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Nitroimidazoles with a halogen-containing side-chain

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Abstract: Syntheses are reported for: nine 2-nitroimidazoles, the abbreviated names all beginning with **E**, based on derivation from Etanidazole); five 2-methyl-5-nitroimidazoles (**M** compounds, derived from Metronidazole); and five 2-methyl-4-nitroimidazoles (labelled **2M4N** compounds). The nitroimidazoles all have an amide side-chain at the N1 atom of the imidazole, 17 of them containing one to five halogen atoms. The aim is to study compounds for comparison with **EF5** (the number showing the presence of five F-atoms), a previously reported, pentafluoropropylacetamide derivative of 2-nitroimidazole that is currently used as a hypoxia marker drug to detect cancerous tumours. The new compounds are characterized by standard methods, including X-ray structural data for the fluorinated **MF5**, **2M4NF5**, and **2M4NF1(-1)** species, the '-1' indicating two C-atoms in an alkylamide chain rather than the three C-atoms in the propylacetamide of **EF5**. Intra- and inter-molecular H-bonding is seen in the solid state structures, likely an important property in biological use; another key property of the nitroimidazoles is their reduction potentials, and the measured CV data confirm that 2NO₂Im compounds with longer side-chains and more F-atoms (like **EF5**) are worth investigating for possible activity as hypoxia-selective, bioreductive agents.

Key words: 2-, 4-, and 5-nitroimidazoles, crystal structures, reduction potentials, hypoxic markers.

Introduction

Two decades ago,¹ our group in conjunction with others reported on an improved synthesis, and an X-ray structure, of **EF5**, a pentafluoropropyl acetamide derivative of 2-nitroimidazole (Chart 1), which is now a well-established biomarker for hypoxia within solid tumours.² This is highly significant because the hypoxic cells (low [O₂]) found in tumours are treatment-resistant (e.g. resistance to radiotherapy), and are thus more aggressive; knowledge of the [O₂] allows for planning of the cancer treatment. Reports on the development of clinical use of **EF5**, and its radioactive ¹⁸F analogue ([¹⁸F]**EF5**) of value in PET imaging, are copious, and cover all aspects of the clinical trial studies; selected reviews and papers, dominated by contributions from Koch's group, are listed.² The related monofluoro analogues **EF1** and [¹⁸F]**EF1** (Chart 1) have also been reported.³ The studies described in this current paper focus mainly on related halogen-containing compounds of 2-nitroimidazole derivatives, and similar derivatives of 2-methyl-5-nitroimidazole, and 2-methyl-4-nitroimidazole; the **E**, **M**, and **2M4N** abbreviations imply derivation, respectively, from Etanidazole (a 2-nitroimidazole, Chart 1), Metronidazole (a 5-nitroimidazole, Chart 1)] and 2-methyl-4-nitroimidazoles. Table 1 shows **EF5**, **EF1**, and all the new nitroimidazoles, the aim of their syntheses being to learn more of potential imaging agents for detection of cancerous tumours. The compound **ImF5**, which is **EF5** minus the NO₂-substituent, was also synthesized. Of note, nitroimidazoles without the N1 side-chain can also exhibit biological activity; e.g. 2NO₂Im itself (Azomycin) is a natural antibiotic and antiprotozoal agent.⁴ We have reported recently on Ru complexes of **EF5**, Etanidazole, Metronidazole, and 2-NO₂-imidazole, regarding their potential use as radiosensitizers.⁵

Chart 1. The structures of **EF5**, **EF1**, Etanidazole, and Metronidazole.

Insert Table 1 somewhere here

The improved synthesis of **EF5** is shown in Scheme 1. The syntheses of most of the new compounds reported in this present paper also involve reaction of a halogen-containing side-chain, but now with carboxylic acid derivatives of the **E**, **M**, and **2M4N** nitroimidazoles; the required nitroimidazole precursors **1-3** (Chart 2) are noted in the Experimental (General).

Scheme 1. Synthesis of **EF5** from 2-nitroimidazole and the side-chain 2-iodo-*N*-(2,2,3,3,3-pentafluoropropyl)acetamide (**IF5**).¹

Experimental

General

Syntheses were carried out under an N_2 flow at room temperature (r.t. $\sim 20^\circ\text{C}$), unless noted otherwise. *N*-(2-Hydroxyethyl)-2-(2-nitro-1*H*-imidazol-1-yl)acetamide (Etanidazole) and 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol (Metronidazole), kindly donated by Drs. C. Koch (Univ. of Pennsylvania) and M. Taylor (MRC, Chilton), respectively, were used as received.

The imidazole precursors (**1-3**, Chart 2) were isolated as powders according to literature methods: 2-(2-nitro-1*H*-imidazol-1-yl)acetic acid (**1**) was synthesized from Etanidazole via

cleavage of the amide bond using MeOH/HCl to yield the methyl ester that was then hydrolyzed using NaOH;^{1,6} 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetic acid (**2**) was obtained via oxidation of Metronidazole with Jones' reagent, after separation from side-products by TLC;⁷ and 2-(2-methyl-4-nitro-1*H*-imidazol-1-yl)propionic acid (**3**) was made by acid hydrolysis of the analogous propionitrile.⁸

Chart 2. The imidazole precursors **1-3** for the **E**, **M**, and **2M4N** derivatives, respectively.

The known 2-nitroimidazoles derivatives **EF5**, **EF1**, and **EBr1**, were made from **1**, as reported,^{1,3} and the respective halogen-containing amines $\text{H}_2\text{NCH}_2\text{CF}_2\text{CF}_3 \cdot \text{HCl}$ (a commercial product from PCR, Inc.), $\text{H}_2\text{N}(\text{CH}_2)_2\text{CH}_2\text{F} \cdot \text{HCl}$,³ and $\text{H}_2\text{N}(\text{CH}_2)_2\text{CH}_2\text{Br} \cdot \text{HBr}$. This last one was kindly donated by Prof. W. Dolbier (Univ. of Florida), who also donated $\text{H}_2\text{NCH}_2(\text{CF}_2)_2\text{Br} \cdot \text{HCl}$ and $\text{H}_2\text{N}(\text{CH}_2)_2\text{CF}_3 \cdot \text{HCl}$. Obtained from Aldrich were $\text{H}_2\text{N}(\text{CH}_2)_2\text{F} \cdot \text{HCl}$, $\text{H}_2\text{N}(\text{CH}_2)_3\text{Cl} \cdot \text{HCl}$, $\text{H}_2\text{N}(\text{CH}_2)_2\text{Cl} \cdot \text{HCl}$, and $\text{H}_2\text{NCH}_2\text{CF}_3 \cdot \text{HCl}$.

Other commercial chemicals were used as purchased, unless stated otherwise. Some solvents were dried using the appropriate drying agent, and distilled prior to use: MeOH (Mg), THF (Na-K alloy), Et₂O (Na), hexanes (Na), acetone (K₂CO₃), CH₂Cl₂ (CaH₂), and MeCN, DMF, and DMSO (molecular sieves); *d*₆-acetone and *d*₆-DMSO (from MSD Isotopes) were used immediately upon opening of an ampule to ensure dryness; D₂O was also an MSD product. Various silica materials from Merck were used for chromatography; preparative TLCs used silica gel 60, 0.5 mm plates (20 cm x 20 cm) and a 20:1 CH₂Cl₂:MeOH eluent, unless stated otherwise. Visualization of the nitroimidazoles was achieved using a UV lamp (Mineralight ® Model UVG-

54). Silica gel (230-400 mesh) was used for column chromatography, and R_f values were measured on Merck silica TLC Al sheets (silica gel 60F₂₅₄). Some products were purified on a Harrison Research model 7924T Chromatotron (a rotating disc TLC) using silica as the stationary phase and an eluent flow rate of ~ 3 mL/min. The thickness of the plate used (1.0 or 2.0 mm) was dependent on the amount of compound used for purification (up to 250 or 750 mg, respectively). This technique was useful for compounds with similar R_f values as band separation could be observed during the elution using a UV lamp.

Elemental analyses (EA) were performed in this University Chemistry department on a Carlo Erba 1106 instrument, with data having an accuracy of $\pm 0.3\%$.

Unless otherwise stated, the ^1H (300 MHz), $^{13}\text{C}\{^1\text{H}\}$ (75.4 MHz) and $^{19}\text{F}\{^1\text{H}\}$ (188 MHz) NMR spectra were recorded at r.t. in d_6 -acetone solution on a Varian XL300 spectrometer. The ^1H and ^{13}C shifts are referenced to those of the Me groups of residual Me_2CO solvent (δ_{H} 2.20 and δ_{C} 2.50), and the $^{19}\text{F}\{^1\text{H}\}$ shift is referenced to that of external $\text{CF}_3\text{CO}_2\text{H}$ in D_2O ; values for the ^1H reference in other solvents are δ 7.24 (CDCl_3), 4.78 (D_2O), 3.30 (CD_3OD), and 2.50 ($(\text{CD}_3)_2\text{SO}$). Peak multiplicities are reported as observed in a given spectrum (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; sex = sextet; spt = septet; m = multiplet; br = broad, including a combination of these symbols, e.g. qt = quartet of triplets). Where overlapping peaks have masked the multiplicity for a specific set of protons, the expected multiplicity is reported in italics (e.g. for NHCH_2CH_2 , the expected doublet of triplets is seen as a quartet and so is recorded as q,*dt*). J values are reported in Hz.

UV-Vis spectra were recorded in MeOH (unless noted otherwise) on an HP 8452A diode array spectrophotometer, and are given as λ_{max} (nm), $[\epsilon_{\text{max}} \times 10^{-3} (\text{M}^{-1}\text{cm}^{-1})]$. IR spectra (listed as cm^{-1}) were recorded (using a KBr disc) on an ATI Mattson Genesis FTIR instrument. The mass spectra

were measured using +LSIMS on a KRATOS Concept IIIHQ instrument. For the compounds that did not yield acceptable EA, a high resolution analysis of the exact elemental composition of the parent peak was sometimes carried out.

