Nitroimidazoles Part 8. Synthesis and Anti-HIV Activity of New 4-Nitroimidazole Derivatives Using the Suzuki Cross-Coupling Reaction

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The development of new HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) offers the possibility of generating structures of increased potency. To this end, a series of 1-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-4-(1,1′-biaryl)-4-yl-piperazine derivatives (**6a–l**) was synthesized *via* the Suzuki coupling reaction. Analogously, coupling of the acid derivative **5**, prepared from **4**, with various amino acid methyl esters in the presence of HOBt/DCC reagents afforded the benzamide derivatives **8–11**. The newly synthesized compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. All compounds are inactive, except compound **6f** which showed inhibition of HIV-1 with $EC_{50} = 2.60\,\mu g\,mL^{-1}$ with a selectivity index (SI) of 9.

Key words: Anti-HIV Activity, Nitroimidazoles, NNRTIs, Piperazine Derivatives, Suzuki Cross-Coupling Reaction

Introduction

Since the first case of acquired immunodeficiency syndrome (AIDS) was reported in 1981, the human immunodeficiency virus (HIV)/AIDS has always been a global health threat and the leading cause of deaths [1]. Therefore, the rapid worldwide spread of AIDS has prompted an intense research effort to discover compounds that could effectively inhibit HIV. In the past two decades, 25 drugs, including nucleoside/nucleotide viral reverse transcriptase inhibitors (NRTIs), non-nucleoside RT inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INIs) and fusion (or entry) inhibitors (FIs) were approved for clinical use [2]. Three NNRTIs, nevirapine [3], delaviridine [4, 5] and efavirenz [6], have been approved by the Food and Drug Administration (FDA) for the treatment of HIV infection. However, these drugs have only limited or transient clinical benefit. Therefore, the rapid emergence of resistant mutants against the NNRTIs allowed only a few compounds to reach the stage of clinical trials [7]. For this reason RT remains a central target in the development of anti-HIV-1 drugs, and of new classes of NNRTIs having high potency as well as being effective against resistant mutants [8, 9].

Several potent heterocyclic NNRTIs have been synthesized with high anti-HIV inhibitory activity, some of which have an imidazole scaffold (for example, capravirine; S-1153, (**1**) (Fig. 1) [10].

Several nitroimidazoles were reported to possess a number of biological activities, with possible applications as, *e. g.*, antibacterial agents [11 – 13], potential radiosensitizers [14], anticancer agents [15, 16] such as Dacarbazine® (DTIC) [17] and misonidazole [18], fungicides and/or as antiprotozoal agents such as clotrinazole [1-(2-chlorotrityl)-1*H*-imidazole] [19, 20] and metronidazole (Flagyl) (**2**) [21].

Some arylpiperazine derivatives possess anti-enterovirus activity [22, 23], such as atevirdine (**3**) (Fig. 1) [24] and vicriviroc, which are currently in Phase II clinical trials [25].

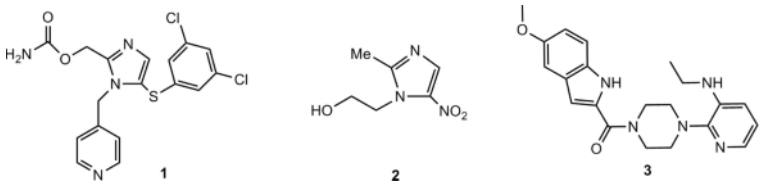
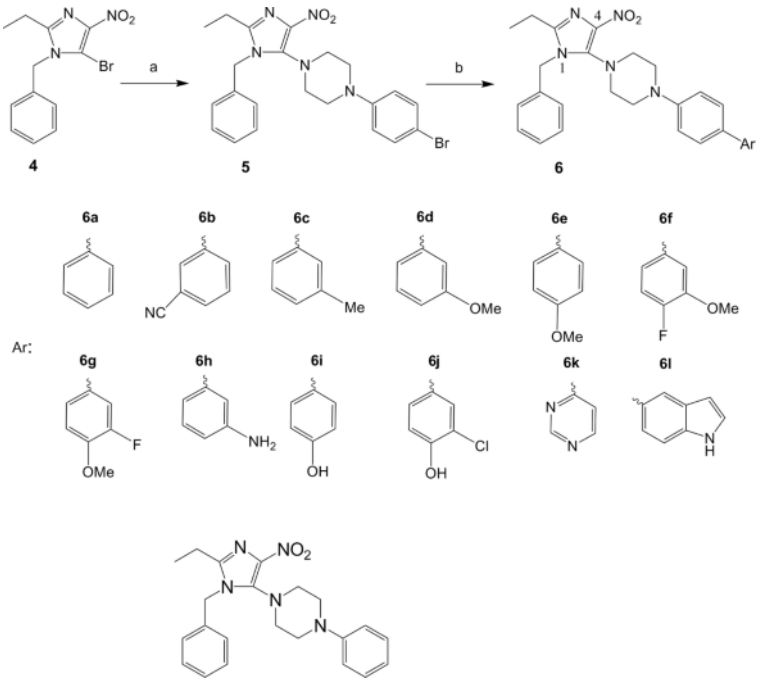


Fig. 1. Chemical structures of capravirine (**1**), metronidazole (Flagyl) (**2**) and ateviridine (**3**).

In our recent work, we have reported new 4-nitroimidazoles with their anti-HIV activity [26 – 32]; meanwhile the efforts have been focused on developing inhibitors based on novel scaffolds, *via* a regioselective palladium(0)-catalyzed cross-coupling reaction [33, 34]. As a result of this strategy, new 4-nitroimidazole derivatives bearing substituted biphenylpiperazine and phenylbenzamide residues have been selected as a lead template in our present study which might lead to the optimization of HIV-1 RT inhibitory activity.

Results and Discussion

Our recent work [26 – 31] has focused on the synthesis of 5-alkyamino, alkylsulfanyl and 2-alkylthio-1-piperazinyl derivatives of 4-nitroimidazoles as potentially active analogs. Scheme 1 depicts the chemistry employed in the preparation of this series of 5-substituted piperazinyl-4-nitroimidazole derivatives starting from **4** by replacement of the bromo substituent by 1-(4-bromophenyl)piperazine in hot DMF furnishing **5** (79 %). The Suzuki coupling reaction has been employed by using the bromo derivative **5** as a key intermediate for the synthesis of our target molecules and the appropriate arylboronic acids (*e. g.* phenyl-, 3-cyanophenyl-, 4-methylphenyl-, 3-methoxyphenyl-, 4-methoxyphenyl-, 4-fluoro-3-methoxyphenyl-, 3-fluoro-4-methoxyphenyl-, 3-aminophenyl-, 4-hydroxyphenyl-, 3-chloro-4-hydroxyphenyl-, pyrimidine-5-, and 5-indole boronic acid) in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 as catalysts to give **6a**–**l** in 42 – 73 % yield. Compounds **6a**–**l** were prepared in a parallel way using a conventional method



Scheme 1. Reagents and conditions: a) 1-(4-bromophenyl)piperazine, DMF, 70 – 80 °C; b) Na_2CO_3, $Pd(PPh_3)_4$, DMF, MWI, 30 min.

