

“4-MC synthesis of 3-heteroarylpropionic acids”

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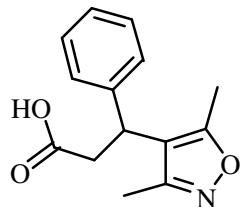
General experimental: ^1H and ^{13}C Spectra were recorded on a 400 MHz spectrometers at ambient temperatures. For ^1H NMR recorded in CDCl_3 chemical shifts (δ_{H}) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet, d, doublet, t, triplet, dd, doublet of doublets, dt, doublet of triplets, tt, triplet of triplets, m, multiplet and br, broad. Coupling constants (J) were recorded in Hertz (Hz) to the nearest 0.5Hz. Infrared (IR) spectra were recorded as thin films between NaCl plates. Absorption maximum (ν_{max}) was reported in wave numbers (cm^{-1}) and only selected peaks are reported. The following abbreviations are used: w, weak, m, medium, s, strong and br, broad.

Flash chromatography was carried out using *silica gel 60* (0.040-0.063mm, 230-400 mesh) as the stationary phase. Thin layer chromatography was carried out on aluminium backed plates pre-coated with *silica gel 60*, which were visualized by quenching of u.v. fluorescence ($\lambda_{\text{max}} = 254 \text{ nm}$) or by staining with either 10% w/v ammonium molybdate in 2M sulphuric acid or basic potassium permanganate solution (followed by heat) as appropriate. Retention factors (R_f) are reported to ± 0.5 .

General one-pot procedure for the preparation of compounds 1a-i (Table 1):

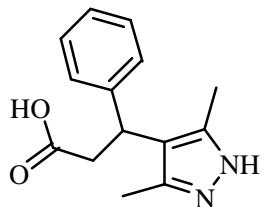
To a stirred solution of 3,5-dimethyl-4-nitroisoxazole **5** (426 mg, 3 mmol) in ethanol (10 mL), was added piperidine (26 mg, 0.3 mmol, 0.1 eq.) and an aromatic aldehyde **6** (3 mmol, 1 eq.). The resulting solution was reacted at 60°C for 1 hours, before acetylacetone **10** (4.5 mmol, 1.5 eq.) was added. The reaction mixture was heated at 60°C for 6 hours and was cooled to room temperature. Then a dinucleophile **9** (3 mmol, 1 eq.) was added and the reaction mixture was heated at 65°C for 7 hours. Finally, to the reaction mixture was added water (10 mL) and sodium hydroxide (0.480 g, 12 mmol) and refluxed at 130°C for 6 hours. The reaction mixture was cooled to room temperature and evaporated *en vacuo*. The brown oil so obtained was diluted with water (10 mL) and washed with chloroform (10 mL). The aqueous layer was acidified to pH≈5 by addition of 1M hydrochloric acid and subsequently extracted with chloroform (2 x 10 mL). This latter organic layer was dried over MgSO_4 , filtered and evaporated to yield pure carboxylic acids.

3-(3,5-Dimethyl-isoxazol-4-yl)-3-phenyl-propionic acid 1a:



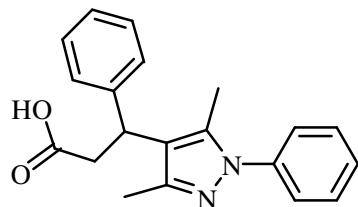
Brown oil (662 mg, 90% yield); ν_{max} (Film)/cm⁻¹: 3220-2950b, 1733s; δ_H (400 MHz, CD₃COCD₃) 7.35-7.17 (5H, m, Ph), 4.44 (1H, app. t, J = 8, CHPh), 3.18 (1H, dd, J = 16, J = 8, CH₂COOH), 2.98 (1H, dd, J = 16, J = 9, CH₂COOH), 2.38 (3H, s, CH₃), 2.11 (3H, s, CH₃); δ_c (100 MHz, CD₃COCD₃) 175.7 (COOH), 165.2 (OCC=C), 158.9 (C=N), 140.2, 128.3 (Ar), 126.6 (Ar), 114.6 (Ar), 37.6 (CH₂), 34.7 (CH), 11.2 (CH₃), 10.4 (CH₃); HRMS found: [M-H] 244.0963, C₁₄H₁₄NO₃ requires 244.0974; *m/z*: 244 (100%, M-H⁺).

3-(3,5-Dimethyl-1H-pyrazol-4-yl)-3-phenyl-propionic acid 1b:



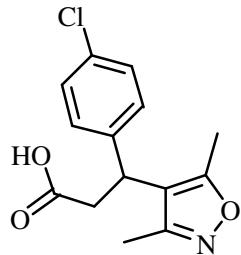
Brown oil (352 mg, 48% yield), ν_{max} (Film)/cm⁻¹: 3250-2950 b, 1738s; δ_H (400 MHz, CD₃COCD₃) 7.35-7.14 (5H, m, Ph), 4.58 (1H, app. t, J = 7, CHPh), 3.16 (1H, dd, J = 16, J = 7, CH₂COOH), 2.97 (1H, dd, J = 8, J = 16, CH₂COOH), 2.38 (6H, s, 2CH₃); δ_c (100 MHz, CD₃COCD₃) 171.0 (COOH), 142.0, 140.3, 128.3 (Ar), 126.5 (Ar), 126.4, 118.3 (Ar), 37.8 (CH₂), 35.1 (CH), 10.3 (2CH₃); HRMS found: M-H⁺ 243.1125, C₁₄H₁₅N₂O₂ requires 243.1134, *m/z*: 245.2 (100%, MH⁺).

3-(3,5-Dimethyl-1phenyl-1H-pyrazol-4-yl)-3-phenyl-propionic acid 1c:



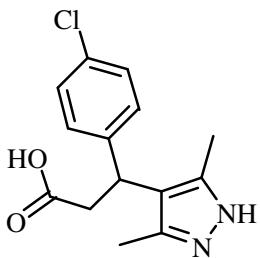
Brown oil (816 mg, 85% yield), ν_{max} (Film)/cm⁻¹: 3135-2940b, 1728s; δ_H (400 MHz, CD₃COCD₃) 7.41-7.24 (10H, m, 2Ph), 4.59 (1H, app. t, J = 8, CHPh), 3.22 (1H, dd, J = 16, J = 7, CH₂COOH), 3.04 (1H, dd, J = 16, J = 9, CH₂COOH), 2.25 (3H, s, CH₃), 2.23 (3H, s, CH₃); δ_c (100 MHz, CD₃COCD₃) 176.5 (COOH), 147.4, 142.2, 139.2, 137.0, 128.9, 128.4, 127.5, 126.3, 125.4, 125.2, 118.9 (Ar), 38.6 (CH), 36.3 (CH₂), 12.7 (CH₃), 11.2 (CH₃); HRMS found: M-H⁺ 319.1451, C₂₀H₁₉N₂O₂ requires 319.1447, *m/z*: 319 (100%, M-H⁺).

3-(4-Chloro-phenyl)-3-(3,5-dimethyl-isoxazol-4-yl)- propionic acid 1d:



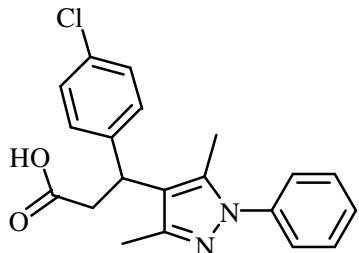
Brown oil (544 mg, 65% yield), ν_{max} (Film)/cm⁻¹: 3100-2945b, 1730s; δ_H (400 MHz, CD₃COCD₃) 7.31 (2H, d, J = 8, Ar), 7.11 (2H, d, J = 8, Ar), 4.40 (1H, app. t, J = 9, ArCH), 3.13 (1H, dd, J = 16, J = 7, CH₂C=O), 2.95 (1H, dd, J = 16, J = 9, CH₂C=O), 2.37 (3H, s, CH₃CO), 2.10 (3H, s, CH₃C=N); δ_c (100 MHz, CD₃COCD₃) 175.8 (COOH), 165.3 (OCC=C), 158.7 (C=N), 138.6 (Ar), 132.5 (Ar), 128.5 (Ar), 127.9 (Ar), 114.4 (Ar), 37.6 (CH₂), 34.2 (CH), 11.2 (CH₃CO), 10.4 (CH₃C=N); HRMS found: M-H⁺ 278.0572, C₁₄H₁₃NO₃Cl requires 278.0584, *m/z*: 278 (100%, M-H⁺).

