Journal of Saudi Chemical Society (2014) **18**, 255–261

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Synthesis and antimicrobial screening of 1,3,4-oxadiazole and clubbed thiophene derivatives

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Received 3 May 2011; accepted 29 June 2011
Available online 5 July 2011

KEYWORDS

1,3,4-Oxdiazole;
Thiophene;
Antibacterial agents;
Antifungal activity;
MIC

Abstract In the present study, a novel series of 2-{5-[4-(1-aza-2-(2-thienyl)vinyl)phenyl](1,3,4-oxadiazol-2-ylthio)}-*N*-arylacetamides **(IV)$_{1–12}$** were synthesized and tested for their antimicrobial activity. Newly synthesized compounds were screened for their antibacterial and antifungal activities on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus pyogenes*, *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*. The chemical structures of newly synthesized compounds were elicited by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The synthesized bio-active compounds exhibited excellent to moderate antimicrobial activity. Compounds **(IV)$_5$**, **(IV)$_6$** and **(IV)$_7$** possess excellent antibacterial activity whereas compounds **(IV)$_6$**, **(IV)$_9$** and **(IV)$_{11}$** possess excellent antifungal activity.

1. Introduction

As resistance to antimicrobial drugs is widespread, there is an increasing need for identification of novel structure leads that may be of use in designing new, potent, and less toxic antimicrobial agents. The multiple pharmacological actions of unique synthetic compounds are a prerequisite for classifying a drug as highly efficacious, because these actions offer possibility of treating various diseases. 1,3,4-Oxadiazoles are an important class of heterocyclic compounds with broad spectrum of biological activities and are commonly utilized pharmacophores due to their metabolic profile and ability to engage in hydrogen bonding. In particular, 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 (Prasad et al., 2008), anti-inflammatory, analgesic (Kashaw et al., 2010), anti-HIV (Sriram et al., 2009), antimycobacterial (Macaey 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. 1,3,4-Oxadiazole-carboxamides containing different lipophilic moieties (i.e. 4-diphenyl, 1-napthyl, phenyl propyl and *n*-hexyl substituents) and additional basic groups which are mainly alkyl and amino alkyl residues have

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1319-6103

Peer review under responsibility of King Saud University.
doi:10.1016/j.jscs.2011.06.020

been recently described as antiplatelet and antithrombotic compounds as well as serotonin antagonist (Bethge et al., 2005). 2-Amino-1,3,4-oxadiazole has demonstrated biological activity as a muscle relaxant (Yale and Losee, 1966), while biarylpyrazolyl oxadiazole behaves as potent, selective, orally bioavailable cannabinoid-1 receptor antagonist for the treatment of obesity (Lee et al., 2008).

Moreover thiophene derivatives are undoubtedly one of the most important class of heterocycles, because some of thiophene skeleton containing molecules have been reported to exhibit interesting pharmaceutical properties including antimicrobial (Queiroz et al., 2006), anticancer (Thomson et al., 2006), anti-inflammatory (Kumar et al., 2004), bacteriostatic and fungistatic activity (Kipnis et al., 1949). Some other derivatives exhibit a strong inhibition of NHE-1 and cardioprotective efficacy (Cho et al., 2005).

Looking at the medicinal importance of 1,3,4-oxadiazole and thiophene moieties, we report here the synthesis of a new class of heterocyclic molecules in which both the moieties are present and attempt to develop potential bioactive molecules. The structures of synthesized compounds were assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. These compounds were evaluated for their antimicrobial screening on different strains of bacteria and fungi.

2. Experimental

2.1. Materials and physical measurements

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. All reaction courses and product mixtures were routinely monitored by aluminium coated thin-layer chromatography (TLC) plates 60 F_{245} (E. Merck) and visualized with ultraviolet (UV) light, or iodine vapour. Melting points were determined on an electro thermal melting point apparatus and are reported uncorrected. Elemental analysis (% C, H, N) was carried out by a Perkin–Elmer 2400 CHN analyser. IR spectra of all compounds have been recorded on a Perkin–Elmer FT-IR spectrophotometer in KBr. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker (400 MH_Z) spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Schimadzu LCMS 2010 spectrophotometer. Anhydrous reactions were carried out in oven-dried glassware in nitrogen atmosphere. In the conventional method, compounds were synthesized by using Random synthesizer. Bookie Rotavapour is used for distillation. The completion of the reaction and the purity of all compounds were checked on aluminium coated TLC plates 60 F_{245} (E. Merck) using hexane-ethyl acetate (7.5:2.5 V/V) as mobile phase and visualized with ultraviolet (UV) light, or iodine vapour.

