30 (t, 3H, CH_2**CH_3**)	163.9 (C=O), 145.2 (C-2), 140.0 (C-4), 138.1 (C-5), 136.5, 135.4, 129.3, 129.2, 129.0, 128.8, 126.9, 126.7, 126.7 (Ar), 49.1, 46.3 (4C, piperazine), 40.2 (**CH_2**Ph), 21.1 (**CH_2**CH_3), 11.4 (CH_2**CH_3**)
18	452 $(M+Na)^+$	7.37–7.27 (m, 3H, ArH), 6.97 (m, 2H, ArH), 5.15 (s, 2H, **CH_2**Ph), 3.70 (s, 3H, OMe), 3.61 (br s., 8H, piperazine), 2.64 (m, 6H, **CH_2**CH_3 + **CH_2CH_2-** COMe), 1.30 (t, 3H, *J* = 7.5 Hz, CH_2**CH_3**)	163.9 (C=O), 145.2 (C-2), 140.0 (C-4), 138.1 (C-5), 136.5, 135.4, 129.3, 129.2, 129.0, 128.8, 126.9, 126.7, 126.7 (Ar), 49.1, 46.3 (4C, piperazine), 40.2 (**CH_2**Ph), 21.1 (**CH_2**CH_3), 11.4 (CH_2**CH_3**)
19	437 $(M+Na)^+$	7.28–7.20 (m, 3H, ArH), 6.99 (m, 2H, ArH), 5.11 (s, 2H, **CH_2**Ph), 3.38, 3.10 (2xs., 8H, piperazine), 2.50 (s, 4H, **CH_2CH_2**$CONH_2$), 2.45 (q, 2H, *J* = 7.5 Hz, *CH_2*CH_3), 1.05 (t, 3H, *J* = 7.5 Hz, **CH_2**CH_3)	174.1 (C=O), 145.2 (C-2), 139.4 (C-4), 138.9 (C-5), 136.7, 129.2, 127.9, 126.6 (Ar), 51.6, 48.9 (4C, piperazine), 41.5 (**CH_2**Ph), 30.1 (CH_2**CH_2**$CONH_2$), 28.9 (CH_2**CH_2**$CONH_2$), 20.5 (**CH_2**CH_3), 11.0 (CH_2**CH_3**)
20	561 $(M+Na)^+$	7.74 (d, 2H, *J* = 7.1 Hz, ArH), 7.55 (d, 2H, *J* = 7.1 Hz, ArH), 7.39–7.31 (m, 7H, ArH), 6.98 (dd, 2H, *J* = 2.0 Hz, 7.2 Hz, ArH), 5.13 (s, 2H, **CH_2**Ph), 4.44 (s, 2H, CO_2**CH_2**), 3.15 (br s., 8H, piperazine), 2.63 (q, 2H, *J* = 7.5 Hz, **CH_2**CH_3), 1.29 (t, 3H, CH_2**CH_3**)	155.1 (**C**O_2CH_2), 144.3 (C-2), 140.9 (C-4), 138.0 (C-5), 134.6, 130.0, 129.7, 129.0, 128.7, 127.7, 127.0, 125.4, 121.0, 120.2, 107.7 (Ar), 65.1 (CO_2**CH_2**), 50.4, 47.4 (4C, piperazine), 43.5 (**CH_2**Ph), 22.6 (**CH_2**CH_3), 14.0 (CH_2**CH_3**)
22	509 $(M+Na)^+$	8.47 (d, 1H, $J_{H,NH}$ = 6.7 Hz, N**H**-indole), 7.54–7.04 (m, 9H, ArH), 6.93 (d, 1H, $J_{H,NH}$ = 6.7 Hz, C**H**-indole), 5.05 (s, 2H, **CH_2**Ph), 3.15–2.55 (m, 14H, piperazine, **CH_2**CH_3 + **CH_2CH_2-** indole), 1.27 (t, 3H, *J* = 7.3 Hz CH_2**CH_3**)	171.5 (C=O), 145.1 (C-2), 139.7 (C-4), 138.2 (C-5), 136.3, 135.3, 129.2, 128.2, 127.0, 125.6, 122.0, 119.0, 11.3 (Ar + indole), 48.9, 46.1 (4C, piperazine), 41.7 (**CH_2**Ph), 33.4 (CO**CH_2**CH_2), 29.0 ($COCH_2$**CH_2**), 21.2 (**CH_2**CH_3), 11.2 (CH_2**CH_3**)

*2-Alkylthio-1-[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]ethanone (***3–9***)*

A solution of **2** (390 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) containing triethylamine (0.10 g, 1.0 mmol) was treated with alkylthiols (1.0 mmol) and the mixture was stirred at 80–90 °C for 4 h. After cooling, the mixture was evaporated to dryness and the residue was recrystallized from EtOH to give the desired ketones.

