Supplementary Information

Organocatalytic synthesis and evaluation of 7-chloroquinoline-1,2,3-triazoyl carboxamides as potential antinociceptive, anti-inflammatory and anticonvulsant agent

Ethel A. Wilhelm^{a,b,*}, Niége C. Machado^a, Andrieli B. Pedroso^a, Bruna S. Goldani^c, Natália Seus^c, Sidnei Moura^d, Lucielli Savegnago^b, Raquel G. Jacob^c and Diego Alves ^{c,*}

^a Universidade Regional Integrada do Alto Uruguai das Missões, URI Campus Santiago, CEP 97700-000, Santiago, RS, Brazil;

^b Grupo de Pesquisa em Neurobiotecnologia - GPN, CDTec, Universidade Federal de Pelotas, UFPel, Pelotas, RS, Brazil;

^c Laboratório de Síntese Orgânica Limpa - LASOL - CCQFA - Universidade Federal de Pelotas – UFPel, CEP 96010-900, Pelotas, RS, Brazil. Tel: +55 (53) 3275-7357;

^d Instituto de Biotecnologia, Universidade de Caxias do Sul, R. Francisco Getulio Vargas 1130, 95070-560, Caxias do Sul – RS, Brasil.

* corresponding author - e-mail: ethelwilhelm@yahoo.com.br and diego.alves@ufpel.edu.br

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Pharmacological Experiments: The experiments were conducted using male Swiss mice (25-35 g) and young male Wistar rats (40–50 g; 21-day-old) maintained at 22 ± 2 °C with free access to water and food, under a 12 h light/dark cycle (with lights on at 6:00 a.m.). Animals were acclimatized to the laboratory for at least 1 h before testing and were used only once during the experiments. All experiments were carried out according to the Guide for the Care and Use of Laboratory Animals, U.S. Department of Health and Human Services (NIH publication no. 85–23, revised 1985). Additionally, the Committee on Care and Use of Experimental Animal Resources, Regional Integrated University of High Uruguay and Missions, Santiago, Brazil, approved the protocols used in this study (005/2012 and 006/2012). The number of animals and the intensity of noxious stimuli used were kept to the minimum necessary to demonstrate the consistent effects of the drug treatments. After experiments, animals were euthanized by cervical displacement.

Drugs: PC and PTZ were purchased from Sigma (St. Louis, MO, USA). All other chemicals were of analytical grade and obtained from standard commercial suppliers. Compound **3a** was dissolved in canola oil and administered by intragastric gavage in a single dose. All other drugs were dissolved in a 0.9% saline solution.

Statistical analysis: Seizure incidence was statistically analyzed by the χ^2 method and Fisher's exact test. Statistical analysis of latency to the seizure onset was performed using one-way analysis of variance (ANOVA), followed by the Newman–Keuls test. Data are expressed as means ± SEM. Values of p < 0.05 were considered statistically significant. The results of the chemical models of nociception are presented as means± SEM, except the ID₅₀ values (i.e., the dose of compound **3a** need to reduce the nociceptive response by 50% relative to the control value), which are reported as geometric means accompanied by their respective 95% confidence limits. Comparisons between experimental and control groups were performed by ANOVA followed by Newman–Keuls' test when appropriated. Values of p < 0.05 were considered as indicative of significance. Maximal inhibition (Imax) values were calculated at the most effective dose used.

Chemistry - General Remarks: Proton nuclear magnetic resonance spectra (¹H NMR) were obtained at 400 MHz on a Bruker DPX-400 NMR spectrometer. Spectra were recorded in CDCl₃ solutions. Chemical shifts are reported in ppm, with tetramethylsilane (TMS) used as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (*J*) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (¹C NMR) were obtained at 100 MHz on a Bruker DPX-400 NMR spectrometer. Spectra were recorded in CDCl₃ solutions. Chemical shifts are reported in ppm in reference to the solvent peak of CDCl₃. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), qua (quartet), dd (double doublet), td (triple doublet), tt (triple triplet), br (broad singlet) and m (multiplet). Mass spectra (MS) were measured on a Bruker Micro TOF-QII spectrometer 10416. Column chromatography was performed using a Merck Silica Gel (230-400 mesh). Thin layer chromatography (TLC) was performed using a 0.25 mm thick Merck Silica Gel GF₂₅₄. For visualization, TLC plates were either placed under ultraviolet light or stained with iodine vapour or acidic vanillin.

