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ORIGINAL ARTICLE

Synthesis, spectral and biological evaluation of some new heterocyclic derivatives incorporating dihydroanthracene moiety

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Abstract The reaction of anthrone **1** with 4-aminoantipyrine and thiosemicarbazide afforded 4-(anthracen-9(10H)-ylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one **2** and anthracen-9(10H)-one thiosemicarbazone **5**, respectively. Oxidation of compound **2** with potassium permanganate gave 4-(anthracen-9(10H)-ylideneamino)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H pyrazole-5-carboxylic acid **3** which on reaction with *o*-phenylenediamine gave 4-(anthracen-9(10H)-ylideneamino)-5-(1H-benzimidazol-2-yl)-1-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one **4**. Furthermore, compound **5** was condensed with different substituted phenacyl bromide to give a series of 2-(anthracen-9(10H)-ylidenehydrazono)-5-substituted-2,3-dihydro-1H-thiazole **6a–g**. Compound **5** also reacted with chloroacetic acid affording 2-(anthracen-9(10H)-ylidenehydrazono)thiazolidin-4-one **7**. The structures of all the products have been determined by elemental analysis and spectral studies. All compounds have been screened for their antibacterial and antifungal studies. The results are summarized in Tables 1 and 2.

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1. Introduction

Research and development of potent and effective antimicrobial agents represents one of the most important advances in therapeutics, not only in the control of serious infections, but also in the prevention and treatment of some infectious complications of other therapeutic modalities such as cancer chemotherapy and surgery. Over the past decade, fungal infection became an important complication and a major cause of morbidity and mortality in immuno-compromised individuals such as those suffering from tuberculosis, cancer or AIDS and in organ transplant cases (Turan-Zitouni et al., 2005).

However, in recent years, much attention has been focused on addressing the problem of multi-drug resistant (MDR) bacteria and fungi resulting from the widespread use and misuse of classical antimicrobial agents (Akbas and Berber, 2005). Such serious global health problem demands a renewed effort seeking the development of new antimicrobial agents effective against pathogenic microorganisms resistant to currently available treatments.

Antibacterial and antifungal activities of the azoles are the most widely studied and some of them are in clinical practice as antimicrobial agents. However, the azole-resistant strains led to the development of a new antimicrobial compounds. In particular pyrazole derivatives are extensively studied and used as antimicrobial agents. Pyrazole is an important class of heterocyclic compounds and many pyrazole derivatives are reported to have a broad spectrum of biological activities, such as anti-inflammatory, antifungal (Prakash et al., 2008), herbicidal (Kudo et al., 1999), antitumour, cytotoxic, molecular modelling (Vera-DiVaio et al., 2009), and antiviral (Storer et al., 1999) activities. Pyrazole derivatives also acts as antiangiogenic agents (Qiao et al., 2004), A3 adenosine receptor antagonists (Baraldi et al., 2003), neuropeptide YY5 receptor antagonists (Stamford and Wu, 2004), kinase inhibitor for treatment of type 2 diabetes, hyperlipidemia, obesity (Brown et al., 2004), and thrombopiotinmimetics (Heerding, 2004).

Antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) was the first pyrazolone derivative used in the management of pain and inflammation, and their derivatives have attracted the attention of several research groups due to their potential activities (Jain et al., 2003). In this context, broad spectra of bioactive antipyrine derivatives have been investigated and diversities of bioactivities such as analgesic (Filho et al., 1998), anti-inflammatory (Ismail et al., 2007), antimicrobial (Mishra, 1999), and anticancer activity (Sondhi et al., 2001) have been reported. The antibacterial activity caught our attention because antimicrobial resistance developed by important pathogens has increased in the last decade (Sutcliffe, 2003). Besides, emerging and re-emerging bacterial infectious diseases still cause death and disability worldwide (Morens et al., 2004).

Benzimidazoles are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio. Extensive biochemical and pharmacological studies have confirmed that benzimidazole molecules are effective against various strains of microorganisms (Kazimierczuk et al., 2002). Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of vitamin-B_{12} (Óniel et al., 2001). This ring system is present in numerous antioxidant (Ayhan-Kilcigil et al., 2007), antiparasitic (Navarrete-Vazquez et al., 2001), antihelmintics (Ravina et al., 1993), antiproliferative (Garuti et al., 2000), and anti-HIV (Rao et al., 2002) activities.