(longer reaction time, 3 – 7 days), giving moderate yields and purity.

The structures of **6a–l** were identified by ^{1}H, and ^{13}C NMR and mass spectra. The ^{1}H and ^{13}C NMR spectra of all prepared compounds are in agreement with the suggested structures. DEPT experiments were employed to differentiate secondary and quaternary carbons from primary and tertiary carbons. The ^{1}H NMR spectra showed rather similar patterns for the benzylic and ethyl protons. The two broad singlets at $\delta = 3.81 - 3.52$ and $2.98 - 2.66$ ppm were assigned to eight piperazine protons. The benzylic protons resonated at $\delta = 5.18 - 5.14$ ppm. In the ^{1}H NMR spectrum of **5**, the protons 3′-H and 5′-H of the aromatic group at C(4)$_{\text{imidazole}}$ appeared as a doublet at $\delta = 6.99$ ppm ($J = 6.9$ Hz), while 2′-H and 6′-H of the same group resonated as a doublet at $\delta = 6.74$ ppm ($J = 6.9$ Hz). The signals of the biaryl protons were further identified by DFQ-COSY spectra [35]. The ^{13}C NMR spectra of **5** and **6a–l** showed signals at $\delta = 150.6 - 145.1$ ppm, attributed to C(2) of the imidazole ring, while the carbon atoms C(4) and C(5) of the same ring resonated at $\delta = 145.4 - 138.6$ and $139.3 - 135.5$ ppm, respectively. The piperazine carbon atoms resonated at $\delta = 50.5 - 49.1$ and $49.4 - 48.8$ ppm, whereas the signals of the benzylic CH_2 carbon atoms appeared at $\delta = 46.6 - 46.1$ ppm. Compound **6b** has been selected for further NMR studies, and its HMBC spectrum [36] revealed a $^{3}J_{C,H}$ coupling between the methylene protons of piperazine at $\delta = 2.63$ ppm and C(5) of the imidazole ring at $\delta = 138.6$ ppm, as well as a $^{2}J_{C,H}$ coupling with the carbons of piperazine at $\delta = 49.6$ ppm.

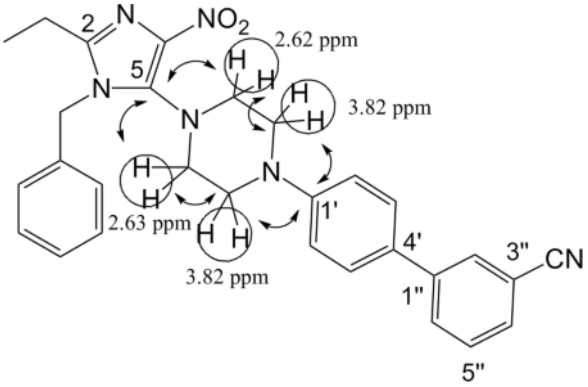


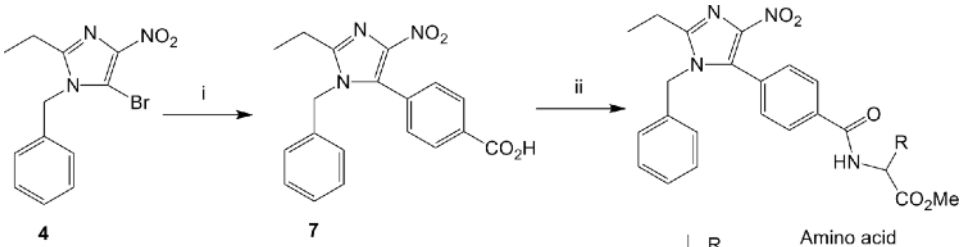
Fig. 2. $J_{C,H}$ correlations in the HMBC NMR spectrum of **6b**.

Additionally, a $^{3}J_{C,H}$ coupling between methylene protons of piperazine at $\delta = 3.82$ ppm and C-1′ of the aromaic ring attached to the piperazine moiety at $\delta = 141.9$ ppm was observed (Fig. 2).

Additional support for the proposed structures comes from mass spectra which showed the correct molecular ions, (M^{+}), as suggested by their molecular formulas.

Next, treatment of **4** with 4-carboxy phenylboronic acid in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 as catalysts, using a Suzuki cross-coupling reaction and by following the method of Vanelle *et al.* [37], afforded **5** in 72 % yield (Scheme 2).

Our work was modified by selecting **5** as a precursor for the synthesis of new benzamide derivatives to examine their antiviral activity in comparison to the biaryl analogs **6a–l**. Thus, treatment of **7** with the acylated amino acid derivatives (glycine, L-serine,



	R	Amino acid
8	H	glycine
9	CH_3	L-alanine
10	CH_2OH	L-serine
11	$CH(Me)_2$	L-valine

Scheme 2. Synthesis of carboxylic esters; i: 1-(4-bromophenyl)piperazine, DMF, 70 – 80 °C; ii: Na_2CO_3, $Pd(PPh_3)_4$, DMF, MWI, 30 min.

L-methionine, L-alanine and L-valine acetates) in the presence of HOBT and DCC as coupling reagents gave **8–11** in 74 % – 67 % yield (Scheme 2).

The structures of **8–11** were determined by their ^{1}H, ^{13}C NMR and mass spectra. The ^{1}H NMR spectra of **8–11** showed a similar pattern of benzylic and ethyl protons of the nitroimidazole scaffold. The low-field doublets at $\delta = 8.32 - 8.11$ ($J_{NH,CH} \sim 5.5$ Hz) were assigned to NH signals. The CH_2 and CH protons of the amino acid residues (CONH*CH*) appeared as doublet, doublet of doublets, or multiplet at $\delta = 4.39$ ($J_{NH,CH2} = 5.8$ Hz), 4.51 ($J_{NH,CH} = 5.5$ Hz, $J_{CH,Me} = 7.2$ Hz), 3.38 (multiplet), and 4.40 ppm ($J_{NH,CH} = 5.1$ Hz, $J_{CH,CHMe2} = 9.5$ Hz), respectively. The other protons of the amino acid moieties were fully analyzed (*cf.* Experimental Section). In the ^{13}C NMR spectra of **8–11**, the carbon atoms of the carboxylate groups resonated in the range $\delta = 172.9 - 171.1$ ppm, while the carbonyl (NHC=O) carbon atoms of the amino acid residues resonated in the range $\delta = 167.1 - 166.6$ ppm. The resonances at $\delta = 39.6$, 56.6, 54.8, and 56.8 ppm were atrributed to the carbon atoms of CH_2-glycine, *C*HMe-alanine, *C*HCH_2OH-serine, and *C*H$CHMe_2$-valine moieties. The *C*HMe, CH_2OH and *C*HMe_2 carbon signals of **10–11** appeared at $\delta = 18.2$, 67.1 and 30.9 ppm, while the dimethyl carbon atoms of **11** resonated at $\delta = 30.9$ ppm. C-2 and C-4 of the imidazole ring resonated in the range $\delta = 149.5 - 148.2$ and $145.8 - 145.2$ ppm, respectively, while C-5 of the same ring appeared in the range $\delta = 140.3 - 139.6$ ppm, and the benzylic CH_2 carbon atoms resonated at $\delta = 46.5 - 46.3$ ppm. A gradient-selected HMBC spectrum of **10** allowed the identification of C-5 of the imidazole ring at $\delta = 140.0$ ppm from the $^{3}J_{C,H}$ correlations to 2′-H and 6′-H of the aromatic residue at $\delta = 8.08$ ppm. Similarly, C=O of the amide group at $\delta = 166.8$ ppm was identified from its a $^{3}J_{C,H}$ correlations to 3′-H and 5′-H of the aromatic residue at $\delta = 7.96$ ppm (Fig. 3), as well as a $^{3}J_{C,H}$ correlation to the *CH*CH_2OH proton at $\delta = 3.58$ ppm. Additionally, The latter proton showed a $^{2}J_{C,H}$ correlation to the CH_2OH carbon atom at $\delta = 67.1$ ppm (Fig. 3). The mass fragmentation patterns were consistent with the suggested structures; however, the FAB-MAS spectra showed the protonated molecular ions of these compounds.

