Pharmacologically active 2-(1H-pyrazol-1-yl)acetamides

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Abstract
Ten title compounds were synthesized by N-alkylation of pyrazoles with 2-iodoacetanilides; they were characterized using spectroscopic methods and pharmacologically tested. Acute toxicity, local anesthetic and anti-arrhythmic activities were assessed using established protocols.

Keywords: Acetamides, pyrazoles, local anesthetics

Introduction

According to findings by Löfgren, a local acetonilide anesthetic, such as lidocaine, should contain a lipophilic aromatic structure, a tertiary hydrophilic amino group, and between these two moieties an anesthesiophoric group (ester, ether, amino, carbonyl, amide). Usually, an amide as the anesthesiophoric group provides higher activity.

In previous papers we reported the synthesis, characterization and pharmacological tests of some N-substituted 2-(1H-pyrazol-1-yl)acetamides. The present paper reports on the synthesis and characterization of N-(chlorophenyl)-substituted 2-(1H-pyrazol-1-yl)acetamides. This research was devised to investigate the influence of the N-(chlorophenyl) substituents on the pharmacological activity of the new compounds was put in evidence.
Results and Discussion

Treatment of N-(chlorophenyl)-2-iodoacetamides 1a,b with pyrazoles 2 in DMF in the presence of sodium carbonate afforded N-(chlorophenyl)-2-(1H-pyrazol-1-yl)acetamides 3 (Scheme 1). Commonly, lidocaine and analogues are prepared by the reaction of 2-chloroacetanilides with amines. 2-Chloroacetanilides obtained by methods reported by Löfgren\textsuperscript{1} and Büchi\textsuperscript{7}, did not react with pyrazoles 2. Therefore, we employed the more reactive 2-iodoacetanilides 1 obtained from 2-chloroacetanilides with sodium iodide in acetone under reflux.\textsuperscript{8}

![Scheme 1](attachment:scheme1.png)

The proposed structures are in good agreement with spectral data. A characteristic feature of the \textsuperscript{1}H-NMR spectra of 3aa and 3ba is the H-4 signal appearing as a doublet of doublets. Also, H-4 in compound 3ae appears as a quartet as a result of a long range coupling with the 5-methyl group with a coupling constant $J = 0.8$ Hz. The multiplicity of H-3 in pyrazoles 3aa and 3ba results from coupling with H-4 ($\textsuperscript{3}J = 1.9$ Hz).

The positions of the methyl and phenyl groups in compound 3ae were determined on the basis of chemical shifts in the \textsuperscript{1}H and \textsuperscript{13}C-NMR spectra, by NOE experiments and by comparison with \textsuperscript{13}C-NMR data for similar compounds.\textsuperscript{9–17} Thus, irradiation of the methylene group resulted in an enhancement by 7% of the 5-methyl signal.

Pharmacological results

The acute toxicity LD$_{50}$ of the compounds ranges within 497-625 mg/kg body weight. Compared with lidocaine all the compounds displayed lower toxicity.

With regard to lidocaine, the compound with the highest anesthetic activity was 3ac with an activity of 81.3\%, whereas the least active compound was 3ad with 44.2\% of the reference substance effect. It was established that compounds having chlorine atoms in the ortho and meta positions of the benzene ring have generally a higher anesthetic activity than those with methyl groups in the same positions.

The compounds with the highest anti-arrhythmic action compared to lidocaine were 3ac and 3ad with the same activity of 61.9\% of the reference compound. The anti-arrhythmic activity decreases when a chlorine atom is present in meta position of the benzene ring, as compared to a methyl group.\textsuperscript{4}
Conclusions

Ten new $N$-substituted 2-(1H-pyrazol-1-yl)acetamides 3 were obtained by $N$-alkylation of pyrazoles 1 with $N$-aryl-2-iodoacetamides 1. Elemental analyses, MS, IR and NMR data are in agreement with the structures of the products 3.

The anesthetic and anti-arrhythmic activities of the new $N$-substituted 2-(1H-pyrazol-1-yl)-acetamides 3 were determined. Their potency was found lower than that of lidocaine and quinidine, but their acute toxicity is significantly lower.

