Nitroimidazoles, Part 3. Synthesis and *anti*-HIV Activity of New *N*-Alkyl-4-nitroimidazoles Bearing Benzothiazole and Benzoxazole Backbones

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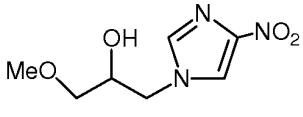
A series of 4-nitroimidazole derivatives bearing substituted piperazines (**5**, **8**, **9**, **12**, **14**, **16**, **17**, and **19** – **21**) were synthesized with the aim to develop new non-nucleoside reverse transcriptase inhibitors (NNRTIs). The newly synthesized compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. All compounds are inactive, except compound **21** which showed inhibition of HIV-1 with EC_{50} 0.20 μg/mL, and therapeutic indexes (SI) of 12.

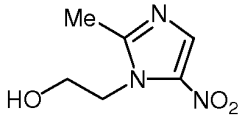
Key words: anti-HIV Activity, Benzothiazoles, Benzoxazoles, 4-Nitroimidazoles, NNRTIs

Introduction

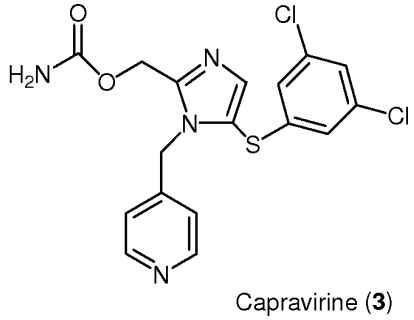
Nitro-substituted haloimidazoles are considered as compounds with important biological activity as antibacterial agents [1, 2], potential radiosensitizers [3] and anticancer agents [4, 5]. Dacarbazine® (DTIC) [6] is synthesized as an alkylating agent for inhibition of *de novo* purine synthesis, while misonidazole **1** [7] has been reported as a potential anticancer agent. Other imidazole derivatives, such as clotrinazole [1-(2-chlorotrityl)-1*H*-imidazole] [8, 9] and metronidazole (Flagyl) **2** [10], have been considered as potent fungicides and/or used as antiprotozoal agents (especially for treatment of *Trichomonas vaginalis*, *Entamoeba histolytica* and *Giardia lamblia*). Capravirine, (S-1153, **3**) is an imidazole analogue with a high *anti*-HIV inhibitory activity [11].



Misonidazole (**1**)



Metronidazole (**2**)



Capravirine (**3**)

The facile replacement of the halogen substituent in the nitro-substituted haloimidazoles prompted many laboratories [12 – 18] to develop new high-yield syntheses leading to interesting imidazole compounds bearing various alkylsulfanyl or alkylamino groups *via* nucleophilic substitution of the halogen by N or S nucleophiles. With the potential biological activity in mind, we synthesized new substituted 4-nitroimidazoles and evaluated their HIV activity.

Results

Our recent work [19, 20] has focused on the substitution of the bromo group of 5-bromo-1-benzyl-2-ethyl-4-nitroimidazole **4** [18] by various primary and secondary amines as well as by alkylsulfanyl precursors [13] to furnish potentially active analogues. In the present work, compound **4** has been selected as start-

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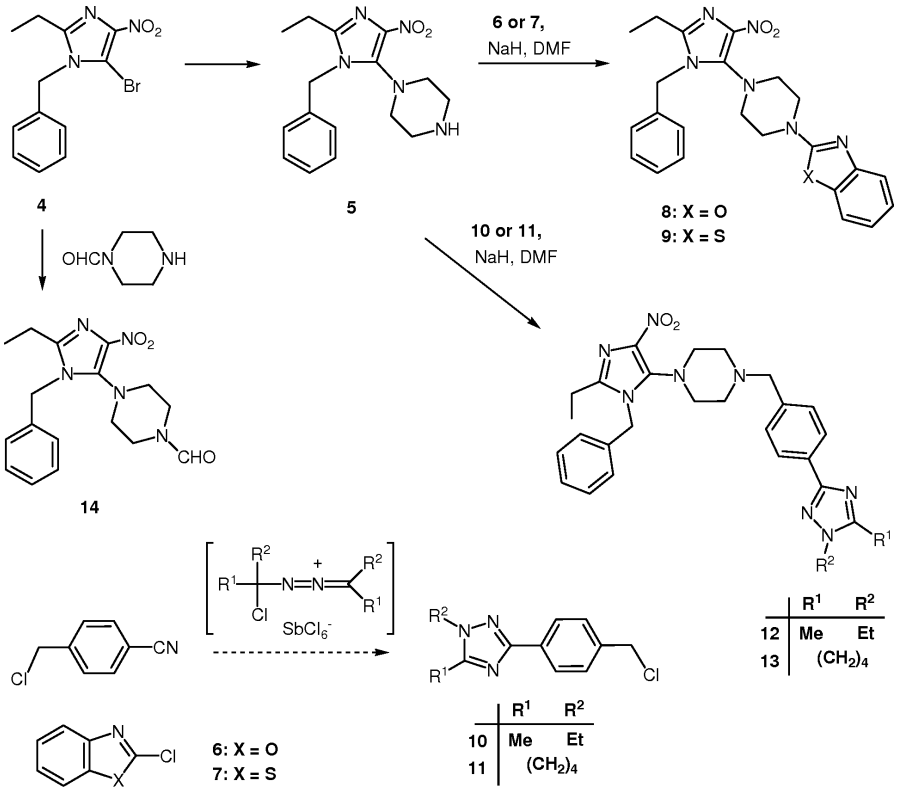


