An Efficient Synthesis of New 5-(1-Aryl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles from 1-Aryl-1*H*-pyrazole-4-carbonitriles *via* [3 + 2] Cycloaddition Reaction

Maurício S. dos Santos,[a] Alice M. R. Bernardino,[b]* Luiz C. S. Pinheiro,[b] Marilene M. Canto-Cavalheiro,[c] and Leonor L. Leon[c]

[a]Universidade Federal de Itajubá, Instituto de Ciências Exatas, Departamento de Física e Química, 37500-903, Itajubá, MG, Brazil
[b]Universidade Federal Fluminense, Instituto de Química, Departamento de Química Orgânica, Programa de Pós-Graduação em Química, Campus do Valonguinho, 24210-150, Niterói, RJ, Brazil
[c]Fundação Oswaldo Cruz, Laboratório de Bioquímica de Tripanosomatídeos, 21040-900, Rio de Janeiro, RJ, Brazil
*E-mail: alicerolim@globo.com

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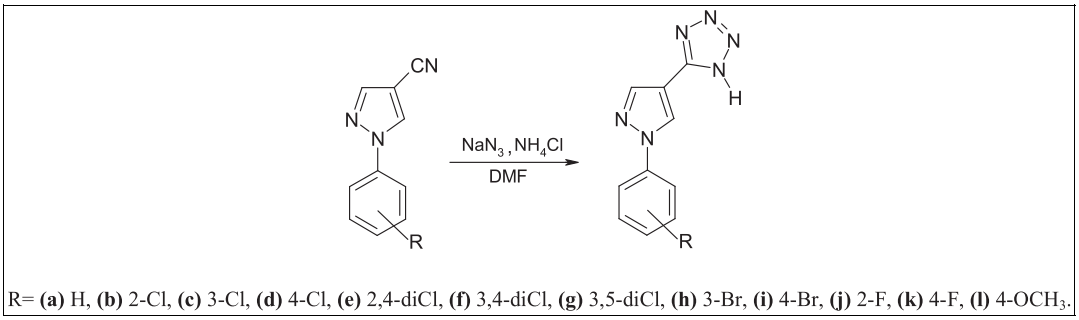

R= **(a)** H, **(b)** 2-Cl, **(c)** 3-Cl, **(d)** 4-Cl, **(e)** 2,4-diCl, **(f)** 3,4-diCl, **(g)** 3,5-diCl, **(h)** 3-Br, **(i)** 4-Br, **(j)** 2-F, **(k)** 4-F, **(l)** 4-OCH_3.

A series of new 5-(1-aryl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles **4a-l** were synthesized *via* [3 + 2] cycloaddition reaction from 1-aryl-1*H*-pyrazole-4-carbonitriles **3a-l**, sodium azide and ammonium chloride, using dimethylformamide (DMF) as solvent, in good yields: 64–85%. The structures of these newly synthesized compounds were determined from the IR, ^{1}H- and ^{13}C-NMR spectroscopic data and elemental analyses.

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INTRODUCTION

Heterocyclic compounds are popular targets for synthetic chemists primarily because of their diverse and potent biological properties [1,2]. Pyrazoles and tetrazoles, in particular, have been highlighted because of the pronounced pharmacological applications. The efficacy of pyrazoles and tetrazoles to behave as COX-2 inhibitors [3], antihyperglycemic [4], cannabinoid antagonists [5], antitumoral [6,7], antiviral [8,9], and antimicrobial [10–12] agents has been reported as well as a large number of synthetic routes have been presented in some monographs and reviews [13–17]. In recent years, tetrazoles have received considerable attention because they play an important role in medicinal chemistry as a pharmacophore due to ability to serve as a bioequivalent (bioisostere) of the carboxylic acid group as well as a synthon [18].

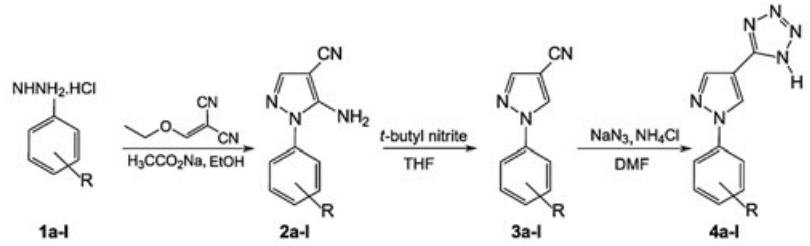
In the course of our search for new pyrazoles and tetrazoles derivatives for evaluation against several biological agents [19–24], we prepared twelve new 5-(1-aryl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles (Scheme 1), and their structures were identified by spectroscopic and elemental analyzes.

