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

Christina Zalaru,[a]* Florea Dumitrascu,[b] Constantin Draghici,[b] Elena Cristea,[c] and Isabela Tarcomnicu[d]

[a]University of Bucharest, Faculty of Chemistry, Department of Organic Chemistry Bucharest, 90-92 Road Panduri, Romania
[b]Institute of Organic Chemistry C.D. Nenitescu, Romanian Academy 202 B, Spl. Independentei, Bucharest, Romania
[c]University of Medicine and Pharmaceutics "Carol Davila", Clinical and Sanitary Chemistry Laboratories, 6-Traian Vuia St., Bucharest, Romania
[d]Pharma Serv International, 52 Sabinelor St., Bucharest, Romania
E-mail: chmzalaru@yahoo.com

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

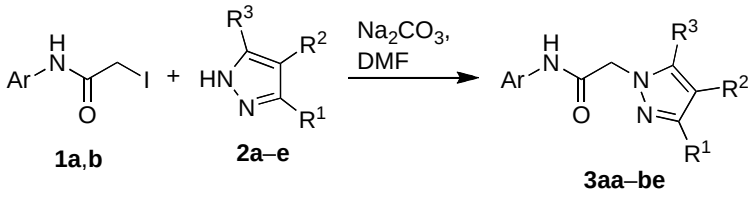
Introduction

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-(1*H*-pyrazol-1-yl)acetamides.[4–6] The present paper reports on the synthesis and characterization of N-(chlorophenyl)-substituted 2-(1*H*-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-(1*H*-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[1] and Büchi[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.[8]



1, 3	Ar
a	2-ClC_6H_4
b	3-ClC_6H_4

2, 3	R^1	R^2	R^3
a	H	H	H
b	Me	H	Me
c	Me	I	Me
d	Me	NO_2	Me
e	Ph	H	Me

Scheme 1

The proposed structures are in good agreement with spectral data. A characteristic feature of the ^{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 (^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 ^{1}H 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.[7,8,18] 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 $60F_{254}$, 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, $CDCl_3$): δ 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, $CDCl_3$): δ 55.6 (CH_2), 107.4 (C-4), 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: λ_{max} (log ε): 208.53 (3.38), 243.17 (2.98) nm. MS (EI): *m*/*z* (%) 81 (100, M^+). Anal. calcd. for $C_{11}H_{10}ClN_3O$: 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-1*H*-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): $\tilde{\nu}$ 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-1*H*-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): $\tilde{\nu}$ 3242 (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 $C_{13}H_{13}ClIN_3O$: N, 10.78. Found: N, 11.07.

***N*-(2-Chlorophenyl)-2-(3,5-dimethyl-4-nitro-1*H*-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): $\tilde{\nu}$ 3260 (m, NH), ν1660 (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 $C_{13}H_{13}ClN_4O_3$: 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-1*H*-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): $\tilde{\nu}$ 3255 (s, NH), 1675 (vs, CO), 1525 (vs, CN, NH), 1470 (w), 1408 (w) cm^{-1}. UV λ_{max} (logε): 206.01 (3.684), 247.95 (3.433) nm. MS (EI): *m/z* (%) 171 (100, M^+). Anal.

calcd. for $C_{18}H_{16}ClN_3O$: 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-(1*H*-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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{11}H_{10}ClN_3O$: 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-1*H*-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, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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 $C_{13}H_{14}ClN_3O$: 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-1*H*-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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{13}H_{13}ClIN_3O$: N, 10.78. Found: N, 11.03.

***N*-(3-Chlorophenyl)-2-(3,5-dimethyl-4-nitro-1*H*-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): δ 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): δ 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 $C_{13}H_{13}ClN_4O_3$: 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-1*H*-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 $C_{18}H_{16}ClN_3O$: 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.

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