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Synthesis, characterization, crystal structure, *in-vitro* anti-inflammatory and molecular docking studies of 5-mercapto-1-substituted tetrazole incorporated quinoline derivative

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ABSTRACT

A novel 5-mercapto-1-substituted tetrazole incorporated quinoline analog was synthesized. The compound 2-Cyclopropyl-4-(4-fluorophenyl)-3-{1-[2-(4-methoxybenzyloxy)ethyl]1*H*-tetrazol-5-ylsulfanylmethyl} quinoline was characterized by IR, Mass, ^{1}H and ^{13}C NMR spectroscopic techniques. Molecular structure was confirmed by using single crystal X-ray diffraction technique. Thermal behavior was studied by using TGA and DSC techniques. Further, *in vitro* anti-inflammatory and *in silico* docking analysis has been carried out to study the activity of the compound.

1. Introduction

Heterocyclic compounds are well known to possess diverse pharmacological properties, such as antimicrobial, antimalarial and anticancer activities. Recently heterocyclic compounds are gaining more attention and playing vital role in the design and development of biologically potent molecules or lead compounds. Heterocyclic compounds play an important role in designing new classes of medicinally important structural entities. Particularly, the quinoline derivatives continuously gain attention due to its structural features [1]. Quinoline nucleus occurs in several natural compounds, which exhibit wide range of biological activity such as anti-inflammatory [2], antimalarial [3], HIV-1 replication inhibitors [4,5], antituberculosis [6,7] and anthelmintic [8]. Interestingly, quinoline scaffold is prevalent in a variety of biologically active compounds as well as in medicinally important naturally products [9]. In addition, quinoline and its derivatives have been observed as promising nuclei to exhibit anticonvulsant properties [10,11]. Moreover, quinoline scaffolds are also utilized in the synthesis of biologically active molecules such as antitumor [12], antiproliferative [13], anticancer [14] and antiparasitic agents [15]. Aforementioned studies unveiled the biological significance and plethoric applications of quinoline derivatives. So we envisioned to synthesis quinoline based molecule in order to examine its anti-inflammatory activity.

Tetrazoles, a unique five membered heterocycles, possess multifarious applications in medicinal, biochemical and biological chemistry [16–20]. Particularly, 1-substituted tetrazole and 5-mercapto substituted tetrazole derivatives have been used in the preparation of pharmacologically active drugs [21–30]. As pharmaceutical compounds, tetrazoles have cholinesterase inhibitor

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activity [31] and it could be a potential bioisostere for carboxylic acid [32]. The tetrazole scaffolds are known to be superior in resisting metabolic degradation [33–36]. Further, tetrazoles are highly flexible ligands, which can serve as pharmacophore replacement of carboxylic acids in medicinal chemistry as well as in supramolecular chemistry, and it can easily adapt to different binding modes [37–40]. Interestingly1-(2-hydroxyethyl)-5-mercapto tetrazole is the pivotal fragment of flomoxef, a cephalosporin drug, due to its significance in antibacterial activity [41]. Studies have shown that, quinoline and tetrazole fused molecules, resulted in wide variety of biological activities such as anti-inflammatory [42], anti-bacterial [43], antimicrobial [44] and antituberclosis [45].

Based on highly promising biological activities of quinoline and tetrazole derivatives, we envisioned to synthesize quinoline and tetrazole fused analog. Herein, we report the synthesis, characterization, single crystal XRD and anti-inflammatory activity of a novel 5-mercapto-1-substituted tetrazole incorporated quinoline derivative. Molecular docking study was also performed on 2-Cyclopropyl-4-(4-fluorophenyl)-3-{1-[2-(4-methoxybenzyloxy)-ethyl]1*H*-tetrazol-5-ylsulfanylmethyl}quinoline with the targeted Human Histamine H1 Receptor (H1R).

2. Experimental

2.1. Materials and methods

All the raw materials and reagents used for synthesis were procured and used without purification. The compound was prepared as per the synthetic method provided in the experimental section.