Scheme 1.

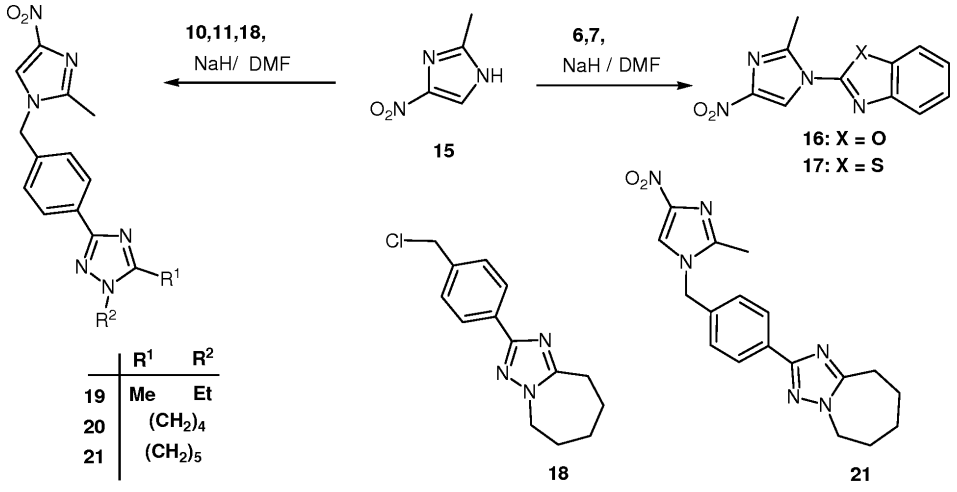
ing material for the synthesis of new substituted imidazole compounds *via* the nucleophilic displacement of the bromine group activated by an adjacent nitro function. Treatment of **4** with piperazine in DMF afforded **5** (72 %), which gave **8** and **9** in 34 and 31 % yield, respectively, on reaction with 2-chlorobenzoxazole (**6**) and 2-chlorobenzothiazole (**7**), respectively, in the presence of NaH/DMF.

On the other hand, treatment of **5** with the 4-(1,2,4-triazol-3-yl)benzyl chloride derivatives [21] **10** and **11** afforded, after purification, compounds **12** and **13** in 64 and 38 % yield, respectively.

Treatment of **4** with piperazine-1-carbaldehyde in DMF afforded after chromatographic purification compound **14** (87 %) (Scheme 1).

The structures of **5** and **8** – **14** were identified by heteronuclear NMR spectroscopic methods including HMBC spectra [22] and mass spectra. The ^{1}H NMR spectra of **5**, **8**, **9** and **12** – **14** showed rather similar patterns. The resonances of the piperazine moiety appeared as two broad singlets at $\delta = 3.89 - 2.65$ and $\delta = 3.51 - 2.56$, the signal of the benzylic protons at $\delta = 5.24 - 5.16$. The aldehyde proton of **14** gave a singlet at $\delta = 8.67$. The ^{13}C NMR spectra of **8** and **9** contained high-field signals at $\delta = 160.8$ and 167.9 which were attributed to C-10 of the oxazole and thiazole rings, respectively. Carbon atom C-2 of the imidazole ring resonated at $\delta = 140.0$. The piperazine carbon atoms were identified at $\delta = 48.4$ and 46.4. Carbon atoms C-4 and C-5 of the imidazole ring gave signals at $\delta = 137.7$ and 135.4. The ^{13}C NMR spectra of **12** and **13** were similar to those of the analogues **8** and **9**. The carbon atoms of the triazole ring were assigned to the signals at $\delta = 159.5$ and 152.3 for **8** and $\delta = 152.2$ and 145.1 for **9**.