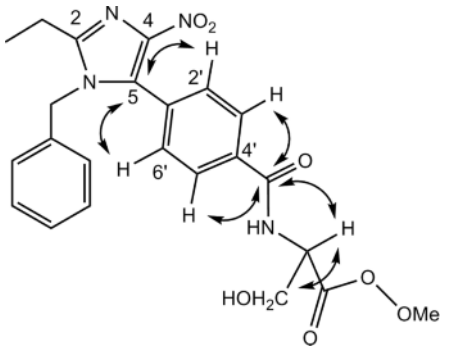


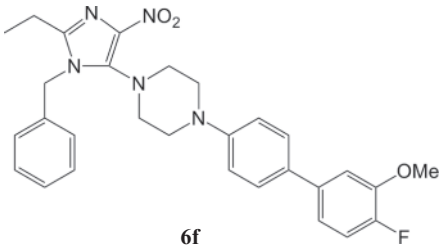
Fig. 3. $J_{C,H}$ correlations in the HMBC NMR spectrum of **10**.

In-vitro anti-HIV assay

Compounds **5**, **6a–l** and **8–11** were tested for their *in-vitro* anti-HIV-1 (strain IIIB) and anti-HIV-2 (strain ROD) activity in human MT-4 cells using the MT-4/MTT assay [38]. The results are summarized in Table 1, in which the data for azidothymidine (AZT) [39] and nevirapine (BOE/BIRG587) [40] are included for comparison purposes.

Compound **6f** was found to be the only compound of the series inhibiting HIV-1 and HIV-2 replication in a cell culture, with an EC_{50} value of $> 2.60\ \mu g\ mL^{-1}$ with a selectivity index (SI) of 9. Compound-induced cytotoxicity was also measured in MT-4 cells parallel with the antiviral activity.

Based on the chemical structure of compound **6f**, this molecule can be proposed to act as non-nucleoside reverse transcriptase inhibitor (NNRTI).



6f

In conclusion, the data in Table 1 suggest that substitution of the bromo residue at position 4 of the nitroimidazole ring by a methoxy-fluoro-biphenyl group may engender an inhibitory activity on HIV-1.

Conclusion

In summary, a series of 5-(substituted-biphenyl-4-yl)piperazine (**6a–l**) and phenylbenzamide (**8–11**)

Table 1. *In-vitro* anti-HIV-1[a] and -HIV-2[b] activity of new 4-nitroimidazioles **5**, **6a–l** and **8–11**.

Compound	Virus strain	EC_{50} ($\mu g\,mL^{-1}$)[c]	CC_{50} ($\mu g\,mL^{-1}$)[d]	SI[e]
5	III_B	>79.7	>79.7	<1
	ROD	>79.7	>79.7	<1
6a	III_B	>22.41	22.41	<1
	ROD	>23.34	23.34	<1
6b	III_B	>9.23	9.23	<1
	ROD	>9.43	9.43	<1
6c	III_B	>125	>125	<1
	ROD	>125	>125	<1
6d	III_B	>63.5	63.5	<1
	ROD	>67.0	67.0	<1
6e	III_B	>17.89	>17.89	<1
	ROD	>17.97	>17.97	<1
6f	III_B	>2.6	23.2	9
	ROD	>23.2	23.2	<1
6g	III_B	>106	106	<1
	ROD	>115	115	<1
6h	III_B	>64.7	64.7	<1
	ROD	>61.1	61.1	<1
6i	III_B	>11.1	11.1	<1
	ROD	>12.3	12.3	<1
6j	III_B	>87.4	87.4	<1
	ROD	>93.1	93.1	<1
6k	III_B	>80.1	80.1	<1
	ROD	>70.1	70.1	<1
6l	III_B	>103	103	<1
	ROD	>102	102	<1
8	III_B	>3.26	3.26	<1
	ROD	>3.26	3.26	<1
9	III_B	>4.69	4.69	<1
	ROD	>4.70	4.70	<1
10	III_B	>3.26	3.26	<1
	ROD	>3.26	3.26	<1
11	III_B	>21.24	21.24	<1
	ROD	>21.24	21.24	<1
AZT	III_B	0.0022	>25	>11 363
	ROD	0.00094	>25	>26 596
Nevirapine	III_B	0.050	>4.00	>80
	ROD	>4.00	>4.00	<1

[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] SI: selectivity index (CC_{50}/EC_{50}).

derivatives of 1-benzyl-2-ethyl-4-nitroimidazole (**4**) were synthesized and evaluated *in-vitro* for their anti-HIV activity. Compound **6f** exhibited moderate anti-HIV activity with SI = 9. Compound **6f**, with a 4-fluoro-3-methoxyphenyl substituent, generally showed higher potency, and a dramatic change in activity was observed with congener **6g** bearing a 3-fluoro-4-methoxyphenyl ring. Otherwise, compounds that were substituted at the aromatic ring by amino, cyano, hydroxy, methoxy, or methyl residues did not show any activity. Therefore, **6f** is a promising agent for further structural modification and pharmacological evaluation.

Experimental Section

General

Melting points were measured on a Mettler FP1 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM500 spectrometer (500 MHz) at 300 K.

NMR spectra were recorded on 400 and 500 MHz (^{1}H) and on 150.91 MHz (^{13}C) spectrometers (Bruker, Germany) with TMS as internal standard and on the δ scale in ppm. Signal assignments for protons were performed by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by ^{1}H-^{13}C COSY or HMBC experiments. All coupling constants (J) are given in Hz. Mass spectra (ESI) were recorded on a TSQ Quantum (Thermo Fisher) instrument and a MAT 8200 spectrometer (Finnegan MAT, USA). Microwave-assisted reactions were carried out in a CEM focused microwave synthesis system (100 – 150 W). Purification of products was performed by preparative thin-layer chromatography (TLC) using 1 mm SIL G-100 UV_{254} glass plates (Macherey-Nagel), and the progress of the reaction was monitored by TLC on Alugram SIL G UV_{254} (Macherey-Nagel).