RESULTS AND DISCUSSION

According to the literature, the key intermediates 1-aryl-1*H*-pyrazole-4-carbonitriles **3a–l** have been synthesized in four steps: first, preparation of 1-aryl-1*H*-pyrazoles; second, Vilsmeier-Haack formylation to give 1-aryl-1*H*-pyrazole-4-carboxaldeydes; third, formation of 1-aryl-1*H*-pyrazole-4-carbaldehyde oximes and fourth, their dehydration to the corresponding derivatives **3a–l** [25,26].

In this work, we synthesized the key intermediates 1-aryl-1*H*-pyrazole-4-carbonitriles **3a–l** in only two steps. Initially, arylhydrazine hydrochlorides **1a–l** reacted with ethoxymethylenemalononitrile and sodium acetate in ethanol gave good yields (77–90%) of 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles **2a–l** [27,28]. The reaction occurs *via* a Michael addition mechanism. In the second step, compounds **2a–l** were subjected to aprotic deamination with *t*-butyl nitrite in tetrahydrofuran (THF) to generate 1-aryl-1*H*-pyrazole-4-carbonitriles **3a–l** in yields of 72–92% [29]. The usefulness of alkyl nitrites as *in situ* diazotising agents has already been demonstrated [30]. These reactions proceed *via* aromatic radicals. The extension of the *in situ* diazotization method to deamination of aromatic amines by aromatic radical abstraction of hydrogen from a suitable solvent is an attractive possibility. THF was chosen as a result of the ease with C—H bonds α to an ether linkage undergo abstraction reactions with aromatic radicals derived in a redox fashion from aromatic diazonium [29,31].

Scheme 1



R= (a) H, (b) 2-Cl, (c) 3-Cl, (d) 4-Cl, (e) 2,4-diCl, (f) 3,4-diCl, (g) 3,5-diCl, (h) 3-Br, (i) 4-Br, (j) 2-F, (k) 4-F, (l) 4-OCH_3.

The inedited targets 5-(1-aryl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles **4a–l** were obtained *via* [3 + 2] cycloaddition by the reaction of the compounds **3a–l** with sodium azide and ammonium chloride in DMF, at 120–130°C [32].

EXPERIMENTAL

All the melting points were determined on a Fisatom 430 melting point apparatus. Analytical thin layer chromatography (TLC) was performed on Merck precoated 60 F254 silica gel plates. IR spectra (KBr pellet) were recorded on Perkin-Elmer BX series FTIR spectrophotometer. NMR spectra were recorded on a Varian Unity 300 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethylsilane as internal standard. Elemental analyzes were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

5-Amino-1-phenyl-1*H*-pyrazole-4-carbonitrile (2a). A mixture of phenyllhydrazine hydrochloride (0.01 mol), ethoxymethylenemalononitrile (0.01 mol), and sodium acetate (0.02 mol) in ethanol (40 mL) was heated under reflux during 1 h. The mixture was poured into cold water. The precipitates were filtered out and recrystallized from ethanol/water. The reaction was accompanied by means of TLC using silica gel plate with fluorescent indicator and hexane/ethyl acetate (1:1) as eluent.

Yield 90%; mp 135–136°C; IR (KBr): 3326, 3224 (NH_2), 2224 (C≡N); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.72 (2H, s), 7.45–7.54 (5H, m), and 7.63 (1H, s); ^{13}C-NMR (75 MHz): δ 73.4, 112.3, 123.1, 127.8, 132.5, 138.8, 143.1, and 149.8. Anal. Calcd. for $C_{10}H_8N_4$ (184.20): C, 65.21; H, 4.38; N, 30.42. Found: C, 65.31; H, 4.42; N, 30.30. The products **2b–l** were similarly prepared.