Next, our efforts have been focused on the *N*-alkylation of 2-methyl-4-nitroimidazole (**15**) by introduction of potential alkyl groups. Thus, treatment of **15** with **6** or **7** and NaH in DMF afforded, after purification, compounds **16** and **17** in 41 and 46 % yield, respectively. A similar treatment of **15** with the benzylic chlorides **10**, **11** or **18** gave N^1-benzylimidazoles **19** – **21** in 27, 38 and 40 % yield, respectively (Scheme 2). The constitution of **16**, **17** and **19** – **21** was derived from their NMR (^{1}H, ^{13}C) and mass spectra. The HMBC spectrum of **21** showed $^2J_{C,H}$ coupling be-



Scheme 2.

tween C-4 of the imidazole ring ($\delta = 136.4$) and 5-H ($\delta = 8.46$). $^3J_{C,H}$ coupling was observed between C-4 and the methylene protons (CH_2Ph) ($\delta = 5.32$). $^2J_{C,H}$ coupling was found between C-2' of the triazole ring ($\delta = 58.5$) and 9'-H_2 ($\delta = 2.94$), and $^3J_{C,H}$ coupling between C-2' and 8'-H_2 ($\delta = 1.74$).

In vitro *anti-HIV assay*

Compounds **8**, **9**, **12**–**14**, **16**, **17** and **19**–**21** 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. The results are summarized in Table 1, in which the data for efavirenz [23] and capravirine [11] are included for comparison purposes. Compound **21** was found to be the only compound in the series inhibiting HIV-1 replication in cell culture. Compound **21** showed an EC_{50} of 0.20 μg/mL and a CC_{50} of 2.40 μg/mL, resulting in a selectivity index of 12.

Based on the chemical structure and the fact that compound **21** inhibits HIV-1, but not HIV-2 replication, this molecule can be proposed to act as an non-nucleoside reverse transcriptase inhibitor (NNRTI). This hypothesis was further confirmed by assaying the compound against a typical NNRTI-resistant HIV-1 strain (double mutation in RT: K103N and Y181C). Compound **21** completely lost its inhibitory activity against this resistant strain.

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

Compound	Virus strain	EC_{50} (μg/ml)[c]	CC_{50} (μg/ml)[d]	SI[e]
8	III_B	> 14.9	16.48 ± 1.32	< 1
	ROD	> 16.2	16.48 ± 1.32	< 1
9	III_B	> 15.9	17.18 ± 1.15	< 1
	ROD	> 16.6	17.18 ± 1.15	< 1
12	III_B	> 15.0	16.75 ± 1.75	< 1
	ROD	> 15.2	16.75 ± 1.75	< 1
13	III_B	> 14.3	15.78 ± 1.09	< 1
	ROD	> 15.6	97.05 ± 13.97	< 1
14	III_B	> 85.1	97.05 ± 13.97	< 1
	ROD	> 117.0	117.0 ± 4.2	< 1
16	III_B	> 28.8	46.88 ± 19.95	< 1
	ROD	> 22.4	46.88 ± 19.95	< 1
17	III_B	> 96.1	≥ 96.1	< 1
	ROD	> 101.0	≥ 96.1	< 1
19	III_B	> 102.0	≥ 102.0	< 1
	ROD	> 118.0	≥ 102.0	< 1
20	III_B	> 14.2	14.8 ± 0.50	< 1
	ROD	> 14.6	14.8 ± 0.50	< 1
21	III_B	0.20 ± 0.08	2.4 ± 0.1	12
	ROD	> 2.9	2.8 ± 0.1	< 1
Efavirenz [23]	III_B	0.003	40	13333
Capravirine [11]	III_B	0.0014	11	7857

[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}).

Experimental Section

Melting points were measured on a Büchi melting point apparatus B-545 (BÜCHI Labortechnik AG, Switzerland) without correction. ^{1}H and ^{13}C NMR spectra were measured on a UltraShield TM NMR-300 MHz Bruker instrument with TMS as internal standard and on the δ scale in ppm. Microanalytical data were obtained with a Vario Elementar apparatus. EI and FAB mass spectra were measured on a GC-MS Shimadzu QP-505A (Japan) spectrometer.