Progress of the reaction was monitored by Thin Layer Chromatography (TLC) using a mixture of *n*-Hexane:Ethyl acetate (7:3) as eluent. Analytical TLC was performed on pre-coated aluminium sheets of silica gel 60 F254 of 0.20 mm thickness (Merck, Germany) and compounds were visualized with UV radiation. The melting point was determined by open capillary tube method on a Buchi melting point apparatus and is uncorrected. FT-IR analysis was done over 4000–400 cm^{-1} with 4 cm^{-1} resolution on a Perkin-Elmer spectrum 65 FT-IR Spectrometer. Eight scans were applied to each sample and the average spectra in transmittance mode is collected and processed through Spectrum software. A mass spectrum was recorded on a PE-SCIEX API-300 LC-MS/MS with Turboion spray mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer using $CDCl_3$ as solvent with TMS (tetramethyl silane) as internal standard.

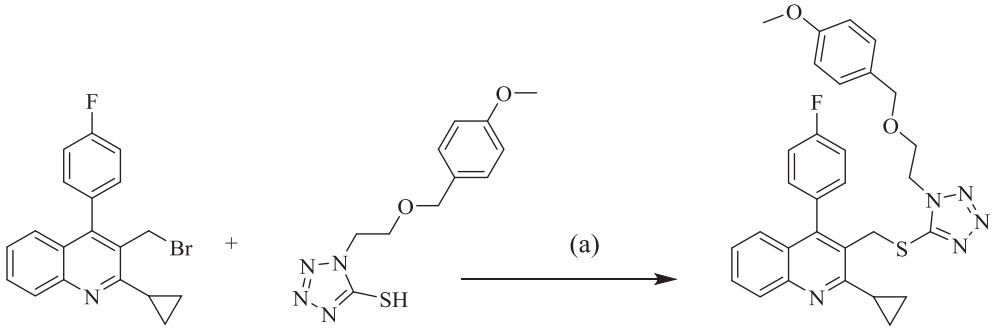
Calorimetric response of the sample was measured using DSC (TA Instruments DSC1000, USA), operating with Universal software (version 4.5A). Prior to analysis, calibration of the instrument was performed using piece of indium (In). The sample (≈2.0–3.0 mg) was weighed and transferred into an aluminum pan and sealed with pin-holed lid. The sample was equilibrated and heated at a rate of 10 °C/min from 25 to 250 °C under nitrogen purge at 40 ml/min.

Thermo gravimetric analysis was performed using TGA (TA Instruments TGA Q500), with Universal software (version 4.5A). TGA system was purged with nitrogen gas at the flow rate of 100 ml/min (60 ml/min for sample and 40 ml/min for balance). About 10 mg of sample was transferred to Aluminium pan and analyzed in the range of 30–350 °C at 10 °C/min temp ramp. Weight calibration of balance was done with certified weights (100 mg and 1000 mg) and temperature calibration was done by using Alumal and Nickel metals. Dry nitrogen was used as a purge gas (sample purge 60 ml/min, balance purge 40 ml/min).

2.2. Synthesis

2.2.1. Preparation of 2-Cyclopropyl-4-(4-fluorophenyl)-3-{1-[2-(4-methoxybenzyloxy)- ethyl]1H-tetrazol-5-ylsulfanylmethyl} quinoline (QS-15)

Anhydrous potassium carbonate (7.76 g, 0.056 mol, 2 eq.) was added to a solution of 3-(bromomethyl)-2-cyclopropyl-4-(4-fluorophenyl)quinoline (10 g, 0.028 mol, 1 eq.) and 1-{2-[(4-methoxybenzyl)oxy]ethyl}-1*H*-tetrazole-5-thiol (7.47 g, 0.028 mol, 1 eq.) in acetone (150 ml) at RT. The reaction mixture was stirred at room temperature for 24 h. The progress of the chemical reaction was monitored by TLC and by completion of the reaction, the reaction mixture was filtered to remove insoluble materials and the clear filtrate was concentrated to thick mass under vacuum at 45–50 °C. The concentrated mass was dissolved in ethyl acetate and washed twice with demineralized water. The organic layer was dried over sodium sulfate and concentrated the clear solution under vacuum at 50–55 °C. To residue methanol (80 mL) was added and the clear solution was stirred for 1 h. The precipitated compound was filtered and washed with chilled methanol (20 mL), which yields 12.8 g (84%) of the final product. The melting point of the compound was determined as 130–132 °C by open capillary method.



(a) Reagents and conditions: Anhydrous K_2CO_3, Acetone at RT

Reaction Scheme 1