Journal of Saudi Chemical Society (2014) **18**, 963–971

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Green synthesis of novel quinoline based imidazole derivatives and evaluation of their antimicrobial activity

N.C. Desai *, A.S. Maheta, K.M. Rajpara, V.V. Joshi, H.V. Vaghani, H.M. Satodiya

Green Chemistry Laboratory, Department of Chemistry, Mahatma Gandhi Campus, Bhavnagar University, Bhavnagar 364 002, India

Received 9 November 2011; accepted 29 November 2011
Available online 6 December 2011

KEYWORDS

Quinoline;
Imidazole;
Antimicrobial activity;
Conventional and microwave method;
MIC

Abstract We have described the conventional and microwave method for the synthesis of *N*-(4-((2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)(aryl)amides **3a–l**. It is observed that the solvent-free microwave thermolysis is a convenient, rapid, high-yielding, and environmental friendly protocol for the synthesis of quinoline based imidazole derivatives when compared with conventional reaction in a solution phase. Antimicrobial activity of the newly synthesized compounds is screened *in vitro* on the following microbial cultures: *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688), *Staphylococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442), *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282), *Aspergillus clavatus* (MTCC 1323). All the synthesized bio-active molecules are tested for their *in vitro* antimicrobial activity by bioassay namely serial broth dilution. Among these compounds **3c**, **3d**, **3f**, **3h** and **3j** show significant potency against different microbial strains. All the compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. On the basis of statistical analysis, it is observed that these compounds give significant co-relation.

1. Introduction

Combat against bacterial infections has resulted in the development of a wide variety of antibiotics. After years of misuse and overuse of antibiotics, bacteria are becoming antibiotic resistant, resulting in a potential global health crisis. Frequently, it is recommended to use new antibacterial agents with enhanced broad-spectrum potency. Therefore, recent efforts have been directed towards exploring novel antibacterial agents (Moustafa et al., 2004). Apart from this, during the past 20 years an increase of invasive fungal infections has

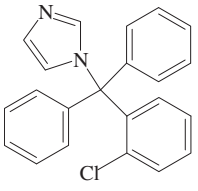
* Corresponding author.
E-mail address: dnisheeth@rediffmail.com (N.C. Desai).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

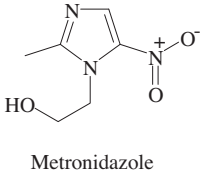
http://dx.doi.org/10.1016/j.jscs.2011.11.021

been observed, particularly in immunosuppressed patients, which are now, cause of morbidity and mortality. Autopsy data in fact indicate that more than half of the patients who die with malignancies are infected with *Candida spp*. and increasing number with other fungi. Since the discovery of amphotericin B, a number of different classes of antifungal agents have been discovered. However, there is still a critical need for new antimicrobial agents to treat life threatening invasive mycoses (Andriole, 1999). In order to overcome this rapid development of drug resistance, new agents should preferably consist of chemical characteristics that clearly differ from those of existing agents. In drug developing programs, an essential component of the search for new leads is the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of critical structural features. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules (Thompson and Ellman, 1996).

