Arabian Journal of Chemistry (2015) xxx, xxx–xxx

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Synthesis, characterization and biological evaluation of some novel nitrogen and sulphur containing organometallic heterocycles

Humaira Parveen [a,*], Raedah Aiyed Suliman Alatawi [a], Nadia Hussein El Sayed [a], Sadaf Hasan [b], Sayeed Mukhtar [a], Asad U. Khan [b]

[a] *Department of Chemistry, Faculty of Science, University of Tabuk, Tabuk, Saudi Arabia*
[b] *Interdisciplinary Biotechnology Unit, Aligarh Muslim University, Aligarh 202002, India*

Received 23 November 2014; accepted 3 May 2015

KEYWORDS

Organometallic heterocyclic compounds;
Antibacterial activity;
Antifungal activity

Abstract A series of some novel sulphur and nitrogen containing ferrocenyl linked heterocyclic compounds were synthesized by multistep reactions and evaluated for *in vitro* antimicrobial activity against 15 ATCC strains out of which 8 were bacterial (*Pseudomonas aeruginosa*, *Streptococcus bovis, Enterococcus faecalis, Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae,* Methicillin-resistant *Staphylococcus aureus* and *Streptococcus mutans*) and 7 were fungal (*Candida albicans, Candida dubliniensis, Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida kefyr and Candida krusei*) strains. The results clearly depict that the compounds (**1**–**12**) gave an average antimicrobial activity against the tested strains with an exception of compound **12** which stood out in terms of its activity against the tested organisms. All these compounds gave a range of MIC value between 32–64 μg/ml against *S. bovis*, *E. coli* and *C. tropicalis* except compound **12** which gave a MIC of 16 μg/ml against each of them. The MIC values of all these compounds against biofilm forming *P. aeruginosa* and *S. mutans* were 64–256 μg/ml and 64–128 μg/ml respectively which is apparently high, concluding that these compounds hold immense potential to be employed as a two in one formulation of antibacterial as well as antifungal agents.

1. Introduction

In the past few decades, the incidence of microbial infection has increased on frightening level over the world as a result of antimicrobial resistance (Ghannoum and Rice, 1999; Fluit et al., 2001; Canuto and Rodero, 2002; Pfaller and Diekema, 2007; Mukherjee et al., 2005; Shapiro et al., 2011). Microbial

* Corresponding author. Tel.: +966 551397507.
E-mail address: h.nabi@ut.edu.sa (H. Parveen).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2015.05.002

Please cite this article in press as: Parveen, H. et al., Synthesis, characterization and biological evaluation of some novel nitrogen and sulphur containing organometallic heterocycles. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.05.002

infections are a growing problem in contemporary medicine and the use of antibiotics is common across the world. Consequently, there is an urgent need to widen antimicrobial agents, which have a broad spectrum of activity against the resistant microorganisms. The current literature is enriched with progressive findings about the synthesis and pharmacological action of fused heterocycles such as pyrazolines and related heterocyclic compounds (Yusuf and Jain, 2014; Kathiravan et al., 2012).

On the other hand, ferrocene and its derivatives, since their discovery have been attracting much attention due to their wide range of applications in catalysis, material sciences (Togni and Hayashi, 1995), biological studies and even in therapy (Jaouen et al., 2006; Lang and Heinze, 2013; Stepnicka, 2008; Scarcia et al., 1988; Hill et al., 1989; Neuse and Kanzawa 1990; Motohashi et al., 1990; Houlton et al., 1991; Top et al., 2001; Klimova et al., 2001; Ma et al., 2001; Delhaes et al., 2001; Weber et al., 2004; Jaouen et al., 2004; Bincoletto et al., 2005; Hillard et al., 2006). Ferroquine, the ferrocenyl derivative of antimalarial drug chloroquine, is currently at the phase II clinical trial stage as the best promise against the chloroquine-resistant strains of *Plasmodium falciparum* (Biot et al., 2005; Dive and Biot, 2008; Biot and Dive, 2010; Supan et al., 2012). Many ferrocenyl compounds also display interesting cytotoxic, anti-tumor, anticancer, antimalarial, antifungal and DNA-cleaving activity (Kealy and Pauson, 1951; Kelly et al., 2007; Fouda et al., 2007). Recently, some new ferrocenyl-substituted heterocyclic compounds have been reported as potential pharmaceuticals (Huang et al., 2014; Arancibia et al., 2014; Harry et al., 2014; Yu et al., 2007; Zora and Görmen, 2007; Zora and Velioğlu, 2008; Fabian et al., 2007; Mochida et al., 2007; Maity et al., 2008). Moreover, the stability and nontoxicity of the ferrocenyl moiety is of particular interest rendering such drugs compatible with other treatment (Biot et al., 2000). In this sense, the integration of one or more ferrocene units into a heterocyclic molecule has long been recognized as an attractive way to endow a novel molecule functionality (Sun et al., 2002; Haung and Wang, 2001). Recent publications also support that combination of pharmacologically active *N*-heterocycles among them pyrazolines and pyrazoles with ferrocene moiety results in favourable change of biological properties, often associated with decreased toxicity (Delhaes et al., 2001; Vázquez López et al., 2004; Fang et al., 2003). Moreover, thiazoles are found in many biologically active compounds, including natural products and pharmaceutical agents (Kashyap et al., 2012; Eicher and Hauptmann, 2003; Siddiqui et al., 2011) and it is well documented that the combination of two or more types of heterocycles into one molecule could afford a novel entity with increased bioactivities (Zhou and Wang, 2012; Wang and Zhou, 2011).