3-(4-Chloro-phenyl)-3-(3,5-dimethyl-1H-pyrazol-4-yl)- propionic acid 1e:



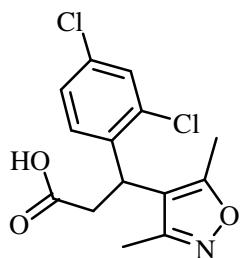
Brown oil (590 mg, 71% yield), ν_{max} (Film)/cm⁻¹: 3160-2915b, 1735s; δ_H (400 MHz, CD₃COCD₃) 7.31 (4H, s, p-Cl-Ph), 4.50 (1H, app t, $J = 8$, CH(p-Cl-Ph)), 3.14 (1H, dd, $J = 15$, $J = 7$, CHCOOH), 2.96 (1H, dd, $J = 15$, $J = 9$, CHCOOH), 2.16 (3H, s, CH₃) 2.06 (3H, s, CH₃); δ_c (100 MHz, CD₃COCD₃) 171.9 (CO), 142.3 (C=N), 140.6 (C=N), 130.6, 128.6 (CH), 127.6 (CH), 115.7, 37.7 (CH₂), 35.4 (CH, p-Cl-ph), 10.37 (2CH₃); HRMS found: M-H⁺ 277.0831, C₁₃H₁₄N₂O₃Cl requires 277.0822, *m/z*: 277 (100%, M-H⁺).

3-(4-Chloro-phenyl)-3-(3,5-Dimethyl-1phenyl-1H-pyrazol-4-yl)-propionic acid 1f:



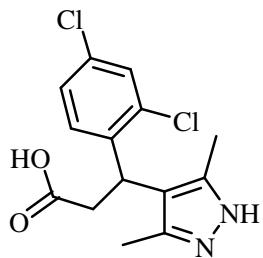
Colourless solid (752 mg, 71% yield), m.p. 74-76°C (ethanol); ν_{max} (Film)/cm⁻¹: 3210-2975b, 1730s; δ_H (400 MHz, CD₃COCD₃) 7.44-7.16 (9H, m, Ph + p-Cl-Ph), 4.54 (1H, app. t, $J = 8$, CH(p-Cl-Ph)), 3.17 (1H, dd, $J = 16$, $J = 7$, CH₂C=O), 3.00 (1H, dd, $J = 16$, $J = 9$, CH₂C=O), 2.25 (6H, s, 2CH₃C=N); δ_c (100 MHz, CD₃COCD₃) 175.6 (COOH), 146.7 (C=N), 140.2, 136.7, 131.8, 128.6 (Ar), 128.2 (Ar), 128.1 (Ar), 127.3 (Ar), 124.8 (Ar), 118.2 (Ar), 38.0 (CH₂), 35.4 (CH), 12.3 (CH₃), 10.8 (CH₃); HRMS found: M-H⁺ 353.1053, C₂₀H₁₈N₂O₂Cl requires 353.1057, *m/z*: 353 (100%, M-H⁺).

3-(2,4-Dichloro-phenyl)-3-(3,5-dimethyl-isoxazol-4-yl)-propionic acid 1g:



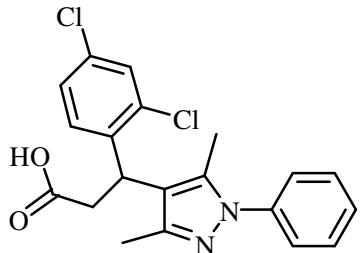
Colourless solid (789 mg, 84% yield); m.p. = 168-170°C (ethanol); ν_{max} (Film)/cm⁻¹: 3200-2955b, 1728s; δ_H (400 MHz, CD₃COCD₃) 7.52 (1H, d, J = 8, *o*-Cl,*p*-Cl-Ph), 7.50 (1H, d, J = 2, *o*-Cl,*p*-Cl-Ph), 7.10 (1H, d, J = 8, J = 2 *o*-Cl,*p*-Cl-Ph), 4.66 (1H, dd, J = 9, J = 6, CHIs), 30.7 (1H, dd, J = 16, J = 6, CH₂COOH) 30.7 (1H, dd, J = 16, J = 9, CH₂COOH), 2.35 (CH₃C=N), 2.15 (CH₃CO); δ_c (100 MHz, CD₃COCD₃) 174.8 (COOH), 165.7 (OCC=C), 158.7 (C=N), 135.8, 134.3, 133.2, 129.7 (Ar), 128.2 (Ar), 126.7 (Ar), 112.3 (Ar), 37.1 (CH₂), 32.3 (CH), 11.5 (CH₃), 10.5 (CH₃); HRMS found: M-H⁺ 312.0196, C₁₄H₁₂NO₃Cl₂ requires 312.0194, *m/z*: 312 (100%, M-H⁺).

3-(2,4-dichloro-phenyl)-3-(3,5-dimethyl-1H-pyrazol-4-yl)- propionic acid 1h :



Colourless solid (571 mg, 61% yield), m.p. 226-227°C ; ν_{max} (Film)/cm⁻¹: 3210-2975b, 1730s; δ_H (400 MHz, CD₃COCD₃) 7.53 (1H, d, J = 2, *o*-Cl,*p*-Cl-Ph), 7.50 (1H, d, J = 8, *o*-Cl,*p*-Cl-Ph), 7.45 (1H, dd, J = 8, J = 2, *o*-Cl,*p*-Cl-Ph), 4.57 (1H, app. t, J = 8, CHAr), 2.96 (1H, dd, J = 15, J = 9, CH₂COOH), 2.83 (1H, dd, J = 15, J = 8, CH₂COOH), 2.50 (1H, s, NH), 2.04 (6H, s, 2CH₃); δ_c (100 MHz, CD₃COCD₃) 206.6 (COOH), 172.4 (C=N), 140.8, 139.2, 134.0, 131.4, 129.9 (Ar), 128.9 (Ar), 126.8 (Ar), 113.5 (Ar), 38.1 (CH₂), 33.6 (CH), 11.3 (CH₃); HRMS found: M-H⁺ 311.0343, C₁₄H₁₃N₂O₂Cl₂ requires 311.0354, *m/z*: 312 (100%, MH⁺).

3-(2,4-Dichloro-phenyl)-3-(3,5-Dimethyl-1phenyl-1H-pyrazol-4-yl)-propionic acid **1i :**



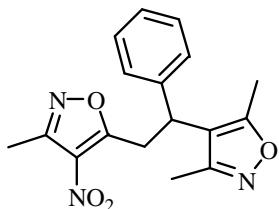
Brown oil (1001 mg, 86% yield), ν_{max} (Film)/cm⁻¹: 3110-2975b, 1732s; δ_{H} (400 MHz, CD₃COCD₃) 7.40-7.27 (8H, m, Ph + *o*-Cl,*p*-Cl-Ph), 4.78 (1H, app. t, J = 8, CHPh), 3.10 (1H, dd, J = 16, J = 7, CH₂COOH), 3.00 (1H, dd, J = 16, J = 9, CH₂COOH), 2.22 (6H, s, 2CH₃); δ_{C} (100 MHz, CD₃COCD₃) 174.9 (COOH), 146.7 (C=N), 138.4, 137.3, 137.2, 134.4, 132.6, 129.5, 128.6 (Ar), 127.5 (Ar), 126.4 (Ar), 124.9, 115.9 (Ar), 37.6 (CH₂), 33.8 (CH), 12.6 (CH₃), 10.9 (CH₃); HRMS found: M-H⁺ 387.0651, C₂₀H₁₇N₂O₂Cl₂ requires 387.0667, *m/z*: 387 (100%, M-H⁺).

General one-pot procedure for the preparation of compounds **2a-i (Table 2)**

To a stirred solution of 3,5-dimethyl-4-nitroisoxazole **5** (426 mg, 3 mmol) in ethanol (10 mL), was added piperidine (26 mg, 0.3 mmol, 0.1 eq.) and an aromatic aldehyde **6** (3 mmol, 1 eq.). The resulting solution was reacted at 60°C for 2 hours, before acetylacetone **10** (4.5 mmol, 1.5 eq.) was added. The reaction mixture was heated at 60°C for 6 hours, then a dinucleophile **9** (3 mmol, 1 eq.) was added. The reaction mixture was heated at 65°C for 7 hours. It was then cooled to room temperature and the solvent was evaporated *en vacuo*. The product was purified by recrystallisation from hot ethanol.