2.2. Preparation methods and physical data of synthesized compounds (*I*) to (*IV*)$_{1–12}$

2.2.1. Procedure for the synthesis of N-amino(4-aminophenyl)carboxamide (*I*)

Compound *N*-amino(4-aminophenyl)carboxamide (**I**) was prepared according to the literature method (Mathew et al., 2006).

2.2.2. Procedure for the synthesis of 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol (*II*)

A mixture of *N*-amino(4-aminophenyl)carboxamide (**I**) (0.1 mol), potassium hydroxide (0.1 mol), carbon disulfide (0.1 mol) and ethanol (20 mL) was heated under reflux until the evolution of hydrogen sulfide ceased . The reaction mixture was cooled to room temperature and poured into ice cold water (100 mL). It was neutralized with dilute hydrochloric acid. The precipitated solid was filtered, washed with water and the dried product was recrystallized from ethanol. Yield: 70%; white powder; m.p.: 257–259 °C; IR (KBr, cm^{-1}): 3350 and 3418 (N–H stretching, primary amine), 3050 (C–H stretching, aromatic ring), 1625, 1587, 1556 (C═N, C═C stretching, aromatic ring), 1206 (C–O–C stretching, oxadiazole); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.31 (s, 2H, NH_2), 6.45–7.60 (m, 4H, Ar–H), 13.21 (s, 1H, SH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 116.4 (C-5, 7), 118.1 (C-3) , 127.6 (C-4, 8) 143.6 (C-6), 161.2 (C-1), 171.3 (C-2); LCMS (*m*/*z*): 193 (M^+). Found: C-49.67, H-3.62, N-21.78; Anal. Calcd. For $C_8H_7N_3OS$ (193.03): C-49.73, H-3.65, N-21.75%.

2.2.3. Procedure for the synthesis of 5-[4-(1-aza-2-(2-thienyl)vinyl)phenyl]-1,3,4-oxadiazole-2-thiol (*III*)

Compound **(II)** (0.1 mol) was dissolved in ethanol (75 mL). Then, thiophene-2-carbaldehyde (0.1 mol) was added drop wise. The reaction mixture was refluxed for 5 h. Excess of solvent was distilled off and the mixture was allowed to cool at room temperature. The separated product was filtered, washed with cold water, dried and recrystallized from ethanol. Yield 78%; white crystal; m.p.: 191–194 °C; IR (KBr, cm^{-1}): 3338 (–NH stretching, secondary amine), 3050 (C–H stretching, aromatic ring), 1627, 1590, 1554 (C═N, C═C stretching, aromatic ring), 1203 (C–O–C stretching, oxadiazole); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.74–7.85 (m, 7H, Ar–H), 8.21 (s, 1H, –CH═N–), 13.24 (s, 1H, SH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 120.1 (C-5, 7), 124.4 (C-3), 127.3 (C-12), 128.2 (C-4, 8), 128.6 (C-13), 130 (C-11), 141.4 (C-10), 147.6 (C-6), 149.7 (C-9), 161.3 (C-1), 171.4 (C-2); LCMS (*m*/*z*): 287 (M^+). Found: C-54.21, H-3.20, N-14.53; Anal. Calcd. For $C_{13}H_9N_3OS_2$ (287.02): C-54.34, H-3.16, N-14.62%.

2.2.4. General Procedure for the synthesis 2-{5-[4-(1-aza-2-(2-thienyl)vinyl)phenyl](1,3,4-oxadiazol-2-ylthio)}-N-arylacetamides (*IV*)$_{1–12}$

In a round bottomed flask, compound **3** (0.01 mol) was dissolved in an aqueous solution of potassium hydroxide (25%). The reaction mixture was heated at 80 °C and different substituted α-chloro acetanilide (0.015 mol) in ethanol (10 mL) was added with constant stirring followed by refluxing it for 2 h. The contents were left overnight. The crystals were filtered, washed with water, dried and recrystallized from ethanol.

2.2.4.1. 2-{5-[4-(1-Aza-2-(2-thienyl)vinyl)phenyl](1,3,4-oxadiazol-2-ylthio)}-N-phenyl-acetamide (IV)$_1$. Yield: 61%; white crystal; m.p.: 270–272 °C; IR (KBr, cm^{-1}): 3334 (–NH stretching, secondary amine), 3087, 3054 (C–H stretching, aromatic ring), 2868 (C–H stretching, $–CH_2–$), 1714 (C═O stretching, amide), 1624, 1586, 1554 (C═N, C═C, aromatic ring stretching), 1450 (C–H bending, $–CH_2–$), 1204 (C–O–C stretching,