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RESEARCH ARTICLE - CHEMISTRY

A Simple Process for the Synthesis of Novel Pyrazolyltriazole and Dihydropyrazolylthiazole Derivatives as Antimicrobial Agents

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Abstract Series of novel 1,2-*bis*((3-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazines **4** and 2-(5-(3-(1,2,3-triazol-4-yl)pyrazol-4-yl) pyrazol-1-yl)thiazoles **13** were synthesized using simple and convenient procedures, and their structures were established. Treatment of pyrazole-4-carbaldehydes **1** with methyl ketones in alkaline medium gave the corresponding (*E*)-1-aryl-3-(3-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-ones **3** in 82–86% yields. Treatment of **3** with hydrazine hydrate gave **4**, in 69–75% yields, rather than the expected 1-aryl-5-methyl-4-(1-aryl-4-(3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazoles. Reactions of **3** with thiosemicarbazide gave the corresponding carbothioamides **9** which in reaction with phenacyl bromides gave the corresponding dihydropyrazolylthiazoles **13** in 82–87% yields. The novel synthesized product exhibits good antimicrobial activities against the tested microorganisms.

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1 Introduction

Pyrazole ring systems are very important and have various applications [1–4]. The most recent processes for the production of pyrazole derivatives involve reactions of 1,2-diols and diarylhydrazones in the presence of an iron-containing catalyst [5], 1,3-diols and alkyl hydrazines in the presence of a ruthenium catalyst [6], aryl aldehydes and tosylhydrazine in the presence of terminal alkynes [7], arylglycines and tosylhydrazine [8], propargylic alcohols and arylhydrazines [9], terminal alkynes and *n*-butyllithium followed by a reaction with aldehydes, iodine and hydroxylamine or hydrazine [10] and 1,3-diketones with hydrazine[11] or arylhydrazines [12].

Various pyrazolyltriazoles [13,14] and pyrazolylthiazoles [15–18] have been synthesized which showed an interesting range of medicinal applications. In the current work, we report the production of novel pyrazolyltriazole and dihydropyrazolylthiazole derivatives, in high yields, as potential antimicrobial agents using a simple and convenient process as part of our interest in synthetic organic chemistry [19–24].

2 Experimental

2.1 General

Electrothermal IA 9000 melting point apparatus was used to detect the melting points. Elemental analyses were performed at Cairo University, Egypt. JASCO FT/IR-6100 was used to record the IR spectra (KBr disks). JOEL-ECA 600MHz

was used to run the ^{1}H and ^{13}C NMR spectra in deuterated dimethyl sulfoxide (DMSO-d_6) relative to the TMS. Mass Varian MAT CH-5 spectrometer was used to perform the mass spectra at 70 eV. The crystallographic data for compounds **4c**, **13a** and **13e** have been deposited at the Cambridge Crystallographic Data Center (CCDC) as CCDC 1521980, CCDC 1521981 and CCDC 1521982, respectively. Compounds **1** were synthesized using literature procedures [25,26].

2.2 Chemistry

*2.2.1 Synthesis of **3***

A solution of **1** (5 mmol) and methyl ketone **2** (5 mmol) in EtOH (70 mL, 90 %) was added slowly to a stirred solution of NaOH (5 mmol) in H_2O (10 mL). The mixture was stirred for 5 h, and the solid obtained was filtered. The products were crystallized from EtOH to afford pure **3**.

*2.2.1.1 (E)-3-(3-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one (**3a**)*

Yield 82%; Mp 201–202 °C. IR (KBr) ν_{max}/cm^{-1} 1674 (C=O). ^{1}H NMR: δ 2.48 (s, 3H, CH_3), 7.39–7.97 (m, 15H, Ar-H), 8.12 (d, 1H, J = 15.0 Hz, CH), 8.51 (d, 1H, J = 15.0 Hz, CH), 9.52 (s, 1H, pyrazole-H). ^{13}C NMR: δ 9.9, 116.5, 116.6 118.5, 118.9, 121.3, 125.4, 127.3, 128.3, 128.4, 128.8, 129.7, 129.8, 132.9, 133.1, 133.9, 135.8, 137.8, 138.9, 144.8, 188.9. MS (EI) m/z (%): 431 (M^+, 60), 77 (100). Anal. Calcd. for $C_{27}H_{21}N_5O$ (431.49): C, 75.16; H, 4.91; N, 16.23%. Found: C, 75.32; H, 4.94; N, 16.52.

*2.2.1.2 (E)-1-(4-Chlorophenyl)-3-(3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl) prop-2-en-1-one (**3b**)*

Yield 84%; Mp 208–209 °C. IR (KBr) ν_{max}/cm^{-1} 1679 (C=O). ^{1}H NMR: δ 2.49 (s, 3H, CH_3), 7.52–7.95 (m, 13H, Ar-H), 8.13 (d, 1H, J = 15.0 Hz, CH), 8.51 (d, 1H, J = 15.0 Hz, CH), 9.52 (s, 1H, pyrazole-H). ^{13}C NMR: δ 9.8, 116.6, 116.8, 118.6, 118.9, 120.9, 127.3, 127.8, 128.5, 128.9, 129.9, 130.2, 133.2, 135.4, 136.1, 136.5, 137.7, 137.9, 138.9, 145.2, 187.8. MS (EI) m/z (%): 485 ($[M^{37}Cl]^+$, 18), 483 ($[M^{35}Cl]^+$, 50), 77 (100). Anal. Calcd. for $C_{27}H_{19}ClFN_5O$ (483.92): C, 67.01; H, 3.96; N, 14.47%. Found: C, 67.27; H, 4.09; N, 14.68.