General Procedure for the Synthesis of 7-chloroquinoline-1,2,3-triazoyl carboxamides 3a-k: To a solution of 4-azido-7-chloroquinoline 1 (0.3 mmol, 0.061 g) in DMSO (0.6 mL), the β -oxo-amides 2a-k (0.3 mmol) were added, followed by the catalyst pyrrolidine (5 mol%). The reaction mixture was stirred in an open vial for the time indicated in Table 2. After completion of the reaction, the crude product was purified by column chromatography on a silica gel using a mixture of hexane/ethyl acetate (5:1) as the eluent to afford the desired products 3a-k. The spectral data of the prepared products are listed below.

Spectral data of the products.



1-(7-Chloroquinolin-4-yl)-5-methyl-*N***-phenyl-1***H***-1,2,3-triazole-4-carboxamide** (3a): Yield: 0.102 g (94%); yellow solid; mp 149-152 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.15 (d, *J* = 4.5 Hz, 1H), 9.13 (br, 1H), 8.30 (d, *J* = 1.9 Hz, 1H), 7.73 (dd, *J* = 8.7 and 1.2 Hz, 2H), 7.59 (dd, *J* = 8.9 and 2.0 Hz, 1H), 7.45 (d, *J* = 4.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.18 (tt, *J* = 7.4 and 1.1Hz, 1H), 2.56 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ = 158.64, 151.36, 149.97, 139.43, 139.02, 138.64, 137.37, 137.24, 129.90, 129.10 (2C), 124.57, 123.64, 122.14, 119.86, 118.79, 9.42. MS (relative intensity) m/z: 365 (31), 363 (M⁺, 100), 245 (26), 243 (74), 232 (46), 215 (53), 179 (26), 162 (80), 127 (31), 77 (29). HRMS calcd for C₁₉H₁₅CIN₅O [M + H]⁺: 364.0959. Found: 364.0954.



1-(7-Chloroquinolin-4-yl)-5-methyl-*N***-(2-tolyl)-1***H***-1,2,3-triazole-4-carboxamide (3b):** Yield: 0.086 g (76%); white solid; mp 190-191 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.15 (d, *J* = 4.3 Hz, 1H), 9.07 (br, 1H), 8.29 (m, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 4.4 Hz, 1H), 7.38 (d, *J* = 8.9 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 7.1 Hz, 1H), 2.56 (s, 3H), 2.45 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ = 158.62, 151.35, 149.96, 139.44, 138.88, 138.79, 137.18, 135.24, 130.53, 129.83, 129.07, 128.58, 126.76, 125.04, 123.68, 122.13, 122.08, 118.75, 17.70, 9.38. MS (relative intensity) m/z: 379 (13), 377 (M⁺, 34), 349 (96), 243 (46), 232 (34), 215 (39), 162 (69), 135 (30), 80 (71), 57 (50), 43 (100). HRMS calcd for C₂₀H₁₇ClN₅O [M + H]⁺: 378.1116. Found: 378.1115.



1-(7-Chloroquinolin-4-yl)-5-methyl-N-(4-tolyl)-1H-1,2,3-triazole-4-carboxamide

(3c): Yield: 0.096 g (85%); white solid; mp 203-204 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.14 (d, *J* = 4.5 Hz, 1H) 9.08 (br, 1H), 8.29 (d, *J* = 2.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.45 (d, *J* = 4.5 Hz, 1H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 2.55 (s, 3H), 2.36 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ = 158.50, 151.35, 149.94, 139.42, 138.87, 138.68, 137.17, 134.78, 134.20, 129.84, 129.56, 129.06, 123.64, 122.12, 119.85, 118.77, 20.87, 9.39. MS (relative intensity) m/z: 379 (31), 377 (M⁺, 86), 243 (39), 232 (74), 215 (34), 162 (59), 135 (26), 127 (28), 107 (38), 98 (37), 80 (72), 57 (41), 43 (100). HRMS calcd for C₂₀H₁₇ClN₅O [M + H]⁺: 378.1116. Found: 378.1109.