Experimental Section

General Procedures. 2-Iodoacetanilides 1 and pyrazoles 2 were prepared according to the literature. Melting points were recorded with a Boetius apparatus. UV spectra (400–4000 nm) were obtained with a VSU-2P Zeiss-Jena Spectrophotometer, using MgO as a standard. IR spectra (KBr pellets) were measured on a Biorad FTS-135 Spectrometer. NMR spectra of solutions in CDCl$_3$, CDCl$_3$/TFA and DMSO-$d_6$ were recorded on a Varian Gemini 300 Spectrometer ($^1$H: 300 MHz, $^{13}$C: 75 MHz) with reference to tetramethylsilane (TMS) as internal standard. GC-MS data were recorded on a Varian Saturn 2000 GC/MS/MS (70 eV). Elemental analyses were determined on Costech Instruments EAS32 (Center for Organic Chemistry, Spl. Independentei 202B, Bucharest 060023, Romania). Reaction progress and product purity were checked by TLC (silica gel 60F$_{254}$, petroleum ether/ethyl ether/methylene chloride/ethyl acetate 7.5:1:2:1, UV visualization).

$N$-(Chlorophenyl)-2-(1H-pyrazol-1-yl)acetamides (3). General procedure. To a solution of $N$-(2- or 3-chlorophenyl)-2-iodoacetamide 1a,b (2.01 g, 6.8 mmol) and pyrazole 2 (6.8 mmol) in DMF (3 mL) was added sodium carbonate (0.72 g, 6.8 mmol). The reaction mixture was stirred and heated at 60 °C for 5 h. Then the solution was neutralized with a 10% sodium carbonate solution. The precipitate formed was filtered off and recrystallized from 2-propanol.

$N$-(2-Chlorophenyl)-2-(1H-pyrazol-1-yl)acetamide (3aa). Colorless crystals (0.41 g, 26%); mp 110–111 °C (2-propanol). $R_f$ = 0.31. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.00 (2H, s, CH$_2$), 6.41 (1H, dd, $J = 2.3$, 1.9 Hz, H-4), 7.03 (1H, td, $J = 7.7$, 1.6 Hz, H-4'), 7.23 (1H, td, $J = 7.7$, 1.6 Hz, H-5'). 7.30 (1H, dd, $J = 8.2$, 1.5 Hz, H-3'). 7.55 (1H, d, $J = 2.2$ Hz, H-5), 7.74 (1H, d, $J = 1.9$ Hz, H-3), 8.75 (1H, bs, NH). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 55.6 (CH$_2$), 107.4 (CH$_2$), 107.4 (CH$_2$), 121.4 (C-6'), 123.0 (C-2'), 125.1 (C-4'), 127.5 (C-5'), 129.1 (C-3'), 131.2 (C-5), 134.0 (C-1'), 141.8 (C-3), 165.3 (CO). IR (KBr): $\tilde{\nu}$ 3275 (s, NH), 1680 (vs, CO), 1540 (vs, CN, NH), 1465 (w), 1410 (w) cm$^{-1}$. UV: $\lambda$$_{max}$ (log $\varepsilon$): 208.53 (3.38), 243.17 (2.98) nm. MS (EI): m/z (%) 81 (100, M$^+$). Anal. calcd. for C$_{11}$H$_{10}$ClN$_3$O: C, 56.05; H, 4.28; Cl, 15.04; N 17.83. Found: C, 56.32; H, 4.76; Cl, 15.37; N, 17.64.
**N-(2-Chlorophenyl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)acetamide (3ab).** Colorless crystals (1.02 g, 57%); mp 120–122 °C (2-propanol). R$_f$ = 0.26. $^1$H NMR (300 MHz, CDCl$_3$): δ 2.27 (3H, s, 3-Me), 2.29 (3H, s, 5-Me), 4.81 (2H, s, CH$_2$), 5.94 (1H, s, H-4), 7.03 (1H, td, J = 7.7, 1.6 Hz, H-4'), 7.25 (1H, td, J = 7.7, 1.6 Hz, H-5'), 7.32 (1H, dd, J = 8.2, 1.5 Hz, H-3'), 8.38 (1H, dd, J = 8.2, 1.5 Hz, H-6'), 8.79 (1H, bs, NH). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 11.0 (5-Me), 13.5 (3-Me), 52.5 (CH$_2$), 106.6 (C-4), 121.3 (C-6'), 123.0 (C-2'), 124.9 (C-4'), 127.6 (C-5'), 129.1 (C-3'), 134.3 (C-1'), 140.7 (C-5), 150.2 (C-3), 165.9 (CO). IR (KBr): v 3262 (s, NH), 1673 (vs, CO), 1533 (vs, CN, NH), 1476 (s), 1421 (w) cm$^{-1}$. UV $\lambda_{\text{max}}$ (log ε): 208.40 (3.40), 242.36 (3.01) nm. MS (EI): m/z (%) 109 (100, M$^+$). Anal. calcd. for C$_{13}$H$_{14}$ClN$_3$O: C, 59.20; H, 5.35; Cl, 13.44; N, 15.93. Found C, 59.52; H, 5.65; Cl, 13.78; N, 16.19.