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

A solution of **4** (3.10 g, 10.0 mmol) in DMF (25 mL) and piperazine (1.03 g, 12.0 mmol) was stirred at 70 – 80 °C for 6 h. After cooling the precipitation was filtered and recrystallized from EtOH to give **5** (2.27 g, 72 %). M. p. 228 – 231 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.38 – 7.18 (m, 5H, ArH), 6.75 (br s, 1H, NH), 5.22 (s, 2H, CH_2Ph), 3.09, 2.98 (2xbr s, 8H, piperazine), 2.56 (q, 2H, J = 7.5 Hz, CH_2CH$_3$), 1.09 (t, 3H, CH$_2$CH_3). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 145.7 (C-2), 139.4 (C-4); 137.0 (C-5), 129.6, 128.3, 127.0 (ar.), 46.6, 43.8 (4 C, piperazine), 41.0 (*C*H$_2$Ph), 20.9 (*C*H$_2$CH$_3$), 11.3 (CH$_2$*C*H$_3$). – MS (EI, 70 eV): *m/z* (%) = 315 (78) [M$^+$]. – $C_{16}H_{21}N_5O_2$ (315.37): calcd. C 60.94, H 6.71, N 22.21; found C 60.75, H 6.59, N 22.03.

*2-[4-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)piperazin-1-yl]benzoxazole (**8**)*

To a solution of **5** (0.32 g, 1.0 mmol) in DMF (15 mL) containing NaH (1.0 mmol) was added a solution of **6** (0.15 g, 1.0 mmol) in DMF (5 mL) and the mixture was stirred at 23 °C for 48 h. The solvent was evaporated and the residue brought to dryness and partitioned between CH_2Cl_2 (40 mL) and water (40 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to dryness and the residue was purified by chromatography (10 g), using CH_2Cl_2-MeOH (9 : 1) as eluent to give **8** (0.15 g, 34 %). M. p. 145 – 147 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.42 – 7.07 (m, 9H, ArH), 5.17 (s, 2H, CH_2Ph), 3.91, 3.50 (2xbr s, 8H, piperazine), 2.68 (q, 2H, J = 7.0 Hz, CH_2CH$_3$), 1.33 (t, 3H, CH$_2$CH_3). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 160.8 (C-10), 148.2 (C-12, Ar-C), 145.3 (C-13, Ar-C), 140.0 (C-2), 137.7 (C-4), 135.4 (C-5), 129.2 – 109.2 (9 C, ar.), 48.7, 46.4 (4 C, piperazine), 45.2 (*C*H$_2$Ph), 21.1 (*C*H$_2$CH$_3$), 11.4 (CH$_2$*C*H$_3$). – MS (EI, 70 eV): *m/z* (%) = 432 (59) [M$^+$]. – $C_{23}H_{24}N_6O_3$ (432.48): calcd. C 63.88, H 5.59, N 19.43; found C 63.57, H 5.46, N 19.21.

*2-[4-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)piperazin-1-yl]benzothiazole (**9**)*

This compound was prepared from **5** (0.32, 1.0 mmol) and **7** (0.17 g, 1.0 mmol), by following the same procedure as for the preparation **8**. Yield: 0.14 g (31 %). M. p. 123 – 125 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.75 – 7.00 (m, 9H, ArH), 5.18 (s, 2H, CH_2Ph), 3.89, 3.51 (2xbr s, 8H, piperazine), 2.68 (q, 2H, J = 7.0 Hz, CH_2CH$_3$), 1.31 (t, 3H, CH$_2$CH_3). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 167.9 (C-10), 145.4 (C-12, Ar-C), 145.1 (C-13, Ar-C), 140.0 (C-2), 137.4 (C-4), 135.4 (C-5), 135.3, 129.4 – 118.1 (ar.), 125.6 (C-12), 48.4, 46.4 (4 C, piperazine), 32.0 (*C*H$_2$Ph), 21.1 (*C*H$_2$CH$_3$), 11.4 (CH$_2$*C*H$_3$). – MS (EI, 70 eV): *m/z* (%) = 484 (88) [M$^+$]. – $C_{23}H_{24}N_6O_2S$ (448.54): calcd. C 61.59, H 5.39, N 18.74; found C 63.37, H 5.46, N 19.21.

