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 acetanilide 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). 1-3 Usually, an amide as the anesthesiophoric group provides higher activity. 1

In previous papers we reported the synthesis, characterization and pharmacological tests of some N-substituted 2-(1H-pyrazol-1-yl)acetamides. 4-6 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 \( N-(\text{chlorophenyl})-2\)-iodoacetamides \(1a,b\) with pyrazoles \(2\) in DMF in the presence of sodium carbonate afforded \( N-(\text{chlorophenyl})-2-(1H\text{-pyrazol-1-yl})\)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 and Büchi 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.\(^8\)

![Scheme 1](image)

The proposed structures are in good agreement with spectral data. A characteristic feature of the \(^1H\)-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 \((^3J = 1.9\) Hz).

The positions of the methyl and phenyl groups in compound \(3ae\) were determined on the basis of chemical shifts in the \(^1H\) and \(^{13}C\)-NMR spectra, by NOE experiments and by comparison with \(^{13}C\)-NMR data for similar compounds.\(^9–17\) 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.\(^4\)
Conclusions

Ten new \(N\)-substituted 2-(1\(H\)-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-(1\(H\)-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.\(^7\,\text{\textsuperscript{8}}\,\text{\textsuperscript{18}}\) 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\textsubscript{254}, petroleum ether/ethyl ether/methylene chloride/ethyl acetate 7.5:1:2:1, UV visualization).

\(N\)-(Chlorophenyl)-2-(1\(H\)-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-(1\(H\)-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\(_2\)), 121.4 (C-6'), 123.0 (C-2'), 125.1 (C-4'), 127.5 (C-3'), 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 e): 208.53 (3.38), 243.17 (2.98) nm. MS (EI): \(m/z\) (%) 81 (100, M\(^+\)). Anal. calcd. for C\(_{11}\)H\(_{10}\)ClN\(_3\): 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). ^1^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 (w), 1421 (w) cm⁻¹. UV λ_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_3O: 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). ^1^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 λ_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_{13}ClN_3O: C, 50.57; H, 4.24; Cl, 10.78. Found: C, 50.79; H, 4.66; Cl, 11.75; N, 16.39.

**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). ^1^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 λ_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_{13}ClN_3O: 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, 3-Ph), 8.35 (1H, dd, J = 8.2, 1.5 Hz, H-6'), 8.95 (1H, bs, NH). ^1^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), 1675 (vs, CO), 1525 (vs, CN, NH), 1470 (w), 1408 (w) cm⁻¹. UV λ_max (log ε): 206.01 (3.684), 247.95 (3.433) nm. MS (EI): m/z (%) 171 (100, M⁺). Anal.
N-(3-Chlorophenyl)-2-(1H-pyrazol-1-yl)acetamide (3ba). 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\(_11\)H\(_{12}\)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 (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\(_{13}\)ClN\(_3\)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\(_2\)), 1530 (vs, NO\(_2\)), 1450 (w), 1410 (w) cm\(^{-1}\). MS (EI): \( m/z\) (%) 154 (100, M\(^+\)). Anal. calcd. for C\(_{13}\)H\(_{13}\)ClNO\(_3\): 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.\(^{19-21}\) The full pharmacological results will be published elsewhere.

**References**