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Synthesis, molecular modeling and anti-inflammatory screening of novel fluorinated quinoline incorporated benzimidazole derivatives using the Pfitzinger reaction

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ABSTRACT

Several new fluorinated quinoline derivatives were synthesized and tested for their anti-inflammatory and ulcerogenic effect. A docking study on the COX-2 binding pocket was carried out for the target compounds to rationalize the possible selectivity of them against COX-2 enzyme. The most active compounds (**3**, **2**, **7** and **11**) were found to be superior to celecoxib as they were devoid of any ulcerogenic activity. Compound **3a** demonstrated the highest anti-inflammatory activity as well as the best binding profiles into the COX-2 binding site. Moreover, compounds **3–12** were screened for antibacterial activity and none of them showed noteworthy activity.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for treatment of inflammation, fever and pain. However, because NSAIDs inhibit both isoforms of cyclooxygenase (COX) (constitutive COX-1 and responsible for cytoprotective effects; induce COX-2 which responsible for inflammatory effects). They are associated with well-known side effects such as gastrointestinal side effects and renal function suppression [1,2]. It is known that selective COX-2 inhibitors can provide anti-inflammatory agents devoid of the undesirable effects associated with classical non-selective NSAIDs [3]. In addition to the role of COX-2 in inflammatory disorders such as rheumatoid arthritis and osteoarthritis, it is also implicated in cancer and angiogenesis. In this regard, several epidemiologic studies have been reported that inhibitors of COX-2 enzyme reduce the risk of colorectal, breast, and lung cancer, and COX-2 are expressed in these cancers [4,5]. As a consequence, increasing interest has been shown towards the synthesis of selective inhibitors of COX-2 by modifying well-known non-selective agents as indomethacin [6], zomepirac [7], flurbiprofen [8], meclofenamic acid [9] or the ketoprofen [10]. From the above findings, we keep looking for anti-inflammatory drugs (COX-2 inhibitors), which remains a mandatory task for medicinal chemistry. The quinoline framework has emerged as a new template for drug design and identification of novel anti-inflammatory agents. They have attracted particular attention owing to their diverse array of pharmacological properties including the ability to target several causes of inflammation. These include targeting of cyclooxygenase-2 (COX-2, prostaglandin inhibition), phosphodiesterase 4 (PDE4, cytokine inhibition) and tumor necrosis factor (TNF)-α converting enzyme (TACE), as well as transient receptor potential vanilloid 1 (TRPV1) antagonists [11].

Fluorine imparts desirable characteristics to drug by modulating both the pharmacokinetics and pharmacodynamics properties of a drug. Incorporation of fluorine into a drug increases the lipophilicity enhancing absorption into biological membranes whereby its small covalent radius can facilitate docking with their drug receptors. In fact the importance of fluorine in bioorganic and medicinal chemistry has been demonstrated by a large number of fluorinated compounds approved by the FDA for medical use [12–14]. Recently, it was reported that more than 138 fluorine

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containing drugs has received FDA approval for human diseases (of which 23, however, have been discontinued from the market), while 33 are currently in use for veterinary applications [15,16]. These statistics make fluorine the "second-favorite substituent" after nitrogen in drug design.

The azole class of drugs, particularly fused imidazoles, occupy a prominent place in medicinal chemistry because of their broad spectrum of pharmacological activities such as anti-inflammatory, analgesic, anticancer, antiulcer, antimicrobial, antiviral, pesticidal, cytotoxicity and anti-arrhythmic activities [17–20]. Omeprazole, Mebendazole, Pimobendan and Albendazole are well-known drugs in the market which contain fused imidazoles as active core moiety.

Promoted by these observations and in continuation of our research on novel quinoline [21] as well as anti-inflammatory compounds against COX-2 [22,23], we report herein the design, synthesis and the preliminary in vivo anti-inflammatory activity of trisubstituted quinoline derivatives linked to different azoles (**2–12**). Also, in an attempt to rationalize the possible selective activity of the target compounds against the COX-2 enzyme, a molecular modeling study was conducted to check the ability of these new scaffolds to bind to the active site of COX-2 isozyme.

