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ORIGINAL ARTICLE

Synthesis and biological evaluation of newer analogues of 2,5-disubstituted 1,3,4-oxadiazole containing pyrazole moiety as antimicrobial agents

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Abstract A series of 2,5-disubstituted-1,3,4-oxadiazole derivatives bearing pyrazole moiety were synthesized by reacting various substituted pyrazole-4-carboxylic acids with different hydrazides in $POCl_3$. All the synthesized compounds **(4a–n)** were characterized by IR, NMR, mass spectra and elemental analyses. Synthesized 1,3,4-oxadiazole derivatives were screened for their antibacterial activity against three different strains, namely *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, while antifungal activity was determined against three different strains *Aspergillus flavus*, *Chrysosporium keratinophilum* and *Candida albicans*. The investigation of antimicrobial screening revealed that compounds **4i** and **4j** exhibited excellent activity when compared with the standard drugs.

1. Introduction

Infectious diseases are one of the leading causes of death worldwide. During the past few decades, new infectious diseases have appeared and old ones previously thought to be controlled have reemerged (Sharma and Jain, 2008). Despite the critical need for new antimicrobial agents, the development of these agents is declining. Solutions encouraging and facilitating the development of new antimicrobial agents are needed.

1,3,4-Oxadiazoles constitute an important family of heterocyclic compounds as they have attracted significant interest in

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medicinal chemistry, pesticide chemistry and polymer science (Bostrom et al., 2012; Mohan et al., 2004; Schulz et al., 1997). Since many of 1,3,4-oxadiazoles display a remarkable biological activity (Zoumpoulakis et al., 2012; Ingale et al., 2012), their synthesis and transformations have been receiving particular interest for a long time (Bondock et al., 2012). Most of the marketed antihypertensive agents such as Tiodazosin (Vardan et al., 1983) and Nesapidil (Schlecker and Thieme, 1988) as well as antibiotics such as Furamizole (Ogata et al., 1971) contain oxadiazole nucleus. During the past years, considerable evidences have accumulated to demonstrate the efficacy of 1,3,4-oxadiazole including antimicrobial (Zoumpoulakis et al., 2012), anti-inflammatory, analgesic (Ingale et al., 2012), anti-HIV (Sriram et al., 2009), antimycobacterial (Macaev et al., 2005), cathepsin K inhibitors (Palmer et al., 2006), tyrosinase inhibitors (Khan et al., 2005), monoamine oxidase (MAO) inhibitors (Ke et al., 2008) and anticonvulsant (Almasirad et al., 2004) properties.

The pyrazole motif makes up the core structure of numerous biologically active compounds (Elguero et al., 2002). Thus, some representatives of this heterocycle have an affinity for the human CRF-1 receptor (Wustrow et al., 1998), exhibit antiviral/anti-tumor (Manfredini et al., 1992; Sunil et al., 2013; Park et al., 2005), antimicrobial (Isloor et al., 2009; Vijesh et al., 2010) antipyretic (Eid et al., 1978), anti-inflammatory (Bekhit et al., 2003), analgesic (Menozzi et al., 1997), fungistatic (Sridhar et al., 2004), fungicidal (Rich and Horsfall, 1952) and anti-hyperglycemic activity (Kees et al., 1996; Bebernitz et al., 2001). Apart from this, pyrazole entity may also be used as nonlinear optical materials (Chandrakantha et al., 2013). Against this background, to extend our research work in heterocyclic synthesis coupled with the significant biological importance of oxadiazoles and pyrazole derivatives, prompted us to undertake the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles. We report herein the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles with an expectation to find new and more potent antimicrobial agents.

2. Experimental

2.1. Materials and methods

All the laboratory grade reagents were obtained commercially. The reaction was monitored by thin layer chromatography, which was performed on Merck precoated plates (silica gel. 60 F_{254}, 0.25 mm) and was visualized by fluorescence quenching under UV light (254 nm). Melting points were determined by the open capillary method and were uncorrected. The IR spectra were recorded on a Thermo Nicolet avatar 330-FT-IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded (DMSO-d_6) on a Bruker (400 and 100 MHz). Chemical shift values are given in δ scales. The mass spectra were recorded on LC–MS-Agilent 1100 series. Elemental analyses were performed on a Flash EA 1112 series CHNS–O Analyzer.