5-[2-(3,5-dymethyl-4-nitroisoxazol-5-yl)-2-phenylethyl]-3-methyl-4-nitroisoxazole

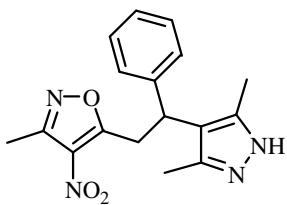
2a:



Couleurless solid (863 mg, 88% yield), $R_f = 0.6$ (ethyl acetate : petroleum spirits 1 : 4), m.p. 94-95 °C (ethanol); ν_{max} (Film)/cm⁻¹: 1519 cm⁻¹ s; δ_H (200 MHz, CD₃COCD₃) 7.13-6.97 (5H, m, Ph), 4.37 (1H, t, $J = 8$, CHPh), 3.71 (2H, d, $J = 8$, CH₂Is), 2.30 (3H, s, CH₃Is), 2.00 (3H, s, CH₃CO), 1.86 (3H, s, CH₃C=N); δ_c (100 Mhz, CD₃COCD₃) 171.9 (OC=CNO₂), 165.4 (CH₃CO), 158.6 (CH₃C=N), 155.3 (CH₃C=N), 139.1 (Ph), 131.5 (NO₂C=C-O) 128.4 (Ph), 126.9 (Ph), 126.5 (Ph), 113.5 (C_{iv}), 36.2 (CHPh), 30.9 (CH₂), 11.2 (CH₃C=N), 11.1 (CH₃C=N), 10.4 (CH₃CO); HRMS found: M+H⁺ 328.1313, C₁₇H₁₈N₃O₄Cl₂ requires 328.1297, *m/z*: 328 (100%, MH⁺).

5-[2-(3,5-Dimethyl-1H-pyrazol-4-yl)-2-phenyl-ethyl]-3-methyl-4-nitro-isoxazole

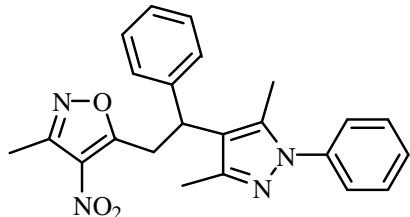
2b:



Colourless solid (831 mg, 85% yield), $R_f = 0.56$ (ethyl acetate), m.p. 148-149 °C (ethanol); ν_{max} (Film)/cm⁻¹: 3200-2810b, 1600m; δ_H (400 MHz, CD₃COCD₃) 7.27-7.25 (5H, m, Ph), 4.69 (1H, m, CHPh), 3.99 (1H, dd, $J = 15$, $J = 10$, CH₂Is), 3.95 (1H, dd, $J = 15$, $J = 7$, CH₂Is), 2.52 (3H, s, CH₃C=N), 2.16 (6H, s, CH₃C=C and CH₃C=N); δ_c (100 Mhz, CD₃COCD₃) 172.2 (C-O), 155.1 (CH₃C=N), 142.3 (CH₃C=N), 140.4 (Ph), 131.4 (NO₂C=C-O), 128.2 (Ph), 127.9 (CH₃CNH), 126.7 (Ph), 126.2 (Ph), 115.3 (C_{iv}), 36.1 (CH), 31.4 (CH₂), 11.2 (CH₃), 10.7 (CH₃) 10.6

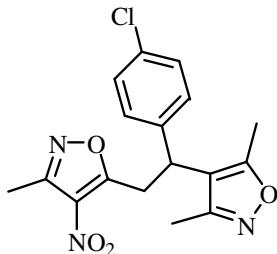
(CH₃); HRMS found: MH⁺ 327.1447, C₁₇H₁₉N₄O₃ requires 327.1457, *m/z*: 327 (100%, M-H⁺).

5-[2-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-phenyl-ethyl]-3-methyl-4-nitro-isoxazole 2c:



Colourless solid (732 mg, 61% yield), R_f = 0.27 (ethyl acetate : petroleum spirits 1 : 3), m.p. = 86-88 °C (ethanol); ν_{max} (Film)/cm⁻¹: 1600m; δ_H (200 MHz, CD₃COCD₃) 7.36–7.25 (10H, m, Ar), 4.74 (1H, t, *J* = 7, CH), 4.03 (2H, d, *J* = 8, CH₂), 2.54 (3H, s, IsCH₃), 2.20 (3H, s, CH₃C=N), 2.15 (3H, s, CH₃C=N); δ_c (100 MHz, CD₃COCD₃) 172.8 (C-O), 155.2 (CH₃C=N), 146.7, 140.6 (Ph), 131.2, 128.6 (Ph), 128.2 (Ph), 127.4 (Ph), 126.7 (Ph), 126.5 (Ph), 124.8 (Ph), 124.7 (Ph), 117.2, 37.5 (CH), 31.1 (CH₂), 12.6 (CH₃), 11.7 (CH₃), 11.2 (CH₃); HRMS found: M+H⁺ 403.1782, C₂₃H₂₃N₄O₃ requires 403.1770, *m/z*: 403 (100%, MH⁺).

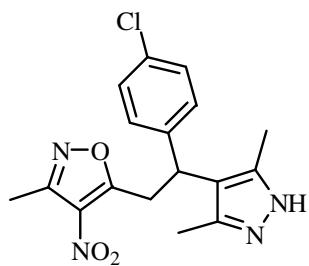
5-[2-(3,5-dimethyl-4-nitroisoxazol-5-yl)-2-(4-chlorophenyl)-ethyl]-3-methyl-4-nitroisoxazole 2d:



Colourless solid (867 mg, 80% yield), R_f = 0.46 (ethyl acetate : petroleum ether 1 : 4); m.p. 133-135 °C (ethanol); ν_{max} (Film)/cm⁻¹: 1600m; δ_H (400 MHz, CD₃COCD₃) 7.40 (2H, d, *J* = 8, *p*-Cl-Ph), 7.18 (2H, d, *J* = 8, *p*-Cl-Ph), 4.58 (1H, t, *J* = 8, CH(*p*-Cl-Ph)), 3.93 (1H, d, *J* = 8, CH₂Is), 3.92 (1H, d, *J* = 8, CH₂Is), 2.55 (3H, s, CH₃Is), 2.32 (3H, s, CH₃CO), 2.09 (3H, s, CH₃C=N); δ_c (100 MHz, CD₃COCD₃) 171.5 (OC=CNO₂),

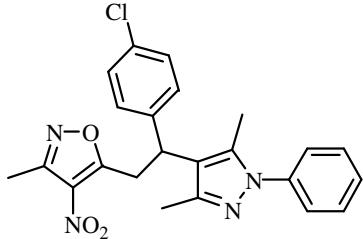
165.5 (CH_3CO), 158.4 ($\text{CH}_3\text{C}=\text{N}$), 155.4 ($\text{CH}_3\text{C}=\text{N}$), 137.6, 132.9, 128.6 (*p*-Cl-Ph), 127.9 (*p*-Cl-Ph), 113.1, 35.7 (CH), 30.8 (CH₂), 11.2 ($\text{CH}_3\text{C}=\text{N}$), 11.1 ($\text{CH}_3\text{C}=\text{N}$), 10.4 (CH_3CO); HRMS found: MH^+ 360.0756, $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4\text{Cl}$ requires 360.0751; *m/z*: 360 (100%, MH^+).

5-[2-(4-Chloro-phenyl)-2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2e:



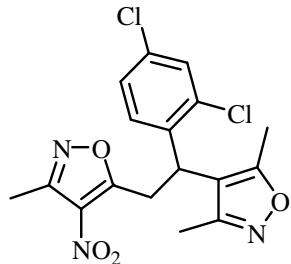
Colourless solid (1,021 mg, 95% yield), $R_f = 0.25$ (ethyl acetate : acetone : petroleum ether 1 : 1 : 8), m.p. 138-143 °C (ethanol); ν_{max} (Film)/cm⁻¹: 3220-2820b, 1602m; δ_{H} (400 MHz, CD_3COCD_3) 7.30 (2H, d, *J* = 8, *p*-Cl-Ph), 7.18 (2H, d, *J* = 8, *p*-Cl-Ph), 4.65 (1H, t, *J* = 7, CH *p*-Cl-Ph), 3.99-3.88 (2H, m, CH_2), 2.53 (3H, s, $\text{CH}_3\text{C}=\text{C}$), 2.15 (6H, s, $\text{CH}_3\text{C}=\text{N}$); δ_{c} (100 MHz, CD_3COCD_3) 172.3 ($\text{OC}=\text{CNO}_2$), 155.2 ($\text{CH}_3\text{C}=\text{N}$), 142.6 ($\text{CH}_3\text{C}=\text{N}$), 138.1 (*p*-Cl-Ph), 132.3 ($\text{NO}_2\text{C}=\text{C}$), 128.3 (*p*-Cl-Ph), 128.1 (*p*-Cl-Ph), 128.0 (*p*-Cl-Ph), 127.9 (CH_3CNH), 115.7 (C_{iv}), 36.4 (CH) 31.2 (CH_2), 11.2 (C=C CH_3), 11.1 (N=C CH_3), 10.9 (N=C CH_3); HRMS found: M-H⁺ 359.0916, $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_3\text{Cl}$ requires 359.0911, *m/z*: 361 (100%, MH^+).