Electrochemistry was performed on 10^{-3} M solutions of compounds with 0.1 M $(\text{Bu}_4\text{N})\text{ClO}_4$ in dry, degassed MeCN under Ar in the 'home-made' cell shown in Fig. S-1; the potential was scanned down at 100 mV/s. The electrode system included Pt working and counter electrodes, and Ag wire (Ag/AgO) as the reference electrode. The amount of AgO deposited on the Ag wire varied as shown by the variable data of 330 to 660 mV *vs.* Ag, for the $\text{FeCp}_2^+/\text{FeCp}_2$ couple, and so FeCp_2 was added as an internal standard. The $\text{FeCp}_2^+/\text{FeCp}_2$ couple in MeCN *vs.* the saturated calomel electrode (SCE) is 424 mV,⁹ hence the conversion factor used to report the compound's $E_{1/2}$ [the average of the reduction and oxidation peaks, $(E_{\text{p.c.}} + E_{\text{p.a.}})/2$] *vs.* the SCE was $424 - E_{1/2}(\text{FeCp}_2)$. The potentiometer was a Pine Biopotentiostat Model AFCBP1 hooked up to an 80 MHz computer running Pine Chem (Version 2.00) CV software.

Synthesis of Side-Chains (Scheme 1 and Chart 3)

Chart 3. The side-chains **IBr** and **ClF5**, and co-products **4** and **5** from synthesis of **IBr**, and **7** from synthesis of **6**; for **IF5**, see Scheme 1.

2-Iodo-N-(2,2,3,3,3-pentafluoropropyl)acetamide (**IF5** in Scheme 1) was synthesized as reported previously as a pale yellow solid from iodoacetic acid and $\text{H}_2\text{NCH}_2\text{CF}_2\text{CF}_3 \cdot \text{HCl}$ in a reaction that uses *N*-methylmorpholine (NMM) and *iso*-butylchloroformate (iBuOCOC l);¹ these abbreviations are used throughout, and details of this type reaction are discussed later.

2-Iodo-N-(3-bromopropyl)acetamide (IBr, Chart 3)

Iodoacetic acid (979 mg, 5.27 mmol) and NMM (576 μ L, 5.27 mmol) were dissolved in THF (20 mL), and *i*BuOCOC₂H₅ (752 μ L, 5.78 mmol) was added. After 40 min, H₂N(CH₂)₂CH₂Br•HBr (1.26 g, 5.79 mmol) and further NMM (639 μ L, 5.85 mmol) were added to give a yellow slurry that on being stirred for 4 h at r.t. became red/brown, prior to precipitation of a yellow solid that was filtered off and washed with THF (3 x 15 mL). Rotoevaporation of the washings yielded a dark red oil that was shown by TLC to be a mixture. Column chromatography first gave a yellow, low concentration band, then a minor red band, and then the orange product band that, after removal of solvent, yielded an orange oil (978 mg, 61 %). LR-MS [DCI(+)]: 306 (M⁺), 255 (I₂), 227 (M⁺-Br), 180 (M⁺-I), 169 [M⁺-NH(CH₂)₂CH₂Br], 128 (I). ¹H NMR: δ 7.90 (s, 1H, NH), 3.77 (s, 2H, ICH₂), 3.52 (t, 2H, CH₂Br), 3.36 (dt, 2H, NCH₂), 2.07 (m, 2H, NCH₂CH₂, with partial overlap with a residual acetone peak). Attempted sublimation at 70 °C, a procedure used to purify **IF5**,¹ generated the cyclic ring compounds **4** and **5** of the same molecular weight (Chart 3): LR-MS [DCI(+)]: 226 (M⁺), 128 (I), 99 (M⁺-I). ¹H NMR, including 2D-cosy (200 MHz, *d*₆-acetone): (**4**) δ 4.81 (t, 2H, OCH₂), 4.12 (s, 1H, ICH), 3.74 (t, 2H, NCH₂), 2.51 (s, 1H, NH), 2.37 (p, *tt*, 2H, CH₂CH₂CH₂); (**5**) δ 4.82 (s, 2H, ICH₂), 3.55 (t, 2H, NCH₂), 3.32 (t, 2H, NCH₂), 2.03 (m, 2H, CH₂CH₂CH₂). Formation of **4** and **5** was also seen on exposure of **IBr** to UV radiation (TLC lamp) at r.t. for 2 d.

2-Chloro-N-(2,2,3,3,3-pentafluoropropyl)acetamide (ClF5, Chart 3)

A 10 mL THF solution of chloroacetic acid (101 mg, 1.08 mmol) and NMM (120 μ L, 1.08 mmol) was stirred for 10 min at 0°C. Subsequent addition of *i*BuOCOC₂H₅ (151 μ L, 1.16 mmol) produced a white precipitate; stirring at 0°C was continued for 30 min when H₂NCH₂CF₂CF₃•HCl (189 mg, 1.10 mmol) and more NMM (128 μ L, 1.17 mmol) were added.

This mixture was stirred at r.t. for 8 h before the white NMM.HCl precipitate⁶ was collected and washed with THF. Removal of filtrate solvent left a pale yellow oil whose TLC analysis revealed two products, one visible under UV light and the other appearing after development using I₂/hexanes. Sublimation at 60 °C under vacuum gave a crystalline, white solid (148 mg, 61 %), and left a dark yellow oil co-product. TLC analysis of the solid revealed a single species, visible under UV light; mp 44-45 °C, but EA gave variable, unacceptable results. LR-MS [DCI(+)]: 225 (M⁺), 190 (M⁺-Cl), 176 (M⁺-CH₂Cl). HR-MS [DCI(+)]: calc. for C₅H₅NO³⁵ClF₅: 224.99799, found 224.99782. IR: 3324 (N-H); 2966, 2872 (C-H); 1653 (C=O); 1206, 1180, 1146, 1067, 1037. ¹H NMR: δ 8.12 (s, 1H, NH), 4.24 (s, 2H, ClCH₂), 4.17 (td, 2H, ³J_{HF} = 6.7, ³J_{HH} = 2.2, CH₂CF₂). ¹⁹F{¹H} NMR: δ -8.21 (t, CF₃), -45.26 (q, CF₂).

I(CH₂)₂NHCH₂CF₂CF₃ (6) and a cyclic ring compound (7, Chart 3)

BH₃•THF (1.0 M, 290 µL, 0.290 mmol) was added to a 5 mL THF solution of **IF5** (4.0 mg, 0.126 mmol), the initial pale yellow colour rapidly becoming bright yellow, but reverting within 15 min to pale yellow; further addition of BH₃•THF (50 µL) now gave a colourless solution that was then refluxed at 80 °C for 1 h. The solution was then cooled to r.t. and MeOH (10 mL) was added to decompose unreacted BH₃. Removal of solvent gave a yellow oil that by TLC revealed several minor products and a major product that was purified via preparative TLC (CH₂Cl₂:MeOH = 50) as a yellow oil, **6** (28 mg, 73 %). ¹H NMR: δ 7.75 (br s, 1H, NH), 4.02 (td, 2H, ³J_{HF} = 10, ³J_{HH} = 2, CH₂CF₂), 3.59 (t, 2H, ICH₂), 3.31 (dt, 2H, CH₂NH). ¹⁹F{¹H} NMR: δ -8.13 (t, CF₃), -45.27 (q, CF₂). After exposure to UV light, the NMR solution became dark red/brown and a new cyclic ring species (**7**) formed. ¹H NMR: δ 4.02 (t, 2H, ³J_{HF} = 10, ³J_{HH} = 1.6, CH₂CF₂), 3.62 (m, 2H, CH_{eq}), 2.05 (m, 2H, CH_{ax}). ¹⁹F{¹H} NMR: δ -8.16 (t, -CF₃), -45.19

(q, CF_2). A minor yellow and minor red band were shown by UV-Vis analysis to be I_3^- and I_2 , respectively.^{10,11}

Synthesis of 2-Nitroimidazole derivatives

2-(2-Nitro-1-H-imidazol-1-yl)-N-(3-bromo-2,2,3,3-tetrafluoropropyl)acetamide [EF4Br]

Addition of NMM (50 μ L, 0.458 mmol) and *i*BuOCOC₂H₅ (63 μ L, 0.483 mmol) to a THF solution (15 mL) of **1** (76.0 mg, 0.442 mmol) gave a yellow slurry; H₂NCH₂CF₂CF₂Br•HCl (120 mg, 0.487 mmol) and more NMM (53 μ L, 0.485 mmol) were then added, and the mixture stirred at r.t. for 5 h to yield a white precipitate that was filtered off and washed with THF (3 x 5 mL). The filtrate and washings were taken to dryness to give a yellow oil that was purified via TLC; the isolated product band contained two species (with almost identical *R_f* values) and so a 2nd preparative TLC was performed (CH₂Cl₂:MeOH = 12). The major band was isolated and eluted with acetone, but dryness of the eluate regenerated the oil; after dissolution in 1 mL EtOAc, addition of hexanes (15 mL) yielded a white precipitate. This was isolated collected, washed with Et₂O (3 x 5 mL) and dried *in vacuo* (42.5 mg, 27%). Anal. Calc.(found) for C₈H₇N₄O₃F₄Br•0.15 Et₂O: C, 27.61 (27.76); H, 2.29 (2.13); N, 14.97 (14.94). LR-MS [DCI(+)]: 365, 363 (M^+ + H), 335, 333 (M^+ - NO), 318, 316 (M^+ - NO₂), 283 (M^+ - Br). HR-MS [DCI(+)] calc. for C₈H₈O₃N₄F₄⁸¹Br (C₈H₇O₃N₄F₄⁷⁹Br): 364.96954 (362.97163); found 364.96834 (362.97100). IR: 3310 (N-H), 3076 (C-H_{Im}), 2960, 2851 (C-H), 1697 (C=O), 1493 (N-O_{asym}), 1370 (N-O_{sym}). UV-Vis: 316 (6.9), 232 (3.5). ¹H NMR: δ 8.18 (br s, 1H, NH), 7.49 (s, 1H, Im-H₅), 7.20 (s, 1H, Im-H₄), 5.31 (s, 2H, CH₂CO), 4.10 (td, 2H, ³*J*_{HF} = 15.6, NHCH₂). ¹⁹F{¹H} NMR: δ 10.04 (t, -CF₂Br), -38.75 (t, CH₂CF₂).

