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# An efficient synthesis of 3′-quinolinyl substituted imidazole-5-one derivatives catalyzed by zeolite and their antimicrobial activity

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**Abstract**

A series of some new quinoline based imidazole-5-one derivatives have been synthesized by the fusion of oxazol-5-ones, various *p*-substituted anilines and zeolite in pyridine. All the derivatives were subjected to an *in vitro* antimicrobial screening against a representative panel of bacteria and fungi and results worth further investigations.


*Keywords:* Imidazolinone; Quinoline; Zeolite; Antimicrobial activity

Over the past few decades, the problems posed by multi-drug resistant microorganisms have reached an alarming level in many countries around the world. The use of most antimicrobial agents is limited, not only by the rapidly developing drug resistance, but also by the unsatisfactory status of the present treatment of bacterial and fungal infections [1]. Infections caused by those microorganisms represent a serious challenge to the medical community; hence, the development of new antimicrobial agents is an important goal. In pursuit of this goal, our research efforts are focused on the development of new structural moieties with promising antimicrobial properties.

A numerous topical computational analysis of the comprehensive medicinal chemistry database found the imidazolinone scaffold to be among the most prolific chemotypes found. Imidazolinone has attracted attention as an important class of heterocyclic compounds in the field of pharmaceuticals. These compounds are widely used as antimicrobial [2], anti-convulsant [3], antiviral [4], antitubercular [5], antioxidant [6], anticancer [7], HIV-1 protease inhibitor [8], CHK1 inhibitor [9], L-DOPA prodrugs [10] and anti-inflammatory [11]. While, quinoline derivatives have been a topic of substantial research interest in contemporary heterocyclic and medicinal chemistry due to their great significance in the view of wide-ranging biological activities which includes antimicrobial [12], antimycobacterial [13], antimalarial [14], anti-inflammatory [15] and anticancer activity [16].

Zeolites are used as catalysts for wide range of processes, from simple drying to complicated catalytic reactions. Zeolite is unique catalyst that contains a framework system of supercages, which are connected by a three-dimensional array of large diameter channels and this array enables a much easier diffusion of reactants and products [17] and employed as mild alternative heterogeneous catalyst for some of these transformation [18]. Zeolite has attracted much attention because of its suitable acidity, eco-friendliness, easy availability and low cost thereby acting as a promising table top reagent. In the following section we will focus on the most significant of these approaches. It must be

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emphasized, that combination of imidazolinone template with other heterocycles is a well-known approach for drug-like molecules' build-up, which allows achieving new pharmacological profile, action strengthening or toxicity lowering. As part of our ongoing research in discovery of new active antimicrobial compounds [19], in this work, we try to study the influence of imidazolinone and quinoline scaffold combination on the antimicrobial effect.

## 1. Experimental

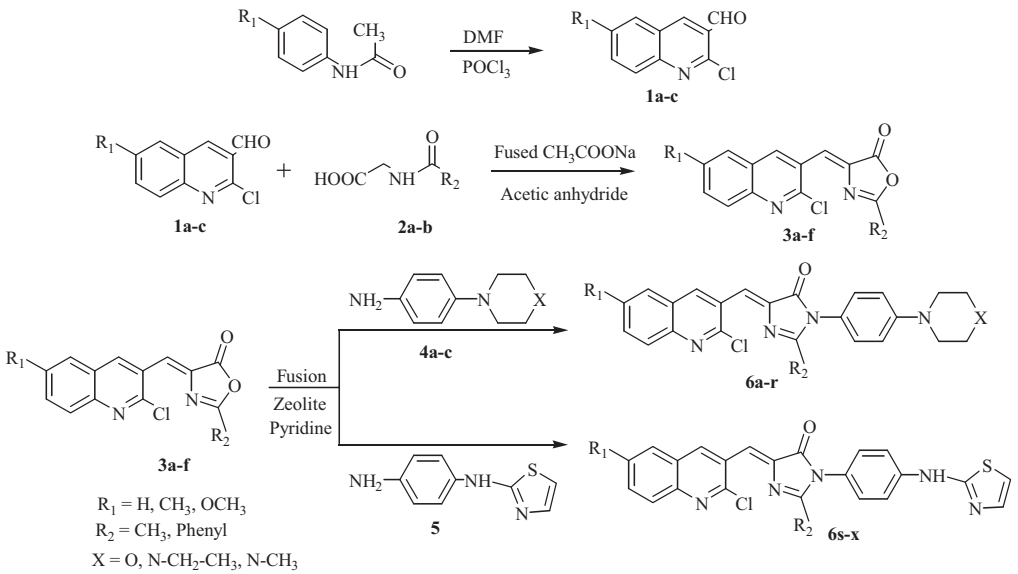
All the reagents were obtained commercially and used with further purification. All melting points were taken in open capillaries in a paraffin bath and are uncorrected. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out by thin layer chromatography (TLC). TLC was run using TLC aluminum sheets silica gel 60 $F_{254}$ (Merck). Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds are within ± 0.4% of theory specified. IR spectra of all the compounds have been recorded on Nicolet Impact 400D FT-IR spectrophotometer using KBr. $^{1}$H NMR and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ on a Bruker AC 300F (300 MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using solvent peak as internal standard at 300 MHz and 75 MHz respectively. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan) (Scheme 1).