*1-[4-(1-Benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]-2-(phenylthio)ethanone (**3**), 1-[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]-2-(4-chlorophenylthio)ethanone (**4**), 1-[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]-2-(4-methoxyphenylthio) ethanone (**5**), 1-[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]-2-(benzylthio)ethanone (**6**), 1-[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]-2-(4-chlorobenzylthio)-ethanone (**7**), 1-[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]-2-(napthalenthio)-ethanone (**8**), and ethyl 2-[2-(4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)piperazin-1-yl)-2-oxoethylthio]acetate (**9**)* were prepared from sodium thiophenolate (132 mg), 4-chlorobenzenethiol (144 mg), 4-methoxybenzenethiol (140 mg), benzylthiol (124 mg), 4-chlorobenzylthiol (158 mg), sodium naphthylthiol (160 mg), and ethyl 3-mercaptopropanoate (134 mg), respectively.

*1-[4-(1-Benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]-2-(naphthalene-1-ylsulphonyl) ethanone (**10**)*

A solution of **8** (200 mg, 0.39 mmol) in CH_2Cl_2 (10 mL) was stirred with *m*-chloroperbenzoic acid (mCPBA) (470 mg, 2.15 mmol) for 6 h at room temperature; it was partitioned with water (10 mL) and the organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was recrystallized from EtOH to give **10**.

*General synthesis of alkyl-[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl)ketones (**11–18, 20**)*

To a solution of **1** (0.32 g, 1.0 mmol) in CH_2Cl_2 (20 mL) containing triethylamine (0.10 g, 1.0 mmol), alkyl carbonyl chloride (1.0 mmol) was added and stirred at room temperature. A few drops of water were added and the solution was stirred for 1 h, then partitioned between $CHCl_3$ (3 x 20 mL) and water (20 mL). The combined organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was recrystallized from EtOH to give the desired ketone derivative.

*[4-(1-Benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]methyl ketone (**11**), [4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl](4-chlorophenyl)ketone (**12**), [4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl](4-fluorophenyl)ketone (**13**), [4-(1-benzyl-2-ethyl--4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl](4-nitrophenyl)ketone (**14**), [4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl](4-methoxyphenyl)ketone (**15**), [4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl](2,4-dichlorophenyl)ketone (**16**), [4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl](thiophen-2-yl)ketone (**17**), methyl 4-[4-(1-benzyl-2-ethyl -4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]-4-oxo-butanoate (**18**),* and *[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl](9H-carbazol-9-yl)methyl carboxylate (**20**)* were prepared from acetyl chloride (79 mg), 4-chlorobenzoyl chloride (175 mg), 4-fluorobenzoyl chloride (158 mg), 4-nitrobenzoyl chloride (185 mg), 4-methoxybenzoyl chloride (171 mg), 2,4-dichlorobenzoyl chloride (210 mg), thiophene-2-carbonyl chloride (147 mg), methyl 3-(chlorocarbonyl)propanoate (151 mg), and 9*H*-carbazyl-9-yl)methyl chloroformate (260 mg), respectively.

*4-[4-(1-Benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]-4-oxo-butanamide (**19**)*

A solution of **18** (208 mg, 0.48 mmol) in NH_3/MeOH solution (10 mL) was stirred at 23 °C for 16 h. The solution was evaporated to dryness and the residue was purified on a short column of silica gel (5 g). Elution with $CHCl_3$-MeOH (9:1) afforded pure **19**.