2-(2-Nitro-1-H-imidazol-1-yl)-N-(3,3,3-trifluoropropyl)acetamide [EF3]

Addition of NMM (96 μ L, 0.873 mmol) to a THF solution (20 mL) of **1** (150 mg, 0.873 mmol) at 0°C gave a colourless solution that was stirred for 10 min, before *i*BuOCOC₁ (125 μ L, 0.961 mmol) was added. Stirring the mixture for 30 min gave a white slurry; H₂N(CH₂)₂CF₃•HCl (199 mg, 0.961 mmol) and more NMM (105 μ L, 0.961 mmol) were then added at r.t. After a further stirring for 5 h at r.t., the resulting white precipitate was removed and washed with THF (3 x 5 mL); the yellow washings were taken to dryness to yield a yellow solid that was recrystallized from EtOAc/hexanes to give white microcrystalline needles (193 mg, 83%). Anal. Calc.(found) for C₈H₉N₄O₃F₃: C, 36.10 (36.35); H, 3.41 (3.35); N, 21.05 (21.05). IR: 3312 (N-H), 3026, 2923, 2851 (C-H), 1669 (C=O), 1493 (N-O_{asym}), 1370 (N-O_{sym}). UV-Vis (DMSO): 328 (9.4); (MeCN) 322 (4940). ¹H NMR: δ 7.81 (br s, 1H, NH), 7.50 (s, 1H, Im-H₅), 7.15 (s, 1H, Im-H₄), 5.25 (s, 2H, CH₂CO), 3.50 (q, 2H, NHCH₂), 2.50 (qt, 2H, ³J_{HF} = 11, CH₂CF₃), ¹⁹F{¹H} NMR: δ 10.84 (s, CF₃).

2-(2-Nitro-1-H-imidazol-1-yl)-N-(2,2,2-trifluoroethyl)acetamide [EF3(-1)]

NMM (109 μ L, 0.996 mmol) and *i*BuOCOC₁ (142 μ L, 1.09 mmol) were added to a THF solution (17 mL) of **1** (172 mg, 0.998 mmol). To the resulting yellow slurry, H₂NCH₂CF₃•HCl (149mg, 1.10 mmol) and NMM (120 μ L, 1.10 mmol) were added, and the mixture was stirred at r.t. for 4 h; the resulting white precipitate was filtered off and washed with Et₂O (3 x 5 mL). The filtrate was taken to dryness to give a yellow oil that was purified using a Chromatotron (THF:acetone = 10). The 4th, most concentrated band was isolated to yield a white solid (208 mg, 83%). Anal. Calc.(found) for C₇H₇N₄O₃F₃•0.15 acetone: C, 34.40 (34.25); H, 3.08 (2.86); N, 21.39 (21.31). IR: 3299 (N-H), 3117 (C-H_{Im}), 2923, 2851 (C-H), 1685 (C=O), 1489 (N-O_{asym}),

1374 (N-O_{sym}). UV-Vis: 316 (8.5). ¹H NMR: δ 8.21 (br s, 1H, NH), 7.53 (s, 1H, Im-H₅), 7.15 (s, 1H, Im-H₄), 5.36 (s, 2H, CH₂CO), 4.06 (qd, 2H, ³J_{HF} = 9.4, CH₂CF₃). ¹⁹F{¹H} NMR : δ 4.30 (s, CF₃).

2-(2-Nitro-1-H-imidazol-1-yl)-N-(2-fluoroethyl)acetamide [EF1(-1)]

NMM (105 μ L, 0.953 mmol) and iBuOCOCl (140 μ L, 1.07 mmol) were added to a THF solution (17 mL) of **1** (154 mg, 0.891 mmol) and, to the yellow slurry, H₂NCH₂CH₂F•HCl (132 mg, 1.33 mmol) and NMM (120 μ L, 1.10 mmol) were added. The mixture was stirred at r.t. for 4 h, and the resulting white precipitate was filtered off and washed with THF (3 x 5 mL). The filtrate and washings were taken to dryness to give a yellow oil that was chromatographed using a Chromatotron (CH₂Cl₂:THF, 10:3). The white solid isolated from the 4th band was recrystallized from 1:1 acetone/Et₂O (124 mg, 64%). Anal. Calc.(found) for C₇H₉N₄O₃F: C, 38.89 (38.88); H, 4.20 (4.25); N, 25.92(25.77). IR: 3296 (N-H), 3120 (C-H_{Im}), 2926, 2851 (C-H), 1669 (C=O), 1488 (N-O_{asym}), 1372 (N-O_{sym}). UV-Vis: 316 (6.2), 212 (4.7). ¹H NMR: δ 7.87 (br s, 1H, NH), 7.50 (s, 1H, Im-H₅), 7.14 (s, 1H, Im-H₄), 5.26 (s, 2H, CH₂CO), 4.48 (dt, 2H, ²J_{HF} = 48, ³J_{HH} = 6.5, CH₂F), 3.55 (dq, *dtd*, 2H, ³J_{HF} = 30, ³J_{HH} = 6.2, NCH₂). ¹⁹F NMR: δ -144.94 (spt, *tt*), ²J_{HF} = 49.1, ³J_{HF} = 26.2, CH₂F). ¹³C NMR: δ 166.89 (CO), 130.92 and 129.92 (Im-C₄ and ₅), 84.70 (d, ¹J_{CF} = 166.5, CH₂F), 54.33 (CH₂CO), 42.89 (d, ²J_{CF} = 21, NCH₂).

2-(2-Nitro-1-H-imidazol-1-yl)-N-(3-chloropropyl)acetamide [EC11]

In 15 mL THF, 103 mg (0.596 mmol) of **1**, 64 μ L (0.581 mmol) of NMM, and 83 μ L (0.636 mmol) of iBuOCOCl, produced a yellow slurry. To this was added 87.1 mg (0.700 mmol) of H₂N(CH₂)₃Cl•HCl and further NMM (71 μ L, 0.650 mmol) before stirring for 3.5 h; this generated a yellow precipitate that was filtered off and washed as above. The filtrate and

washings were taken to dryness and the resulting yellow oil was analyzed by preparative TLC, the major band yielding a white solid (94.5 mg, 64%). Anal. Calc.(found) for $C_8H_{11}N_4O_3Cl$: C, 38.96 (39.36); H, 4.50 (4.64); N, 22.71 (22.70). IR: 3287 (N-H), 3099 (C-H_{Im}), 2946, 2868 (C-H), 1657 (C=O), 1484 (N-O_{asym}), 1368 (N-O_{sym}). UV-Vis: 316 (6.1), 216 (3.4). 1H NMR: δ 7.70 (br s, 1H, NH), 7.49 (s, 1H, Im- H_5), 7.14 (s, 1H, Im- H_4), 5.23 (s, 2H, CH_2CO), 3.66 (t, 2H, CH_2Cl), 3.39 (q,dt, 2H, NCH_2), 1.98 (p,tt, 2H, $CH_2CH_2CH_2$).

2-(2-Nitro-1-H-imidazol-1-yl)-N-(2-chloroethyl)acetamide [EC11(-1)]

The procedure was as above but using 100 mg (0.585 mmol) of **1**, 15 mL of THF, 65 μ L (0.590 mmol) of NMM, and 84 μ L (0.644 mmol) of $iBuOCOCl$, to produce the yellow slurry, followed by addition of 74.6 mg (0.64 mmol) of $H_2N(CH_2)_2Cl \cdot HCl$ and further NMM (72 μ L, 0.659 mmol), and stirring for 4.5 h. The generated white precipitate was filtered off and washed and, from the major TLC band of the yellow oil product, a white solid was isolated (93.9 mg, 69%). Anal. Calc.(found) for $C_7H_9N_4O_3Cl$: C, 36.14 (36.17); H, 3.90 (3.92); N, 24.08 (24.04). LR-MS [EI(+)]: 233 (M^+), 196 ($M^+ - Cl$), 186 ($M^+ - NO_2$). IR: 3292 (N-H), 3117 (C-H_{Im}), 2926, 2851 (C-H), 1665 (C=O), 1489 (N-O_{asym}), 1373 (N-O_{sym}). UV-Vis: 316 (5.8), 218 (3.7). 1H NMR (d_6 -DMSO): δ 8.64 (br t, 1H, NH), 7.53 (s, 1H, Im- H_5), 7.20 (s, 1H, Im- H_4), 5.15 (s, 2H, CH_2CO), 3.61 (t, 2H, CH_2Cl), 3.44 (q,dt, 2H, NCH_2). ^{13}C NMR: δ 166.17 (CO), 128.90 and 127.58 (Im- $C_{4\&5}$), 51.63 (CH_2CO), 43.46 (CH_2Cl), 40.90 (NCH_2).