5-[2-(4-Chloro-phenyl)-2-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2f:



Colourless solid (938 mg, 72% yield), $R_f = 0.32$ (ethyl acetate : petroleum spirits 1 : 4), m.p. 143-144 °C (ethanol); ν_{max} (Film)/cm⁻¹: 1601m; δ_H (400 MHz, CD₃COCD₃) 7.34-7.24 (9H, m, Ph + p-Cl-Ph), 4.69 (1H, t, $J = 8$, CH₂p-Cl-Ph), 4.05 (1H, d, $J = 8$, CH₂Is), 3.98 (1H, d, $J = 8$, CH₂Is), 2.55 (3H, s, CH₃C=N), 2.17 (3H, s, CH₃CO), 2.14 (3H, s, CH₃C=N); δ_c (100 MHz, CD₃COCD₃) 172.4 (OC=CNO₂), 155.3 (CH₃C=N), 146.6 (Ar), 139.1 (Ar), 138.6 (Ar), 136.7 (Ar), 132.3 (Ar), 131.5 (OC=CNO₂), 128.7 (Ar), 128.4 (Ar), 128.1 (Ar), 127.4 (Ar), 124.8 (Ar), 116.7 (Ar), 37.0 (CH), 31.1 (CH₂), 12.2 (CH₃C=C), 11.2 (CH₃C=N), 10.8 (CH₃C=N); HRMS found: MH⁺ 435.1219, C₂₃H₂₀N₄O₃Cl requires 435.1224; *m/z*: 435 (100%, MH⁺).

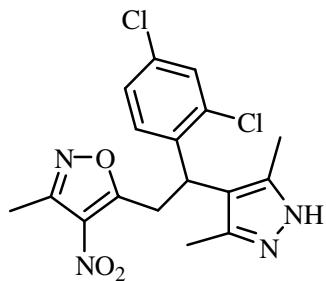
5-[2-(3,5-dimethyl-4-nitroisoxazol-5-yl)-2-(2,4-dichlorophenyl)-ethyl]-3-methyl-4-nitroisoxazole 2g:



Colourless solid (1,002 g, 85% yield), $R_f = 0.25$ (ethyl acetate : petroleum spirits 1 : 4), m.p. 125-126 °C (ethanol); ν_{max} (Film)/cm⁻¹: 1601; δ_H (400 MHz, CD₃COCD₃) 7.43 (1H, d, $J = 2$, CH-o-Cl,p-Cl-Ph), 7.41 (1H, d, $J = 8$, Ar), 7.33 (1H, dd, $J = 8, J = 2$, Ar), 4.85 (1H, t, $J = 8$, CH(o-Cl,p-Cl-Ph)), 4.01 (1H, dd, $J = 15.0, J = 8$, CH₂Is), 3.80 (1H, dd, $J = 15, J = 8$ CH₂Is), 2.55 (3H, s, CH₃), 2.32 (3H, s, CH₃), 2.09 (3H, s,

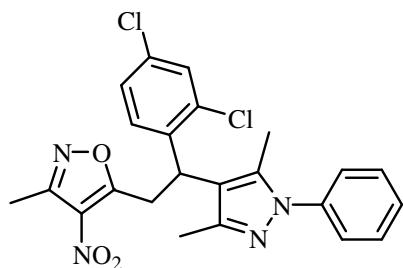
$\underline{\text{CH}_3}$); δ_c (100 MHz, CD_3COCD_3) 170.8 ($\text{OC}=\text{CNO}_2$), 165.8 (CH_3CO), 158.4 ($\text{CH}_3\text{C}=\text{N}$), 155.4 ($\text{CH}_3\text{C}=\text{N}$), 134.8, 134.4, 131.8 ($\text{OC}=\text{CNO}_2$), 129.9 (Ar), 128.3 (Ar), 126.8 (Ar), 111.6 ($\text{CH}_3\text{C}=\text{N}$), 33.6 ($\underline{\text{CH}}$, Ar), 30.6 ($\underline{\text{CH}_2}$), 11.4 ($\underline{\text{CH}_3}$), 10.4 ($\underline{\text{CH}_3}$); HRMS found: MH^+ 394.0348, $\text{C}_{17}\text{H}_{14}\text{N}_3\text{O}_4\text{Cl}_2$ requires 394.0361, m/z : 396 (30%, MH^+).

5-[2-(2,4-Dichloro-phenyl)-2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2h:



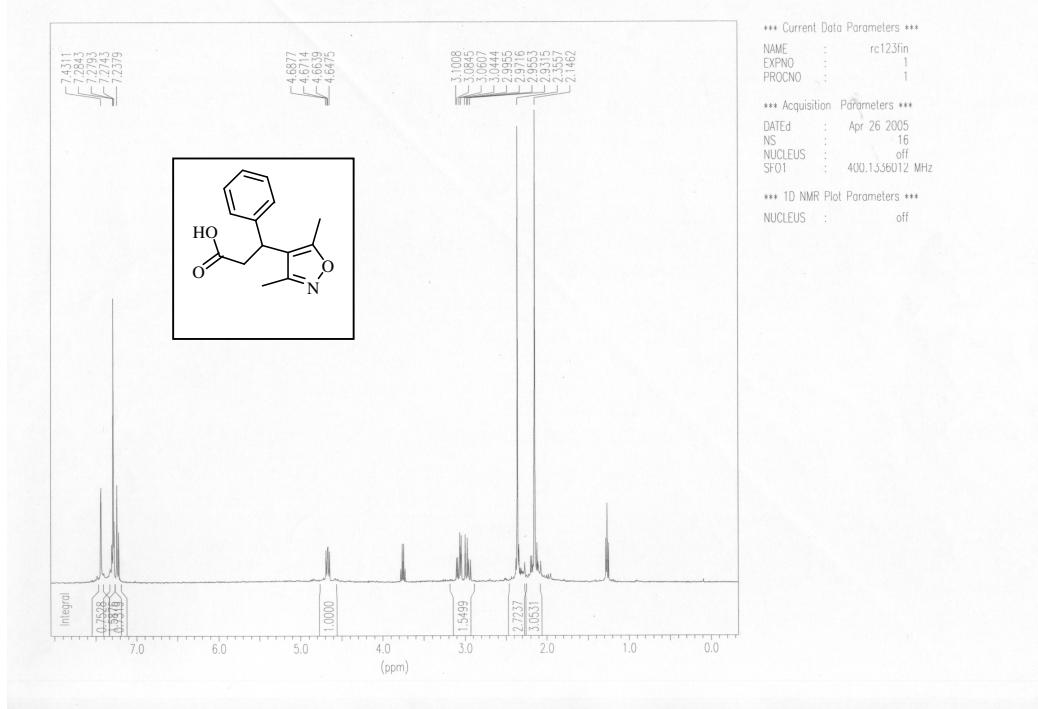
Colourless solid (720 mg, 61% yield), R_f = 0.2 (ethyl acetate : petroleum spirits 1 : 4), m.p. 151-152 °C (ethanol); ν_{max} (Film)/cm⁻¹: 3230-2860b, 1601m; δ_H (400 MHz, CD_3COCD_3) 7.42 (1H, d, J = 8, *o*-Cl,*p*-Cl-Ph), 7.40 (1H, d, J = 2, *o*-Cl,*p*-Cl-Ph), 7.30 (1H, dd, J = 8, J = 2, *o*-Cl,*p*-Cl-Ph), 4.91 (1H, t, J = 9, CHCH_2), 4.02 (1H, dd, J = 14, J = 9, CH_2Is), 3.80 (1H, dd, J = 14, J = 9, CH_2Is), 2.54 (3H, s, CH_3), 2.17 (6H, s, 2 CH_3); δ_c (100 MHz, CD_3COCD_3) 171.7 ($\text{OC}=\text{CNO}_2$), 155.3 ($\text{CH}_3\text{C}=\text{N}$), 142.0, 136.3, 134.3, 133.1, 130.9, 129.6 (Ar), 128.5 (Ar), 126.5 ($\text{OC}=\text{CNO}_2$), 113.1 (Ar), 34.5 ($\underline{\text{CH}}$), 31.1 ($\underline{\text{CH}_2}$), 11.2 (CH_3), 11.1 (CH_3), 10.7 (CH_3); HRMS found: MH^+ 393.0523, $\text{C}_{17}\text{H}_{15}\text{N}_4\text{O}_3\text{Cl}_2$ requires 393.0521, m/z : 395(100%, MH^+).