*2.2.1.3 (E)-3-(3-(1-(4-Bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-tolyl)prop-2-en-1-one (**3c**)*

Yield 86%; Mp 168–169 °C. IR (KBr) ν_{max}/cm^{-1} 1680 (C=O). ^{1}H NMR: δ 2.43 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.37–7.92 (m, 13H, Ar-H), 8.12 (d, 1H, J = 15.1 Hz, CH), 8.55 (d, 1H, J = 15.1 Hz, CH), 9.49 (s, 1H, pyrazole-H). ^{13}C NMR: δ 9.9, 21.3, 116.6, 116.8, 118.4, 118.8, 120.7, 125.3, 127.1, 127.7, 128.3, 129.6, 130.2, 131.8, 132.8, 133.1, 135.7, 136.7, 137.8, 138.8, 144.8, 187.8. MS (EI) m/z (%): 525 ($[M^{81}Br]^+$, 20), 523 ($[M^{79}Br]^+$, 21), 77 (100). Anal. Calcd. for$C_{28}H_{22}BrN_5O$ (524.41): C, 64.13; H, 4.23; N, 13.35%. Found: C, 64.28; H, 4.52; N, 13.65.

*2.2.1.4 (E)-3-(3-(1-(4-Chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-tolyl)prop-2-en-1-one (**3d**)*

Yield 83%; Mp 189–190 °C. IR (KBr) ν_{max}/cm^{-1} 1677 (C=O). ^{1}H NMR: δ 2.44 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.35–7.91 (m, 13H, Ar-H), 8.13 (d, 1H, J = 15.0 Hz, CH), 8.53 (d, 1H, J = 15.0 Hz, CH), 9.51 (s, 1H, pyrazole-H). ^{13}C NMR: δ 9.9, 21.2, 116.6, 116.8, 118.4, 118.9, 120.7, 125.3, 127.1, 127.6, 128.3, 129.6, 130.2, 131.8, 132.8, 133.2, 135.7, 136.7, 137.8, 138.8, 144.7, 187.7. MS (EI) m/z (%): 481 ($[M^{37}Cl]^+$, 14), 479 ($[M^{35}Cl]^+$,44), 77 (100). Anal. Calcd. for $C_{28}H_{22}ClN_5O$ (479.96): C, 70.07; H, 4.62; N, 14.59%. Found: C, 70.18; H, 4.48; N, 14.80.

*2.2.2 Synthesis of **4***

Hydrazine hydrate (5 mmol; 80%) was added to **3** (1 mmol) in EtOH (30 mL), and the mixture was refluxed for 6 h. The solid formed on cooling was filtered, washed with EtOH and dried to give pure **4**.

*2.2.2.1 1,2-Bis((3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazine (**4a**)*

Yield 75%; Mp 197–199 °C. ^{1}H NMR: δ 2.49 (s, 6H, 2 CH_3), 7.61–8.01 (m, 20H, Ar-H), 8.53 (s, 2H, 2 CH=N), 9.52 (s, 2H, pyrazole-H). ^{13}C NMR: δ 9.9, 118.6, 118.9, 120.9, 125.4, 128.5, 129.8, 130.9, 132.9, 135.7, 136.8, 137.8, 138.9, 144.9, 187.9. MS (EI) m/z (%): 654 (18), 132 (100). Anal. Calcd. for $C_{38}H_{30}N_{12}$ (654.73): C, 69.71; H, 4.62; N, 25.67%. Found: C, 69.94; H, 4.79; N, 25.77.

*2.2.2.2 1,2-Bis((3-(5-methyl-1-(4-tolyl)-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazine (**4b**)*

Yield 73%; Mp 208–209 °C. ^{1}H NMR: δ 2.43 (s, 6H, 2 CH_3), 2.49 (s, 6H, 2 CH_3), 7.47–7.96 (m, 18 H, Ar-H), 8.50 (s, 2H, 2 CH=N), 9.53 (s, 2H, pyrazole-H). MS (EI) m/z (%): 682 (18), 132 (100). Anal. Calcd. for $C_{40}H_{34}N_{12}$ (682.78): C, 70.36; H, 5.02; N, 24.62%. Found: C, 70.54; H, 4.89; N, 24.37.

*2.2.2.3 1,2-Bis((3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazine (**4c**)*

Yield 69%; Mp 202–205 °C. ^{1}H NMR: δ 2.48 (s, 6H, 2 CH_3), 7.50–8.13 (m, 18 H, Ar-H), 8.52 (s, 2H, 2 CH=N), 9.51 (s, 2H, pyrazole-H). ^{13}C NMR: δ 9.8, 118.6, 116.8,