2-(2-Nitro-1-H-imidazol-1-yl)-N-(2-bromoethyl)acetamide [EBr1(-1)]

After 237 mg (1.37 mmol) of **1**, 25 mL of THF, 154 μ L (1.40 mmol) of NMM, and 196 μ L (1.50 mmol) of $iBuOCOCl$, were mixed to produce a yellow slurry, 312 mg (1.53 mmol) of $H_2N(CH_2)_2Br \cdot HBr$ and further NMM (167 μ L, 1.53 mmol) were added, and the mixture was

stirred for 4.0 h. The generated white precipitate was filtered off and now washed with Et₂O (3 x 5 mL). The yellow filtrate and washings were taken to dryness, and the residue was chromatographed on a silica gel column. The desired product (vs. starting material and side-products) was collected in the first 3 fractions, whose purity was confirmed by TLC analysis; these fractions yielded a pale yellow solid (269 mg, 71%). Anal. Calc.(found) for C₇H₉N₄O₃Br•0.5 THF: C, 35.90 (36.04); H, 3.63 (found 3.92); N, 17.53 (17.60). IR: 3293 (N-H), 3108 (C-H_{Im}), 2923, 2854 (C-H), 1668 (C=O), 1488 (N-O_{asym}), 1370 (N-O_{sym}). UV-Vis: 316 (6.4), 214 (3.5). ¹H NMR: δ 7.99 (br s, 1H, NH), 7.53 (s, 1H, Im-H₅), 7.17 (s, 1H, Im-H₄), 5.28 (s, 2H, CH₂CO), 3.64 (q,dt, 2H, NCH₂), 3.52 (t, 2H, CH₂Br). ¹³C NMR: δ 172.75 (CO), 134.84 and 134.26 (Im-C_{4&5}), 58.60 (CH₂CO), 48.24 (N-CH₂), 37.88 (CH₂Br).

2-(2-Nitro-1-H-imidazol-1-yl)-N-(propyl)acetamide [EPrA]

The procedure was as above but using 80.8 mg (0.469 mmol) of **1**, 10 mL of THF, 50 µL (0.467 mmol) of NMM, and 70 µL (0.536 mmol) of iBuOCOCl, to produce the yellow slurry, followed by addition of 46.6 mg (0.488 mmol) of H₂N(CH₂)₂CH₃Cl•HCl and further NMM (56 µL, 0.513 mmol), and then stirring for 4.5 h. The generated white precipitate was filtered off and washed, and the filtrate and washings were taken to dryness and the white solid product (30.1 mg, 30 %) was isolated using preparative TLC (CH₂Cl₂:MeOH = 10). Anal. Calc.(found) for C₈H₁₂N₄O₃: C, 45.28 (45.21); H, 5.70 (5.58); N, 26.40 (26.67). IR: 3290 (N-H), 3113 (C-H_{Im}), 2969, 2878 (C-H), 1662 (C=O), 1490 (N-O_{asym}), 1361 (N-O_{sym}). UV-Vis: 316 (5.6), 228 (3.1). ¹H NMR: δ 7.52 (br s, 1H, NH, overlapping with peak at 7.50), 7.50 (s, 1H, Im-H₅), 7.13 (s, 1H, Im-H₄), 5.20 (s, 2H, CH₂CO), 3.20 (q,dt, 2H, NCH₂), 1.52 (sex,qt, 1H, CH₂CH₃), 0.89 (t, 3H, CH₃).

2-(2-Nitro-1-H-imidazol-1-yl)-N-(iso-amyl)acetamide [EIAA]

The procedure was as above but using 81.2 mg (0.472 mmol) of **1**, 10 mL THF (10 mL), 50 μ L (0.467 mmol) of NMM, and 70 μ L (0.536 mmol) of *i*BuOCOC₂H₅ 70 μ L, to give the yellow slurry to which H₂N(CH₂)₂CH(CH₃)₂ (59 μ L, 0.508 mmol) was added. The stirring, filtration, THF washing of the white solid, and isolation by preparative TLC, exactly as for **EPrA**, gave a white solid (77.3 mg, 68%). Anal. Calc.(found) for C₁₀H₁₆N₄O₃: C, 49.99 (49.64); H, 6.71 (6.56); N, 23.32 (22.98). IR: 3267 (N-H), 3127 (C-H_{Im}), 2958, 2875 (C-H), 1656 (C=O), 1490 (N-O_{asym}), 1374 (N-O_{sym}). UV-Vis: 316 (7.1), 228 (4.0). ¹H NMR: δ 7.52 (br s, 1H, NH) overlapping with δ 7.50 (s, 1H, Im-H₅), 7.11 (s, 1H, Im-H₄), 5.20 (s, 2H, CH₂CO), 3.27 (q,dt, 2H, NHCH₂), 1.65 (m, 1H, CH(CH₃)₂), 1.38 (q,dt, 2H, CH₂CH₂), 0.88 (d, 6H, CH(CH₃)₂).

Synthesis of 2-Methyl-5-Nitroimidazoles

2-(2-Methyl-5-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide [MF5]

To a suspension of **2** (130 mg, 0.70 mmol) in 25 mL THF at 0°C, NMM (80 μ L, 0.73 mmol) was added and the colourless solution then stirred: after 10 min, *i*BuOCOC₂H₅ (130 μ L, 1.00 mmol) was added, and after 30 min a pale yellow slurry was seen. The ice-bath was removed, and H₂NCH₂CF₂CF₃•HCl (149 mg, 0.87 mmol) and NMM (95 μ L, 0.87 mmol) were added, and the mixture stirred for 3 h. The off-white precipitate that formed was filtered off and washed with THF (3 x 5 mL); the filtrate and washings were taken to dryness to give a yellow oil that was purified via column chromatography using THF as eluent. The 1st band was pale yellow, and the 2nd colourless one contained **MF5**; this band was taken to dryness to yield a white solid (117 mg, 53 %), and X-ray quality crystals were grown by evaporation of a concentrated MeOH solution. Anal. Calc.(found) for C₉H₉N₄O₃F₅: C, 34.19 (34.25); H, 2.87 (2.99); N, 17.53 (17.53). IR: 3212 (N-H), 3028 (C-H_{Im}), 2921, 2851 (C-H), 1670 (C=O), 1473 (N-O_{asym}), 1368 (N-O_{sym}).

UV-Vis: 310 (8.1), 230 (3.7), 212 (3.9). ^1H NMR (CD_3OD): δ 8.07 (s, 1H, Im- H_4), 5.24 (s, 2H, CH_2CO), 4.08 (t, 2H, CH_2CF_2), 2.54 (s, 3H, Im- CH_3); (CDCl_3) δ 7.93 (s, 1H, Im- H_4), 6.28 (br s, 1H, NH), 4.93 (s, 2H, CH_2CO), 3.97 (dt, 2H, CH_2CF_2), 2.47 (s, 3H, Im- CH_3). $^{19}\text{F}\{^1\text{H}\}$ NMR (CD_3OD): δ -7.56 (t, CF_3), -44.63 (q, CF_2); (CDCl_3) δ -8.17 (t, CF_3), -45.79 (q, CF_2).

2-(2-Methyl-5-nitro-1H-imidazol-1-yl)-N-(2,2,2-trifluoroethyl)acetamide [MF3(-1)]

The synthesis is similar to that given above for **MF5**: used were **2** (252 mg 1.359 mmol), THF (15 mL), NMM (150 μL , 1.361 mmol), and $i\text{BuOCOC}\text{Cl}$ (192 μL , 1.472 mmol), and the resulting slurry was stirred at 0°C prior to addition of $\text{H}_2\text{NCH}_2\text{CF}_3 \cdot \text{HCl}$ (202 mg, 1.490 mmol) and NMM (164 μL , 1.489 mmol). The mixture was then warmed to r.t. and stirred for 4.5 h to form a precipitate that was filtered off, and the filtrate taken to dryness. Purification of the desired product from the residue was achieved via column chromatography, with the THF being added dropwise (slowly) to ensure the separation of the **MF3(-1)** from several side-products (as seen from TLC). The third and most concentrated band was eluted from the column, with several fractions being combined and taken to dryness to give an off-white solid (291 mg, 80 %). Anal. Calc.(found) for $\text{C}_8\text{H}_9\text{N}_4\text{O}_3\text{F}_3$: C, 36.10 (36.24); H, 3.41 (3.25); N, 21.05 (20.01). IR: 3304 (N-H), 3117 (C- H_{Im}), 2960, 2871 (C-H), 1678 (C=O), 1471 (N- O_{asym}), 1373 (N- O_{sym}). UV-Vis: 310 (8.6), 230 (3.5), 210 (4.0). ^1H NMR: δ 8.26 (br s, 1H, NH), 7.92 (s, 1H, Im- H_4), 5.25 (s, 2H, CH_2CO), 4.05 (qd, 2H, CH_2CF_3), 2.43 (s, 3H, Im- CH_3). $^{19}\text{F}\{^1\text{H}\}$ NMR: δ 4.76 (s, $-\text{CF}_3$).

2-(2-Methyl-5-nitro-1H-imidazol-1-yl)-N-(2-fluoroethyl)acetamide [MF1(-1)]

The procedure is the same as that given above for **MF3(-1)**, and uses the same amounts of **2**, THF, NMM, and $i\text{BuOCOC}\text{Cl}$, with subsequent addition of $\text{H}_2\text{NCH}_2\text{CH}_2\text{F} \cdot \text{HCl}$ (155 mg, 1.560 mmol) and NMM (164 μL , 1.489 mmol) to the resulting white slurry at 0°C , before an identical

way to isolate the precipitate and work-up using column chromatography with dropwise THF: **MF1(-1)** was the 4th and most concentrated band that yielded a pale yellow solid (207 mg, 66 %). Anal. Calc.(found) for C₈H₁₁N₄O₃F: C, 41.74 (41.85); H, 4.82 (4.80); N, 24.34 (24.11). IR: 3288 (N-H), 3110 (C-H_{Im}), 2956, 2874 (C-H), 1668 (C=O), 1463 (N-O_{asym}), 1367 (N-O_{sym}). UV-Vis: 310 (9.2), 226 (4.7), 210 (5.4). ¹H NMR: δ 7.80 (br s, 2H, NH + Im-H₄), 5.16 (s, 2H, CH₂CO), 4.50 (dt, 2H, CH₂F, ²J_{HF} = 42), 3.55 (dq, ddt, 2H, NHCH₂, ³J_{HF} = 26), 2.45 (s, 3H, Im-CH₃). ¹⁹F NMR (282 MHz) δ -144.91 (spt, tt, ²J_{HF} = 50.5, ³J_{HF} = 25.7, CH₂F).