**N-(2-Chlorophenyl)-2-(4-iodo-3,5-dimethyl-1H-pyrazol-1-yl)acetamide (3ac).** Colorless crystals 0.97 g, 37%); mp 158–160 °C (2-propanol). R$_f$ = 0.37. $^1$H NMR (300 MHz, CDCl$_3$): δ 2.29 (3H, s, 3-Me), 2.33 (s, 3H, 5-Me), 4.88 (2H, s, CH$_2$), 7.04 (1H, td, J = 7.7, 1.5 Hz, H-4'), 7.26 (1H, td, J = 7.7, 1.5 Hz, H-5'), 7.33 (1H, dd, J = 8.2, 1.5 Hz, H-3'), 8.35 (1H, dd, J = 8.2, 1.5 Hz, H-6'), 8.60 (1H, bs, NH). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 12.1 (5-Me), 14.1 (3-Me), 53.7 (CH$_2$), 64.7 (C-4), 121.4 (C-6'), 123.1 (C-2'), 125.0 (C-4'), 127.7 (C-5'), 129.2 (C-3'), 134.1 (C-1'), 142.5 (C-5), 152.1 (C-3), 165.2 (CO). IR (KBr): v 3262 (m, NH), 1668 (vs, CO), 1539 (vs, CN, NH), 1475 (w), 1418 (w) cm$^{-1}$. UV $\lambda_{\text{max}}$ (log ε): 205.84 (3.821), 240.33 (3.485) nm. MS (EI): m/z (%) 235 (100, M$^+$). Anal. calcd. for C$_{13}$H$_{15}$ClN$_3$O: N, 10.78. Found: N, 11.07.

**N-(2-Chlorophenyl)-2-(3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)acetamide (3ad).** Colorless crystals (0.43 g, 29%); mp 155–156 °C (2-propanol). R$_f$ = 0.13. $^1$H NMR (300 MHz, CDCl$_3$, TFA): δ 2.60 (3H, s, 3-Me), 2.74 (3H, s, 5-Me), 5.23 (2H, s, CH$_2$), 7.17 (1H, td, J = 7.7, 1.5 Hz, H-4'), 7.30 (1H, td, J = 7.7, 1.5 Hz, H-5'), 7.42 (1H, dd, J = 8.2, 1.5 Hz, H-3'), 8.02 (1H, dd, J = 8.2, 1.5 Hz, H-6'), 8.60 (1H, bs, NH). $^{13}$C-NMR (75 MHz, CDCl$_3$, TFA): δ 11.6 (5-Me), 13.3 (3-Me), 52.0 (CH$_2$), 123.4 (C-6'), 125.2 (C-2'), 127.3 (C-4'), 127.9 (C-5'), 129.7 (C-3'), 131.8 (C-4), 132.4 (C-1'), 143.7 (C-5), 148.4 (C-3), 165.1 (CO). IR (KBr): v 3260 (m, NH), v1660 (vs, CO), 1540 (m, CN, NH), 1570 (m, NO$_2$), 1355 (vs, NO$_2$), 1465 (w), 1405 (w) cm$^{-1}$. UV $\lambda_{\text{max}}$ (log ε): 207.33 (3.374), 245.10 (3.117), 276.91 (2.844) nm. MS (EI): m/z (%) 154 (100, M$^+$). Anal. calcd. for C$_{13}$H$_{15}$ClN$_3$O$_2$: C, 50.57; H, 4.24; Cl, 11.48; N, 18.15. Found: C, 50.79; H, 4.66; Cl, 11.75; N, 18.39.