*3-(1*H*-Indol-3-yl)-1-[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl]propan-1-one (**22**)*

To a cold solution of **1** (630 mg, 2.0 mmol), at –5 °C, in MeCN (10 mL), 3-(1*H*-indol--3-yl)propanoic acid (**21**) (378 mg, 2.0 mmol), hydroxybenzotriazole (HOBt) (270 mg, 2.0 mmol) and *N*,*N*′-dicyclohexyl-carbodiimide (DCC) (413 mg, 2.0 mmol) were added successively. The reaction mixture was stirred at 0 °C for 1 h, at 5 °C for 1 h, and at 23 °C for 16 h. Dicyclohexylurea (DCU) was filtered and the filtrate was evaporated to dryness. The residue was stirred with ethyl acetate, filtered, washed successively with saturated NaCl solution, 5% $NaHCO_3$ solution, 1.0 mol L^{-1} HCl, and finally with water. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness to give **22**.

Cytotoxicity and in vitro *anti-HIV assays*

Compounds **2–20** and **22** were tested for their *in vitro* anti-HIV-1 (strain III_B) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells using the MT-4/MTT assay (21). The results are summarized in Table III, in which the data for efavirenz (22) and capravirine (6) were included for comparison.

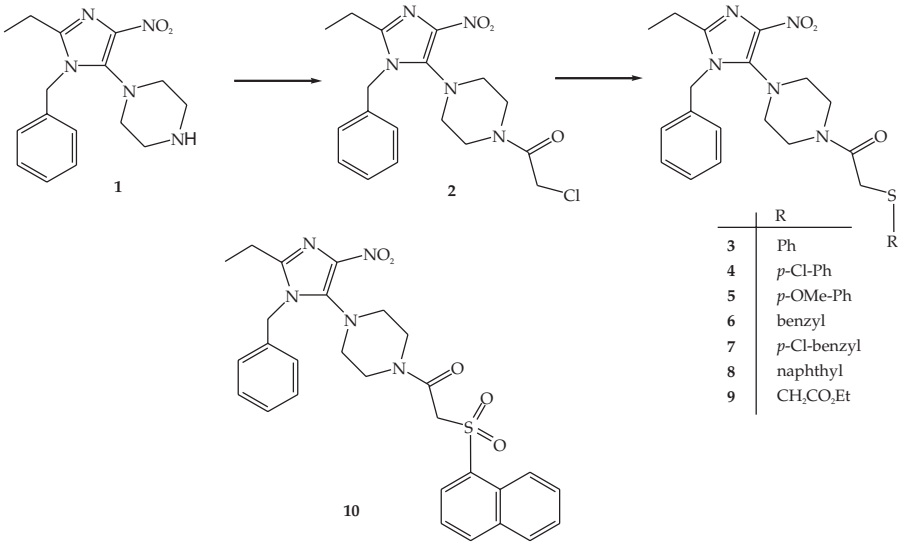
All cytotoxicity and anti-HIV activity assays were performed in 96-well microtiter plates (Falcon 3072; Becton Dickinson, USA). Determination of cytotoxicity involved plating of 4×10^4 CEM cells (100 μL) into each well in the presence of a given amount of the test compound (100 μL). The cells were allowed to proliferate for 96 h at 37 °C in a humidified atmosphere in which the CO_2 concentration was controlled. At the end of the incubation period, the cells were counted in a Coulter counter (model ZB; Coulter Electronics Ltd., UK). The 50% cytotoxic concentration (μg mL^{-1}) (CC_{50}) was defined as the concentration of compound that inhibited CEM cell proliferation by 50%. The procedures used to assess the anti-HIV activity in cell culture were based on assessment of the inhibition of HIV-induced giant cell formation in CEM cell cultures at day 4 postinfection by microscopic examination. Briefly, CEM cells were suspended at 250,000 cells mL^{-1} in culture medium and infected with HIV at approximately 100 times the 50% cell culture infectious dose ($CCID_{50}$) per mL. Then, 100 μL of the infected cell suspension was added to 200-μL microtiter plate wells containing 100 μL of an appropriate dilution of the test compound. After 4 days of incubation at 37 °C, the cell cultures were examined for syncytium formation. The 50% effective concentration (EC_{50}, μg mL^{-1}) was defined as the compound concentration required to inhibit virus-induced syncytium formation by 50%. The selectivity index *SI* is defined as CC_{50}/EC_{50}.