2-(2-Methyl-5-nitro-1H-imidazol-1-yl)-N-(2-chloroethyl)acetamide [**MCl1(-1)**]

The procedure is very similar to that given above for **MF5**, but using 301 mg (1.62 mmol) of **2**, 20 mL of THF, 165 μ L (1.62 mmol) of NMM, and 220 μ L (1.73 mmol) of iBuOCOCl, with subsequent addition at 0 °C of H₂N(CH₂)₂Cl•HCl (200 mg, 1.73 mmol) and NMM (184 μ L, 1.73 mmol) to the white slurry. After a work-up (stirring at r.t. for 5.5 h), the precipitate filtrate yielded an orange-pink oil that was purified using preparative TLC (CH₂Cl₂:MeOH = 10). The major band (lowest R_f) gave a white, microcrystalline solid (190 mg, 47 %). but EA gave variable, unacceptable results. LR-MS [DCI(+)] : 249, 247 (M⁺ + H), 202, 200 (M⁺ - NO₂). HR-MS [DCI(+)] calc. for C₈H₁₁N₄O₃³⁷Cl (C₈H₁₁N₄O₃³⁵Cl): 249.05684 (247.05980); found 249.05725 (247.05896). IR: 3312 (N-H), 3028 (C-H_{Im}), 2921, 2851 (C-H), 1670 (C=O), 1473 (N-O_{asym}), 1368 (N-O_{sym}). UV-Vis: 310 (6.9), 232 (2.9), 210 (3.7). ¹H NMR: δ 7.94 (br s, 2H, NH + Im-H₄), 5.16 (s, 2H, CH₂CO), 3.69 (t, 2H, CH₂Cl), 3.61 (q, dt, 2H, NHCH₂), 2.46 (s, 3H, Im-CH₃).

2-(2-Methyl-5-nitro-1H-imidazol-1-yl)-N-(2-bromoethyl)acetamide [**MBr1(-1)**]

Reaction conditions are the same as those given for the synthesis of **MF1(-1)**, but using 108 mg, (0.586 mmol) of **2**, 10 mL of THF, 65 μ L, (0.590 mmol) of NMM, and 83 μ L (0.636 mmol)

of $i\text{BuOCOCl}$, with $\text{H}_2\text{N}(\text{CH}_2)_2\text{Br}\cdot\text{HBr}$ (135 mg, 0.660 mmol) and NMM (73 μL , 0.663 mmol) being added to the white slurry at 0°C prior to the eventual, preparative TLC work-up using acetone; the major band yielded an off-white solid (137 mg, 80 %). Anal. Calc.(found) for $\text{C}_8\text{H}_{11}\text{N}_4\text{O}_3\text{Br}$: C, 33.01 (33.69); H, 3.81 (3.75); N, 19.25 (18.66). [Calc. with 0.1 mole acetone C, 33.58; H, 3.94; N 18.87]. IR: 3295 (N-H), 3100 (C-H_{Im}), 2926, 2854 (C-H), 1661 (C=O), 1458 (N-O_{asym}), 1372 (N-O_{sym}). UV-Vis: 310 (8.9), 228 (3.7), 210 (4.8). ^1H NMR: δ 7.91 (br s, 2H, $\text{NH} + \text{Im-H}_4$), 5.16 (s, 2H, CH_2CO), 3.65 (q, *dt*), 2H, NHCH_2), 3.53 (t, 2H, CH_2Br), 2.45 (s, 3H, Im-CH_3).

Synthesis of 2-Methyl-4-Nitroimidazoles

3-(2-Methyl-4-nitro-1-H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)propionamide [2M4NF5]

DMF was added dropwise (~ 3 mL) to the white slurry of **3** (305 mg, 1.53 mmol) in THF (10 mL) to give a colourless solution. NMM (169 μL , 1.53 mmol) was then added and the mixture stirred for 10 min at 0°C before addition of $i\text{BuOCOCl}$ (215 μL , 1.65 mmol); continued stirring for ~ 30 min generated a pale yellow slurry. $\text{H}_2\text{NCH}_2\text{CF}_2\text{CF}_3\cdot\text{HCl}$ (311 mg, 1.82 mmol) and more NMM (200 μL , 1.83 mmol) were then added at r.t., and further stirring for 4 h formed a white precipitate that was filtered off and washed with THF (3 x 5 mL). The filtrate was reduced in volume to ~ 5 mL before Et_2O (~ 15 mL) was added. The resulting yellow precipitate was removed by filtration and, from storage of the filtrate at 0°C overnight, formed were pale yellow crystals (403 mg, 83%) that became X-ray quality from slow evaporation of a concentrated MeOH solution. Anal. Calc.(found) for $\text{C}_{10}\text{H}_{11}\text{N}_4\text{O}_3\text{F}_5$: C, 36.37 (36.67); H, 3.36 (3.45); N, 16.97 (16.69). IR: 3260 (N-H), 3128 (C-H_{Im}), 3079, 2921 (C-H), 1674 (C=O), 1506 (N-O_{asym}), 1400 (N-O_{sym}). UV-Vis: 300 (6.2), 224 (3.6), 210 (4.2). ^1H NMR (d_6 -DMSO): δ 8.69 (t, 1H,

NH), 8.22 (s, 1H, Im- H_5), 4.23 (t, 2H, CH_2CO), 3.96 (td, 2H, $^3J_{HF} = 16.5$, CH_2CF_2), 2.78 (t, 2H, Im- CH_2), 2.38 (s, 3H, Im- CH_3). $^{19}F\{^1H\}$ NMR (d_6 -DMSO): δ -7.06 (t, CF_3), -43.99 (q, CF_2).

3-(2-Methyl-4-nitro-1-H-imidazol-1-yl)-N-(2,2,2-trifluoroethyl)propionamide [2M4NF3(-1)]

The synthesis followed that for **2M4NF5**, but using 308 mg (1.55 mmol) of **3**, 10 mL THF, ~3 mL DMF, 170 μ L (1.55 mmol) NMM, and 220 μ L (1.68 mmol) $iBuOCOCl$; 234 mg (1.73 mmol) $H_2NCH_2CF_3 \cdot HCl$ and 190 μ L (1.74 mmol) NMM were added to the resulting yellow/pink slurry. Collection of the THF filtrate from a white solid, Et_2O addition, and overnight storage yielded a white, microcrystalline solid (377 mg, 87%). Anal. Calc.(found) for $C_9H_{11}N_4O_3F_3$: C, 38.58 (38.79); H, 3.96 (3.93); N, 19.99 (19.78). IR: 3263 (N-H), 3122 (C- H_{Im}), 3076, 2946 (C-H), 1675 (C=O), 1506 (N- O_{asym}), 1400 (N- O_{sym}). UV-Vis: 300 (6.3), 224 (3.8), 212 (3.9). 1H NMR (d_6 -DMSO): δ 8.70 (t, 1H, NH), 8.21 (s, 1H, Im- H_5), 4.20 (t, 2H, CH_2CO), 3.90 (sex, qd), 2H, CH_2CF_3), 2.73 (t, 2H, Im- CH_2), 2.37 (s, 3H, Im- CH_3). $^{19}F\{^1H\}$ NMR (d_6 -DMSO): δ 5.63 (s, CF_3).

3-(2-Methyl-4-nitro-1-H-imidazol-1-yl)-N-(2-fluoroethyl)propionamide [2M4NF1(-1)]

The procedure again followed that for **2M4NF5**, using 308 mg, (1.55 mmol) of **3**, 10 mL THF, ~3 mL DMF, 170 μ L (1.55 mmol) NMM, and 220 μ L (1.68 mmol) $iBuOCOCl$; 174 mg (1.74 mmol) $H_2N(CH_2)_2F \cdot HCl$ and 190 μ L (1.74 mmol) NMM were added to the slurry. Collection of the THF filtrate from a white solid, Et_2O addition, and overnight storage this time yielded a cloudy, white mixture that on sonication for 5 min at 5 $^{\circ}C$ yielded a white microcrystalline solid (290 mg, 77%); X-ray quality crystals were grown from evaporation of a concentrated MeOH solution. Anal. Calc.(found) for $C_9H_{13}N_4O_3F$: C, 44.25 (44.38); H, 5.37 (5.34); N, 22.94 (22.75). IR: 3298 (N-H), 3110 (C- H_{Im}), 3073, 2947 (C-H), 1668 (C=O), 1504

(N-O_{asym}), 1396 (N-O_{sym}). UV-Vis: 300 (9.1), 210 (7.0). ¹H NMR (*d*₆-DMSO): δ 8.28 (t, 1H, NH), 8.23 (s, 1H, Im-*H*₅), 4.37 (dt, 2H, CH₂F, ²J_{HF} = 56), 4.19 (t, 2H, CH₂CO), 3.31 (dq, *ddt*), 2H, CH₂CH₂F, ³J_{HF} = 28), 2.69 (t, 2H, ImCH₂), 2.38 (s, 3H, Im-CH₃). ¹⁹F NMR (*d*₆-DMSO): δ -142.64 (spt, *tt*, ²J_{HF} = 49.2, ³J_{HF} = 24.2).