*1-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)4-(4-bromophenyl)piperazine (**5**)*

To a stirred solution of **4** (3.10 g, 10.0 mmol) in DMF (25 mL) was added 1-(4-bromophenyl)piperazine (1.03 g, 12.0 mmol), and the solution was heated at 70 – 80 °C for 6 h. The solution was evaporated to dryness, the residue was washed with diethyl ether and purified by TLC using $CHCl_3$ as eluent to give **5**. Yield: 3.71 g (79%) as a brown powder; m. p. 153 – 156 °C (dec). – ^{1}H NMR ($CDCl_3$): δ = 7.36 – 7.32 (m, 5H, Ar-H), 6.99 (d, J = 6.9 Hz, 2H, $H(3)_{arom-Br}$ + $H(5)_{arom-Br}$), 6.74 (d, J = 6.9 Hz, 2H, $H(2)_{arom-Br}$ + $H(6)_{arom-Br}$), 5.15 (s, 2H, CH_2Ph), 4.12 – 2.70 (br s, 8H, $H_{piperazine}$), 2.62 (q, J = 7.5 Hz, 2H, CH_2CH_3), 1.30, (t, 3H, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): δ = 150.2 (C-2), 145.0 (N-$C(1)_{arom}$), 139.9 (C-4), 138.7 (C-5), 135.5 (CH_2-$C(1)_{arom}$), 131.9, 129.2, 128.2, 125.8 (C_{arom}), 118.0 (N-$C(2)_{arom}$ + N-$(C6)_{arom}$), 112.3 (C-Br), 49.6, 49.1 ($C_{piperazine}$), 46.1 (CH_2Ph), 21.1 (CH_2CH_3), 11.3 (CH_2CH_3). – MS ((+)-FAB): m/z = 469/471 $[M+H]^+$. –

$C_{22}H_{24}BrN_5O_2$ (470.36): calcd. C 56.18, H 5.14, N 14.89; found C 56.27, H 5.30, N 15.05.

General procedure for preparation of 1-(1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-4-(1,1′-biaryl-4-yl)piperazines ***6a–l***

A suspension of **5** (235 mg, 0.50 mmol), substituted arylboronic acid (0.70 mmol), tetrakis(triphenylphosphane)-palladium ($Pd(Ph_3)_4$) (22 mg, 5% mmol), and Na_2CO_3 (212 mg, 2.00 mmol) in DMF-water 1 : 1 (40 mL) was heated at 70 – 80 °C for 6 h or under MWI for 30 min. After cooling, the mixture was evaporated to dryness, and the residue was partitioned between ethyl acetate (3 × 30 mL) and water (30 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness, and the crude product was purified by preparative TLC.

*1-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-(1-[1,1′-biphenyl]-4-yl)piperazine (****6a****)*

From phenylboronic acid (85 mg). Yield: 170 mg (73%), orange crystals; m. p. 189 – 191 °C (dec.). – ^{1}H NMR ($CDCl_3$): $\delta = 7.67 - 7.63$ (m, 1H, Ar-H), 7.53 – 7.50 (m, 4H, Ar-H), 7.46 – 7.26 (m, 7H, Ar-H), 6.99 (d, 2H, $J = 7.2$ Hz, Ar-H), 5.15 (s, 2H, CH_2Ph), 3.93, 2.63 (2 × br s, 8H, $H_{piperazine}$), 2.61 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.29 (t, 3H, $J = 7.5$ Hz, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 145.1$ (C-2 + N-C(1)$_{arom}$), 138.7 (C-5 + C(1′)$_{arom}$+ C-4), 135.5 (CH_2-C(1)$_{arom}$), 132.1, 132.0, 131.9, 129.2, 128.7, 128.5, 128.4, 128.2, 127.9, 126.7, 126.6, 125.8 (C_{arom}), 50.1, 48.9 ($C_{piperazine}$), 46.3 (CH_2Ph), 21.1 (CH_2CH_3), 11.3 (CH_2CH_3). – MS ((+)-FAB): $m/z = 468$ $[M+H]^+$. – $C_{28}H_{29}NO_2$ (467.23): calcd. C 71.93, H 6.25, N 14.98; found C 71.77, H 6.39; N 15.08.

*1-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-4-(3′-isocyano-[1,1′-biphenyl]-4-yl)piperazine (****6b****)*

From 3-cyanophenylboronic acid (103 mg). Yield: 160 mg (65%), dark-brown crystals; m. p. 153 – 156 °C (dec.). – ^{1}H NMR ($CDCl_3$): $\delta = 7.81$ (s, 1H, Ar-H), 7.76 (t, 1H, $J =$ 1.3 Hz, Ar-H), 7.56 – 7.55 (m, 1H, Ar-H), 7.51 – 7.32 (m, 6H, Ar-H), 7.03 – 7.00 (m, 4H, Ar-H), 5.17 (s, 2H, CH_2Ph), 3.82, 2.82 (2 × br s, 8H, $H_{piperazine}$), 2.63 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.31 (t, 3H, $J = 7.5$ Hz, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 145.4$ (C-2 + N-C(1)$_{arom}$), 141.9 (C(1′)$_{arom}$), 139.8 (C-4), 138.6 (C-5), 135.5 (CH_2-C(1)$_{arom}$), 130.7, 130.0, 129.9, 129.5, 129.3, 128.2, 127.8, 125.3 (C_{arom}), 118.9 (CN), 116.7, 116.6 (C(1)$_{arom}$), 112.9 (C(4′)$_{arom}$-CN), 49.6, 48.9 ($C_{piperazine}$), 46.2 (CH_2Ph), 21.1 (CH_2CH_3), 11.3 (CH_2CH_3). – MS ((+)-FAB): $m/z = 493$ $[M+H]^+$. – $C_{29}H_{28}N_6O_2$ (492.57): calcd. C 70.71, H 5.73, N 17.06; found C 70.53, H 5.66, N 17.30.

*1-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-4-(4′-methyl-[1,1′-biphenyl]-4-yl)piperazine (****6c****)*

From 3-methylphenylboronic acid (95 mg). Yield: 0.10 gm (42%), light-brown crystals; m. p. 145 – 148 °C (dec.). – ^{1}H NMR ($CDCl_3$): $\delta = 7.51$ (d, 2H, $J = 8.6$ Hz, Ar-H), 7.38 – 7.28 (m, 7H, Ar-H), 7.15 – 7.06 (m, 2H, Ar-H), 7.00 (d, 2H, $J = 7.2$ Hz, Ar-H), 5.16 (s, 2H, CH_2Ph), 3.70 – 2.79 (br s, 8H, $H_{piperazine}$), 2.63 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 2.40 (s, 3H, CH_3), 1.31 (t, 3H, $J =$ 7.5 Hz, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 145.1$ (C-2 + N-C(1)$_{arom}$), 140.3 (C(1′)$_{arom}$), 138.9 (C-4 + C(4′)$_{arom}$), 136.9 (C-5 + CH_2-C(1)$_{arom}$), 129.4, 129.2, 129.1, 128.9, 128.6, 128.2, 128.0, 127.9, 127.5, 127.4, 127.1, 126.0, 125.8, 123.7 (C_{arom}), 50.5, 48.9 ($C_{piperazine}$), 46.4 (CH_2Ph), 21.5 (CH_2CH_3), 11.3 (CH_2CH_3). – MS ((+)-FAB): $m/z = 482$ $[M+H]^+$. – $C_{29}H_{31}N_5O_2$ (481.59): calcd. C 72.33, H 6.49, N 14.54; found C 72.50, H 6.32, N 14.80.