1-Phenyl-1*H*-pyrazole-4-carbonitrile (3a). The reaction mixture of *t*-butyl nitrite (4 mL) with dry THF (10 mL) was stirred and refluxed under 20 min. Then 5-amino-1-aryl-1*H*-pyrazole-4-carbonitrile (0.005 mol) was added and the mixture was stirred and refluxed for about 2 h. From the reaction mixture THF and *t*-butyl nitrite was evaporated. The residue was recrystallized with a mixture of ethanol/water. The purity of the compound was checked by means of TLC using silica gel plate with fluorescent indicator and hexane/ethyl acetate (1:1) as eluent.

Yield 82%; mp 91–92°C; IR (KBr): 2240 (C≡N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, t, *J* = 7.8 Hz), 7.51 (2H, t, *J* = 7.8 Hz), 7.68 (2H, t, *J* = 7.8 Hz), 8.00 (1H, s), and 8.31 (1H, s); ^{13}C-NMR (75 MHz) δ 93.5, 112.7, 119.5, 127.9, 131.4, 137.8, 140.0, and 143.7. Anal. Calcd. for $C_{10}H_7N_3$ (169.19): C, 70.99; H, 4.17; N, 24.84. Found: C, 71.05; H, 4.26; N, 24.74. Other carbonitriles **3b–l** were similarly obtained.

General procedure for the synthesis of compounds 5-(1-aryl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles 4a–l. 5-Amino-1-aryl-1*H*-pyrazole-4-carbonitrile **3a** (0.002 mol) was mixed with sodium azide (0.004 mol), ammonium chloride (0.004 mol), and DMF (15 mL). The reaction mixture was heated at 120–130°C, during 14 h and poured into cold water. The precipitate formed was filtered and recrystallized from ethanol/water. The compound **4a** was obtained in good yield: 78%. The reaction was accompanied by means of TLC using silica gel plate with fluorescent indicator and hexane/ethyl acetate (1:1) as eluent. Compounds **4b–l** were prepared similarly.

5-(1-Phenyl-1*H*-pyrazole-4-yl)-1*H*-tetrazole (4a). Yield 78%; mp 217°C; IR (KBr): 3130 (NH), 1638 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 7.52 (1H, t, *J* = 7.5 Hz), 7.67 (2H, t, *J* = 7.5 Hz), 8.05 (2H, d, *J* = 7.5 Hz), 8.41 (1H, s), and 9.26 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 108.3, 119.2, 128.0, 128.2, 130.1, 139.0, 139.8, and 149.4. Anal. Calcd. for $C_{10}H_8N_6$ (212.22): C, 56.60; H, 3.80; N, 39.60. Found: C, 56.68; H, 3.91; N, 39.47.

5-[1-(2′-Chlorophenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole (4b). Yield 72%; mp 189–190°C; IR (KBr): 3111 (br, NH), 1630 (C═N, tetrazole). ^{1}H-NMR (300 MHz, DMSO) δ 7.67–7.70 (2H, m), 7.80–7.88 (2H, m), 8.44 (1H, s), and 8.92 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 107.9, 128.2, 128.3, 128.5, 130.8, 130.9, 132.1, 137.7, 139.7, and 149.3. Anal. Calcd. for $C_{10}H_7N_6Cl$ (246.66): C, 48.70; H, 2.86; N, 34.07. Found: C, 48.68; H, 2.90; N, 34.11.

5-[1-(3′-Chlorophenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole (4c). Yield 81%; mp 238–239°C; IR (KBr): 3117 (NH), 1639 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 7.56–7.60 (1H, m), 7.70 (1H, t, *J* = 8.1 Hz), 8.04–8.07 (1H, m), 8.18 (1H, t, *J* = 2.1 Hz), 8.44 (1H, s), and 9.37 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 108.8, 117.7, 117.8, 127.0, 128.2, 131.6, 140.1, 140.2, 144.3, and 149.3. Anal. Calcd. for $C_{10}H_7N_6Cl$ (246.66): C, 48.70; H, 2.86; N, 34.07. Found: C, 48.66; H, 2.91; N, 34.12.

5-[1-(4′-Chlorophenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole (4d). Yield 72%; mp 239–240°C; IR (KBr): 3112 (NH), 1631 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 7.72 (2H, d, *J* = 9.0 Hz), 8.07 (2H, d, *J* = 9.0 Hz), 8.40 (1H, s), and 9.25 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 108.4, 119.8, 125.6, 129.6, 132.7, 136.3, 138.8, and 149.8. Anal. Calcd. for $C_{10}H_7N_6Cl$ (246.66): C, 48.70; H, 2.86; N, 34.07. Found: C, 48.65; H, 2.90; N, 34.13.