RESULTS AND DISCUSSION

Various 5-alkylamino and 5-alkylsulfanyl derivatives of imidazole derivatives (17, 18) have been prepared recently in our laboratory *via* nucleophilic displacements of the bromine group activated by an adjacent nitro group. Our efforts are continued in preparation of such compounds bearing piperazines substituted by alkylsulfanyl and amido groups to furnish potentially active analogues. 1-(Benzyl-2-ethyl-4-nitro-1*H*-imidazole--5-yl)piperazine **1** has been selected for the synthesis of our target, amide molecules, by treatment with different acyl chlorides. Thus, treatment of **1** with 2-chloroacetyl chloride in the presence of triethylamine at room temperature afforded **2** (50%).

Treatment of **2** with alkylthiols: sodium thiophenolate, 4-chlorobenzenethiol, 4-methoxybenzenethiol, benzylthiol, 4-chlorobenzylthiol, sodium naphthylthiol, ethyl 3-mercaptopropanoate at 80–90 °C in the presence of triethylamine gave compounds **3–9** (58–72%). Oxidation of **8** with mCPBA in the presence of a base furnished, after purification, the sulphone **10** (76%) (Scheme 1).

Structures of the newly synthesized compounds **2–9** were assigned by the ^{1}H, ^{13}C NMR and mass spectra. The ^{1}H NMR spectra showed rather similar patterns for the phenyl and ethyl protons, while the singlets in the region δ 5.17–5.12 ppm were attributed to methylene of the benzyl group. Resonances of the piperazine moiety appeared



	R
3	Ph
4	*p*-Cl-Ph
5	*p*-OMe-Ph
6	benzyl
7	*p*-Cl-benzyl
8	naphthyl
9	CH_2CO_2Et

Sheme 1

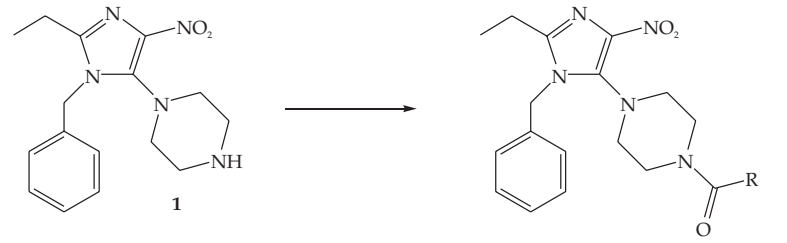
as broad singlets at δ 3.60–3.41 ppm. The CH_2Cl and CH_2S protons of **2** and **3–9** appeared as singlets at δ 4.12 and 3.84–3.48 ppm, respectively, the benzylic protons of **8** at δ 3.20 ppm and SCH_2CO_2Et protons of **9** at δ 3.38 ppm, while the CH_2SO_2 proton of **10** resonated at δ 4.36 ppm. In the ^{13}C NMR spectra of **2–10**, C-2 and C-4 of the imidazole ring resonated at δ 145.2–145.1, and δ 139.9–135.5 ppm, respectively. CH_2Cl carbon appeared at δ 42.3 ppm, while CH_2S carbon of **3–9** resonated in the region δ 38.1–33.6 ppm. The higher-field resonances at the region δ 169.8–165.1 ppm were attributed to the carbonyl group.

Further, other models of imidazole derivatives bearing keto substituted piperazine residues were prepared. Thus, treatment of **2** with alkyl carbonyl chlorides: acetyl chloride, 4-chlorobenzoyl chloride, 4-fluorobenzoyl chloride, 4-nitrobenzoyl chloride, 4-methoxybenzoyl chloride, 2,4-dichlorobenzoyl chloride, thiophene-2-carbonyl chloride, methyl 3-(chlorocarbonyl)propanoate, and (9*H*-carbazyl-9-yl)methyl chloroformate in the presence of triethylamine at room temperature afforded **11–20** in 40–81% yield. The amide **19** was prepared (91%) from treatment of **18** with NH_3/MeOH at room temperature (Scheme 2).

The assignment of protons and carbons of the imidazole ring was deduced from comparison with compounds **11–19** and our previously reported data on nitroimidazoles (17).