*1-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-4-(3′-methoxy-[1,1′-biphenyl]-4-yl)piperazine (****6d****)*

From 3-methoxyphenylboronic acid (106 mg). Yield: 120 mg (48%), dark-brown crystals; m. p. 144 – 147 °C (dec.). – ^{1}H NMR ($CDCl_3$): $\delta = 7.50$ (d, 2H, $J =$ 8.8 Hz, Ar-H), 7.38 – 7.73 (m, 4H, Ar-H), 7.15 – 7.13 (m, 1H, Ar-H), 7.08 (t, 1H, $J = 1.9$ Hz, Ar-H), 7.00 (d, 2H, $J = 7.0$ Hz, Ar-H); 6.95 (d, 2H, $J = 8.8$ Hz, Ar-H), 6.86 – 6.83 (m, 1H, Ar-H), 5.15 (s, 2H, CH_2Ph), 3.85 (s, 3H, OCH_3), 3.76 – 2.76 (br s, 8H, $H_{piperazine}$), 2.63 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.31 (t, 3H, $J = 7.5$ Hz, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 159.9$ (C(3′)$_{arom}$-OMe), 150.6 (C-2), 145.0 (N-C(1)$_{arom}$), 142.3 (C(1′)$_{arom}$), 138.8 (C-4), 135.5 (CH_2-C(1)$_{arom}$+ C-5), 132.6, 129.9, 129.7, 129.2, 128.2, 127.8, 125.8 (C_{arom}), 119.1 (C(6′)$_{arom}$), 112.3 (C(2′)$_{arom}$+ C(4′)$_{arom}$), 111.9 (C(2)$_{arom}$+ C(6)$_{arom}$), 55.3 (OCH_3); 49.6, 49.2 ($C_{piperazine}$), 46.1 (CH_2Ph), 21.1 (CH_2CH_3), 11.3 (CH_2CH_3). – MS ((+)-FAB): $m/z = 498$ $[M+H]^+$. – $C_{29}H_{31}N_5O_3$ (497.59): calcd. C 70.00, H 6.28, N 14.07; found C 70.19, H 6.50, N 13.89.

*1-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-4-(4′-methoxy-[1,1′-biphenyl]-4-yl)piperazine (****6e****)*

From 4-methoxyphenylboronic acid (106 mg). Yield: 140 mg (56%), yellow crystals; m. p. 216 – 219 °C (dec.). – ^{1}H NMR ($CDCl_3$): $\delta = 7.46 - 7.44$ (m, 4H, Ar-H), 7.36 – 7.30 (m, 3H, Ar-H), 6.99 (d, 3H, $J = 7.1$ Hz, Ar-H), 6.93 (d, 3H, $J = 8.8$ Hz, Ar-H), 5.14 (s, 2H, CH_2Ph), 3.82 (s, 3H, OCH_3), 3.81 – 2.66 (br s, 8H, $H_{piperazine}$), 2.61 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.29 (t, 3H, $J = 7.5$ Hz, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 159.1$ (C(4)$_{arom}$-OMe), 147.8 (C-2), 145.1 (N-C(1)$_{arom}$), 140.9 (C-4), 139.3 (N-C(1′)$_{arom}$), 138.8 (CH_2-C(1)$_{arom}$), 135.5 (C-5), 134.4, 129.3, 128.3, 127.6, 127.4, 125.8 (C_{arom}), 117.0, 116.9 (C(2)$_{arom}$+

$C(6)_{arom}$), 114.2 ($C(3')_{arom}$+ $C(5')_{arom}$), 55.4 (OCH_3), 50.2, 49.1 ($C_{piperazine}$), 46.2 (CH_2Ph), 21.2 (CH_2CH_3), 11.4 (CH_2CH_3). – MS ((+)-FAB): $m/z = 498$ $[M+H]^+$. – $C_{29}H_{31}N_5O_3$ (497.59): calcd. C 70.00, H 6.28, N 14.07; found C 70.21, H 6.43, N 14.26.

*1-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-4-(4′-fluoro-3′-methoxy-[1,1′-biphenyl]-4-yl)piperazine (**6f**)*

From 4-fluoro-3-methoxyphenylboronic acid (119 mg). Yield: 180 mg (70%), light-brown crystals; m. p. 126 – 129 °C (dec.). – ^{1}H NMR ($CDCl_3$): $\delta = 7.46$ (d, 2H, $J = 8.4$ Hz, Ar-H), 7.40 – 7.28 (m, 4H, Ar-H), 7.11 – 7.07 (m, 3H, Ar-H), 7.05 – 7.03 (m, 1H, Ar-H), 7.01 (d, 2H, $J = 7.1$ Hz, Ar-H), 5.17 (s, 2H, CH_2Ph), 3.93 (s, 3H, OCH_3), 3.73 – 2.82 (br s, 8H, $H_{piperazine}$), 2.62 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.31 (t, 3H, $J = 7.5$ Hz, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 153.8$, 151.7 (d, $J_{C4',F} = 250$ Hz, $C(4')_{arom}$-F), 147.7 (C-2), 147.6 (N-$C(1)_{arom}$), 145.2 ($C(1')_{arom}$), 138.6 (C-4 + CH_2-$C(1)_{arom}$), 135.8 (C-5 + $C(1')_{arom}$), 129.4, 129.2, 128.7, 128.2, 127.8, 127.1, 126.0, 125.8 (C_{arom}), 116.2, 116.1 ($C(3')_{arom}$+ $C(5')_{arom}$), 112.1 ($C(2)_{arom}$+ $C(6)_{arom}$), 56.3 (OCH_3), 50.4, 48.8 ($C_{piperazine}$), 46.3 (CH_2Ph), 21.1 (CH_2CH_3), 11.3 (CH_2CH_3). – MS ((+)-FAB): $m/z = 514/516$ $[M+H]^+$. – $C_{29}H_{30}FN_5O_3$ (515.58): calcd. C 67.65, H 5.86, N 13.58; found C 67.42, H 5.98, N 13.37.

