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Research paper

Synthesis and biological screening of novel 2-morpholinoquinoline nucleus clubbed with 1,2,4-oxadiazole motifs

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ABSTRACT

Novel series of 2-morpholinoquinoline scaffolds (**6a-n**), containing the 1,2,4-oxadiazole and moiety, was designed and synthesized in good yield (76–86%). The synthesized compounds were screened for their preliminary *in vitro* antimicrobial activity against a panel of pathogenic strains of bacteria and fungi. Molecular docking and pharmacokinetic study were carried out for the prepared compounds. The cytotoxicity of the synthesized compounds was tested at different concentrations using bioassay of *S. pombe* cells at the cellular level. The effect of synthesized compounds on the DNA integrity of *S. pombe* was observed on agarose gel. Compounds **6d**, **6e**, **6g**, **6h, 6j** and **6n** exhibited excellent antimicrobial potency as compared to the standard drugs (i.e Ampicillin, Norfloxacin, Chloramphenicol, Ciprofloxacin). Compounds **6d**, **6e**, **6g**, **6k** and **6n** were found to have significant antifungal activity as compared to griseofulvin. Compounds **6f**, **6i**, **6k**, **6l** were found very less cytotoxic, while compounds **6d**, **6e**, **6g**, **6h** were found to exhibit maximum toxicity. The rest of the synthesized compounds were found to be moderately toxic.

1. Introduction

The occurrence of microbial and fungal infections has increased notoriously in current years [1,2]. Resistance to antimicrobial agents has increased health concerns cost and resulted in mortality and morbidity from treatment failures [3,4]. The development of novel structure leads remains a key challenge for medicinal chemists to design new, effective and broad spectrum antimicrobial and antifungal. The search for new antimicrobial drugs is an area characterized by active investigation with the goal of overcoming the phenomenon of multiple drug resistance strains of bacteria and fungi [5–7]. There is an imperative need to discover and develop novel antibacterial and antifungal agent with novel mechanism of action and enhanced activity profile, high potency without or with at least reduced systemic adverse effects. Aforementioned consequences motivated us to construct quinoline and morpholine core in one molecule which may play vital roles as significant building blocks in the targeted compounds bearing 1,2,4-oxadiazole moiety (**6a**–**n**).

Quinoline is the key building core for many naturally occurring (cinchona alkaloids) compounds and pharmacologically active substances. It demonstrates a broad range of biological activity such as antimalarial [8], antituberculosis [9], anti-HIV [10], antifungal, antibacterial, antiprotozoic and antibiotic activities [11]. *N*-Functionalized morpholine motifs have been recognized to possess diversified biological activities such as antiemetic [12,13], antidiabetic [14], inflammatory migraine and asthma [15,16], platelet aggregation inhibitors [17]. Moreover, 1,2,4-oxadiazole, known as an ester isostere, is present in a variety of biologically active compounds, such as benzodiazepine receptor ligands, muscarinic receptor agonists and 5-HT3 receptor antagonists [18]. 1,2,4-

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Oxadiazole derivatives possess human tryptase inhibitory activity [19], antitrypanosomal activity [20], genotoxic activity [21], peptide inhibitory activity [22], β-amyloid imaging agents in Alzheimer's disease [23], potential combretastatin A-4 (CA-4) analogs [24], antihyperglycemic activity [25] and oxadiazoles mannich bases show antimyco-bacterial activity [26].

In continuation of our efforts to synthesize some novel heterocyclic motifs with biological interest [27–40], herein we report the design, synthesis, antimicrobial evaluation, cytotoxicity and genotoxicity of quinoline based 1,2,4-oxadiazole scaffold. Potent 1,2,4-oxadiazole moiety is linked to quinoline moiety at C-3 position to observe the synergistic effect of these rings towards antimicrobial activity. The molecules (6a-n) were found to be more effective on *bacillus subtilis* stain. This stain being bacteria, it was thought appropriate to study molecular docking with the receptor, *Bacillus subtilis* HmoB (PDB ID: 4OZ5).

2. Chemistry

The synthesis of novel series of quinoline based 1,2,4-oxadiazole scaffolds was performed as outlined in Scheme 1. Table 1 shows type of substituent present on the targeted scaffolds **6a-n**.The starting material 2-chloroquinoline-3-carbaldehydes **1a-b** was prepared according to Vilsmeier-Haack reaction as reported earlier [41]. 2-Chloro-3-formylquinoline **1a-b** in THF was added to (30%, 8 mL) aqueous ammonia solution followed by sublimed iodine and the reaction mixture was stirred at room temperature for 30 min, to obtain 2-chloro-6-substitutedquinoline-3-carbonitrile **2a-b** [42]. 6-Substituted-2-morpholinoquinoline-3-carbonitrile **3a-b** was prepared by refluxing thus prepared **2a-b** and morpholine in presence of anhydrous K_2CO_3 as the basic catalyst in DMF as the solvent. These derivatives **3a-b** were treated with $NH_2OH{\cdot}HCl$ in presence of sodium carbonate in ethanol:water (7:3). The mixture was warmed on a water bath for 4–5 h to obtain corresponding amidoximes **4a-b.** The obtained amidoximes were refluxed for 2 h with aromatic acids **5a-g** in presence of dichloromethane using coupling reagent Ethyl-(*N′,N′-dimethylamino*)propylcarbodiimide hydrochloride (EDC·HCl) under nitrogen atmosphere to obtain the intermediate (**4a'-b'**). Refluxing thus obtained solid in ethanol and sodium acetate in water for 3 h afforded corresponding 1,2,4-oxadiazoles derivatives **6a-n**.