*1-[4-(1-Ethyl-5-methyl-1H-1,2,4-triazol-3-yl)benzyl-4-1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl]piperazine (**12**)*

This compound was prepared from **5** (0.32, 1.0 mmol) and **10** (0.24 g, 1.0 mmol), analogously to the preparation of **8**. Yield: 0.33 g (64 %). M. p. 152 – 154 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36 – 7.01 (m, 9H, ArH), 5.16, 5.01 (2xs, 4H, 2xCH_2Ph), 3.20, 2.56 (2xbr s, 8H, piperazine), 4.16, 2.65 (2xq, J = 7.3 Hz, 2xCH_2CH$_3$), 2.68 (q, 2H, J = 7.0 Hz, CH_2CH$_3$), 1.31 (t, 3H, CH$_2$CH_3). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 159.5 (C-3', triazole), 152.3 (C-5', triazole), 140.2 (C-2, imidazole), 138.9 (C-4, imidazole), 135.4 (2xC, Ar), 132.6 (C-5, imidazole), 130.0 – 125.6 (10 C, ar.), 48.4, 46.4 (4C, piperazine), 32.0 (*C*H$_2$Ph), 49.2, 48.6 (4 C, piperazine), 46.4, 40.2 (2x*C*H$_2$Ph), 43.5 (*C*H$_2$CH$_3$, triazole), 20.1 (*C*H$_2$CH$_3$, imidazole), 13.8, 13.6 (2xCH$_2$*C*H$_3$), 11.8 (C$_5$-*Me*). – MS (EI, 70 eV): *m/z* (%) = 514 (85) [M$^+$]. – $C_{28}H_{34}N_8O_2$ (514.62): calcd. C 65.35, H 6.66, N, 21.77; found C 65.07, H 6.49, N 21.53.

*2-[4-((4-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)piperazin-1-yl)methyl)phenyl]-5,6,7,8-tetrahydro[1,2,4]-triazolo-[1,5-a]pyridine (**13**)*

This compound was prepared from **5** (0.32, 1.0 mmol) and **11** (0.25 g, 1.0 mmol), by following the same procedure as for **8**. Yield: 0.20 g (38 %). M. p. 148 – 150 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.20, 7.52 (2xd, 4H, J = 5.0 Hz, ArH), 7.38 – 7.04 (m, 5H, ArH), 5.16, 4.29 (2xs, 4H, 2xCH_2Ph), 4.29 (m, 2H, 5'-H$_2$, triazole), 3.24 (br s, 4H, piperazine), 2.65 (br s, 8H, 9'-H$_2$, triazole + piperazine + CH_2CH$_3$), 2.22 (m, 2H, 6'-H$_2$, triazole), 2.09 (m, 2H, 8'-H$_2$, triazole), 1.35 (m, 2H, 7'-H$_2$, triazole), 1.30 (t, 3H, J = 7.2 Hz, CH$_2$CH_3). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 152.2 (C-2', triazole), 145.1 (C-10', triazole), 140.8 (C-2, imidazole), 138.9 (C-4, imidazole), 135.4 (2 C, ar.), 131.0.6 (C-5, imidazole), 130.9 – 125.7 (10C, ar.), 49.2, 47.9 (4C, piperazine), 45.5 (C-5', triazole), 46.4, 41.0 (2x*C*H$_2$Ph), 29.7 (C-7', triazole), 23.0 (C-9', triazole), 22.1 (C-8'), 21.1 (C-6', triazole), 18.7 (*C*H$_2$CH$_3$, imidazole), 11.4 (CH$_2$*C*H$_3$). – MS (EI, 70 eV): *m/z* (%) = 526 (85) [M$^+$]. – $C_{29}H_{34}N_8O_2$ (526.63): calcd. C 66.14, H 6.51, N 21.28; found C 65.84, H 6.47, N 21.11.