5-[2-(2,4-Dichloro-phenyl)-2-(3,5-dimethyl-1phenyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2i:

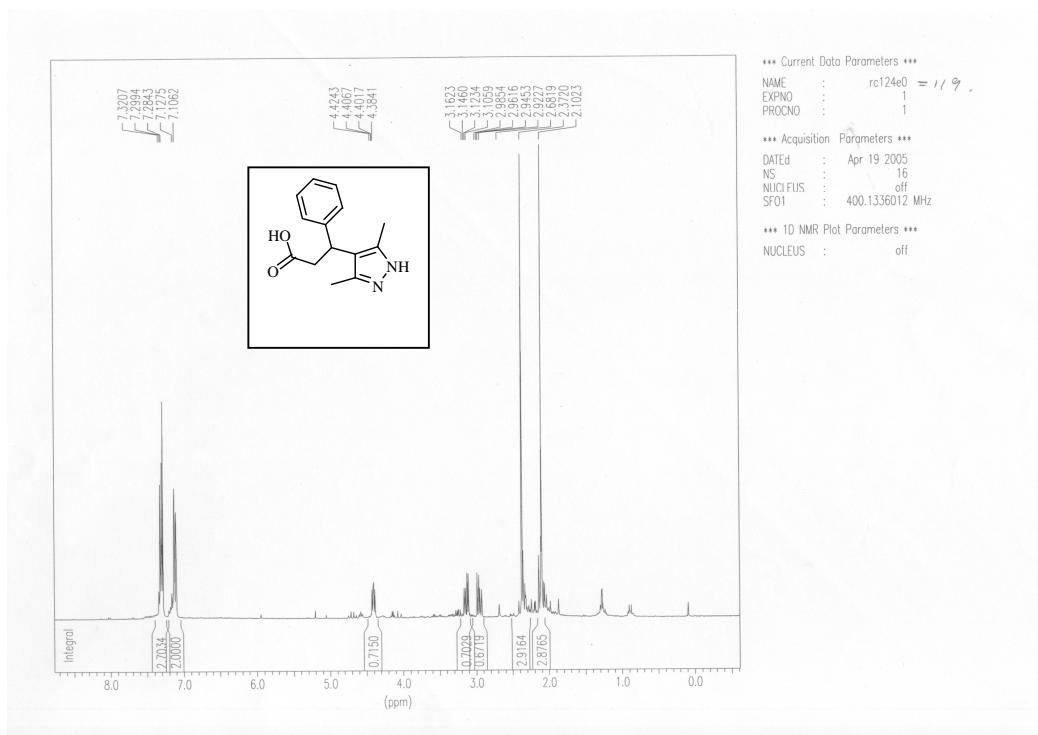


Colourless solid (1.039 g, 74% yield), $R_f = 0.4$ (ethyl acetate : petroleum spirits 1 : 4), m.p. 72-73 °C (ethanol); ν_{max} (Film)/cm⁻¹: 1601m; δ_H (400 MHz, CD₃COCD₃) 7.51 – 7.30 (8H, m, Ar), 4.94 (1H, t, $J = 8$, ArCH), 4.08 (1H, dd, $J = 15, J = 8$, CH₂), 3.87 (1H, dd, $J = 15, J = 8$, CH₂), 2.55 (3H, s, CH₃C=N), 2.22 (3H, s, CH₃), 2.18 (3H, s, CH₃) ; δ_c (100 Mhz, CD₃COCD₃) 171.7 (OC=CNO₂), 155.29 (CH₃C=N), 146.5, 138.3, 137.3, 136.1, 134.4, 133.2, 130.3 (Ar), 129.7 (Ar), 128.7 (Ar), 128.6 (Ar), 127.6, 126.6 (Ar), 125.0 (Ar), 115.0 (Ar), 35.1 (CH), 31.0 (CH₂), 12.5 (CH₃), 11.2 (CH₃), 10.8 (CH₃); HRMS found: M-H⁺ 469.0826, C₂₃H₁₉N₄O₃Cl₂ requires 469.0834, m/z : 471 (100%, MH⁺).

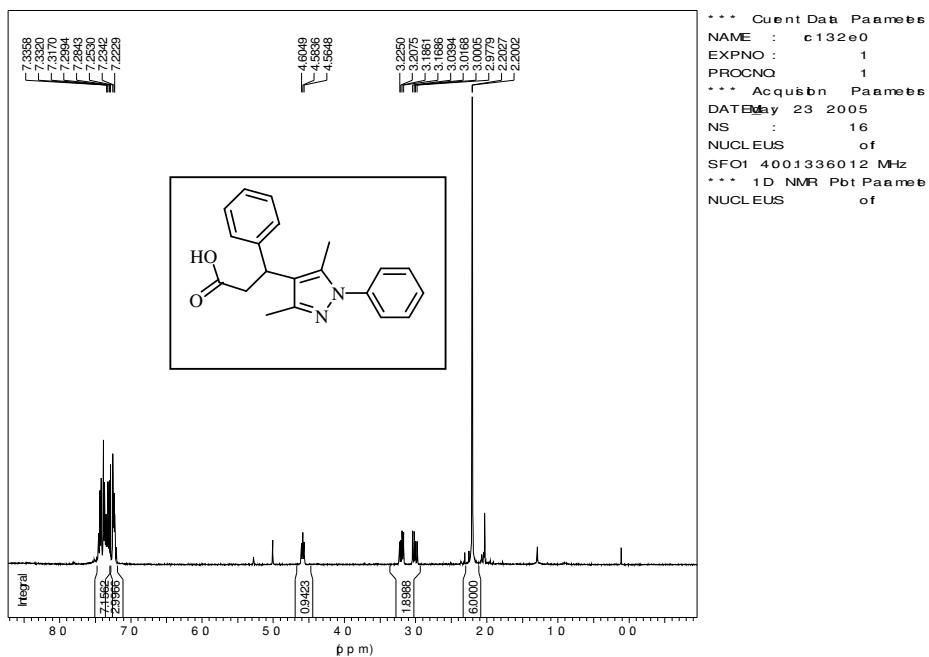
3-(3,5-Dimethyl-isoxazol-4-yl)-3-phenyl-propionic acid 1a



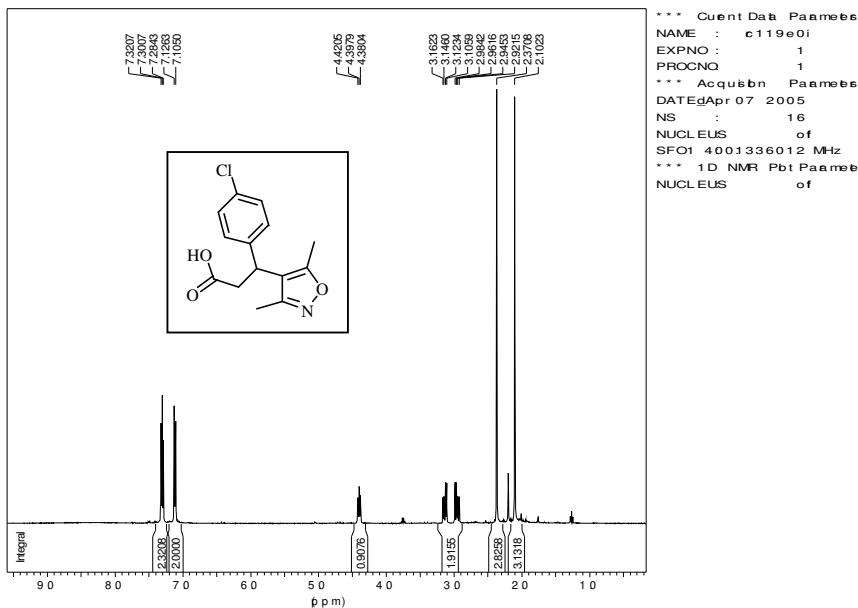
3-(3,5-Dimethyl-1H-pyrazol-4-yl)-3-phenyl-propionic acid 1b:



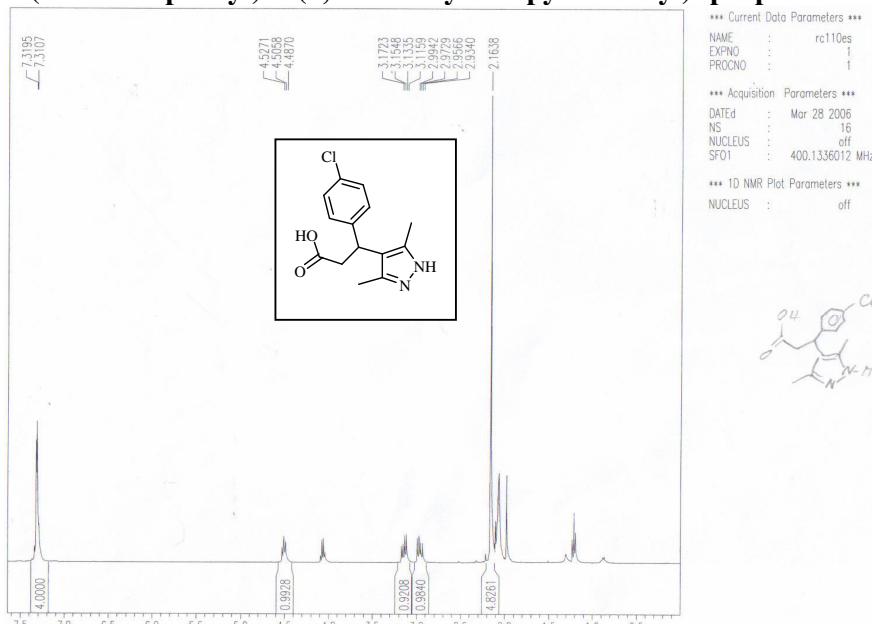
3-(3,5-Dimethyl-1phenyl-1H-pyrazol-4-yl)-3-phenyl-propionic acid 1c