The choice of substituents **R** and $\mathbf{R_1}$ introduced in the synthesized compounds **6a-n** is based on the most influential aspect of lipophilicity as it determines solubility, reactivity and formulation of pharmaceuticals as well as metabolism of drugs.

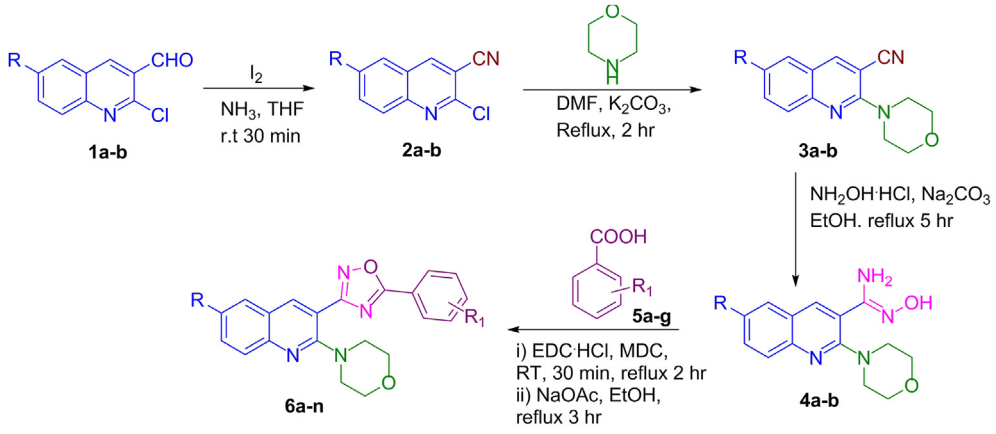
Table 1
Type of substituent on 2-morpholinoquinoline based 1,2,4-oxadiazoles scaffolds **6a-n**.

Comp	R	R_1	Comp	R	R_1
6a	-H	-H	**6h**	-H	4-Cl
6b	$-CH_3$	-H	**6i**	$-CH_3$	$3-CF_3$
6c	-H	$4-CF_3$	**6j**	$-CH_3$	4-Br
6d	$-CH_3$	$4-NO_2$	**6k**	-H	4-Br
6e	$-CH_3$	4-Cl	**6l**	-H	$4-OCH_3$
6f	$-CH_3$	$4-CF_3$	**6m**	$-CH_3$	$4-OCH_3$
6g	-H	$4-NO_2$	**6n**	-H	$3-CF_3$

The formation of 4-(3-(5-phenyl-1,2,4-oxadiazol-3-yl)quinolin-2-yl)morpholine **6a** can be explained by the plausible mechanism illustrated in Scheme 2. An *O-acylisourea* intermediate **5a'** is formed by the reaction of carboxylic acid and the EDC·HCl. The *O-acylisourea* being an extremely reactive species readily reacts with amidoxime **4a** to obtain *N-acyl*-intermediate **4a'**. EDC·HCl is transformed to the corresponding water soluble urea **6**. Finally 4-(3-(5-phenyl-1,2,4-oxadiazol-3-yl)quinolin-2-yl)morpholine **6a** was achieved by cyclodehydration of intermediate **4a'-b'**.

2.1. Analytical results

The formation of synthesized compounds was confirmed by ^1H NMR, FT-IR, mass spectrometry and elemental analysis. The ^1H NMR spectra of the targeted morpholinoquinoline based 1,2,4-oxadiazole scaffolds **6a-n** showed two triplets in the range of 3.14–3.45 ppm and 3.90 ppm due to protons of $-CH_2-N-CH_2-$ and $-CH_2-O-CH_2-$ of morpholine ring respectively. The aromatic region resonates in the range of 7.39–8.90 ppm (Ar–H) as multiplet. In IR spectra, the absorption bands in the range of 1634–1617 cm^{-1} was observed for all the compounds which may be due to $-C{=}N$ stretching. $-C{=}C-$ stretching appeared at 1599-1592 cm^{-1}. The absorption around 3069-3051 cm^{-1} is due to aromatic C–H stretching. IR spectra of the synthesized scaffolds exhibited characteristic absorption bands in the range 1233–1211 cm^{-1} due to the presence of ether linkage. The mass spectrum of all the compounds showed molecular ion peak (M+1) corresponding to their respective molecular weights, which additionally confirmed the molecular frame work.



Scheme 1. Synthesis of 2-morpholinoquinoline integrated 1,2,4-oxadiazole scaffolds.