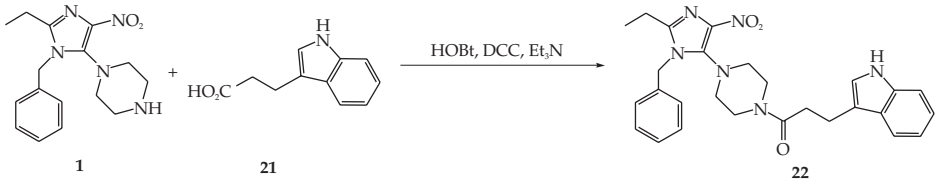
A suitable coupling method (23) was employed for the formation of amide by reaction of the carboxylic acid group with amine, using 1-hydroxybenzotriazole (HOBt) (24, 25) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) (26) as coupling reagents.

Therefore, our work was modified by selecting the 3-(1*H*-indol-3-yl)propanoic acid **21** as a precursor for the synthesis of new derivatives to examine the antiviral activity by



	R
11	Me
12	*p*-Cl-Ph
13	*p*-F-Ph
14	*p*-NO_2-Ph
15	p-OMe-Ph
16	2,4-Cl_2-Ph
17	2-thiophene
18	$(CH_2)_2CO_2Me$
19	$(CH_2)_2CONH_2$

Sheme 2



1 **21** **22**

Sheme 3

comparison with the amide analogues **3**–**20**. Compound **22** was prepared in 56% yields from coupling of **1** with **21** in the presence of HOBt and DCC as coupling reagents (Scheme 3).

The structure of **22** was determined from the ^{1}H-, ^{13}C NMR and mass spectra. The piperazine, CH_2CH_3, and CH_2CH_2-indole protons (14H) appeared as multiplet in the region δ 3.15–2.55 ppm, the signal of the benzylic protons at δ 5.05 ppm. The HC-indole proton resonated at δ 6.93 ppm as a doublet ($J_{H,NH}$ = 6.7 Hz). The ^{13}C NMR spectrum of **22** showed signals at higher δ 171.5 ppm field, attributed to the carbonyl group whereas the resonances at δ 145.1 and 139.7 ppm were assigned to C-2 and C-4, respectively. Resonances at δ 41.7 and 33.4 pm were assigned to the CH_2CH_2-indole carbons.

Reverse transcriptase (RT) is a key enzyme, which plays an essential and multifunctional role in the replication of HIV-1 and thus is considered to be an attractive target for inhibition of HIV-1 replication (27). Non-nucleosides reverse transcriptase inhibitors (NNRTIs), a group of structurally diverse compounds, have been reported to directly inhibit the enzyme in an allosteric fashion by binding to a pocket near the polymerase active site (28). To date, many classes of NNRTIs have been identified, *e.g.* capravirine and efavirenz have been approved for the treatment of HIV-1 infection. However, NNRTI-containing regimens are compromised by rapid emergence of drug-resistant strains carrying the amino acid mutations surrounding the NNRTI binding pocket.

Our target was the synthesis of new 4-nitroimidazoles, leading to inhibition of HIV by inhibition of RT and reduction of the drug-resistance strains. Compounds **2** and **9** were found to be most active among the tested compounds inhibiting HIV replication in cell culture. Compound **2** showed inhibition of HIV-1 with an effective concentration (EC_{50}) of 0.45 μg mL^{-1} and HIV-2 with EC_{50} of 0.50 μg mL^{-1}, while compound **9** showed inhibition of HIV-2 with EC_{50} of 2.48 and a CC_{50} of 10.67 ± 0.19 μg mL^{-1}, resulting in a selectivity index of 4.

Based on the chemical structure and the fact that compound **9** inhibits HIV-1, but not HIV-2, replication, this molecule can be proposed to act as an non-nucleoside reverse transcriptase inhibitor (NNRTI).

In our study 4-nitroimidazoles, we have explored the SARs of substituents in a series of 4-nitroimidazoles (parts II–IV) in order to identifity novel NNTRIs capable of inhibiting both HIV-1 and HIV-2 replication. The docking study suggested the importance of a piperazine group on the imidazole ring substituted by aliphatic carbonyl groups such as $COCH_2Cl$, $CO(CH_2)_nR$ or sulphonamides for potent inhibitory activity against RT.