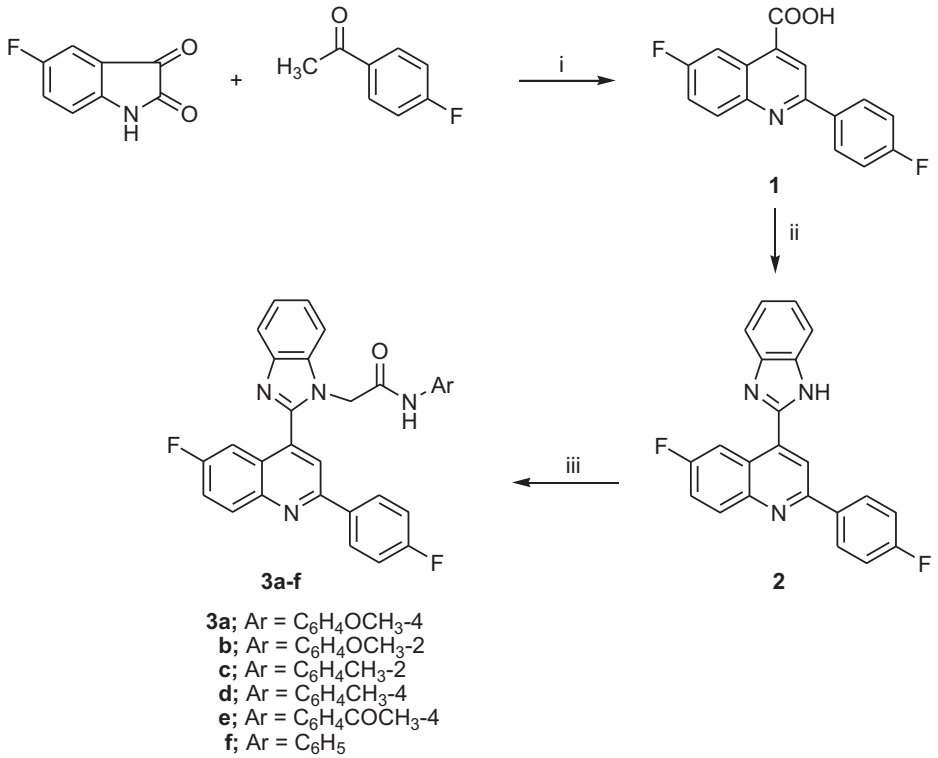
2. Results and discussion

The reaction sequence used to synthesize the target compounds is outlined in Schemes 1–4. The versatile Pfitzinger reaction was utilized to synthesize pertinent 6-fluoro-2-(4-fluorophenyl)quinoline-4-carboxylic acid **1** in a very good yield by reacting 5-fluoroisatin with 4-fluoroacetophenone in aqueous ethanol [24]. This compound has previously been produced by a Doebner reaction using substituted aniline, 4-fluorobenzaldehyde, pyruvic acid and a catalytic amount of trifluoroacetic acid in ethanol media [17]. Infrared spectrum of compound **1** showed a characteristic band at 3390 cm^{-1} which is due to the –OH stretching of carboxylic acid in addition to the presence of a band at 1690 cm^{-1} due to C=O stretching of acid group. ^{1}H-NMR spectrum showed a singlet at δ 14.0 ppm corresponding to the acidic-COOH proton of quinoline, a singlet at δ 8.54 ppm due to quinolone H-3 proton in addition to the presence of multiplet at δ 6.95–8.2 ppm assigned to 4-fluorophenyl aromatic protons. These data were in accordance with the reported spectral data of Isloor et al. [17].

The target quinoline incorporated benzimidazole derivative **2** was synthesized by the reaction of the acid **1** with 1,2-benzenediamine (*o*-phenylenediamine) in polyphosphoric acid media. The crude product was purified by column chromatography. Compound **2** was confirmed by the presence of absorption band at 3350 cm^{-1} which is due to NH stretching of benzimidazole (Scheme 1). Compounds **3a–f** were obtained by heating compound **2** with the appropriate 2-chloro-*N*-arylacetamides [25] in *N*,*N*-dimethylformamide (DMF) containing anhydrous potassium carbonate. Compounds **3a–f** have benzimidazole ring in which different quinolines were linked to it through acetamides linker (Scheme 1).

Compounds **3a–f** were confirmed by the presence of absorption bands at 3255 cm^{-1} due to stretching NH, 1687 cm^{-1} due to stretching C=O of amide.

Quinoline-4-carboxylic acid (**1**) was treated with methyl iodide in acetone in the presence of potassium carbonate to obtain the corresponding ester (**4**). This ester was then hydrazinolyzed with hydrazine hydrate in ethanol to give the corresponding carbohydrazide precursor (**5**) in good yield, and the correct synthesis of



Reagents and conditions: i; 33% KOH/EtOH, ii; o-phenylenediamine, PPA, iii; $ArNHCOCH_2Cl$/KOH, iv; DMF/K_2CO_3

Scheme 1. Synthesis of 4-(1*H*-benzo[d]imidazol-2-yl)-6-fluoro-2-(4-fluorophenyl)quinoline **2** and *N*-(substituted-phenyl)-2-(2-(6-fluoro-2-(4-fluorophenyl)-quinolin-4-yl)-1*H*-benzimidazol-1-yl)acetamides **3a–f**.