Thiazolidin-4-ones are an important group of heterocyclic compounds, having valuable biological activities in the areas of medicine. Recently, antimicrobial and antimycobacterial activities (de Aquino et al., 2008; Verma and Saraf, 2008; Küçükgüzel et al., 2006) of this framework containing compounds were explored well whereas their 2,3-disubstituted analogues have proved to be predominantly effective non-nucleoside HIV reverse transcriptase inhibitors (Barreca et al., 2001). Likewise, thiazole and their 2-substituted derivatives were also reported to exhibit diverse biological properties such as antituberculous and antimicrobial activities (Karegoudar et al., 2008). Moreover, it has been found in the drug development program for the treatment of inflammation (Suryavanshi and Pai, 2006) and HIV (Balzarini et al., 2009).

In view of the above-mentioned findings and as a continuation of our efforts (Salimon and Salih, 2010) to identify new candidates that may be of value in designing new, potent, selective and less toxic antimicrobial agents, we report herein the synthesis of some new heterocyclic derivatives starting from anthrone in order to investigate their antimicrobial activity (Fig. 1).

2. Experimental

2.1. Measurements

Melting points were determined in open glass capillaries on a Gallenkamp apparatus and are uncorrected. The percentage compositions of the elements (CHNS) for the compounds were determined using an elemental analyzer CHNS Model Fison EA 1108. The infrared spectra were recorded as potassium bromide discs using a Perkin-Elmer spectrophotometer GX. The ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded using the JEOL JNM-ECP 400 spectrometer in DMSO-d_6 as the solvent, using TMS as an internal standard, and chemical shifts are expressed as δ_{ppm}. All the reactions were followed by TLC (Silica gel, aluminum sheers 60 F_{254}, Merck).

2.2. Synthesis of of 4-(anthracen-9(10H)-ylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (2)

A mixture of anthrone **1** (10.5 g, 0.012 mol), 30 mL glacial acetic acid and 4-aminoantipyrine (8.76 g, 0.012 mol) was heated under reflux for 10 h. The reaction mixture was filtered off and recrystalized from ethanol (5.43 g, 55%); mp 67–69 °C; IR (KBr) cm^{-1} 3089 (C–H aromatic), 2954, 2824 (C–H aliphatic), 1678 (C═O), 1621 (C═N). ^{1}H NMR (400 MHz-DMSO-d_6-ppm) δ 1.67 (s, 3H, CH_3), 2.05 (s, 2H, CH_2), 8.11–8.17 (d, 1H, Ar–H), 7.94–8.03 (d, 1H, Ar–H), 7.55–7.64 (d, 1H, Ar–H), 7.51–7.65 (d, 1H, Ar–H), 7.24–7.33 (d, 1H, Ar–H), 7.26–7.33 (d, 1H, Ar–H), 7.23–7.28 (t, 1H, Ar–H), 7.17–7.20 (t, 1H, Ar–H), 7.06–7.13 (t, 1H, Ar–H), 6.90–6.96 (t, 1H, Ar–H), 6.82–6.88 (t, 1H, Ar–H), 6.71–6.75 (t, 1H, Ar–H), 6.66–6.69 (t, 1H, Ar–H).^{13}C NMR (400 MHz-DMSO-d_6-ppm) δ 13.05, 13.11 (2C, 2 CH_3), 14.51 (1C, CH_2), 61.53 (1C, C═N), 131.24–135.98 (18C, aromatic carbons), 166.70 (C, C═O). Anal. Found (calc.) for $C_{30}H_{37}N_3O$ (%): C, 79.09 (79.08); H, 8.20 (8.19); N, 9.23 (9.22).

2.3. Synthesis of 4-(anthracen-9(10H)-ylideneamino)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H pyrazole-5-carboxylic acid (3)

Compound **2** (20 g, 0.04 mol) is added to a solution of (6.32 g, 0.04 mol) of potassium permanganate and (3.32 g, 0.04 mol) sodium carbonate in (85 mL) water and the mixture is heated under reflux until the color of the permanganate has disappeared (15 h). The reaction mixture was filtered while still hot to get rid of the MnO_2 precipitate. The cooled filtrate is