**N-(2-Chlorophenyl)-2-(5-methyl-3-phenyl-1H-pyrazol-1-yl)acetamide (3ae).** Colorless crystals (0.56 g, 25%); mp 93–95 °C (2-propanol). R$_f$ = 0.43. $^1$H NMR (300 MHz, CDCl$_3$): δ 2.36 (3H, d, J = 0.8 Hz, 5-Me), 4.92 (2H, s, CH$_2$), 6.49 (1H, q, J = 0.8 Hz, H-4), 7.00 (1H, td, J = 7.7, 1.5 Hz, H-4'), 7.21–7.44 (5H, m, H-3', H-5', H-3–5 3-Ph), 7.82-7.85 (2H, m, H-2,6 3-Ph), 8.35 (1H, dd, J = 8.2, 1.5 Hz, H-6'), 8.95 (1H, bs, NH). $^{13}$C-NMR (CDCl$_3$, 75 MHz): δ 11.2 (5-Me), 52.9 (CH$_2$), 104.0 (C-4), 121.3 (C-6'), 123.2 (C-2'), 125.0 (C-4'), 125.6, 128.0, 128.5, 132.7 (6C, 3-Phenyl), 127.5 (C-5'), 129.0 (C-3'), 134.2 (C-1'), 141.4 (C-5), 152.6 (C-3), 165.4 (CO). IR (KBr): v 3255 (s, NH), 1673 (vs, CO), 1525 (vs, CN, NH), 1470 (w), 1408 (w) cm$^{-1}$. UV $\lambda_{\text{max}}$ (log ε): 206.01 (3.684), 247.95 (3.433) nm. MS (EI): m/z (%) 171 (100, M$^+$). Anal.
calcd. for C$_{18}$H$_{16}$ClN$_3$O: C, 66.35; H, 4.95; Cl, 10.88; N, 12.90. Found: C, 66.61; H, 5.27; Cl, 11.17; N, 13.18.

**N-(3-Chlorophenyl)-2-(1H-pyrazol-1-yl)acetamide (3b).** Colorless crystals (0.15 g, 8%); mp 60-62 °C (2-propanol). $R_f = 0.10$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 4.94 (2H, s, CH$_2$), 6.39 (1H, dd, $J = 2.3$ Hz, 1.9, H-4'), 7.06-7.10 (1H, m, H-4'), 7.21 (1H, t, $J = 7.9$ Hz, H-5'), 7.28-7.32 (m, 1H, H-6'), 7.55 (d, 1H, $J = 2.3$ Hz, H-5), 7.57 (t, 1H, $J = 2.0$ Hz, H-2'), 7.71 (1H, d, $J = 1.9$ Hz, H-3), 8.73 (1H, bs, NH). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 55.4 (CH$_2$), 106.9 (C-4), 118.0 (C-6'), 120.0 (C-2'), 124.8 (C-4'), 129.9 (C-5'), 131.6 (C-5), 134.5 (C-3'), 138.1 (C-1'), 141.6 (C-3), 165.1 (CO). IR (KBr): $\tilde{\nu}$ 3260 (m, NH), 1680 (vs, CO), 1534 (vs, CN, NH), 1480 (w), 1409 (w) cm$^{-1}$. MS (EI): $m/z$ (%) 81 (100, M$^+$). Anal. calcd. for C$_{11}$H$_{10}$ClN$_3$O: C, 56.06; H, 4.28. Cl, 15.04; N, 17.38. Found: C, 56.37; H, 4.41. Cl, 15.41; N, 17.62.

**N-(3-Chlorophenyl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)acetamide (3bb).** Colorless crystals (0.45 g, 25%); mp 110–111 °C (2-propanol). $R_f = 0.23$. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$: 2.27, 2.29 (6H, 2s, 3-Me, 5-Me), 4.76 (2H, s, CH$_2$), 5.92 (1H, s, H-4), 7.05-7.09 (1H, m, H-4'), 7.21 (1H, t, $J = 7.9$ Hz, H-5'), 7.29-7.33 (1H, m, H-6'), 7.58 (1H, t, $J = 2.0$ Hz, H-2'), 8.70 (1H, bs, NH). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$: 11.1 (5-Me), 13.6 (5-Me), 52.3 (CH$_2$), 106.4 (C-4), 118.0 (C-6'), 120.0 (C-2'), 124.7 (C-4'), 130.0 (C-5'), 134.6 (C-3'), 138.4 (C-1'), 141.1 (C-5), 150.3 (C-3), 165.7 (CO). IR (KBr): $\tilde{\nu}$ 3278 (s, NH), 1698 (vs, CO), 1570 (vs, CN, NH), 1480 (w), 1409 (w) cm$^{-1}$. MS (EI): $m/z$ (%) 109 (100, M$^+$). Anal. calcd. for C$_{13}$H$_{14}$ClN$_3$O: C, 59.21; H, 5.35; Cl, 13.44; N, 15.93. Found: C, 59.39; H, 5.73; Cl, 13.67; N, 16.22.

