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ORIGINAL ARTICLE

Synthesis and biological activities of Bis alkyl 1,3,4-oxadiazole incorporated azo dye derivatives

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KEYWORDS

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Abstract 3,5-Bis(alkyl-1,3,4-oxadiazole-2-yl azo dyes were synthesized by a multi-step reaction sequence. Structures of newly synthesized compounds were characterized and confirmed by IR, NMR, and Mass spectral studies. The synthesized compounds were screened for their antimicrobial and *in vitro* antioxidant properties. The results of this investigation revealed that the newly synthesized compounds are potent antibacterial and antioxidant agents. All the synthesized compounds exhibit significant biological activity and certainly hold a greater promise for discovering potent biologically active molecules.

1. Introduction

In recent years, fungal and bacterial infections have become an important complication and a major cause of morbidity and mortality. The growing incidence of fungal and bacterial resistance to existing antibiotics poses a serious medical problem in treating pathogenic infections. Several five-membered hetero cyclic drugs possess diverse biological effects. Nitrogen and oxygen containing five membered azoles are important bioactive agents, due to their vast pharmacological and industrial applications. Synthesis of such heterocyclic compounds is of pharmaceutical importance and a foremost task for chemists. 1,3,4-Oxadiazole derivatives are heterocyclic compounds which exhibit remarkable pharmacological activities. It has been known that the activity of azo linkage increases with the incorporation of a suitable heterocyclic moiety. Heterocyclic azo compounds are well known for their medicinal importance and are recognized for their use as antineoplastics (Child et al., 1977), antidiabetics (Garg and Praksh, 1972), antiseptics (Browing et al., 1926), anti-inflammatory, antibacterial (Khedr et al., 2011; Nikhil et al., 2011) and other useful chemotherapeutic agents (Bae et al., 2003; Sanjay et al., 2007). Azo dyes are used as hypnotic drugs for the nervous system, in detecting

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cancer as chemotherapeutic agents and are involved in the structure of nucleic acids in living cells (Zeynel et al., 2008). Azo dyes are known to be involved in a number of biological reactions such as inhibition of DNA, RNA, protein synthesis, carcinogenesis and nitrogen fixation (Browing et al., 1926; Rajendra et al., 1998). Evans blue and Congo red are being studied as HIV inhibitors. This effect is believed to be caused by binding of azo dyes to both protease and reverse transcriptase of this dreadful virus (Fatma and Eser, 2007). 1,2,3-Oxadiazoles can also act as HIV integrase inhibitors (Sicardi et al., 1980).

1,3,4-Oxadiazoles are five membered heterocyclic compounds having significant position in synthetic and medicinal chemistries due to their wide array of biological activities such as anti fungal (Parkash et al., 2010) antimicrobial (Sridhara et al., 2010), anti-inflammatory, analgesic (Akhter et al., 2009; Idrees et al., 2009; Tozcoparan et al., 2000), hypolipidemic (Jayashankar et al., 2009) anti tubercular (Kumar et al., 2010; Kucukguzel et al., 2002), anti-convulsant (Singh and Pankaj, 2010; Bhat et al., 2010), and cytotoxic agents (Padmavathi et al., 2009), also as prostaglandin receptor antagonists (George et al., 2000) and anti oxidant agent (Abdu Musad et al., 2011; Bondock et al., 2009).

In view of the above mentioned findings and our previous findings on synthesis and pharmacological activities of heterocyclic compounds (Keshavayya et al., 2011a,b, 2006, 2007), in the present study we made an efficient attempt to synthesize alkyl bis 1,3,4-oxadiazole substituted azo dyes coupled with quinoline, possessing potent biological activities. Structures of the synthesized compounds were confirmed by ^{1}H NMR, IR and Mass spectral studies. Synthesized compounds were screened for their antimicrobial and *in vitro* antioxidant properties.