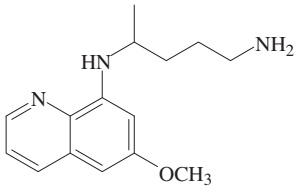
Nitrogen bridgehead-fused heterocycles containing an imidazole ring are common structural motifs in pharmacologically important molecules, with activities spanning a diverse range of targets. The pharmacological interest of the imidazole ring has been established, nitroimidazoles being extensively used in therapy against amoebic, trichomonal, giardial and anaerobic infections or as hypoxic cell radiosensitizers (Nair and Nagarajan, 1983). Metronidazole and substituted imidazoles are well-tolerated drugs that are potentially active against Leishmania, but their use in the treatment of cutaneous and visceral leishmaniasis has produced conflicting results (Gangneux et al., 1999). Clotrimazole is an antifungal medication commonly used in the treatment of fungal infections such as vaginal yeast infections, oral thrush and ringworm. The imidazole moiety which incorporates both p-excessive and p-deficient characteristics has proven to be a master key in the range of drug target families (Abdel-Meguid et al., 1994; Muller, 2003). Compounds incorporating the imidazole scaffold are known as inhibitors of p38 MAPK (Laufer et al., 2004), JNK (Lisnock et al., 2002), B-Raf kinase (Takle et al., 2006), transforming growth factor β-1 (TGF-β1) type 1 receptor kinase (Laping et al., 2002) and acyl-CoA: cholesterol O-acyl transferase (ACAT) (Riddell et al., 1996). Imidazoles substituted with 2-arylamino functionality have been reported to have potent and selective agonist activity at α_2-adrenoceptors (Munk et al., 1997).



Clotrimazole



Metronidazole



Primaquine

The quinoline ring system is an important structural unit in naturally occurring quinoline alkaloids, therapeutics and synthetic analogues with interesting biological activities. Some derivatives containing quinoline ring system have been shown to possess useful pharmacological activities, for example Dibucaine hydrochloride is an anaesthetic, Primaquine is an antimalarial agent, Apomorphine is antiparkinsonian and Oxamniquine is schistosomicidal. Quinoline derivatives have been developed for the treatment of many diseases like malaria (Lutz et al., 1946), HIV (Ahmed et al., 2010), tumour (Atwell et al., 1989) and antibacterial infections (Munawar et al., 2008). Recently, substituted quinolines have also been reported to act as antagonists for endothelin (Cheng et al., 1996), $5HT_3$ (Anzini et al., 1995), NK-3 (Giardina et al., 1997) and leukotriene D4 receptor (Gauthier et al., 1990). They also function as inhibitors of gastric (H^+/K^+)-ATPase (Ife et al., 1992), dihydroorotate dehydrogenase (Chen et al., 1990) and 5-lipoxygenase (Musser et al., 1987).

The exploitation of microwaves for assisting different organic reactions has blossomed into an important tool in synthetic organic chemistry. In the present programme our aim is to develop an efficient procedure for the synthesis of new heterocyclic systems containing imidazole and quinoline derivatives. Due to the timeless ease of workability and eco-friendliness, microwaves provide alternative to environmentally unacceptable procedures. Microwave energy offers numerous benefits in performing synthesis including increased reaction rates, yield enhancements and cleaner chemistries. Due to greater selectivity, rapid transfers of energy, significant practical simplicity and pure product, microwave assisted reactions have greater advantage over conventional methods. Toxicity of conventional method prompted us to explore other green processes. Reactions without using solvent usually with closed vessel in microwave reaction system are currently popular among the synthetic chemists to create eco-friendly atmosphere.

In continuation to this, it is our ongoing project to synthesize bio-active heterocyclic compounds (Desai et al., 2011b, 2011c, 2011d, 2014, 2011f). Due to this high level of importance and utility, an ever increasing amount of research has been focused on the functionalization of imidazole and quinoline moieties. We have synthesized a series of *N*-(4-((2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)(aryl)amides (**3a–l**) (Scheme 1) by conventional and microwave methods. The conditions of conventional and microwave methods are shown in Table 1. The structures of synthesized compounds are assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. These compounds are evaluated for their antimicrobial screening on different strains of bacteria and fungi.

2. Experimental part

2.1. Materials and physical measurements

Completion of reaction and purity of all compounds were checked on aluminium coated TLC plates 60 F_{245} (E. Merck) using *n*-hexane:ethyl acetate (7.5:2.5 V/V) as mobile phase and visualized under ultraviolet (UV) light or iodine vapour. Melting points were determined on an electro thermal melting point apparatus and were reported uncorrected. Elemental analysis (% C, H, N) was carried out by a Perkin-Elmer 2400 CHN ana-