*1-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-4-(3′-fluoro-4′-methoxy-[1,1′-biphenyl]-4-yl)piperazine (**6g**)*

From 3-fluoro-4-methoxyphenylboronic acid (119 mg). Yield: 0.130 mg (50%), gray crystals, m. p. 126 – 129 °C (dec.). – ^{1}H NMR ($CDCl_3$): $\delta = 7.42$ (d, 2H, $J = 8.6$ Hz, Ar-H), 7.35 – 7.24 (m, 6H, Ar-H), 7.00 – 6.98 (m, 4H, Ar-H), 5.15 (s, 2H, CH_2Ph), 3.89 (s, 3H, OCH_3), 3.70 – 2.75 (br s, 8H, $H_{piperazine}$), 2.61 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.29 (t, 3H, $J = 7.5$ Hz, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 153.6$, 151.6 (d, $J_{C3'-F} = 250$ Hz, $C(3')_{arom}$-F), 146.6 (C-2), 146.5 (N-$C(1)_{arom}$), 145.1 ($C(1')_{arom}$), 139.7 (C-4), 138.7 (CH_2-$C(1)_{arom}$), 135.7 (C-5), 134.0, 129.2, 128.2, 127.4, 125.8 (C_{arom}), 122.0, 116.4, 115.5, 114.3 (m, $C(3')_{arom}$+ $C(4')_{arom}$), 113.8 ($C(2)_{arom}$+ $C(6)_{arom}$), 56.4 (OCH_3), 50.0, 49.0 ($C_{piperazine}$), 46.2 (CH_2Ph), 21.1 (CH_2CH_3), 11.3 (CH_2CH_3). – MS ((+)-FAB): $m/z = 514/516$ $[M+H]^+$. – $C_{29}H_{30}FN_5O_3$ (515.58): calcd. C 67.65, H 5.86, N 13.58; found C 67.71, H 5.75, N 13.34.

*4′-[4-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)piperazin-1-yl]-[1,1′-biphenyl]-3-amine (**6h**)*

From 3-aminophenylboronic acid (96 mg, 0.70 mmol). Yield: 150 mg (62%), dark-yellow crystals; m. p. 209 – 212 °C (dec.). – ^{1}H NMR ($CDCl_3$): $\delta = 7.45$ (d, 2H, $J = 8.8$ Hz, Ar-H), 7.36 – 7.30 (m, 3H, Ar-H), 7.17 (t, 1H, $J = 7.8$ Hz, Ar-H), 6.98 (d, 2H $J = 7.1$ Hz, Ar-H), 6.94 – 6.90 (m, 3H, Ar-H), 6.84 (t, 1H, $J = 1.9$ Hz, Ar-H), 6.61 – 6.59 (m, 1H, Ar-H), 5.14 (s, 2H, CH_2Ph), 3.68 (br s, 2H, NH_2), 3.63 – 2.65 (br s, 8H, $H_{piperazine}$), 2.61 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.29 (t, 3H, $J = 7.5$ Hz, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 150.4$ ($C(4')$-NH_2), 146.7 (C-2), 145.0 (N-$C(1)_{arom}$), 142.0 ($C(1')_{arom}$), 138.9 (C-4), 135.9 (C-5 + CH_2-$C(1)_{arom}$), 133.0, 129.6, 129.2, 128.2, 127.8, 127.7, 125.8 (C_{arom}), 117.1 ($C(6')_{arom}$), 116.4 ($C(5')_{arom}$), 113.5 ($C(2')_{arom}$), 113.3 ($C(2)_{arom}$+ $C(6)_{arom}$), 49.6, 49.2 ($C_{piperazine}$), 46.1 (CH_2Ph), 21.1 (CH_2CH_3), 11.3 (CH_2CH_3). – MS ((+)-FAB): $m/z = 483$ $[M+H]^+$. – $C_{28}H_{30}N_6O_2$ (482.58): calcd. C 69.69, H 6.27, N 17.41; found C 69.55, H 6.40, N 17.20.

*4′-[4-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-piperazin-1-yl]-[1,1′-biphenyl]-4-ol (**6i**)*

From 4-hydroxyphenylboronic acid (97 mg, 0.70 mmol. Yield: 120 mg (50%), colorless crystals; m. p. 219 – 221 °C (dec.). – ^{1}H NMR ([D_6]DMSO): $\delta = 9.42$ (s, 1H, OH), 7.43 – 7.30 (m, 7H, Ar-H), 7.11 (d, 2H, $J = 7.2$ Hz, Ar-H), 6.95 (d, 2H, $J = 8.9$ Hz, Ar-H), 6.79 (d, 2H, $J = 8.7$ Hz, Ar-H), 5.17 (s, 2H, CH_2Ph), 3.55 – 2.95 (br s, 8H, $H_{piperazine}$), 2.58 (q, 2H, $J = 7.4$ Hz, CH_2CH_3), 1.14 (t, 3H, CH_2CH_3). – ^{13}C NMR ([D_6]DMSO): $\delta = 156.7$ ($C(4')$-OH), 150.0 (C-2), 145.2 (N-$C(1)_{arom}$), 140.0 (C-4), 139.1 (C-5), 136.8 (CH_2-$C(1)_{arom}$), 131.6, 129.3, 128.0, 127.3, 126.9, 126.7 (C_{arom}), 116.6, 116.1 ($C(3')_{arom}$+ $C(5')_{arom}$), 113.7 ($C(2)_{arom}$ + $C(6)_{arom}$), 49.1, 48.8 ($C_{piperazine}$), 46.2 (CH_2Ph), 20.7 (CH_2CH_3), 11.1 (CH_2CH_3). – MS ((+)-FAB): $m/z = 484$ $[M+H]^+$. – $C_{28}H_{29}N_5O_3$ (483.56): calcd. C 69.55, H 6.04, N 14.48; found C 69.78, H 6.23, N 14.77.

*4′-[4-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)piperazin-1-yl]-3-chloro-[1,1′-biphenyl]-4-ol (**6j**)*

From 3-chloro-4-hydroxyphenylboronic acid (121 mg, 0.70 mmol). Yield: 150 mg (58%), light-yellow crystals; m. p. 207 – 210 °C (dec.). – ^{1}H NMR ($CDCl_3$): $\delta = 7.49$ (d, 1H, $J = 2.0$ Hz, Ar-H), 7.41 (d, 2H, $J = 8.8$ Hz, Ar-H), 7.36 – 7.33 (m, 4H, Ar-H), 7.05 (d, 1H, $J = 8.5$ Hz, Ar-H), 7.00 (d, 1H, $J = 7.0$ Hz, Ar-H), 6.93 (d, 2H, $J = 8.7$ Hz, Ar-H), 5.71 (br s, 1H, OH), 5.16 (s, 2H, CH_2Ph), 3.81 – 2.76 (br s, 8H, $H_{piperazine}$), 2.63 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.30 (t, $J = 7.5$ Hz, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 150.4$ ($C(4')$-OH), 150.2 (C-2), 145.1 (N-$C(1)_{arom}$), 138.8 (C-4), 135.7 (C-5 + CH_2-$C(1)_{arom}$), 134.5 ($C(1')_{arom}$), 129.2, 128.7, 128.2, 127.8, 127.3, 126.8 (C_{arom}), 125.8 (C-Cl), 120.2 ($C(5')_{arom}$), 113.5, 113.2 ($C(2)_{arom}$+ $C(6)_{arom}$), 49.6, 49.2 ($C_{piperazine}$), 46.1 (CH_2Ph), 21.1 (CH_2CH_3), 11.3 (CH_2CH_3). – MS ((+)-FAB): $m/z = 517/519$ $[M+H]^+$. – $C_{28}H_{28}ClN_5O_3$ (518.01): calcd. C 64.92, H 5.45, N 13.52; found C 65.15, H 5.61, N 13.73.