3-(2-Methyl-4-nitro-1-H-imidazol-1-yl)-N-(2-chloroethyl)propionamide [2M4NCl1(-1)]

The initial procedure again followed that for **2M4NF5**, but now using 306 mg (1.54 mmol) of **3**, 10 mL THF, ~3 mL DMF, 169 μ L (1.54 mmol) NMM, and 220 μ L (1.68 mmol) *i*BuOCOC₂H₅; H₂N(CH₂)₂Cl•HCl 195 mg (1.69 mmol) and 188 μ L (1.69 mmol) NMM were added to the slurry. However, the THF filtrate from a white solid was now taken to dryness to give a white, oily residue whose TLC analysis showed several side-products. The major band of preparative TLC yielded a colourless oil, to which addition of ~3 mL of MeOH and then 15 mL of Et₂O generated a white slurry; storage at r.t. for 2 h, followed by sonication (5 min at 5 °C) and then filtration, gave a white, microcrystalline solid (315 mg, 79%). Anal. Calc.(found) for C₉H₁₃N₄O₃Cl: C, 41.47 (41.83); H, 5.03 (4.81); N, 21.49 (20.64). IR: 3258 (N-H), 3119 (C-H_{Im}), 3079, 2923 (C-H), 1666 (C=O), 1499 (N-O_{asym}), 1384 (N-O_{sym}). UV-Vis: 302 (6.7), 226 (3.9), 212 (4.3). ¹H NMR: δ 8.03 (s, 1H, Im-*H*₅), 7.60 (br s, 1H, NH), 4.38 (t, 2H, CH₂CO) 3.60 (t, 2H, CH₂Cl), 3.51 (q, *dt*, 2H, CH₂CH₂Cl), 2.84 (t, 2H, Im-CH₂), 2.44 (s, 3H, Im-CH₃).

2-(2-methyl-4-nitro-1-H-imidazol-1-yl)-N-(2-bromoethyl)propionamide [2M4NBr1(-1)]

The procedure was exactly the same as given for **2M4NCl1(-1)**, but using H₂N(CH₂)₂Br•HBr (347 mg, 1.70 mmol) as the amine salt. The work-up via an oil and slurry yielded colourless crystals (98 mg, 21%). Anal. Calc.(found) for C₉H₁₃N₄O₃Br: C, 35.43 (35.62); H, 4.29 (4.28); N, 18.36 (18.65). IR: 3259 (N-H), 3115 (C-H_{Im}), 3072, 2918 (C-H), 1660 (C=O), 1499 (N-O_{asym}), 1399 (N-O_{sym}). UV-Vis: 300 (7.4), 226 (4.4), 210 (5.6). ¹H NMR: δ 8.03 (s, 1H, Im-*H*₅), 7.67 (br

s, 1H, NH), 4.36 (t, 2H, CH₂CO), 3.56 (q,dt, 2H, CH₂CH₂Br), 3.44 (t, 2H, CH₂Br), 2.83 (t, 2H, Im-CH₂), 2.42 (s, 3H, Im-CH₃).

2-(Imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide [ImF5] (EF5 minus the NO₂)

IF5 (117 mg, 0.366 mmol) was added to a yellow slurry of sodium imidazolate (31.2 mg, 0.344 mmol) in DMF (5 mL), and the mixture was stirred for 4 h at 70 °C. Reduction of volume *in vacuo* yielded a yellow oil that was then loaded onto a preparative TLC plate. Two major bands with similar R_f values were visible only after development using I₂; the isolated brown solid from the bands was heated to 120 °C *in vacuo* in a sublimation apparatus when a yellow oil deposited onto a cold finger maintained at 5 °C (36.5 mg, 41%). The oil, on exposure to air, became dark purple, but re-dissolution in acetone and exposure to air gave a bright yellow colour; removal of the acetone regenerated the dark purple colour. LR-MS [EI]: 257 (M⁺), 81 (M⁺-C(O)N(H)CH₂CF₂CF₃). HR-MS [EI] calc. for C₈H₈N₃OF₅: 257.05875; found 257.05903. ¹H NMR: δ 7.96 (br s, 1H, NH), 7.65 (s, 1H, ImH₂), 7.16 (s, 1H, ImH₅), 6.97 (s, 1H, ImH₄), 4.92 (s, 2H, NCH₂), 4.10 (td, 2H, ³J_{HF} = 17, ³J_{HH} = 6.4, N(H)CH₂). ¹⁹F{¹H} NMR: δ -8.16 (t, CF₃), -44.87 (q, CF₂).

X-ray crystallographic analyses

As for **EF5**,¹ X-ray analyses of complexes **MF5**, **2M4NF5**, and **2M4NF1(-1)** were carried out at 295 K on a Rigaku AFC6S CCD diffractometer with graphite-monochromated CuKα radiation (1.54178 Å). The new structures were solved by direct methods,¹² with all refinements being performed using a SHELXL program¹³ via the Olex2 interface.¹⁴ All non H-atoms were refined anisotropically, and all other H-atoms were generally placed in calculated positions, although H2 of **MF5**, and the H3 atoms of **2M4NF5** and **2M4NF1(-1)** were located in a

difference map and refined isotropically. The ORTEP plots and selected bond lengths and angles of the new structures are shown in Figs. 1-3, and Fig.4 shows corresponding data for **EF5** (with more details than reported in 1998). Full experimental parameters and details of the structures are given in CIF format in the Supplementary Information.

Results and Discussion

Synthesis of the nitroimidazole side-chains

Nitroimidazoles themselves can exhibit biological activity in biological systems,⁴ but a limitation is their relatively low solubility in aqueous systems. Addition of side-chains at the N1 position of the nitroimidazole ring (Chart 1) can increase the partition coefficient of the nitroimidazoles and hence their lipophilicity, ability to cross cell membranes,¹⁵ and efficacy as hypoxia-selective cytotoxins or radiosensitizers, but unfortunately increased lipophilicity can give increased neurotoxicity, the major factor that limits clinical dose.¹⁶ Nevertheless, **EF5** (Chart 1) is a proven hypoxia-selective species,² and the best synthesis uses **IF5** (Scheme 1) that is easily purified via sublimation, but has to be stored in the absence of light because of slow decomposition. As the C–Cl bond is more resistant than C–I to cleavage by UV radiation,¹¹ **ClF5** (Chart 3) was synthesized and, of interest, was visible on the TLC plate only on exposure to UV light that did not decompose the compound. Use of **ClF5** for synthesis of **EF5** gives a lower yield than using **IF5** (60 vs.78%), but is simpler in a practical sense.

The amide bond in **IF5** was reduced to $\text{I}(\text{CH}_2)_2\text{NHCH}_2\text{CF}_2\text{CF}_3$ (**6**) using $\text{BH}_3 \cdot \text{THF}$, as reported for amido side-chains of nitroimidazoles;¹⁷ however, **6** was less stable than **IF5**, and its yellow solution at r.t. in daylight slowly turned dark red-brown. ^1H NMR spectra in d_6 -acetone revealed a slow loss of **6**, with generation of new signals; a 10-day old NMR sample showed three TLC bands, the ^1H NMR spectrum of the first being consistent with compound **7** (Scheme

2), formed from **6** by loss of HI that in the presence of UV light liberates I₂, and UV-Vis data on solutions of the darker TLC bands show the presence of I₂ and I₃⁻.^{10,11} Of note, **7** has an aziridine ring analogous to that in **RSU1069** (used as a DNA alkylating agent) that is similarly formed from the bromoethylamine derivative **RB6145** (Scheme 2).¹⁸

Scheme 2. Formation of aziridine ring upon exposure of **6** to UV light.

The interest in using halogen exchange reactions to form radio-labelled species for PET hypoxia imaging¹⁹ prompted us to synthesize the monobromo species IBr (Scheme 3), but this is only stable at < 10 °C in the dark, because of reactive C–Br and C–I bonds, and exposure to heat and/or UV light gives decomposition to **4** and **5**, as seen by ¹H NMR. The NH singlet at δ 7.90 for IBr is replaced by one at δ 2.51, typical for a cyclic amine NH proton,²⁰ and the other shifts are consistent with structure **4**. Analogous cyclization products have been suggested previously, but with no supporting spectroscopic data.²¹ The formation of a short-lived species **5** (Scheme 3) is also supported by the ¹H NMR data, but it rearranges to **4** presumably because of the strained four-membered ring. Cyclization products from the cleavage of the C–I bond of IBr are not seen.

Scheme 3. Cyclization of IBr in the presence of heat or UV-radiation.

Synthesis of nitroimidazoles

Several 2-, 4- and 5NO₂-Im derivatives have been synthesized previously and tested as radiosensitizers.²² Our studies, prompted by clinical applications of **EF5**,² and successful syntheses of **EF1** and **EBr1**,³ describe isolation of the new nitroimidazole compounds listed in Table 1. Overall yields for the 2-, 5-, and 4-nitroimidazole derivatives were reasonable, 80% of each of the **E**, **M**, and **2M4** types being isolated in > 50% yield. Our publication on the **EF5** synthesis (Scheme 1)¹ included use of side-chain **IF5**, whose synthesis is shown in Scheme 4. All the nitroimidazoles were made using the same basic process for addition of an amine unit but, instead of iodoacetic acid, the imidazole-substituted acetic acids (**1-3**, Chart 2) are used,

Scheme 4. Synthesis of **IF5**.

these being made from available nitroimidazoles; Scheme 5 shows a reasonable mechanism, based on that suggested for **IF5** production.^{3,6} In the mixed anhydride generated from the carboxylic acid and *i*BuOCOC₂Cl, the more reactive carbonyl group is nearest the imidazole, and thus the isobutyl carbonate is the preferred leaving group on reaction with the NH₂R₁ amine; this leads to formation of the amide bond. NMM consumes the H⁺ from the anhydride formation and

the amine acid salt. Other methodologies for syntheses of nitroimidazole derivatives continue to appear.²³

Scheme 5. Addition of side-chain via an amide linkage; *note*, the **2M4N** compounds have an extra CH₂ (not shown) between the Im ring and the CO₂H group (see Table 1).