**N-(3-Chlorophenyl)-2-(4-iodo-3,5-dimethyl-1H-pyrazol-1-yl)acetamide (3bc).** Colorless crystals (1.21 g, 46%); mp 157–159 °C (2-propanol). $R_f = 0.31$. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$: 2.29, 2.34 (6H, 2s, 3-Me, 5-Me), 4.84 (s, 2H, CH$_2$), 7.07–7.11 (1H, m, H-4'), 7.22 (1H, t, $J = 7.9$ Hz, H-5'), 7.26-7.30 (1H, m, H-6'), 7.56 (1H, t, $J = 2.0$ Hz, H-2'), 8.59 (1H, bs, NH). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$: 12.5 (5-Me), 14.1 (5-Me), 53.4 (CH$_2$), 64.5 (C-4), 117.9 (C-6'), 120.0 (C-2'), 124.8 (C-4'), 129.9 (C-5'), 134.6 (C-3'), 138.1 (C-1'), 142.6 (C-5), 151.8 (C-3), 164.9 (CO). IR (KBr): $\tilde{\nu}$ 3260 (s, NH), 1690 (s, CO), 1540 (vs, CN, NH), 1468 (w), 1413 (w) cm$^{-1}$. MS (EI): $m/z$ (%) 235 (100, M$^+$). Anal. calcd. for C$_{13}$H$_{13}$ClIIN$_3$O: N, 10.78. Found: N, 11.03.

**N-(3-Chlorophenyl)-2-(3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)acetamide (3bd).** Colorless crystals (0.53 g, 28%); mp 167–168 °C (2-propanol). $R_f = 0.55$. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta$: 2.39, 2.56 (6H, 2s, 3-Me, 5-Me), 5.09 (2H, s, CH$_2$), 7.12-7.16 (1H, m, H-4'), 7.35 (1H, t, $J = 8.0$ Hz, H-5'), 7.41-7.45 (1H, m, H-6'), 7.77 (1H, t, $J = 2.0$ Hz, H-2'), 10.64 (1H, bs, NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$: 11.4 (5-Me), 13.7 (3-Me), 52.5 (CH$_2$), 117.6 (C-6'), 118.8 (C-2'), 123.5 (C-4'), 130.4 (C-4), 130.5 (C-5'), 133.3 (C-3'), 139.7 (C-1'), 142.5 (C-5), 145.3 (C-3), 164.6 (CO). IR (KBr): $\tilde{\nu}$ 3260 (vs, NH), 1670 (vs, CO), 1595 (vs, CN, NH), 1578 (m, NO$_2$), 1350 (vs, NO$_2$), 1450 (w), 1410 (w) cm$^{-1}$. MS (EI): $m/z$ (%) 154 (100, M$^+$). Anal. calcd. for C$_{13}$H$_{13}$ClN$_4$O$_3$: C, 50.58; H, 4.24; Cl, 11.48; N, 18.15. Found: C, 50.84; H, 4.61; Cl, 11.80; N, 18.47.

**N-(3-Chlorophenyl)-2-(5-methyl-3-phenyl-1H-pyrazol-1-yl)acetamide (3be).** Colorless crystals (0.44 g, 20%); mp 134–135 °C (2-propanol). $R_f = 0.31$. IR (KBr): $\tilde{\nu}$ 3263 (s, NH), 1682
(vs, CO), 1520 (vs, CN, NH), 1468 (w), 1407 (w) cm$^{-1}$. MS (EI): $m/z$ (%) 171 (100, M$^+\)). Anal. calcd. for C$_{18}$H$_{16}$ClN$_3$O: C, 66.36; H, 4.95; Cl, 10.88; N, 12.90. Found: C, 66.58; H, 5.21; Cl, 11.20; N, 13.11

**Pharmacology**
Acute toxicity (LD$_{50}$), infiltration, local anesthetic action and anti-arrhythmic action were measured using standard techniques.\textsuperscript{19-21} The full pharmacological results will be published elsewhere.

**References**