In view of these observations and as a part of our ongoing search devoted to the synthesis of biologically active heterocycles (Iqbal et al., 2009; Parveen et al., 2010, 2011) we report herein some novel 5-ferrocenyl-3-substituted aryl-4,5-dihydro-1H-pyrazol-1-carbothioamides (**1**–**6**) and their cyclized products 2-(5-ferrocenyl-3-aryl-4,5-dihydro-1H-pyrazol-1-yl)-4-(4-substituted-aryl) thiazoles (**7**–**12**), as useful leads towards the development of potent antimicrobial agents.

2. Results and discussion

2.1. Synthesis

The aforementioned compounds were prepared according to the synthetic sequences illustrated in Scheme 1. The ferrocenyl chalcones **(a**–**f)**, were prepared by a classic Claisen–Schmidt condensation of substituted acetophenones/1-phenyl butane-1-one/2-acetyl ferrocene with ferrocene carboxaldehyde in the presence of KOH and absolute ethanol. The cyclization of ferrocenyl chalcones **(a**–**f)**, with thiosemicarbazide and sodium hydroxide in the presence of absolute ethanol yielded their corresponding pyrazoline analogues 5-ferrocenyl-3-aryl-4,5-dihydro-1H-pyrazole-1-carbothioamides **(1**–**6)**, which were further cyclized with 2-bromo-4′fluro acetophenone to yield their corresponding 2-(5-ferrocenyl-3-aryl-4,5-dihydro-1H-pyrazol-1-yl)-4-(4-substituted-phenyl)thiazoles **(7**–**12)**. According to the mechanism, the formation of pyrazoline analogues is favoured via thiosemicarbazone formation, which undergoes cyclization under basic condition to form desired pyrazoline ring in all the compounds.

All the synthesized compounds were characterized by spectroscopic methods such as IR, ^{1}H NMR ^{13}C NMR and Mass and the purity of compounds was confirmed by elemental analysis and melting points. All compounds showed sharp melting points and the elemental analysis was found in accordance with ±0.3%. The analytical data are presented in the experimental section.

In the IR spectra of ferrocenyl chalcones **(a**–**f)**, the appearance of characteristic bands at 1642–1655 cm^{-1} and 1568–1580 cm^{-1} due to α, β unsaturated carbonyl group and C═C, respectively, suggested the condensation of substituted ketones/1-phenyl butane-1-one/2-acetyl ferrocene with ferrocene carboxaldehyde. The structures of all these compounds were further confirmed by ^{1}H NMR spectra. The appearance of doublets in the region of δ 6.75–7.35 ppm for Hα and 6.82–7.71 ppm for Hβ with coupling constant (J) in the range of 15.2–16 Hz showed that they are transisomers. The rest of protons appeared in the expected region and their values are shown in the data given in experimental section. Additional support for the structures of the compounds **(a**–**f)**, was obtained from ^{13}C NMR. A characteristic signal for the ferrocenyl chalcones (C═O) appeared in the range of δ 189.81–192.00 ppm. The signals at δ 120.23–122.43 and 142.46–146.82 ppm confirmed the presence of α, β unsaturated keto function in all compounds **(a**–**f)**.

Selected diagnostic bands of the IR spectra of pyrazoline analogues **(1**–**6)** of ferrocenyl chalcones **(a**–**f)** showed useful information about the structures of the compounds. All the compounds showed intense bands in the region 1032–1078 cm^{-1} due to ν (C═S) stretch of the thiocarboxamide group. The IR spectra of all the compounds showed ν (C═N) stretch at 1524–1587 cm^{-1} because of the ring closure. In addition, the absorption bands at 1125–1215 cm^{-1} were attributed to the ν (C—N) stretch vibrations, which also confirmed the formation of the desired pyrazoline ring in all the compounds. The structures of the pyrazoline analogues were further supported by their ^{1}H NMR spectra which provided diagnostic tools for the positional elucidation of the protons. Assignments of the signals are based on the chemical shifts and intensity patterns. The pyrazoline protons H_a and H_b

Please cite this article in press as: Parveen, H. et al., Synthesis, characterization and biological evaluation of some novel nitrogen and sulphur containing organometallic heterocycles. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.05.002