To obtain better agreement between the calculated and experimental elemental analyses for **EF4Br**, **EF3(-1)**, **EBr1(-1)**, and **MBr1(-1)**, 0.15 Et₂O, 0.15 Me₂CO, 0.5 THF, and 0.1 Me₂CO solvates were added, respectively, to the formulations; these solvents were used in the syntheses of the compounds. ¹H NMR data sometimes provided qualitative evidence for the presence of the solvents, and MS data also sometimes provided the value of the parent peak for the non-solvated molecule. The NMR, IR, and CV data all support the basic, solvent-free formulations.

Characterization of the nitroimidazole derivatives

Only 5 bond lengths were initially listed with the **EF5** structure that was not discussed.¹ More details of the structure are shown here (Fig. 4), and the new structures of **MF5**, **2M4NF5**, and **2M4NF1(-1)** are shown in Figs. 1-3. All four compounds crystallize in a primitive monoclinic space group, and the bond lengths and angles are all within the normal ranges.²⁴ The packing of

the **EF5** molecules within the unit cell results in a layered effect via intermolecular H-bonding stabilizing the lattice; involved is H-bonding between H3 and O1 (of the carbonyl), and N2 with an H-atom on C6. For **MF5**, the intermolecular interactions are H2...N3, and an H-atom on C4 with O1, and there are weaker intramolecular ones: an H-atom on C3 with O2 (of the NO₂) and an H-atom on C7 with O1 (of the C=O), the stronger and weaker H-bonds being considered as ~ 2.1 and ~ 2.6 Å, respectively. In **2M4NF5**, disorder is seen for the CF₂ and CF₃ groups, and there is just a single intramolecular interaction between the carbonyl-O1 and an H-atom of C8, the 4-NO₂ group being too remote from the side-chain for any H-bonding; intermolecular H-bonding is again seen between H3 and N2, and a 'new' methyl-H4...F1 interaction plays a role in the lattice structure. The F1-atom in **2M4NF1(-1)** similarly undergoes intermolecular H-bonding with the 2-Me group, and there are other intermolecular interactions between the NH proton and an NO₂ oxygen and an imidazole-N.

Fig. 1. Structural diagram of **MF5**. Selected bond lengths and angles. Bond lengths (Å): N4–O3, 1.222(2); N1–C3, 1.455(2); N2–C6, 1.345(3); N2–C7, 1.441(3); C7–C8, 1.497(3); C8–C9, 1.517(4); C8–F1, 1.347(3); C9–F4, 1.318(3). Bond angles (°): C(5)–N(4)–O(3), 117.54(18); C(5)–N(4)–O(2), 119.18(18); C2–N(1)–C5, 105.02(16); C2–N1–C3, 125.56(16); C6–N2–C7, 121.42(19); C3–N1–C5, 129.26(16); N2–C7–C8, 114.06(19); F1–C8–C9, 106.5(2); F1–C8–F2, 107.3(2); F3–C9–F4, 106.9(2).

Fig. 2. Structural diagram of **2M4NF5**. Selected bond lengths and angles. Bond lengths (Å): N4–O3, 1.218(2); N1–C5, 1.473(2); C5–C6, 1.496(3); C6–C7, 1.509(2); N3–C7, 1.338(2); N3–C8, 1.436(5); C9–C10, 1.514(5); C9–F1, 1.334(4); C10–F4, 1.317(5). Bond angles (°): O3–N4–O2, 123.54(17); C2–N4–O3, 119.15(16); C2–N4–O2, 117.3(17); C3–N1–C1, 107.88(15); C1–N1–C5, 127.64(16); C7–N3–C8, 118.1(3); C5–N1–C3, 124.44(15); N3–C8–C9, 110.5(4); F1–C9–F2, 107.1(4); F1–C9–C10, 107.7(3); F4–C10–F5, 107.5(5).

Fig. 3. Structural diagram of **2M4NF1(-1)**. Selected bond lengths and angles. N4–O3, 1.230(3); N1–C5, 1.466(3); C5–C6, 1.514(3); C6–C7, 1.516(3); N3–C7, 1.322(3); N3–C8, 1.451(3); C9–F1, 1.384(3). Bond angles (°): O3–N4–O2, 123.1(2); C2–N4–O3, 118.1(2); C2–N4–O2, 118.9(2); C3–N1–C1, 107.81(18); C1–N1–C5, 127.6(2); C7–N3–C8, 121.6(2); C5–N1–C3, 124.63(18); N3–C8–C9, 112.8(2); C8–C9–F1, 108.3(2).

Fig. 4. Structural diagram of **EF5** (Ref. 1). Selected bond lengths and angles. Bond lengths (Å): N4–O3, 1.223(4); N1–C4, 1.457(4); C4–C5, 1.521(4); N3–C5, 1.335(4); N3–C6, 1.440(4); C7–C8, 1.514(5); C7–F1, 1.352(4); C(8)–F(3), 1.321(5). Bond angles (°): O3–N4–O2, 123.8(3); C1–N4–O3, 117.3(3); C1–N4–O2, 119.2(3); C3–N1–C1, 105.3(3); C3–N1–C4, 123.2(3); C5–N3–C6, 122.7(3); N3–C6–C7, 111.0(3); F1–C7–F2, 106.9(3), F1–C7–C8, 106.9(3); C7–C8–F3, 111.5(3); F3–C8–F4, 109.0(3).

The ^1H NMR spectra for the 2-nitroimidazoles (**E** species, including data reported for **EF5** in CD_3OD and $d_6\text{-DMSO}$,¹ and **EF1** in $d_6\text{-acetone}$)²⁵ reveal that the chemical ^1H shifts of the $2\text{NO}_2\text{Im-CH}_2$ moiety are all similar (Im-H_5 : δ 7.49 $\rightarrow$ 7.66; Im-H_4 : δ 7.08 $\rightarrow$ 7.21; CH_2CO : δ 5.15 $\rightarrow$ 5.36), showing that varied attached side-chains have little effect on these shifts. The NH proton shift varies more (δ 7.52 $\rightarrow$ 9.05), and likely reflects some proton exchange with trace H_2O in the $d_6\text{-acetone}$ NMR solvent.²⁰ For **ImF5**, the compound identical to **EF5** less the electron-withdrawing NO_2 substituent (Chart 1), the imidazole-ring chemical shifts are, as expected, more significantly upfield to those of **EF5**; e.g. for Im-H_5 , δ 7.66 (**EF5**)¹ $\rightarrow$ 7.16 (**ImF5**); the ^1H shifts for the $\text{CH}_2\text{CF}_2\text{CF}_3$ group are not affected by the presence or absence of the NO_2 group. The δ values for the CH_2 group(s) in the side-chain generally depend on adjacent atoms, although the δ 4.06 for the N(H)CH_2 of both **EF5** and **EF3(-1)** implies no difference in the effects of C_2F_5 and CF_3 . However, the corresponding δ values for **EF3** and **EF1** show upfield shifts (δ 4.06 $\rightarrow$ 3.50 $\rightarrow$ 3.38, respectively), revealing effects of the proximity and number of electronegative F-atoms; the trend continues when, with no side-chain halogens, δ = 3.20 and 3.27, respectively for **EPrA** and **EIAA**. The most pronounced F-atom effects are seen for **EF1** (Fig. S-2) and **EF1(-1)** (Fig. S-3), where the CH_2F protons, easily identified as a doublet of triplets with $^2J_{\text{HF}}$ values of 66 and 48 Hz, respectively, are shifted downfield to $\delta \sim 4.50$; the F-atom also interacts strongly with the adjacent CH_2 , as indicated by respective $^3J_{\text{HF}}$ values of 42 and 30 Hz. For compounds that vary only in the terminal halogen in the side-chain, the shifts of the CH_2X protons (**EF1**, δ 4.51; **ECl1**, δ 3.66; **EBr1**, δ 3.50) decrease, as expected, with decreasing Pauling electronegativity (EN) of the halogen atom (F, 4.0; Cl, 3.0; Br, 2.8); the same trend is seen for the **EX1(-1)** compounds, as well as for the $^{13}\text{C}\{^1\text{H}\}$ shifts [**EF1(-1)**, δ 84.70; **ECl1(-1)**, δ 43.46; **EBr1(-1)**, δ 37.88].

The $^{19}\text{F}\{^1\text{H}\}$ NMR spectra do not show such straightforward trends: e.g. the CF_3 shifts of **EF5** and **EF3** are $\delta -4.34$ and 10.84 , respectively, where the respective adjacent groups are CF_2 and CH_2 , and so the upfield **EF5** shift is surprising. The expected electronegativity trend is seen in the δ values of -41.31 for the CF_2 of **EF5**, and -142.50 for CH_2F of **EF1**; i.e. more F-atoms on a C-atom shift the signal further downfield. ^1H and ^{19}F NMR spectral data for the 4-nitro-(**2M4N**) and 5-nitroimidazole (**M**) compounds reveal trends similar to those observed for the **E** derivatives. The closer the NO_2 is to the imidazole proton leads to a downfield shift of the ^1H signal, e.g. **MF5** (Im- H_4 , δ 7.93) vs. **EF5** (Im- H_4 , δ 7.21). For both **MX1(-1)** and **2M4NX1(-1)** (where X = F, Cl and Br), shift differences are analogous to those of the **EX1(-1)** compounds, with increasing EN giving a downfield shift for the CH_2X protons.