2.2. Synthesis

2.2.1. General procedure for the synthesis of 3-(4-substitutedphenyl)-1H-pyrazole-4-carboxylic acid (3)

3-Substituted-pyrazole-4-carbaldehydes (0.01 mol) were dissolved by stirring in a solution of 2 g of NaOH in 40 ml of water. The mixture was cooled to 15 °C, and a solution of $KMnO_4$ (0.0088 mol) in 40 ml of water was quickly added. The mixture was stirred for 30 min at 20 °C and then heated to 100 °C until the solution becomes completely decolorized. The solution was cooled and filtered to remove MnO_2 precipitate. Then the filtrate was acidified with Conc. HCl to pH 3. The resulting solid was filtered off, washed with water and dried (Lebedev et al., 2005).

2.2.2. General procedure for the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles (4a–n)

An equimolar mixture of respective substituted acid hydrazides **(2)** (0.001 mol) and 3-(4-substituted phenyl-1H-pyrazole-4-carboxylic acids **(3)** (0.001 mol) was dissolved in 5 ml of dry phosphorous oxychloride. The resulted solution was further refluxed for 8–9 h. Excess of phosphorous oxychloride was then distilled off and the mixture was gradually poured into crushed ice with stirring. The separated solid was filtered, washed thoroughly with cold water, 20% $NaHCO_3$ solution and recrystallized from a mixture of DMF and water.

2.3. Characterization of synthesized compounds

2.3.1. 2-(4-Chlorophenyl)-5-(3-phenyl-1H-pyrazol-4-yl)-1,3,4-oxadiazole (4a)

Color: off white amorphous solid. Yield 66%, m.p. 223–225 °C. IR (KBr, υ_{max} cm^{-1}): 3143 (N–H-str), 3053 (C–H-str), 1593 (C═N), 1531 (C═C), 1087 (C–O–C); ^{1}H-NMR (DMSO-d_6): δ 13.79 (s, 1H, pyrazole-NH), 8.7 (s, 1H, pyrazole-5H), 7.55–8.0 (m, 9H, Ar–H). MS: m/z = 321 (M-1). Anal. calcd. for $C_{17}H_{11}ClN_4O$: C, 63.26; H, 3.44; N, 17.36. Found: C, 63.23; H, 3.49; N, 17.30%.

2.3.2. 2-(4-Chlorophenyl)-5-(3-(4-chlorophenyl)-1H-pyrazol-4-yl)-1,3,4-oxadiazole (4b)

Color: off white amorphous solid. Yield 68%, m.p. 126–128 °C. IR (KBr, υ_{max} cm^{-1}): 3160 (N–H-str), 3021 (C–H-str), 1603 (C═N), 1554 (C═C), 1090 (C–O–C); ^{1}H-NMR (DMSO-d_6): δ 13.71 (s, 1H, pyrazole-NH), 8.67 (s, 1H, pyrazole-5H), 7.52–8.23 (m, 8H, Ar–H). MS: m/z = 357 (M+), 359 (M+2), 361 (M+4). Anal. calcd. for $C_{17}H_{10}Cl_2N_4O$: C, 57.16; H, 2.82; N, 15.69. Found: C, 57.11; H, 2.86; N, 15.65%.

2.3.3. 2-(4-Chlorophenyl)-5-(3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1,3,4-oxadiazole (4c)

Color: off white amorphous solid. Yield 75%, m.p. 273–275 °C. IR (KBr, υ_{max} cm^{-1}): 3182 (N–H-str), 3077 (C–H-str), 1609 (C═N), 1542 (C═C), 1089 (C–O–C); ^{1}H-NMR (DMSO-d_6): δ 13.73 (s, 1H, pyrazole-NH), 8.5 (s, 1H, pyrazole-5H), 7.32–7.98 (m, 8H, Ar–H). ^{13}C-NMR: 162.59, 160.78, 136.97, 131.38, 131.30, 130.04, 129.87, 128.60, 122.78, 115.77, 115.55, 103.14. MS: m/z = 341(M+1), 343 (M+2). Anal. calcd. for $C_{17}H_{10}ClFN_4O$: C, 59.92; H, 2.96; N, 16.44. Found: C, 59.96; H, 2.90; N, 16.49%.

2.3.4. 2-(4-Chlorophenyl)-5-(3-(4-methoxyphenyl)-1H-pyrazol-4-yl)-1,3,4-oxadiazole (4d)

Color: off white amorphous solid. Yield 73%, m.p. 176–178 °C. IR (KBr, υ_{max} cm^{-1}): 3143 (N–H-str), 3014 (C–H-str), 1605 (C═N), 1516 (C═C), 1088 (C–O–C); ^{1}H-NMR (DMSO-d_6):