Research Article

Synthesis of ١,٢,٤-triazole-٣-thiol derivative

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Abstract
Several new quinoline-٤-carboxylic acid derivatives were synthesized via pfitzinger reaction and tested for their anti-inflammatory and ulcerogenic effects compared to NSAIDs. Replacement of the ulcerogenic carboxylic (COOH) functional group with its less acidic bioisostere ١,٢,٤-triazole ring is expected to lower the ulcerogenic potentials of quinoline-٤-carboxylic acid derivatives as well as NSAIDs.
Key Words*:* ١,٢,٤-triazole-٣-thiol, Quinoline, Anti-inflammatory

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Introduction
Quinoline is nitrogen containing heterocyclic aromatic compound. Quinoline derivatives have a wide therapeutic applications such as anti-malarial[١], analgesic[٢], anticancer[٣], anti-inflammatory activities[٤] and in treating of alzheimer's disease[٥].

There are so many reported procedures for the synthesis of quinoline ring[٦], the main core of quinoline ring has been synthesized via well-known named chemical reactions as Skraup[٧], Doebner-Von Miller[٨], Friedländer[٩], Pfitzinger[١٠], Conrad-Limpach[١١] and Combes syntheses[١٢]. Nowadays scientists are focusing on introduction of novel and safe therapeutic drugs with new scaffolds of clinical importance.

Triazole ring has been incorporated into a variety of pharmacologically active drugs, it can be synthesized via numerous chemical reactions as Pellizari Reaction[١٣] and Einhorn-Brunner synthesis[١٤]. Triazoles have many therapeutic applications such as anti-microbial[١٥], anti-inflammatory[١٦], anticancer[١٧], anticonvulsant[١٨] and anti-malarial activities[١٩].

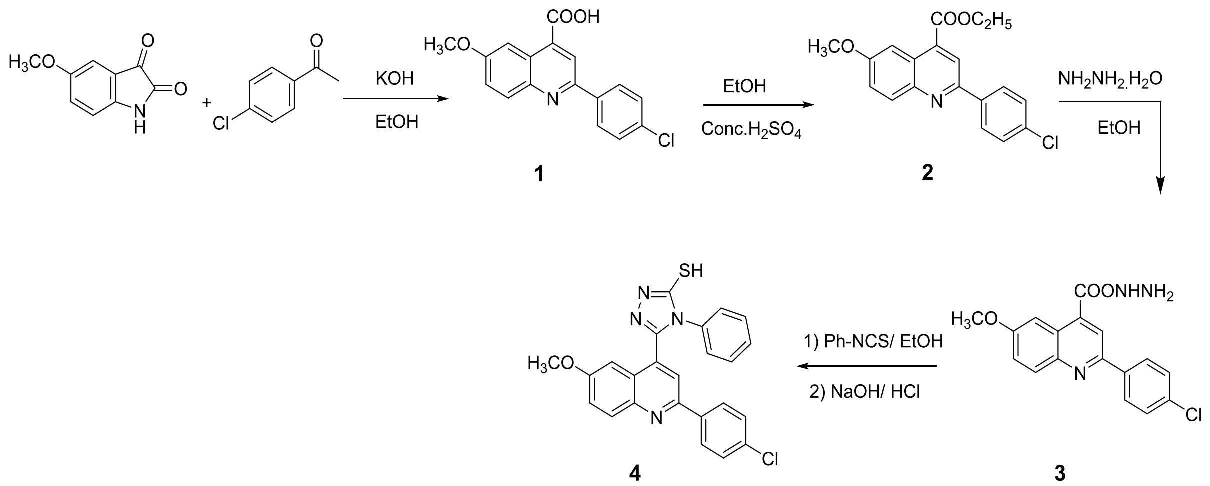
Results and discussion
Chemistry
The synthesis of the target compound ٥-(٢-(٤-chlorophenyl)-٦-methoxyquinolin-٤-yl)-٤-phenyl-٤*H*-١,٢,٤-triazole-٣-thiol ٤ is illustrated in Scheme١.

Synthesis of ٢-(chlorophenyl)quinoline-٤-carboxylic acid ١ was carried out according to the reported method[٢٠] by heating at reflux of ٥-methoxyisatin with *p*-chloroacetophenone in aqueous ethanol affording compound ١ in a good yield. Treatment of the acid ١ with absolute ethanol in presence of conc. $H_{٢}SO_{٤}$ affording the corresponding esters **٢.** Refluxing of ester with hydrazine monohydrate affording the carbohydrazide derivative ٣. Structure of the formed compounds have been confirmed by their reported melting points.