*4-(1-Benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)piperazin-1-carbaldehyde (**14**)*

A solution of **5** (0.34 g, 3.0 mmol) in DMF (30 mL) containing piperazine-1-carbaldehyde (0.93 g, 3.0 mmol) was heated at 70 – 80 °C for 6 h. After cooling overnight, the crystals were collected to give **14** (0.89 g, 87 %). M. p. 297 – 299 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.67 (s, 1H, CHO), 7.41 – 7.03 (m, 5H, ArH), 5.24, (s, 2H, CH_2Ph),

3.33, 3.07 (2xbr s, 8H, piperazine), 2.53 (q, $J = 7.2$ Hz, CH_2CH$_3$), 1.14 (t, 3H, CH$_2$CH_3). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 160.9$ (CHO), 145.2 (C-2), 137.9 (C-4), 135.4 (C-5), 129.3, 128.4, 127.1, 123.7 (ar.), 49.6, 48.7, 46.3, 45.7 (4 C, piperazine), 40.2 (*C*H$_2$Ph), 21.1 (*C*H$_2$CH$_3$), 11.4 (CH$_2$*C*H$_3$). – MS (EI, 70 eV): *m/z* (%) = 343 (75) [M$^+$]. – $C_{17}H_{21}N_5O_3$(343.38): calcd. C 59.46, H 6.16, N 20.40; found C 59.15, H, 6.08, N 12.75.

*2-(2-Methyl-4-nitro-1H-imidazol-1-yl)benzoxazole (**16**)*

To a solution of **15** (0.13 g, 1.0 mmol) in DMF (15 mL) containing NaH (1.0 mmol) was added a solution of **6** (0.15 g, 1.0 mmol) in DMF (5 mL) and the mixture was stirred at 120 – 130 °C for 12 h. After cooling, the reaction mixture was worked up as described for **8**. Yield: 0.10 g (41 %). M. p. 182 – 184 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.92$ (s, 1H, 5-H), 7.87 – 7.83 (m, 3H, ArH), 7.51 – 7.48 (m, 2H, ArH), 2.79 (s, 3H, 2-CH$_3$). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 151.5$ (C-2'), 149.1 (C-3a'), 146.8 (C-2), 146.5 (C-7a'), 140.3 (C-4), 126.2 (C-5), 126.2, 120.4, 120.2, 111.6 (ar.), 16.1 (2-CH$_3$). – MS (EI, 70 eV): *m/z* (%) = 241 (68) [M$^+$]. – $C_{11}H_8N_4O_3$ (244.21): calcd. C 54.10, H 3.30, N 22.94; found C 53.93, H 3.18, N 22.67.

*2-(2-Methyl-4-nitro-1H-imidazol-1-yl)benzothiazole (**17**)*

This compound was prepared from **15** (0.13 g, 1.0 mmol) and **7** (0.17 g, 1.0 mmol), by following the same procedure as for **16**. Yield: 0.12 g (46 %). M. p. 220 – 222 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.26$ (s, 1H, 5-H), 8.26 – 8.09 (m, 3H, ArH), 7.65 – 7.53 (m, 2H, ArH), 2.71 (s, 3H, 2-CH$_3$). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 156.1$ (C-2'), 149.9 (C-7a'), 146.0 (C-3a'), 146.0 (C-2), 134.2 (C-4), 127.8 (C-5), 126.9, 123.5, 123.2, 121.8 (ar.), 15.8 (2-CH$_3$). – MS: *m/z* = 260 (M$^+$). – $C_{11}H_8N_4O_2S$ (260.27): calcd. C 50.76, H 3.10, N 21.53; found C 50.54, H 2.98, N 21.42.

*1-Ethyl-5-methyl-3-[((2-methyl-4-nitro-1H-imidazol-1-yl)methyl)phenyl]-1H-1,2,4-triazole (**19**)*

This compound was prepared from **15** (0.13 g, 1.0 mmol) and **10** (0.24 g, 1.0 mmol), by following the same procedure as for **8**. Yield: 0.09 g (27 %). M. p. 166 – 168 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.46$ (s, 1H, 5-H), 7.96 (d, 2H, $J = 8.0$ Hz, ArH), 7.32 (d, 2H, $J = 8.0$ Hz, ArH), 5.33 (s, 2H, CH_2Ph), 4.15 (q, 2H, $J = 7.4$ Hz, CH_2CH$_3$), 2.44 (s, 3H, 2-Me, imidazole), 2.29 (s, 3H, 5'-Me, triazole), 1.36 (t, 3H, CH$_2$CH_3). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 159.2$ (C-3', triazole), 153.0 (C-5', triazole), 145.6 (C-2, imidazole), 136.5 (C-4, imidazole), 136.4 (C-Ar); 131.5 (C-5, imidazole), 128.1, 126.4, 123.1 (5xC-Ar), 49.9 (*C*H$_2$Ph), 43.2 (*C*H$_2$CH$_3$), 15.3 (CH$_2$*C*H$_3$), 13.3 (5'-Me, triazole), 11.8 (2-CH$_3$, imidazole). – MS (EI, 70 eV): *m/z* (%) = 260 (70) [M$^+$]. – $C_{16}H_{18}N_6O_2$ (326.35): calcd. C 58.88, H 5.56, N 25.75; found C 58.55, H 5.43, N 25.53.