Table III. In vitro *anti-HIV-1*[a] *and HIV-2*[b] *activity of some new nitroimidazoles*

Compd.	Virus strain	EC_{50} (μg mL^{-1})[c,d]	CC_{50} (μg mL^{-1})[d,e]	*SI*[d]
2	III_B	> 0.41	0.45 ± 0.04	< 1
	ROD	> 0.50		< 1
3	III_B	> 1.74	4.17 ± 3.40	< 1
	ROD	> 2.74		< 1
4	III_B	> 2.17	4.80 ± 4.76	< 1
	ROD	> 1.94		< 1
5	III_B	> 6.02	7.77 ± 3.68	< 1
	ROD	> 5.29		< 1
6	III_B	7.64	8.14 ± 1.96	< 1
	ROD	> 6.48		< 1
7	III_B	> 5.95	7.35 ± 2.55	< 1
	ROD	> 5.81		< 1
8	III_B	> 4.48	12.69 ± 14.64	< 1
	ROD	> 3.99		< 1
9	III_B	> 2.58	10.67 ± 0.19	4
	ROD	> 10.64		< 1
10	III_B	> 17.70	30.23 ± 24.53	< 1
	ROD	> 14.50		< 1
11	III_B	> 63.70	≥ 63.10	< 1
	ROD	> 63.10		< 1
12	III_B	> 21.20	31.67 ± 17.02	< 1
	ROD	> 22.50		< 1
13	III_B	> 57.50	64.53 ± 7.79	< 1
	ROD	> 63.20		< 1
14	III_B	> 84.70	98.23 ± 22.32	< 1
	ROD	> 86.00		< 1
15	III_B	> 64.70	71.53.± 7.20	< 1
	ROD	> 71.80		< 1
16	III_B	> 14.60	17.73 ± 5.51	< 1
	ROD	> 14.50		< 1
17	III_B	> 49.00	58.93 ± 12.52	< 1
	ROD	> 54.80		< 1
18	III_B	> 29.80	44.67 ± 19.02	< 1
	ROD	> 38.10		< 1
19	III_B	> 78.90	≥ 78.90	< 1
	ROD	> 93.70		< 1
20	III_B	> 11.30	17.95 ± 13.34	< 1
	ROD	> 9.24		< 1
22	III_B	> 15.20	19.73 ± 7.68	< 1
	ROD	> 15.40		< 1
Efavirenz	III_B	> 0.003	40	13333
Capravirine	III_B	> 0.0014	11	7857

Solvent – DMSO. *SI*: Selectivity index (CC_{50}/EC_{50}).
[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 2-induced cytopathogenic effect.
[d] Compound concentration that reduces the viability of mock-infected MT-4 cells by 50%.
[e] Average and average ± SD, $n = 2$, for EC_{50} and CC_{50}, resp.

CONCLUSIONS

The anti-HIV activity of compound **9** was assessed against an NNRTI-resistant strain (RT K103N and Y181C) revealing a total loss of the inhibitory activity on HIV replication, confirming the typical first generation NNRTI mode of action of this compound. The structure-activity relationships (SARs) of 4-nitroimidazole derivatives have suggested the importance of a piperazine group on the imidazole ring substituted by aliphatic carbonyl groups such as $COCH_2Cl$, $CO(CH_2)_nR$ or sulphonamides for potent inhibitory activity against RT. This could lead to the discovery of more potent and selective analogues that will allow the elucidation of their molecular mode of action.

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S A Ž E T A K

Nitroimidazoli. V. Sinteza i anti-HIV djelovanje novih 5-supstituiranih piperazinil-4-nitroimidazol derivata

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Iz 4-nitro-5-piperazinil derivata imidazola **1** sintetizirana je serija 2-alkiltio-1-[4-(1--benzil-2-etil-4-nitro-1*H*-imidazol-5-il)-piperazin-1-il]etanona (**3–9**) i alkil-[4-(1-benzil-2--etil-4-nitro-1*H*-imidazol-5-il)-piperazin-1-il)ketona (**11–20**) te indol analog **22**, s ciljem da se razviju novi nenukleozidni inhibitori reverzne transkriptaze (NNRTI). Novosintetiziranim spojevima ispitano je djelovanje na HIV-1 i HIV-2 u MT-4 stanicama. Spoj **4** pokazao je značajno djelovanje na HIV-1 (EC_{50} 0,45 mg mL^{-1}) i HIV-2 (0,50 mg mL^{-1}), a spoj **11** na HIV-1 (EC_{50} 2.48 mg mL^{-1}, SI = 4).

Ključne riječi: anti-HIV djelovanje, 4-nitroimidazoli, NNRTIs, piperazin

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