1-(7-Chloroquinolin-4-yl)-N-(2-methoxyphenyl)-5-methyl-1H-1,2,3-triazole-4-

carboxamide (3d): Yield: 0.102 g (87%); white solid; mp 200-201 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.73 (s, 1H), 9.15 (d, J = 4.4 Hz, 1H), 8.52 (d, J = 7.8 Hz, 1H), 8.29 (s, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.44-6.95 (m, 3H), 3.97 (s, 3H), 2.56 (s, 3H). ¹³C NMR (CDCl₃, 100

MHz) $\delta = 158.53$, 151.35, 149.97, 148.36, 139.50, 139.03, 138.78, 137.16, 129.81, 129.05, 127.19, 124.10, 123.76, 122.19, 120.89, 119.66, 118.76, 110.05, 55.75, 9.41. MS (relative intensity) m/z: 395 (6), 393 (M⁺, 18), 362 (100), 243 (21), 215 (18), 162 (33), 135 (16). HRMS calcd for C₂₀H₁₇ClN₅O₂ [M + H]⁺: 394.1065. Found: 394.1071.



^{O--} **1-(7-Chloroquinolin-4-yl)**-*N*-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4carboxamide (3e): Yield: 0.102 g (87%); brown solid; mp 193-195 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.15 (d, *J* = 4.0 Hz, 1H), 9.05 (s, 1H), 8.29 (s, 1H), 7.65-7.57 (m, 3H), 7.46 (d, *J* = 4.1 Hz, 1H), 7.35 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 3.83 (s, 3H), 2.55 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ = 158.46, 156.53, 151.36, 149.94, 139.44, 138.79, 138.68, 137.18, 130.43, 129.85, 129.07, 123.65, 122.13 (2C), 121.61, 118.77,

114.19 (2C), 55.43, 9.38. MS (relative intensity) m/z: 395 (30), 393 (M⁺, 91), 234 (32), 232 (100), 189 (32), 162 (50), 122 (27), 99 (20). HRMS calcd for $C_{20}H_{17}ClN_5O_2$ [M + H]⁺: 394.1065. Found: 394.1063.



N-(2-chlorophenyl)-1-(7-chloroquinolin-4-yl)-5-methyl-1H-1,2,3-triazole-4-

carboxamide (3f): Yield: 0.106 g (89%); white solid; mp 153-154 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.70 (s, 1H), 9.15 (d, *J* = 4.4 Hz, 1H), 8.53 (dd *J* = 8.2 and 1.4 Hz 1H), 8.29 (d, *J* = 1.8 Hz, 1H), 7.59 (dd, *J* = 8.9 and 1.8 Hz, 1H), 7.48-7.29 (m, 4H), 7.10 (td, *J* = 7.8 and 1.4 Hz, 1H), 2.56 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ = 158.61, 151.31, 149.92, 139.34, 139.11, 138.53, 137.17, 134.23, 129.83, 129.20, 129.03, 127.58, 124.83, 123.66, 123.32, 122.08, 121.26, 118.73, 9.38. MS (relative intensity) m/z: 399 (2), 397 (M⁺, 3), 364 (33), 362 (100), 243 (32), 215 (20), 162 (33), 135 (15), 127 (18), 99 (19). HRMS calcd for C₁₉H₁₄Cl₂N₅O [M + H]⁺: 398.0569. Found: 398.0568.



الأ N-(4-chlorophenyl)-1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-

carboxamide (3g): Yield: 0.113 g (95%); white solid; mp 179-180 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.17 (d, *J* = 4.5 Hz, 1H), 9.11 (s, 1H), 8.31 (s, 1H), 7.69 (d *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.9 Hz, 1H), 7.45 (d, *J* = 4.5 Hz, 1H), 7.36 (t, *J* = 9.0 Hz, 3H), 2.56 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ = 158.63, 151.40, 150.05, 139.39, 139.17, 138.47, 137.32, 136.00, 129.99, 129.58, 129.21, 129.18, 123.58, 122.14, 121.03, 118.79, 9.44. MS (relative intensity) m/z: 399 (66), 397 (M⁺, 100), 243 (86), 232 (92), 215 (52), 189 (27), 162 (95), 135 (40), 127 (55), 99 (50), 57 (39). HRMS calcd for C₁₉H₁₄Cl₂N₅O [M + H]⁺: 398.0569. Found: 398.0579.