Other techniques used to characterize the nitroimidazoles were MS, and UV-Vis and IR spectroscopies. The UV-Vis spectra in MeOH revealed as the major band the NO_2 group at 316, 310 and 300 nm, respectively, for the 2NO_2 -, 5NO_2 -, and 4NO_2 -derivatives. MS was used when acceptable elemental analyses were not obtained for the compounds. The MS data usually showed a weak parent peak, and a major peak that corresponded to M^+-NO_2 , suggesting that the Im- NO_2 bond is easily cleaved. For the IR spectra, only stretching frequency bands for the side-chain N-H and C=O moieties, and the imidazole N-O are assigned, based on data from IR texts;^{20,26} the data suggest that there is a weak electronic influence of the side-chain substituents on the N-H and C=O stretching frequencies, but not on the more distant NO_2 group. The asymmetric and symmetric ν_{NO} bands typically spanned the respective ranges of 1484-1506, and 1361-1400 cm^{-1} , with the wave numbers decreasing slightly in the order $4\text{NO}_2 > 2\text{NO}_2 > 5\text{NO}_2$, but this might result from effects of the varying side-chain; the 4NO_2 group is the furthest removed and the possibility of an H-bonding interaction with the side-chain via is unlikely. For

the 2NO₂Im compounds **EF1**, **ECI1** and **EBr1** [each with C(O)NH(CH₂)₂CH₂X moieties)] there is no essentially change in ν_{NH} or ν_{CO} with variation in X. Where two CH₂-groups (*vs.* three) separate the halogen from the amide functionality, ν_{NH} and ν_{CO} both are shifted to somewhat higher values; e.g. ν_{CO} values are 1669 and 1660 cm⁻¹, respectively, for **EF1(-1)** and **EF1**.

Electrochemistry of nitroimidazoles

The efficacy of nitroimidazoles as radiosensitizers and hypoxia-selective cytotoxins depends significantly on the 1-electron reduction potential of the nitro moiety^{2c,27} that has been measured by pulse radiolysis in neutral aqueous media (the so-called ' E_7^1 ').²⁸ The NO₂-group undergoes reduction steps to give finally the amine (Scheme 6), the degree of reduction being determined enzymatically.²⁹ The stability of the initially formed radical anion also depends on pH, which decreases below physiological values during radiation with a corresponding increase in DNA damage;³⁰ hypoxic cells have increased [CO₂], and this lowers slightly the pH. In oxic cells (high [O₂]), the radical anion is re-oxidized as the reduction potential of O₂ is more positive than that of the nitroimidazole, and radiotherapy becomes ineffective³¹ - see also the Introduction. This initial reduction step is key to initiation of the nitroimidazole action as a hypoxia marker, although the active species may be a subsequently reduced species.^{27a,32} The $E_{1/2}$ values measured in MeCN (Table 2) are not E_7^1 , but the approximate correlation $E_7^1 \approx E_{1/2} - 241$ mV has been established;³³ the measured $E_{1/2}$ values were converted to a potential versus the SCE. Of note, the reduction potentials are measured in MeCN and so do not correlate with those reported in aqueous solution. Values can be compared to those known for Etanidazole in aqueous solution ($E_7^1 = -388$ mV, *vs.* NHE²⁸) and in MeCN ($E_{1/2} = -1077$ mV *vs.* SCE, Table 2).

Scheme 6. Stepwise reduction of 2-nitroimidazole to 2-aminoimidazole.

Insert Table 2 somewhere here

In the CV plots (e.g. Fig. S-4 for **EF1**, a 2NO₂Im), the cathodic and anodic peak currents are unequal, and the potential difference between them is significantly > 59 mV, implying that the electron transfer to and from the nitroimidazole is not completely reversible. The 4NO₂Im and 5NO₂Im compounds show even more irreversible behaviour (Fig. S-5). Nevertheless, the $E_{1/2}$ values (electron affinity) decrease as the NO₂ changes from the 2 → 5 → 4 positions: -977 to -1116, -1068 to -1163, and -1300 to -1415 mV), respectively, and is readily apparent for the pentafluorinated species **EF5**, **MF5** and **2M4NF5** with respective $E_{1/2}$ values of -977, -1068 and -1300 mV. The same effect has been reported within reduction potentials of the isomeric nitroimidazoles RGW-601 (2NO₂ImR), nimorazole (5NO₂ImR), and RGW-611 (4NO₂ImR), where R = CH₂CH₂N(CH₂CH₂)₂O, the E_7^1 values being -390, -457 and -554 mV, respectively;^{15c} this report also noted that the side-chain has little effect on the reduction potential, any electron-withdrawing groups being sufficiently distant from the Im ring, and having little inductive effect on the NO₂ group. However, for **EF5** and the other nitroimidazoles containing more than a single side-chain F-atom, our data show a side-chain influence on $E_{1/2}$: for Etanidazole (no F-atoms) $E_{1/2}$ -1077 mV, whereas **EF5** has the expected highest value of -977 mV, with successive removal of F-atoms giving more negative $E_{1/2}$ values (Table 2).

Surprisingly, for the monohalogenated compounds **EX1** and **EX1(-1)** ($X = \text{F}, \text{Cl}$ and Br), $E_{1/2}$ is decreased (by ~ 80 mV) when one methylene is removed. Overall, the CV data imply that pursuit of $2\text{NO}_2\text{Im}$ compounds with longer side-chains and more F-atoms for use as hypoxia-selective bioreductive agents would appear, at least in the absence of biological factors such as relative toxicities, to be most advantageous. This is consistent, for example, with the current clinic use of **EF5**, although **EF3** and **EF5** have very similar, moderate toxicity values in oxic and hypoxic conditions.³⁴

Conclusions

Nineteen, new 2-nitro-, 4-nitro-, and 5-nitroimidazoles, that have a halogen-containing amide side-chain at an imidazole N-atom, are reported, together with their reduction potentials. The compounds are analogous to the known **EF5** (a 2-nitroimidazole), a well-established hypoxic marker that has the highest reduction potential, known to be a key factor in its biological activity. Intra- and inter-molecular H-bonding, evident in three solid state structures, including that of **EF5** (a finding not previously reported), could well play a role in biological applications.

Supplementary data

Supplementary material contains Figs.S1–S5, showing the CV cell, ^1H NMR spectra of **EF1** and **EF1(-1)** in d_6 -acetone, and CV plots for **EF1** and **MC11(-1)**. CCDC numbers 1570083 and 1570086 contain the crystallographic data for compounds **MF5**, **2M4NF5**, **2M4NF1(-1)**, and **EF5**, respectively; these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article are available through the journal Web site at <http://dx.doi.org/10.1039/C6CY00000A>.

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Table 1. Groups of nitroimidazoles ^{a, b}

2NO ₂ Im compounds	R	Compound
CH ₂ CF ₂ CF ₃	EF5
	CH ₂ CF ₂ CF ₂ Br	EF4Br
	CH ₂ CH ₂ CF ₃	EF3
	CH ₂ CF ₃	EF3(-1)
	CH ₂ CH ₂ CH ₂ F	EF1
	CH ₂ CH ₂ F	EF1(-1)
	CH ₂ CH ₂ CH ₂ Cl	ECl1
	CH ₂ CH ₂ Cl	ECl1(-1)
	CH ₂ CH ₂ CH ₂ Br	EBr1^c
	CH ₂ CH ₂ Br	EBr1(-1)
	CH ₂ CH ₂ CH ₃	EPrA
	CH ₂ CH ₂ CH(CH ₃) ₂	EIAA
2Me5NO ₂ Im compounds
CH ₂ CF ₂ CF ₃	MF5
	CH ₂ CF ₃	MF3(-1)
	CH ₂ CH ₂ F	MF1(-1)
	CH ₂ CH ₂ Cl	MCl1(-1)
	CH ₂ CH ₂ Br	MBr1(-1)
2Me4NO ₂ Im compounds
CH ₂ CF ₂ CF ₃	2M4NF5
	CH ₂ CF ₃	2M4NF3(-1)
	CH ₂ CH ₂ F	2M4NF1(-1)
	CH ₂ CH ₂ Cl	2M4NCl1(-1)
	CH ₂ CH ₂ Br	2M4NBr1(-1)

^a **E**, **M**, and **2Me4N**, imply derivatives of Etanidazole, Metronidazole, and 2-methyl-4-nitroimidazole, respectively; these are followed by the type and number of halogen atoms on the terminal R alkyl group attached to the amide N-atom (e.g. **EF4Br** has the terminal propyl group CH₂CF₂CF₂Br); a **(-1)** at the end means a terminal R = ethyl group, i.e. one CH₂ shorter (e.g. **EF1(-1)** has a terminal CH₂CH₂F).

^b Compounds **EF5**, **EF1**, Etanidazole (a 2NO₂Im), and Metronidazole (a 5NO₂Im), are shown in Chart1.

^c **EBr1**, reported previously, is the precursor to **EF1** (ref.3).

Table 2. Reduction potentials ($E_{1/2}$ in mV) for the nitroimidazoles (in MeCN) vs. SCE.^{a,b}

	Etanidazole	EF5	EF3	EF3(-1)	EF1	EF1(-1)	EC11	EC11(-1)	EBr1	EBr1(-1)
	-1077	-977	-1024	-1015	-1037	-1115	-1036	-1119	-1038	-1116
Metronidazole	MF5	MF3(-1)	MF1(-1)	MC11(-1)	MBr1(-1)	2M4NF5	2M4NF3(-1)	2M4NF1(-1)	2M4NC11(-1)	2M4NBr1(-1)
	-1092	-1068	-1074	-1150	-1163	-1157	-1300	-1344	-1415	-1389
									-1398	

^a $E_{1/2}$ is the average of the reduction and oxidation peaks referenced to the $\text{FeCp}_2^+/\text{FeCp}_2$ couple; e.g., see Figs. S-4 and S-5.

^b Reproducibility was $\pm 3\text{mV}$ for 3 separate solutions of the same nitroimidazole .

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