*4-(4-(4-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-piperazin-1-yl)phenyl)pyrimidine (**6k**)*

From pyrimidine-5-boronic acid (87 mg, 0.70 mmol). Yield: 130 mg (55 %), orange oil. – ^{1}H NMR ($CDCl_3$): $\delta =$ 9.10 (s, 1H, Ar-H), 8.29 (br s, 2H, Ar-H), 7.69 – 7.10 (m, 9H, Ar-H), 5.18 (s, 2H, CH_2Ph), 3.52 – 2.98 (br s, 8H, $H_{piperazine}$), 2.64 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.32 (t, 3H, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 156.8$ ($C(1')_{pyrimidine}$), 154.4 ($C(3')_{pyrimidine}$), 153.2 ($C(5')_{pyrimidine}$), 148.2 (C-2), 145.4 (N-$C(1)_{arom}$), 138.8 (C-4), 135.7 (C-5 + CH_2-$C(1)_{arom}$), 132.3, 129.5, 128.7, 128.7, 128.5, 128.0, 126.0 (C_{arom}), 113.6, 113.2 ($C(6')_{pyrimidine}$ + $C(2)_{arom}$ + $C(6)_{arom}$), 49.4, 49.2 ($C_{piperazine}$), 46.4 (CH_2Ph), 21.4 (CH_2CH_3), 11.6 (CH_2CH_3). – MS ((+)-FAB): $m/z = 470$ $[M+H]^+$. – $C_{26}H_{27}N_7O_2$ (469.54): calcd. C 66.51, H 5.80, N 20.88; found C 66.30, H 5.66, N 20.59.

*5-(4-(4-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-piperazin-1-yl)phenyl)-1H-indole (**6l**)*

From 5-indoleboronic acid (113 mg, 0.70 mmol). Yield: 110 mg (43 %), dark-brown crystals; m. p. 103 – 106 °C (dec.). – ^{1}H NMR ($CDCl_3$): $\delta = 8.28$ (br s, 1H, NH), 7.80 (s, 1H, Ar-H), 7.69 – 7.65 (m, 2H, Ar-H), 7.61 – 7.53 (m, 2H, Ar-H), 7.48 – 7.43 (m, 4H, Ar-H), 7.40 – 7.37 (m, 3H, Ar-H), 7.35 – 7.32 (m, 1H, Ar-H), 7.29 – 7.26 (m, 1H, Ar-H), 5.16 (s, 2H, CH_2Ph), 3.52 – 2.87 (br s, 8H, $H_{piperazine}$), 2.64 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 1.32 (t, 3H, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 150.6$ (C-2), 145.0 (N-$C(1)_{arom}$), 138.6 (C-4), 135.8 (C-5 + CH_2-$C(1)_{arom}$), 134.1 ($C(7a)_{indole}$), 131.9, 129.3, 128.7, 128.6, 128.5, 128.3, 127.8, 127.5, 125.8 (C_{arom}), 124.9 ($C(2)_{indole}$), 121.6 ($C(4)_{indole}$), 115.5 ($C(6)_{indole}$), 113.2 ($C(2)_{arom}$ + $C(6)_{arom}$), 111.6 ($C(7)_{indole}$), 100.9 ($C(3)_{indole}$), 50.1, 49.4 ($C_{piperazine}$), 46.3 (CH_2Ph), 21.2 (CH_2CH_3), 11.5 (CH_2CH_3). – MS ((+)-FAB): $m/z = 507$ $[M+H]^+$. – $C_{30}H_{30}N_6O_2$ (506.60): calcd. C 71.13, H, 5.97, N 16.59; found C 71.29, H 6.09, N 16.80.

*4-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)benzoic acid (**7**)*

This compound was prepared according to the procedure for the preparation of **5** from **4** (618 mg, 2.00 mmol) and 4-carboxylphenylboronic acid (398 mg, 2.40 mmol). Yield: 506 mg (72 %); m. p. 161 – 164 °C (dec.). – ^{1}H NMR ([D_6]DMSO): $\delta = 8.02$ (d, 2H, $J = 7.1$ Hz, $H(2)_{arom}$ + ($H(6)_{arom}$), 7.89 (d, 2H, $J = 7.1$ Hz, $H(3)_{arom}$ + $H(5)_{arom}$), 7.26 – 7.21 (m, 3H, H_{arom}), 5.36 (s, 2H, CH_2Ph), 2.69 (q, 2H, $J = 7.4$ Hz, 2H, CH_2CH_3), 1.26, (t, 3H, CH_2CH_3). – ^{13}C NMR ($CDCl_3$): $\delta = 168.4$ (CO_2H), 148.9 (C-2), 145.5 (C-5), 140.7 (C-4), 137.5 ($C(1)_{arom}$ + CH_2-$C(1)_{arom}$), 129.9, 128.8, 128.5, 127.9, 127.7, 127.6, 127.4, 125.1 (C_{arom}), 46.3 (CH_2Ph), 21.2 (CH_2CH_3), 11.6 (CH_2CH_3). – MS ((+)-FAB): $m/z = 352$ $[M+H]^+$. – $C_{19}H_{17}N_3O_4$ (351.36): calcd. C 64.95, H, 4.88, N 11.96; found C 64.69, H 4.77, N 11.74.

*Synthesis of 4-nitroimidazoles bearing amino acid esters (**8–11**)*

General procedure. – To a cold solution of the amino acid ester (2.0 mmol) at −5 °C in MeCN (20 mL), **7** (703 mg, 2.0 mmol), hydroxybenzotriazole (HOBt) (270 g, 2.0 mmol) and *N*,*N*′-dicyclohexyl-carbodiimide (DCC) (412 mg, 2.00 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 off, and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate, and the solution was filtered and washed successively with saturated NaCl solution, 5 % $NaHCO_3$ solution, 1 M HCl, followed by washing with saturated NaCl solution and finally with water. The solution was dried (Na_2SO_4), filtered, evaporated to dryness and the residue purified on a SiO_2 column to give the desired products.