F 1-(7-chloroquinolin-4-yl)-N-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4carboxamide (3h): Yield: 0.094 g (82%); yellow solid; mp 143-145 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.16 (d, J = 4.3 Hz, 1H), 9.12 (s, 1H), 8.30 (s, 1H), 7.70 (dd J = 8.1 and 4.3 Hz, 2H), 7.59 (d, J = 8.9 Hz, 1H), 7.46 (d, J = 4.2 Hz, 1H), 7.34 (d, J = 8.9 Hz, 1H), 7.09 (t, J = 8.3 Hz, 2H), 2.56 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) $\delta = 159.46$ (d, $J_{C-F} = 243.9$ Hz), 158.60, 151.36, 149.98, 139.38, 139.05, 138.48, 137.24, 133.36 (d, $J_{C-F} = 2.8$ Hz), 129.91, 129.13, 123.59, 121.63 (d, $J_{C-F} = 7.9$ Hz), 121.58, 118.77, 115.76 (d, $J_{C-F} = 22.5$ Hz), 9.39. MS (relative intensity) m/z: 383 (25), 381 (M⁺, 75), 243 (46), 232 (46), 215 (30), 162 (56), 135 (29), 99 (27), 83 (39), 69 (100), 57 (49), 43 (44). HRMS calcd for C₁₉H₁₄CIFN₅O [M + H]⁺: 382.0865. Found: 382.0865.



^{NO₂} 1-(7-chloroquinolin-4-yl)-5-methyl-*N*-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-

carboxamide (3i): Yield: 0.098 g (80%); yellow solid; d.p. 251 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.42 (s, 1H), 9.18 (d, *J* = 4.2 Hz, 1H), 8.32-8.29 (m, 3H), 7.93 (d, *J* = 9.2 Hz, 2H), 7.61 (dd, *J* = 8.9 and 2.1 Hz, 1H), 7.47 (d, *J* = 4.5 Hz, 1H), 7.33 (d, *J* = 8.9 Hz, 1H), 2,58 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ = 158.84, 151.40, 150.05, 143.73, 143.24, 139.77, 139.21, 138.06, 137.41, 136.08, 129.26, 125.25, 123.44, 122.04, 119.19, 118.79, 9.51. MS (relative intensity) m/z: 410 (25), 408 (M⁺, 70), 243 (100), 216 (65), 203 (26), 162 (95), 135 (40), 127 (36), 99 (37), 40 (69). HRMS calcd for C₁₉H₁₄ClN₆O₃ [M + H]⁺: 409.0810. Found: 409.0811.



1-(7-chloroquinolin-4-yl)-*N*,5-diphenyl-1*H*-1,2,3-triazole-4-carboxamide (3j): Yield: 0.108 g (85%); white solid; mp 215-216 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.26 (s, 1H), 8.94 (d, *J* = 4.3 Hz, 1H), 8.22 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.56 (t, *J* = 9.1 Hz, 2H), 7.39-7.25 (m, 7H), 7.18-7.13 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ = 157.57, 151.06, 149.92, 141.55, 139.98, 138.52, 137.40, 137.00, 130.41, 129.89, 129.65, 129.06, 128.98, 128.45, 124.56, 124.27, 123.94, 122.16, 119.94, 119.13. MS (relative intensity) m/z: 427 (6), 425 (M⁺, 19), 305 (100), 294 (23), 242 (81), 162 (36), 135 (24), 89 (52). HRMS calcd for C₂₄H₁₇ClN₅O [M + H]⁺: 426.1116. Found: 426.1116.



1-(7-chloroquinolin-4-yl)-N-phenyl-5-(trifluoromethyl)-1H-1,2,3-triazole-4-

carboxamide (3k): Yield: 0.029 g (23%); white solid; mp 144-146 °C. ¹H NMR (CDCl₃, 400 MHz) δ = 9.1 (d, J = 4.4 Hz, 1H), 9.14 (s, 1H), 8.33 (s, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.63 (dd, J = 7.7 and 1.3 Hz, 1H), 7.55-7.52 (m, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.27-7.18 (m, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ = 154.93, 151.13, 149.73, 141.98, 139.79, 137.51, 136.81, 130.36, 130.04, 129.23, 127.43, 125.26, 122.59, 122.03, 120.02, 118.78, 118.54 (q, J_{C-F} = 271.90 Hz). MS (relative intensity) m/z: 419 (34), 417 (M⁺, 100), 297 (29), 270 (69), 250 (17), 162 (33), 120 (34), 93 (56), 77 (56). HRMS calcd for C₁₉H₁₂ClF₃N₅O [M + H]⁺: 418.0676. Found: 418.0676.

SELECTED SPECTRA



¹H NMR (400 MHz, CDCl₃) spectrum of *1-(7-Chloroquinolin-4-yl)-5-methyl-N-phenyl-1H-1,2,3-triazole-4-carboxamide (3a)*









































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