Heating at reflux of the carbohydrazide ٣ and phenyl isothiocyanate in ethanol followed by the addition of ٢N NaOH and acidification with conc. HCl affording the final ١,٢,٤-triazole-٣-thiol derivative ٤**.**

The purity of compound ٤ has been checked by TLC and the structure was confirmed by ^{١}H-NMR and ^{١٣}C-NMR spectra.

Scheme١: Synthesis of ٥-(٢-(٤-chlorophenyl)-٦-methoxyquinolin-٤-yl)-٤-phenyl-٤*H*-١,٢,٤-triazole-٣-thiol (٤**).**



The ١H-NMR spectrum for the ١,٢,٤-triazole-٣-thiol derivative ٤ is characterized by the appearance of SH proton at ١١.٦٢ ppm and the protons of the methoxy group ($OCH_{٣}$) at ٣.٩٤ppm.

In ١٣C-NMR spectrum, the methoxy carbon ($OCH_{٣}$) appeared at ٥٥.٨١ ppm and the ١,٢,٤-triazole carbon attached to the thiol group (C—SH) appeared at ١٥٩.٢٥ ppm and this is may be attributed to the high electronegativity of sulfur atom.

Experimental

General

Melting points were determined on Stuart electro-thermal melting point apparatus and were uncorrected. ١H-NMR and ١٣C-NMR spectra were recorded in Umm-al-Qura University, Saudi Arabia using TMS as reference standard and $CDCl_{٣}$ as solvent. Chemical shifts are expressed in parts per million (ppm) and coupling constants (*J*) are expressed in Hertz.

Synthesis of compounds ١-٣.

٢-(٤-Chlorophenyl)-٦-methoxyquinoline-٤-carboxylic acid, ethyl ٢-(٤-chlorophenyl)-٦-methoxyquinoline-٤-carboxylate and ٢-(٤-chlorophenyl)-٦-methoxyquinoline-٤-carbohydrazide were prepared according to the reported procedures. [٢١]

Synthesis of ٥-(٢-(٤-chlorophenyl)-٦-methoxyquinolin-٤-yl)-٤-phenyl-٤*H*-١,٢,٤-triazole-٣-thiol (٤).

Equimolar quantities of the carbohydrazide **٣** (١٠٠ mmol) and phenyl isothiocyanate (١٠٠ mmol) in ١٢٥ ml of absolute ethanol were heated at reflux for ٤ h. The solvent was evaporated under reduced pressure. Then ١٠٠ ml of ٢N NaOH solution was added and the obtained solution was refluxed for ٣h. The reaction mixture was cooled and acidified to pH ٢ with concentrated HCl. The solid that precipitated was filtered off, washed with water, and recrystallized from ethanol. Compound ٤ was obtained as a white solid, (in٧٩٪ yield), m.p. ٢٣٨-٢٤٠°C; ١H NMR (٥٠٠ MHz, $CDCl_{٣}$) δ (ppm) ١١.٦٣ (s, ١H, SH), ٨.٢٧-٨.١٥ (m, ١H, Ar-H), ٧.٧٧-٧.٧٢ (m, ٢H, Ar-H), ٧.٥٦– ٧.٥٠ (m, ٢H, Ar-H), ٧.٤٨-٧.٤٢ (m, ٤H, Ar-H), ٧.٣٤-٧.٣٢ (m, ١H, Ar-H), ٧.٢٨ (s, ٢H, Ar-H), ٧.٢١ (d, *J* = ٧.٩ Hz, ١H, Ar-H), ٣.٩٥ (s, ٣H, $-OCH_{٣}$); ١٣C NMR (١٢٥ MHz, $CDCl_{٣}$) δ (ppm) ١٥٩.٢٦, ١٤٣.٧٢, ١٣٣.٦٨, ١٣٣.٠٩, ١٣٠.٧٥, ١٣٠.٢٤, ١٢٩.٧٨, ١٢٩.١٢, ١٢٨.٤٢, ١٢٨.٣٧, ١٢٨.١٣, ١٢٧.٦١, ١٢٧.٤٠, ١٢٦.٩٠, ١٢٦.٠٦, ١٢٣.٨٩, ١٢٠.٥٤, ١٠٣.٠٦, ١٠٢.٤٧, ٥٥.٨٢.

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