*Methyl 2-(4-(1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-benzamido)acetate (**8**)*

From glycine methyl ester (178 mg). Yield: 565 mg (67 %); m. p. 138 – 140 °C. – ^{1}H NMR ([D_6]DMSO): $\delta = 8.11$ (d, 1H, $J_{NH,CH2} = 5.8$ Hz, NH); 8.02 (d, 2H, $J = 7.1$ Hz, $H(2)_{arom}$ + $H(6)_{arom}$), 7.89 (d, 2H, $J = 7.1$ Hz, $H(3)_{arom}$ + $H(5)_{arom}$), 7.26 – 7.21 (m, 5H, H_{arom}), 5.33 (s, 2H, CH_2Ph), 4.39 (d, 2H, $J_{NH,CH2} = 5.8$ Hz, CH_2-glycine), 3.70 (s, 3H, CO_2Me), 2.65 (q, 2H, $J = 7.3$ Hz, 2H, CH_2CH_3), 1.25, (t, 3H, CH_2CH_3). – ^{13}C NMR ([D_6]DMSO): $\delta = 171.8$ (CO_2Me); 167.1 ($NC_{glycine}$ =O); 149.2 (C-2); 145.2 (C-5), 139.8 (C-4), 137.1 (CH_2-$C(1)_{arom}$), 135.9 ($C(1')_{arom}$), 134.5, 131.9, 129.2, 128.2, 127.2, 125.5 (C_{arom}), 51.6 (CO_2Me); 46.3 (CH_2Ph), 39.6 (CH_2-glycine), 21.0 (CH_2CH_3), 11.4 (CH_2CH_3). –MS ((+)-FAB): $m/z = 445$ $[M+Na]^+$. – $C_{22}H_{22}N_4O_4$ (422.16): calcd. C 62.55, H 5.25, N 13.26; found C 62.32, H 5.16, N 12.97.

*Methyl 2-(4-(1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-benzamido)propanoate (**9**)*

From L-alanine methyl ester (206 mg). Yield: 628 mg (72 %); m. p. 143 – 147 °C. – ^{1}H NMR ([D_6]DMSO): $\delta = 8.28$ (d, 1H, $J_{NH,CH2} = 5.5$ Hz, NH); 8.11 (d, 2H, $J = 7.0$ Hz, $H(2)_{arom}$ + $H(6)_{arom}$), 7.91 (d, 2H, $J = 7.0$ Hz, $H(3)_{arom}$ + $H(5)_{arom}$), 7.29 – 7.24 (m, 5H, H_{arom}), 5.38 (s, 2H, CH_2Ph), 4.51 (dd, 1H, $J_{NH,CH} = 5.5$ Hz, $J_{CH,Me} = 7.2$ Hz, CH-alanine), 3.73 (s, 3H, CO_2Me), 2.67 (q, 2H, $J = 7.5$ Hz, 2H, CH_2CH_3), 1.39 (d, 3H, $J_{CH,Me} = 7.2$ Hz, $CH_{alanine}$-*Me*), 1.24 (t, 3H, CH_2CH_3). – ^{13}C NMR

([D$_6$]DMSO): $\delta = 172.9$ (CO_2Me); 166.6 ($NC_{alanine}$ =O); 149.5 (C-2); 145.4 (C-4), 139.6 (C-5), 137.1 (CH_2-(C(1)$_{arom}$), 135.9 (C(1′)$_{arom}$), 134.5, 131.9, 129.2, 128.2, 127.2, 125.5 (C_{arom}), 46.5 (CH_2Ph), 56.6 (CH-alanine), 52.0 (CO_2Me), 21.3 (CH_2CH_3), 18.2 (CH*Me*), 11.5 (CH_2CH_3). –MS ((+)-FAB): $m/z = 437$ $[M+H]^+$. – $C_{23}H_{24}N_4O_4$ (436.46): calcd. C 63.29, H 5.54, N 12.84; found C 62.98, H 5.44, N 12.65.

*Methyl 2-(4-(1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-benzamido)-3-hydroxypropanoate (**10**)*

From L-serine methyl ester (238 mg). Yield: mg (74 %); m. p. 156 – 157 °C. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 8.16$ (br s, 1H, NH); 8.08 (d, 2H, $J = 7.2$ Hz, H(2)$_{arom}$ + H(6)$_{arom}$), 7.96 (d, 2H, $J = 7.2$ Hz, H(3)$_{arom}$ + H(5)$_{arom}$), 7.27 – 7.23 (m, 5H, H_{arom}), 5.41 (s, 2H, CH_2Ph), 4.53 (m, 2H, CH_2OH), 4.10 (t, 1H, $J_{OH,CH2} = 5.5$ Hz, CH_2OH), 3.58 (m, 1H, CH-serine), 3.70 (s, 3H, CO_2Me), 2.69 (q, 2H, $J = 7.4$ Hz, CH_2CH_3), 1.25 (t, 3H, CH_2CH_3). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 171.1$ (CO_2Me), 166.8 (NC_{serine} =O), 148.6 (C-2), 145.3 (C-4), 140.0 (C-5), 137.3 (CH_2-C(1)$_{arom}$), 135.8 (C(1′)$_{arom}$), 134.1, 131.2, 129.0, 128.2, 127.5, 127.2, 125.7 (C_{arom}), 46.4 (CH_2Ph), 67.1 (CH_2OH), 54.8 ($CHCH_2$OH), 51.7 (CO_2Me), 21.2 (CH_2CH_3), 11.3 (CH_2CH_3). – MS ((+)-FAB): $m/z = 426$ $[M+H]^+$. – $C_{23}H_{24}N_4O_6$ (425.46): calcd. C 61.05, H 5.35, N 12.38; found C 61.24, H 5.26, N 12.49.

*Methyl 2-(4-(1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-benzamido)-3-methylbutanoate (**11**)*

From L-valine methyl ester (262 mg). Yield: 641 mg (69 %); m. p. 145 – 18 °C. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 8.32$ (d, 1H, $J_{NH,CH} = 5.1$ Hz, NH); 8.12 (d, 2H, $J = 7.4$ Hz, H(2)$_{arom}$ + H(6)$_{arom}$), 7.97 (d, 2H, $J = 7.4$ Hz, H(3)$_{arom}$ + H(5)$_{arom}$), 7.29 – 7.24 (m, 5H, H_{arom}), 5.45 (s, 2H, CH_2Ph), 4.41 (dd, 1H, $J_{CH,CHMe2} = 9.5$ Hz, $J_{NH,CH} = 5.1$ Hz, CHCHCMe$_2$), 3.66 (s, 3H, CO_2Me), 2.09 (m, 1H, CHMe$_2$), 2.71 (q, 2H, $J = 7.5$ Hz, 2H, CH_2CH_3), 1.23 (t, 3H, CH_2CH_3), 0.83, 0.80 (2× s, 6H, 2× Me). - ^{13}C NMR ([D$_6$]DMSO): $\delta = 171.8$ (CO_2Me), 166.6 (NC_{valine} =O), 148.2 (C-2), 145.8 (C-4), 140.3 (C-5), 137.4 (CH_2-(C(1)$_{arom}$), 135.8 (C(1′)$_{arom}$), 134.4, 131.1, 129.2, 129.1, 127.7, 127.5, 125.7 (C_{arom}), 46.7 (CH_2Ph), 56.8 (CHCHMe$_2$), 52.1 (CO_2Me), 46.5 (CH_2Ph), 30.9 (CHMe$_2$), 20.9 (CH_2CH_3), 18.8, 17.7 (2× Me), 11.3 (CH_2CH_3). – MS ((+)-FAB): $m/z = 487$ $[M+Na]^+$. – $C_{25}H_{28}N_4O_5$ (464.51): calcd. C 64.64, H 6.08, N 12.06; found C 64.42, H 5.98, N 11.87.

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