*5,6,7,8-Tetrahydro-2-[4-((2-methyl-4-nitro-1H-imidazol-1-yl-)methyl)phenyl]-[1,2,4]-triazolo[1,5-a]pyridine (**20**)*

This compound was prepared from **15** (0.13 g, 1.0 mmol) and **11** (0.25 g, 1.0 mmol), by following the same procedure as for **8**. Yield: 0.13 g (38 %). M. p. 148 – 150 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.16$ (d, 2H, $J = 8.2$, ArH), 7.71 (s, 1H, 5-H), 7.22 (d, 2H, $J = 8.2$, ArH), 7.32 (d, 2H, $J = 8.2$ Hz, ArH), 5.15 (s, 2H, CH_2Ph), 4.25 (m, 2H, 5'-H$_2$-triazole), 3.06 (m, 8'-H$_2$, triazole), 2.41 (s, 3H, 2-Me, imidazole), 2.07 (m, 2H, 7'-H$_2$, triazole), 2.03 (m, 2H, 6'-H$_2$, triazole). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta =$ 160.1 (C-2', triazole), 158.0 (C-9', triazole), 145.0 (C-2, imidazole), 138.0 (C-4, imidazole), 136.1 (C-Ar), 131.2 (C-5, imidazole), 127.6, 120.0 (5 C-Ar), 50.7 (*C*H$_2$Ph), 47.5 (5'-CH$_2$-5', triazole), 29.7 (CH$_2$-8', triazole), 22.9 (CH$_2$-7', triazole), 19.7 (CH$_2$-6', triazole), 13.3 (5'-Me, triazole). – MS (EI, 70 eV): *m/z* (%) = 338 (85) [M$^+$]. – $C_{17}H_{18}N_6O_2$ (338.36): calcd. C 60.34, H 5.36, N 24.84; found C 60.16, H 5.19, N 24.49.

*6,7,8,9-Tetrahydro-2-[4-((2-methyl-4-nitro-1H-imidazol-1-yl-)methyl)phenyl]-*5H*-[1,2,4]-triazolo[1,5-a]azepine (**21**)*

This compound was prepared from **15** (0.13 g, 1.0 mmol) and **18** (0.13 g, 1.0 mmol), by following the same procedure as for **8**. Yield: 0.14 g, (40 %). M. p. 208 – 210 °C. – ^{1}H NMR (600 MHz, HMBC, $CDCl_3$): $\delta = 8.46$ (s, 1H, H-5), 7.95 (d, 2H, $J = 8.1$ Hz, ArH), 7.31 (d, 2H, $J = 8.1$ Hz, ArH), 5.32 (s, 2H, CH_2Ph), 4.28 (m, 2H, 5'-H$_2$-triazole), 2.94 (m, 2H, 9'-H$_2$, triazole), 2.28 (s, 3H, 2-Me, imidazole), 1.84 (m, 2H, 6'-H$_2$, triazole), 1.74 (m, 2H, 8'-H$_2$, triazole), 1.64 (m, 2H, 7'-H$_2$, triazole). – ^{13}C NMR (150.0 MHz, $CDCl_3$): $\delta = 158.5$ (C-2', triazole), 158.1 (C-10', triazole), 145.6 (C-2, imidazole), 136.4 (C-4, imidazole), 133.3 (C-Ar), 131.5 (C-5, imidazole), 128.2, 126.4, 123.0 (5 C-Ar), 51.0 (C-10', triazole), 50.0 (*C*H$_2$Ph), 47.5 (CH$_2$-5', triazole), 29.9 (CH$_2$-7', triazole), 27.6 (CH$_2$-9', triazole), 27.0 (CH$_2$-8', triazole), 25.0 (CH$_2$-6', triazole), 13.3 (5'-Me, triazole). – MS (EI, 70 eV): *m/z* (%) = 352 (70) [M$^+$]. – $C_{18}H_{20}N_6O_2$ (352.39): calcd. C 61.35; H 5.72; N 23.85; found C 61.08, H 5.63, N 23.57.

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