2. Results and discussion

As depicted in Scheme 1, 1,3,4-oxadiazole azo dye derivatives were synthesized by a multi-step reaction sequence. 1,3,4-Oxadiazoles were prepared by reacting 5-nitro bis iso-phthalic dihydrazide with appropriate long chain fatty acids in the presence of phosphorous oxychloride gives 5-nitro alkyl bis 1,3,4-oxadiazoles in good yields. 5-Nitro alkyl bis 1,3,4-oxadiazoles were allowed to react with Zn/HCl using ethanol as a solvent to convert the nitro group to amine. The newly synthesized amine group was diazotized and coupled with 8-hydroxy quinoline to obtain bis alkyl 1,3,4-oxadiazole substituted azo dye **4 (a–f)**. The synthesized compounds were recrystallized using methanol. The purity of the compounds was checked by TLC. The structures of the newly synthesized compounds were characterized by ^{1}H NMR, IR and Mass spectra studies. The synthesized compounds were found in good agreement with the spectral data. The elemental analysis results were matched within $\pm 0.4\%$ of the theoretical values.

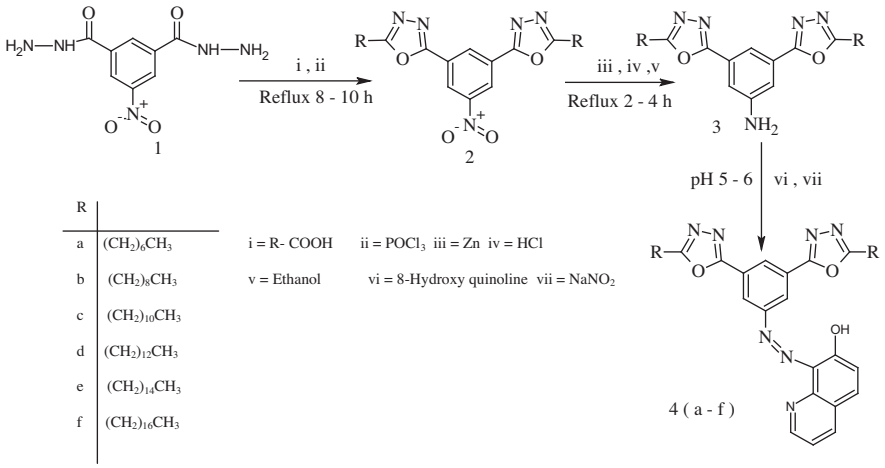
The IR spectra of **1** showed an absorption peak at 3336.4 cm^{-1} due to hydrazide, a peak at 1507.1 cm^{-1} due to NO_2 and a peak at 1633.3 cm^{-1} due to C═O absorption. These spectral data of synthesized 5-nitro, iso-phthalic dihydrazide stand in good agreement with those reported in the literature (Palekar et al., 2009). The IR spectrum of the compound **2** showed absorption peak at 1561.4 cm^{-1} due to C═N stretching vibration. The absence of C═O peak at 1633.3 cm^{-1} and $NHNH_2$ at 3336.4 cm^{-1} confirms the formation of oxadiazoles. The ^{1}H NMR spectrum revealed a singlet at δ 13–16 due to ─OH protons, δ 2–3 due to long chain aliphatic protons and δ 6–8 due to aromatic proton. The IR spectrum of compounds **4 a–f** showing an absorption peak at 3300–3400 cm^{-1}, was attributed to ─OH, at 1600–1700 cm^{-1}, due to N═N, absorption at 1500–1600 and C═N at 2921 (aliphatic chain). The IR, ^{1}H NMR and mass spectral data were found in good agreement with the newly synthesized compounds.

3. Pharmacology

Azoles exert antifungal activity through inhibition based on the structure of the active site of oxadiazoles and extensive investigation of the structure–activity relationships (SAR) of azole has revealed that the oxadiazole ring, having oxygen, nitrogen and the hydroxyl group was the pharmacophore of antifungal agents [**41**].

3.1. Evaluation of minimal inhibitory concentrations (MICs)

Evaluation of MIC values of all the compounds **4a–f** was carried out using concentrations ranging from 2.5 to 20 mg/mL. Compound **4c** showed significant inhibition at 2.5 mg/mL against *Pseudomonas aureginosa, Escherichia coli,* and *Candida parapsilosis*. While, compounds 4a and **4d** showed maximum



Scheme 1