5-[1-(2′,4′-Dichlorophenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole (4e). Yield 73%; mp 230°C; IR (KBr): 3107 (NH), 1629 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 7.76 (1H, dd, *J* = 8.7;2.4 Hz), 7.84 (1H, d, *J* = 8.7 Hz), 8.05 (1H, d, *J* = 2.4 Hz), 8.45 (1H, s),

and 8.91 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 108.6, 119.7, 128.5, 130.2, 130.7, 131.5, 133.1, 137.0, 138.7, and 149.4. Anal. Calcd. for $C_{10}H_6N_6Cl_2$ (281.11): C, 42.73; H, 2.15; N, 29.90. Found: C, 42.66; H, 2.20; N, 29.98.

5-[1-(3′,4′-Dichlorophenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole (4f). Yield 80%; mp 243–245°C; IR (KBr): 3141 (NH), 1637 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 7.92 (1H, d, *J* = 9.0 Hz), 8.07 (1H, dd, *J* = 9.0;2.7 Hz), 8.37 (1H, d, *J* = 2.7 Hz), 8.46 (1H, s), and 9.38 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 108.6, 119.9, 128.0, 129.2, 130.9, 132.6, 132.9, 135.1, 138.7, and 149.3. Anal. Calcd. for $C_{10}H_6N_6Cl_2$ (281.11): C, 42.73; H, 2.15; N, 29.90. Found: C, 42.68; H, 2.21; N, 29.95.

5-[1-(3′,5′-Dichlorophenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole (4g). Yield 85%; mp 258–260°C; IR (KBr): 3100 (NH), 1639 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 7.69 (1H, d, *J* = 2.1 Hz), 8.18 (2H, d, *J* = 2.1 Hz), 8.37 (1H, s), and 9.30 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 108.5, 119.8, 127.9, 128.4, 130.1, 131.5, 131.0, 134.3, 137.6, and 149.5. Anal. Calcd. for $C_{10}H_6N_6Cl_2$ (281.11): C, 42.73; H, 2.15; N, 29.90. Found: C, 42.69; H, 2.10; N, 29.98.

5-[1-(3′-Bromophenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole (4h). Yield 83%; mp 255–256°C; IR (KBr): 3120 (NH), 1639 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 7.63 (1H, t, *J* = 8.1 Hz), 7.71 (1H, d, *J* = 8.1 Hz), 8.10 (1H, d, *J* = 8.1 Hz), 8.31 (1H, t, *J* = 2.1 Hz), 8.43 (1H, s), and 9.37 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 108.8, 118.0, 121.7, 122.3, 128.2, 130.0, 131.8, 140.2, 140.3, and 149.4. Anal. Calcd. for $C_{10}H_7N_6Br$ (291.11): C, 41.26; H, 2.42; N, 28.87. Found: C, 41.13; H, 2.31; N, 29.01.

5-[1-(4′-Bromophenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole, (4i). Yield 69%; mp 249–250°C; IR (KBr): 3111 (NH), 1632 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 7.86 (2H, d, *J* = 9.0 Hz), 8.05 (2H, d, *J* = 9.0 Hz), 8.42 (1H, s), and 9.23 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 109.8, 120.0, 121.8, 128.3, 133.2, 138.6, 140.5, and 150.0. Anal. Calcd. for $C_{10}H_7N_6Br$ (291.11): C, 41.26; H, 2.42; N, 28.87. Found: C, 41.12; H, 2.33; N, 28.98.

5-[1-(2′-Fluorophenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole (4j). Yield 64%; mp 194–195°C; IR (KBr): 3101 (NH), 1634 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 7.50–7.56 (1H, m), 7.61–7.68 (2H, m), 7.99 (1H, t, *J* = 8.1 Hz), 8.47 (1H, s), and 8.96 (1H, d, *J* = 2.4 Hz); ^{13}C-NMR (75 MHz, DMSO) δ 108.6, 117.8, 125.8, 126.5, 127.7, 127.8, 130.2, 131.8, 140.0, and 149.7. Anal. Calcd. for $C_{10}H_7N_6F$ (230.21): C, 52.18; H, 3.06; N, 36.51. Found: C, 52.13; H, 2.99; N, 36.60.