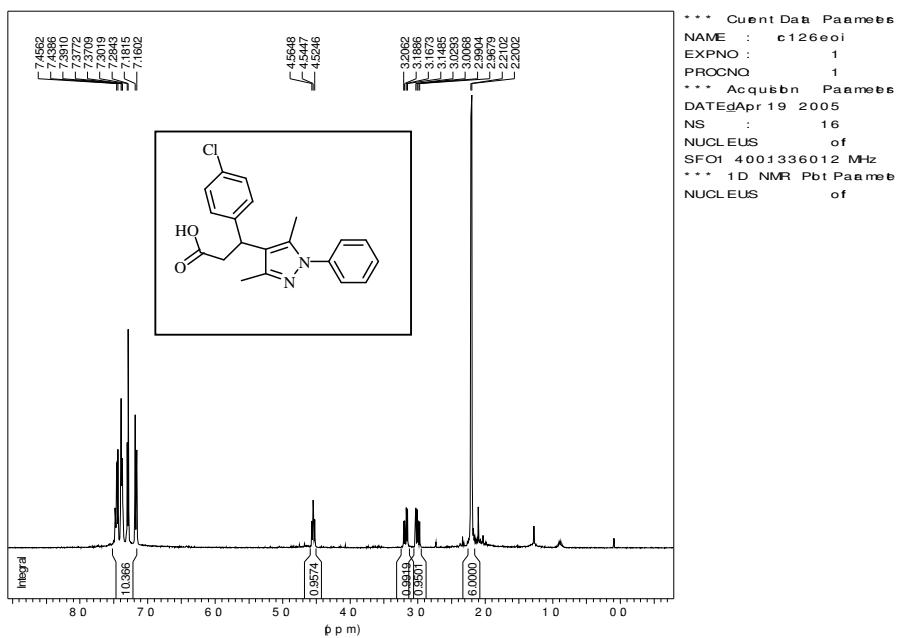
3-(4-Chloro-phenyl)-3-(3,5-dimethyl-isoxazol-4-yl)- propionic acid 1d:



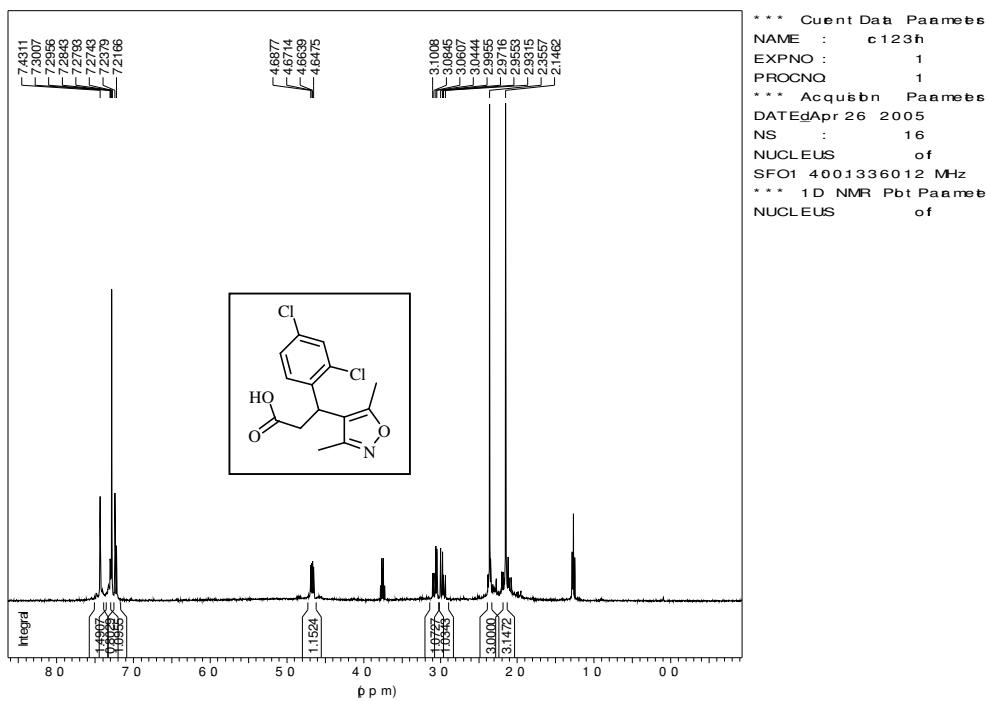
3-(4-Chloro-phenyl)-3-(3,5-dimethyl-1H-pyrazol-4-yl)- propionic acid 1e:



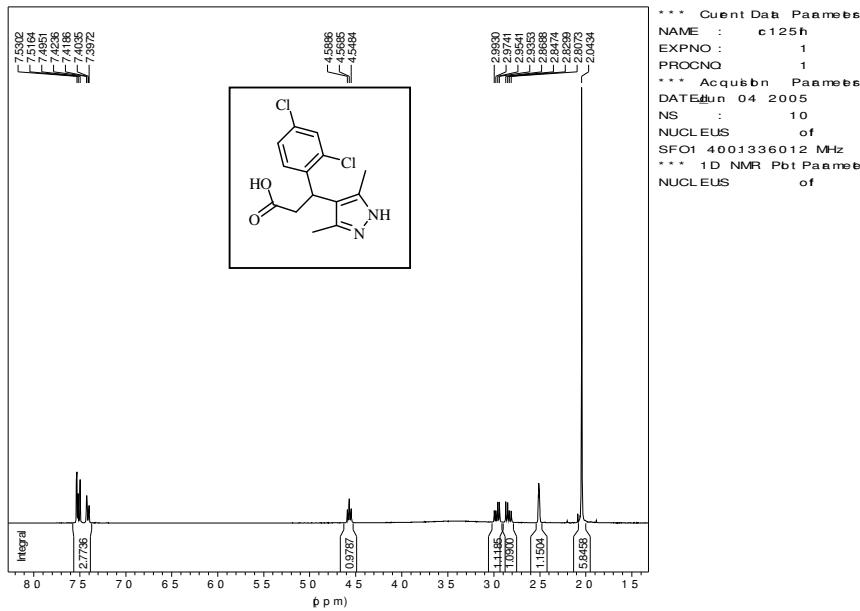
3-(4-Chloro-phenyl)-3-(3,5-Dimethyl-1phenyl-1H-pyrazol-4-yl)-propionic acid 1f:



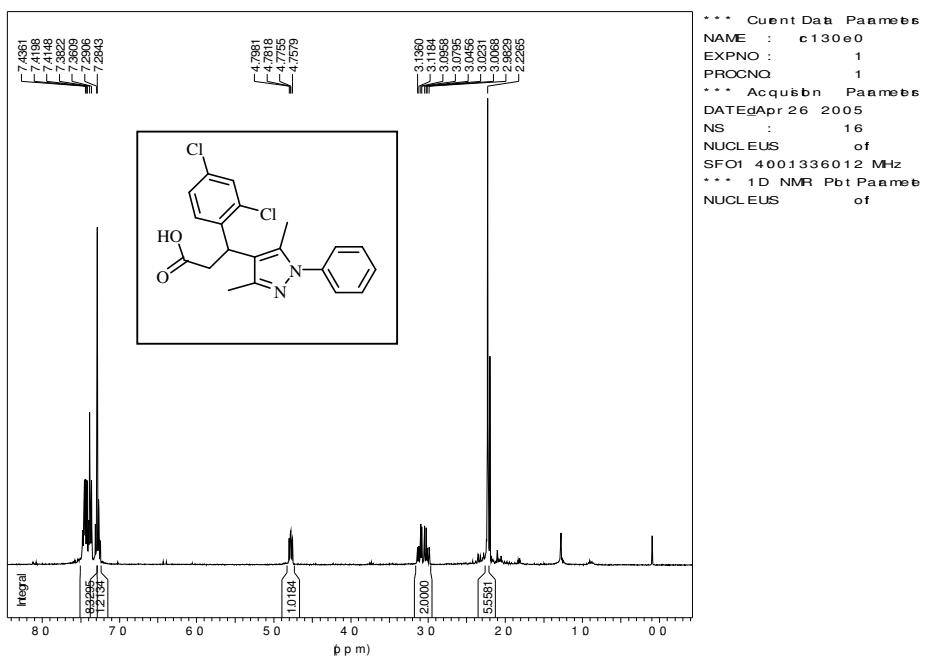
3-(2,4-Dichloro-phenyl)-3-(3,5-dimethyl-isoxazol-4-yl)-propionic acid 1g:



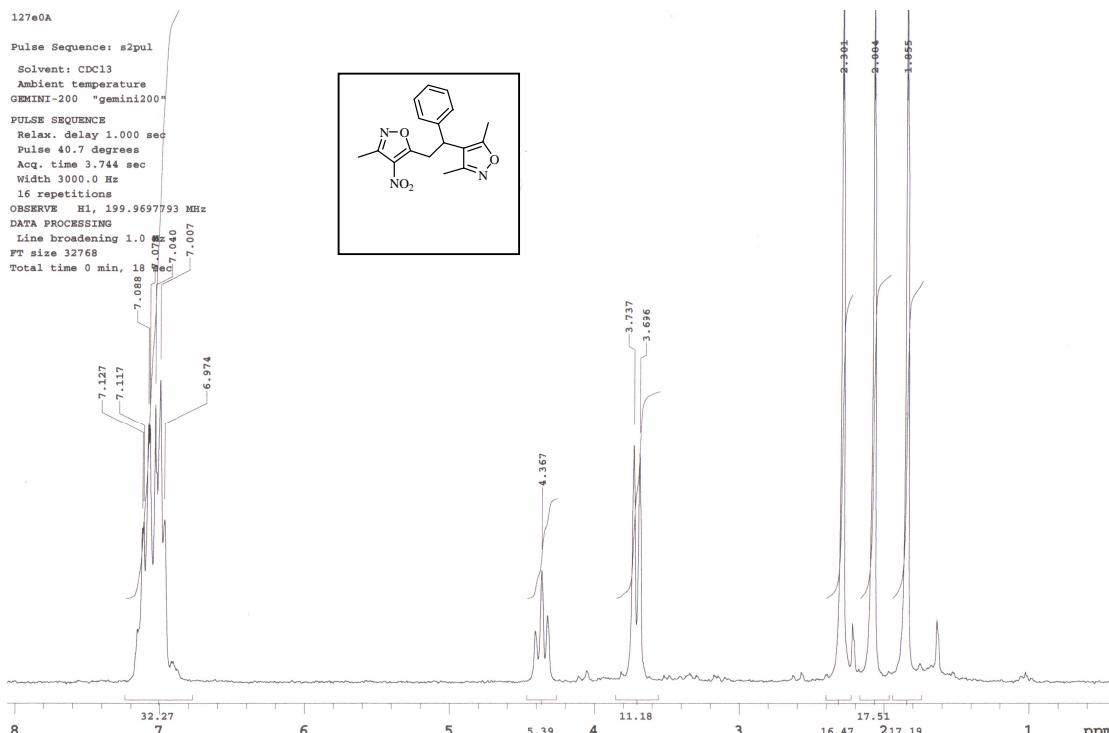
3-(2,4-dichloro-phenyl)-3-(3,5-dimethyl-1H-pyrazol-4-yl)- propionic acid 1h :



3-(2,4-Dichloro-phenyl)-3-(3,5-Dimethyl-1phenyl-1H-pyrazol-4-yl)-propionic acid 1i :

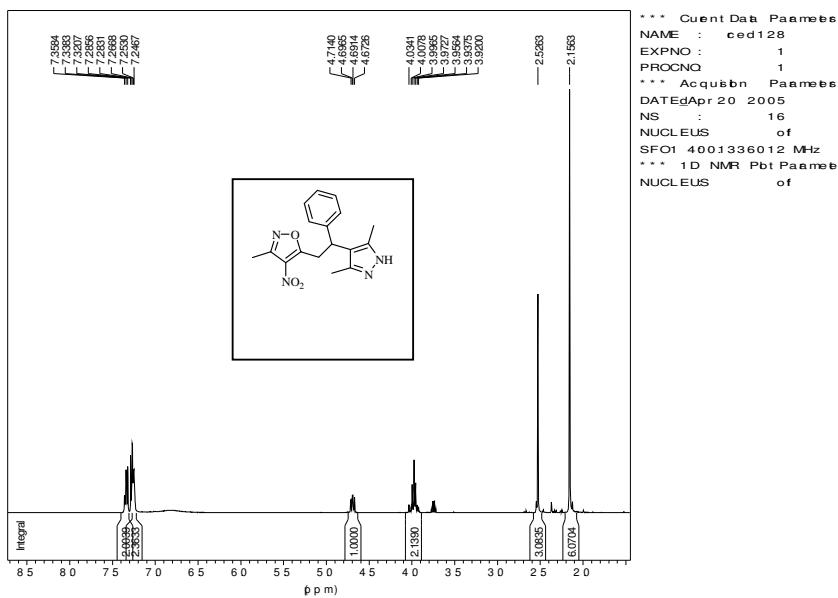


5-[2-(3,5-dymethyl-4-nitroisoxazol-5-yl)-2-phenylethyl]-3-methyl-4-nitroisoxazole 2a:

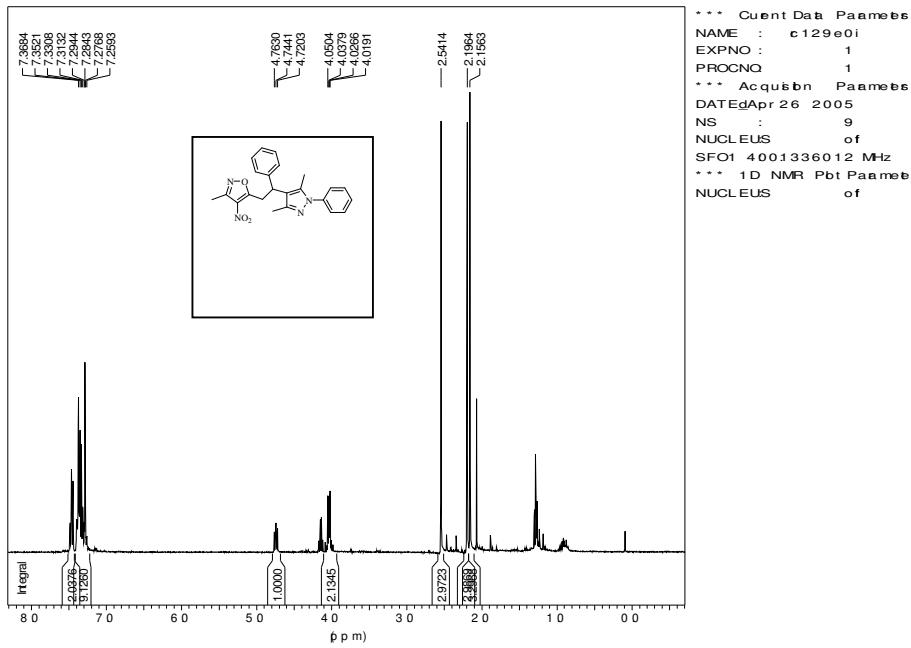


5-[2-(3,5-Dimethyl-1H-pyrazol-4-yl)-2-phenyl-ethyl]-3-methyl-4-nitro-isoxazole

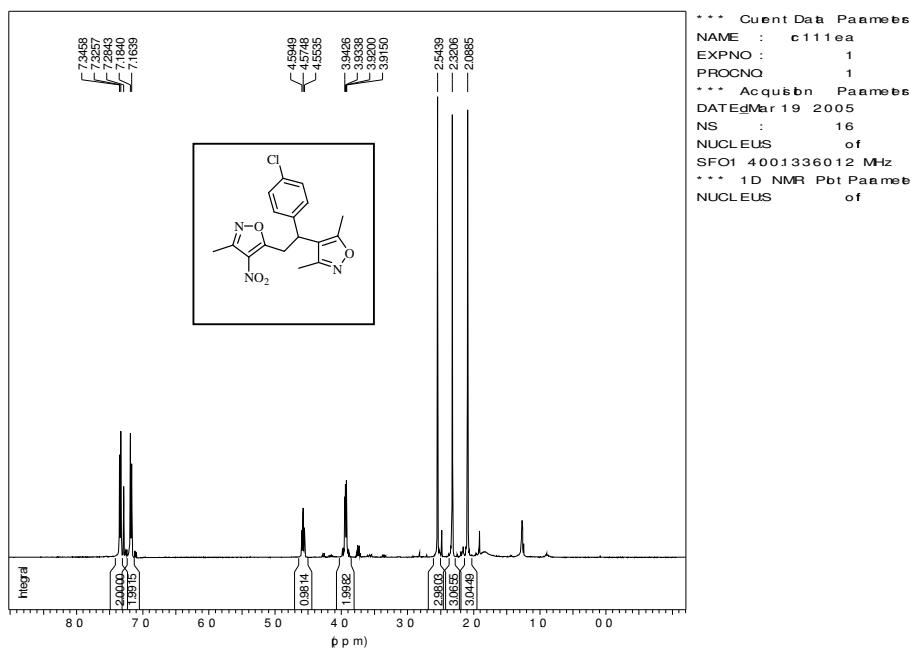
2b:



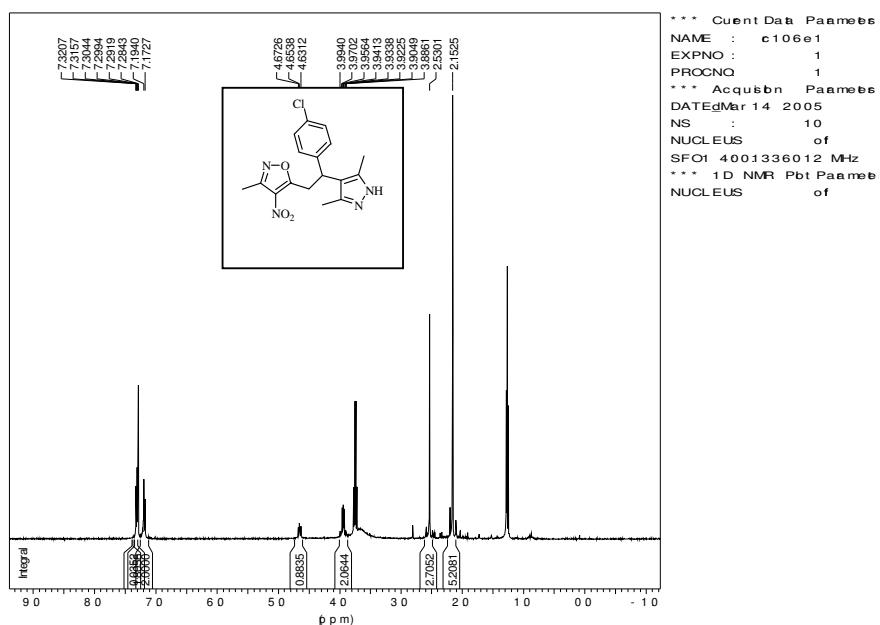
5-[2-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-phenyl-ethyl]-3-methyl-4-nitro-isoxazole 2c:



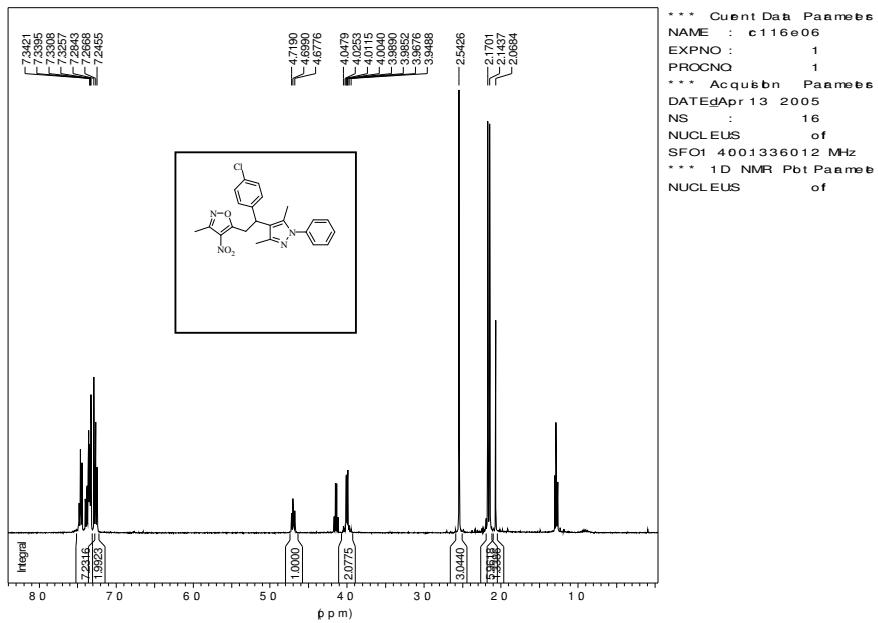
5-[2-(3,5-dimethyl-4-nitroisoxazol-5-yl)-2-(4-chlorophenyl)-ethyl]-3-methyl-4-nitroisoxazole 2d:



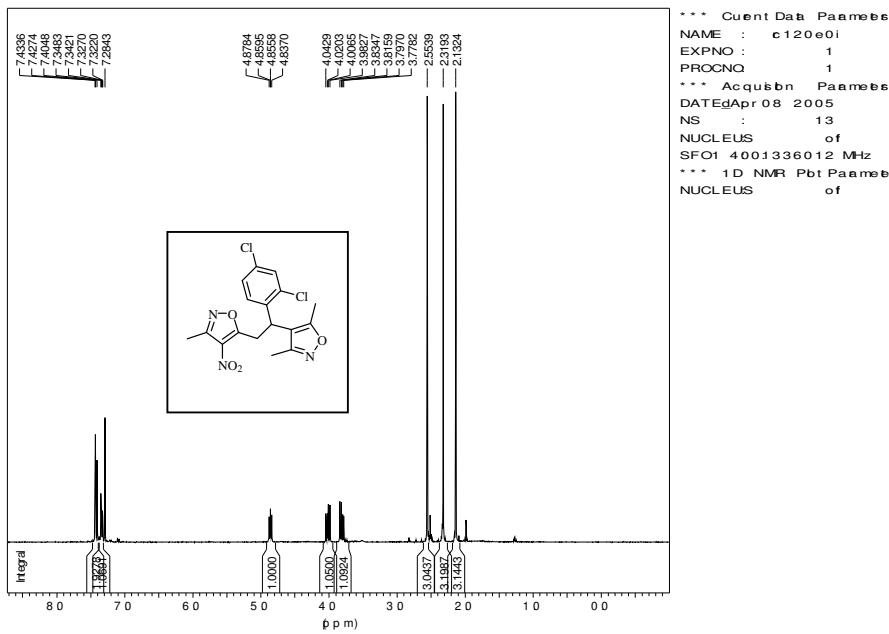
5-[2-(4-Chloro-phenyl)-2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2e:



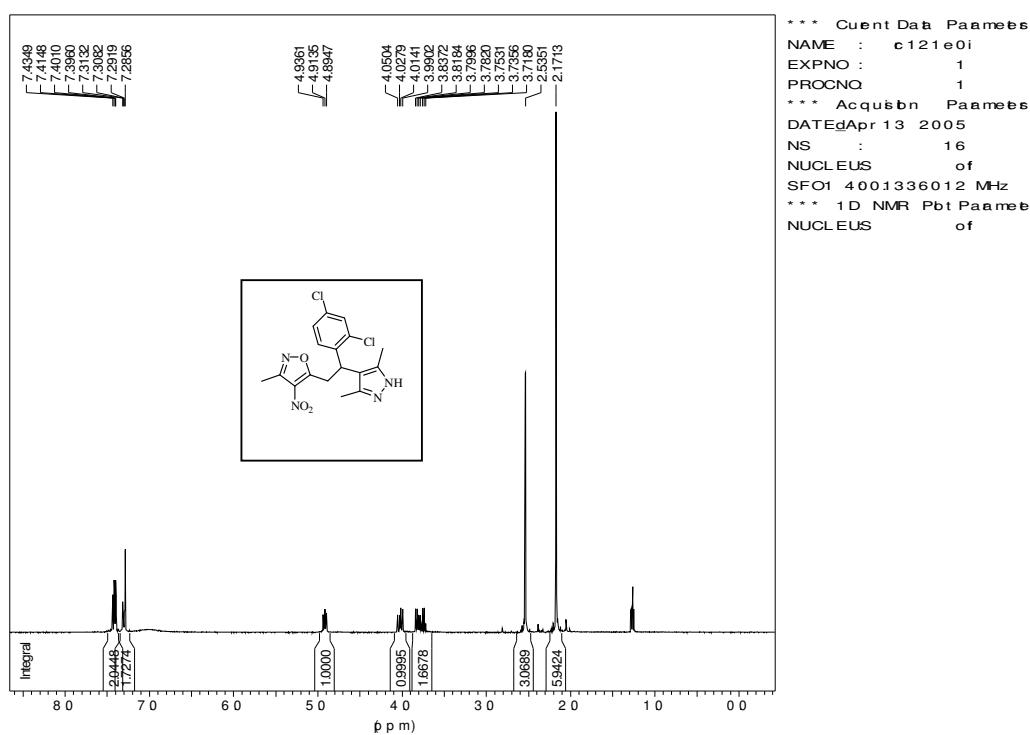
5-[2-(4-Chloro-phenyl)-2-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2f:



5-[2-(3,5-dimethyl-4-nitroisoxazol-5-yl)-2-(2,4-dichlorophenyl)-ethyl]-3-methyl-4-nitroisoxazole 2g:



5-[2-(2,4-Dichloro-phenyl)-2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2h:



5-[2-(2,4-Dichloro-phenyl)-2-(3,5-dimethyl-1phenyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2i:

