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SYNTHESIS AND CHARACTERIZATION OF NOVEL BENZIMIDAZOLE CONNECTED PYRAZOLES AS NOVEL ANTIBACTERIAL AGENTS

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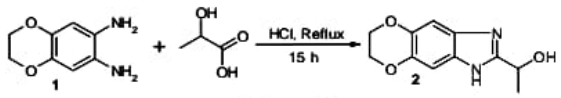
ABSTRACT
A facile and convenient method has been reported for the synthesis of six novel 2-(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naph-thalene and its derivatives **(5a-f)** from 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthalene-2-yl)-3-phenyl-propenones **(4a-f)** by involving 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthalene-2-yl)-ethanol **(2)** and 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthaene-2-yl)-ethanone **(3)** as intermediates and 2,3-dihydro-benzo[1,4]dioxine-6,7-diamine **(1)** as starting compound. The chemical structures of the synthesized compounds were confirmed by IR, ^{1}H-NMR, mass spectral study and elemental analysis. All the synthesized hybrids were evaluated for their *in vitro* antibacterial activity against different bacterial strains.

KEYWORDS: Pyrazoles, antibacterial activity.

INTRODUCTION
As with many other five-membered heterocyclic compounds, pyrazoles and their derivatives attract increasing attention in the fields of pharmacology and medicine because of their various bioactivities, including antifungal[1], anti-inflammatory[2], antiviral[3], antioxidant[4], cytotoxic[5], antihypertensive[6], A3 adenosine receptor antagonistic[7], antibacterial[8], tranquilizing, psychoanaleptic, muscle-relaxant, hypnotic, antidepressant, ulcerogenic and analgesic activities.[9] They are also highly significant in agrichemistry and many of these compounds have been widely used, given their fungicidal[10], insecticidal[11] and herbicidal activities.[12] Pyrazole carboxamide derivatives are important heterocyclic compounds in the development of medicines and pesticides because of their broad spectrum of biological activities, including insecticidal[13], fungicidal[14] and acaricidal activity.[15]

In the present work as continuation of our active research in the area of heterocyclic compounds, we planned to develop a novel series of 2-(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-6,7-dihydro-1*H*-5,8- dioxa-1,3-diaza-cyclopenta[*b*]naph-thalenes (5a-f), because of the important biological properties associated with this moiety. The reaction sequences used for the synthesis of target compounds are shown in scheme 1-4. The chemical structure of all compounds will be identified by different techniques, such as elemental analysis, Fourier transform infrared spectroscopy (FT-IR), nuclear magnetic resonance (NMR) and mass spectrometry (MS).

Thus, the raw material, 2,3-dihydro-benzo[1,4]dioxine-6,7-diamine (1) was reacted with lactic acid in presence of hydrochloric acid solution at reflux temperature for 15 h with uniform stirring on water bath to give the initial intermediate, 1-(6,7-dihydro-1*H*-5,8-dioxa-1,3-diaza-cyclopenta[*b*] naphthalene-2-yl)-ethanol (2) in good yield. The structure of this intermediate was characterized by IR, ^{1}H-NMR, Mass spectra and elemental analysis. Its IR spectrum showed strong absorption bands at 3325 and 3125 cm^{-1} due to (O-H) and (N-H) groups respectively. In addition, the appearance of two absorption bands at 1456 and 1232 cm^{-1} corresponding to the C=N and C-O stretching vibrations. In the ^{1}H-NMR spectrum, the characteristic O-H and N-H resonated both as singlets at δ10.28 ppm and δ 4.79 ppm respectively by disappearing two NH_2 groups. Final proof for the structure was obtained by recording its mass spectrum, which exhibited a molecular ion peak at m/z 220 corresponding to its molecular weight.



Scheme 1

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Design, synthesis, and anticancer evaluation of 1,2,4-oxadiazole functionalized quinoline derivatives

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Abstract
A library of 1,2,4-oxadiazole functionalized quinoline derivatives (**13a–j**) were synthesized and their structures were confirmed by ^{1}H NMR, ^{13}CNMR and Mass Spectral analysis. Further, these compounds were evaluated for their anticancer activity against four human cancer cell lines, namely MCF-7 (breast), A549 (lung), DU-145 (prostate) and MDA MB-231 (breast) using Etoposide as the positive control. Most of these derivatives exhibited more potent activity towards the four cancer cell lines compared to Etoposide. Amongst all the compounds tested, compounds **13b, 13c, 13h, 13i** and **13j** exhibited promising activity. Further of these compounds **13b, 13i** and **13j** exhibited excellent activity, when compared with Etoposide.

Keywords Lenvatinib · Proxazole · Quinoline · 1,2,4-oxadiazole · Anticancer activity

Introduction

Cancer, caused due to uncontrolled cell proliferation is one of the major health concerns and the leading cause of death in both developed and under developed countries (Eckhardt 2002; Lee et al. 2002). One of the treatment strategies for cancer is chemotherapy which employs the use of cytotoxic drugs (Lu et al. 2012). Tubulin binding agents are one of the finest chemotherapeutic agents that were used in cancer chemotherapy. Microtubules are important cytoskeletal proteins which play a crucial role in cellular functions including division, shape of cell, motility, mitosis and internal transport (De Martino et al. 2004; Plattner and Desai 2006). Hence, they act as important therapeutic targets in cancer (Jordan and Wilson 1998). Mitotic agents that inhibit polymerization of tubulin, were found to simultaneously control cancer.

Nitrogen heterocyclic are central to medicinal chemistry because of the biological activities exhibited by many of these compounds (Wen et al. 2013; Athri and Wilson 2009; George Rosenker et al. 2015) and act as anticancer agents in cancer chemotherapy (Agarwal et al. 2016; Ahsan et al. 2015; Durgesh et al. 2018a, 2018b, 2018c; Hatti et al. 2015a, 2015b; Reddy et al. 2016a, 2016b; Shahinshavali et al. 2019; Spandana et al. 2019a, 2019b; Sreenivasulu et al. 2017; 2018; 2019; Subramanyam et al. 2018; Madhavi et al. 2016; Madhavi et al. 2017a, 2017b; Pragathi et al. 2019; Spandana et al. 2019a, 2019b; Subramanyam et al. 2018; Suma et al. 2019; Yakantham et al. 2019). Quinoline derivatives, as fused-six membered heterocyclic scaffolds have significantly received huge attention from many researchers for development of new therapeutic agents in the field of medicinal chemistry due to the broad spectrum of biological properties they exhibit. Earlier reports have shown quinoline derivatives exhibiting anticancer (Solomon and Lee 2011), antimalarial (Joshi et al. 2005), analgesic (Abadi et al. 2005), antiallergic (Roma et al. 2000), anti-AIDs (Benard et al. 2004), tyrosine kinase inhibition (Maguire et al. 1994), antipsychotic (Zajdel et al. 2014), antiviral (Kumar et al. 2014), antiinflammatory (Gupta and Mishra 2016) and antiAlzheimer's (Najafi et al. 2016) properties. Lenvatinib (**1**, Fig. 1) is US-FDA approved anticancer drug containing quinoline nucleus and is used for treatment of cancer (Matsuki et al. 2018).

Similarly, 1,2,4-oxadiazoles are most privileged five-membered heterocyclic moieties that can be fabricated into a variety of novel therapeutic agents (Hemming et al. 2008),

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