5-[1-(4′-Fluorophenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole (4k). Yield 82%; mp 258–259°C; IR (KBr): 3136 (NH), 1635 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 7.52 (2H, t, *J* =8.7 Hz), 8.09 (2H, dd, *J* = 9.3;4.8 Hz), 8.40 (1H, s), and 9.25 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 108.6, 117.4, 121.5, 128.0, 135.7, 135.8, 139.8, and 149.3. Anal. Calcd. for $C_{10}H_7N_6F$ (230.21): C, 52.18; H, 3.06; N, 36.51. Found: C, 52.10; H, 3.01; N, 36.58.

5-[1-(4′-Methoxyphenyl)-1*H*-pyrazole-4-yl)]-1*H*-tetrazole (4l). Yield 69%;mp 229–231°C; IR (KBr): 3121 (NH), 1634 (C═N, tetrazole); ^{1}H-NMR (300 MHz, DMSO) δ 3.93 (3H, s), 7.22 (2H, d, *J* = 9.0 Hz), 7.94 (2H, d, *J* = 9.0 Hz), 8.36 (1H, s), and 9.14 (1H, s); ^{13}C-NMR (75 MHz, DMSO) δ 55.8, 108.2, 114.5, 121.8, 127.7, 132.7, 139.3, 149.5, and 158.1. Anal. Calcd. for $C_{11}H_{10}N_6O$ (242.24): C, 54.54; H, 4.16; N, 34.69. Found: C, 54.35; H, 4.25; N, 34.51.

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REFERENCES AND NOTES

[1] Katritzky, A. R. Chem Rev 2004, 104, 2125.

[2] Gupta, R. R.; Khan, M. T. H. Topics Heterocyclic Chemistry: Bioactive Heterocycles IV; Springer: Berlin, 2007; Vol. 10, p 1.

[3] Bekhit, A. A.; Ashour, H. M. A.; Ghany, Y. S. A.; Bekhit, A. E. A.; Baraka, A. Eur J Med Chem 2008, 43, 456.

[4] Kees, K. L.; Fitzgerald, J. J.; Steiner, K. E.; Mattes, J. F.; Mihan, B.; Tosi, T.; Mondoro, D.; McCaleb, M. L. J Med Chem 1996, 39, 3920.

[5] Kotagiri, V. K.; Suthrapu, S.; Reddy, J. M.; Rao, C. P.; Bollugoddu, V.; Bhattacharya, A.; Bandichhor, R. Org Process Res Dev 2007, 11, 910.

[6] Fancelli, D.; Moll, J.; Varasi, M.; Bravo, R.; Artico, R.; Berta, D.; Bindi, S.; Cameron, A.; Candiani, I.; Cappella, P.; Carpinelli, P.; Croci, W.; Forte, B.; Giorgini, M. L.; Klapwijk, J.; Marsiglio, A.; Pesenti, E.; Rocchetti, M.; Roletto, F.; Severino, D.; Soncini, C.; Storici, P.; Tonani, R.; Zugnoni, P.; Vianello, P. J Med Chem 2006, 49, 7247.

[7] Bavetsias, V.; Marriott, J. H.; Melin, C.; Kimbell, R.; Matusiak, Z. S.; Boyle, F. T.; Jackman, A. L. J Med Chem 2000, 43, 1910.

[8] Barreca, M. L.; De Luca, L.; Iraci, N.; Chimirri, A. J Med Chem 2006, 49, 3994.

[9] Walker, M. A.; Johnson, T.; Ma, Z.; Banville, J.; Remillard, R.; Kim, O.; Zhang, Y.; Staab, A.; Wong, H.; Torri, A.; Samanta, H.; Lin, Z.; Deminie, C.; Terry, B.; Krystal, M.; Meanwell, N. Bioorg Med Chem Lett 2006, 16, 2920.

[10] Bekhit, A. A.; Ashour, H. M. A.; Ghany, Y. S. A.; Bekhit, A. E. A.; Baraka, A. Eur J Med Chem 2008, 43, 456.

[11] Aly, A. A. Chin J Chem 2005, 83, 5.

[12] Chohan, Z. H.; Supuran, C. T.; Scozzafava, A. J. Enzyme Inhib Med Chem 2004, 19, 79.

[13] Yet, L. Comprehensive Heterocyclic Chemistry III: Pyrazoles; Elsevier: USA, 2008; p 1.

[14] Elguero, J. Comprehensive Heterocyclic Chemistry: Pyrazoles and their Benzo Derivatives; Elsevier: USA; 1984; p 167.

[15] Borges, J. C.; Oliveira, C. D.; Pinheiro, L. C. S.; Marra, R. K. F.; Khan, M. A.; Wardell, J. L.; Wardell, S. M. S. V.; Bernardino, A. M. R. J Braz Chem Soc 2007, 18, 1571.

[16] Stanovnik, B.; Svete, J. Science of Synthesis; Thieme: Stuttgart, 2002; Vol. 12, p 15.

[17] Stanovnik, B.; Svete, J. Chem Rev 2004, 104, 2433.

[18] Ostrovskii, V. A.; Koldobskii, G. I.; Trifonov, R. E. Comprehensive Heterocyclic Chemistry III: Tetrazoles; Elsevier: USA, 2008; p 257.

[19] Santos, M. S.; Gomes, A. O.; Bernardino, A. M. R.; Souza, M. C.; Khan, M. A.; Brito, M. A.; Castro, H. C.; Abreu, P. A.; Rodrigues, C. R.; Léo, R. M. M.; Leon, L. L.; Canto-Cavalheiro, M. M. J Braz Chem Soc 2011, 22, 352.

[20] Charret, K. S.; Rodrigues, R. F.; Bernardino, A. M. R.; Gomes, A. O.; Carvalho, A. V.; Canto-Cavalheiro, M. M.; Leon, L. L.; Amaral, V. F. Am J Trop Med Hyg 2009, 80, 568.

[21] Pinheiro, L. C. S.; Abreu, P. A; Afonso, I. F.; Leal, B.; Corrêa, L. C. D.; Borges, J. C; Marques, I. P.; Lourenço, A. L.; Sathler, P.; Santos, A. L.; Medeiros, C. A.; Cabral, L. M.; Júnior, M. L. O.; Romeiro, G. A.; Ferreira, V. F.; Rodrigues, C. R.; Castro, H. C.; Bernardino, A. M. R. Curr Microbiol 2008, 57, 463.

[22] Bernardino, A. M. R.; Castro, H. C.; Frugulhetti, I. C. P. P.; Loureiro, N. I. V.; Azevedo, A. R.; Pinheiro, L. C. S.; Souza, T. M. L.; Giongo, V.; Passamani, F.; Magalhães, U. O.; Albuquerque, M. G.; Cabral, L. M.; Rodrigues, C. R. Bioorg Med Chem 2008, 16, 313.

[23] Bernardino, A. M. R.; Gomes, A. O.; Charret, K. S.; Freitas, A. C. C.; Machado, G. M. C.; Canto-Cavalheiro, M. M.; Leon, L. L.; Amaral, V. F. Eur J Med Chem 2006, 41, 80.

[24] Mello, H.; Echevarria, A.; Bernardino, A. M. R.; Canto-Cavalheiro, M. M.; Leon, L. L. J Med Chem 2004, 47, 5427.

[25] Finar, I. L.; Lord, G. H. J Chem Soc 1957, 3314.

[26] De la Hoz, A.; Diaz-Ortiz, A.; Elguero, J.; Martínez, L. J.; Moreno, A.; Sánchez-Migallón, A. Tetrahedron 2001, 57, 4397.

[27] Cheng, C. C.; Robins, R. K. J Org Chem 1956, 21, 1240.

[28] Dooley, M. J.; Quinn, R. J.; Scammells, P. J. Aust J Chem. 1989, 42, 747.

[29] Cadogan, J. I. G.; Molina, G. A. J Chem Soc Perkin Trans I 1973, 541.

[30] Friedman, L.; Logullo, F. M. J Am Chem Soc 1963, 85, 1549.

[31] Cadogan, J. I. G.; Roy, D. A.; Smith, D. M. J Chem Soc (C) 1966, 1249.

[32] Sharon, A.; Pratap, R.; Tiwari, P.; Srivastava, A.; Maulik, P. R.; Ram, V. J. Bioorg Med Chem Lett 2005, 15, 2115.