### *1.1. General procedure for the synthesis of title compounds (**6a–x**)*

A mixture of an appropriate oxazol-5-ones **3a–f** (1 mmol), various *p*-substituted anilines **4a–c/5** (1 mmol) and 0.2 g zeolite (20%) were taken in pyridine (5 mL). The reaction mixture was refluxed on an oil bath for 3–4 h. After the completion of reaction (checked by TLC), the reaction mixture was cooled to room temperature and poured over crushed ice and acidified with dilute HCl. The separated precipitates were filtered and washed with hot water till neutral pH to get title compounds **6a–x**.

## 2. Results and discussion

The imidazolin-5-ones **6a–x** were synthesized using zeolite catalyst with good yield (52–72%). While optimizing, the yield was very poor without catalyst. Presence of zeolite in the reaction revealed good yield. Moreover, equivalence optimization for best yield concluded to use just 20% of zeolite in reaction. Oxazol-5-ones **3a–f** were prepared by heating of substituted 2-chloro-3-formyl quinolines **1a–c** (0.01 mmol), benzoyl/acetyl glycine




Scheme 1. General synthetic procedure of imidazoline-5-one **6a–x**.

(0.01 mmol), anhydrous sodium acetate (0.03 mmol) and acetic anhydride (0.025 mmol) according to literature procedure reported by us [20]. The required 2-chloro-3-formyl quinoline was prepared by literature procedure [21].

IR spectra of **6a** exhibited absorptions at 705 $cm^{-1}$ for (C–Cl stretching), 1115 $cm^{-1}$ for (C–O stretching of morpholine ring), 1610 $cm^{-1}$ for (C=N stretching) and 1650 $cm^{-1}$ for (C=O group). The $^1H$ NMR of compound **6a** showed singlet at $\delta$ 2.13 for ($CH_3$) proton as well as multiplet at $\delta$ 2.70 and 3.32 for ($CH_2$–N–$CH_2$) and ($CH_2$–O–$CH_2$), respectively. Aromatic protons resonate as multiplets at $\delta$ 6.82–8.01. The $^{13}C$ NMR spectrum of compound **6a** showed signals at $\delta$ 23.12 for ($CH_3$), 66.57 for ($CH_2$–N–$CH_2$), 77.53 for ($CH_2$–O–$CH_2$) carbon, 110.91 for (CH) and 115.04, 120.82, 121.24, 121.78, 126.47, 128.71, 129.10, 129.45, 129.72, 130.76, 131.29, 133.90, 134.61, 138.12, 138.69 for aromatic carbon. The carbonyl carbon was observed at $\delta$ 167.45. The elemental analysis values and mass spectral data of some selected compounds are in good agreement with theoretical data. Similarly, all these compounds were characterized on the basis of spectral studies.

### 2.1. Antimicrobial assay

The *in vitro* antimicrobial activity was carried out against 24 h old cultures of three bacteria and two fungi by disc diffusion method [22]. Compounds **6a–x** have been tested for their antibacterial activity against *Escherichia coli* as Gram-negative bacteria and *Bacillus subtilis* and *Bacillus cereus* as Gram-positive bacteria and antifungal activity against *Aspergillus parasiticus* and *Sclerptum rolfsii*. Nutrient agar and potato dextrose were used to culture the bacteria and fungus respectively. The compounds were tested at 1000 ppm in DMF solution. Ampicillin and Griseofulvin were used as standards for comparison of antibacterial and antifungal activities, respectively. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 h for bacteria at 35 °C and 48 h for fungus at 28 °C. The results are summarized in Table 1.

Table 1
Antimicrobial activity of compounds (**6a–x**).

| Compounds | Antibacterial activity zone of inhibition (mm) | | | Antifungal activity zone of inhibition (mm) | |
|---|---|---|---|---|---|
| | *E. coli* | *B. subtilis* | *B. cereus* | *A. parasiticus* | *S. rolfsii* |
| **6a** ($R_1$=H, $R_2$=$CH_3$, X=O) | ++ | – | – | +++ | +++ |
| **6b** ($R_1$=H, $R_2$=$CH_3$, X=N–$CH_2CH_3$) | + | – | – | + | + |
| **6c** ($R_1$=H, $R_2$=$CH_3$, X=N–$CH_3$) | + | | – | | |
| **6d** ($R_1$=H, $R_2$=Ph, X=O) | ++ | – | + | +++ | +++ |
| **6e** ($R_1$=H, $R_2$=Ph, X=N–$CH_2CH_3$) | + | – | + | + | + |
| **6f** ($R_1$=H, $R_2$=Ph, X=N–$CH_3$) | + | + | – | +++ | ++ |
| **6g** ($R_1$=$CH_3$, $R_2$=$CH_3$, X=O) | + | + | – | +++ | ++ |
| **6h** ($R_1$=$CH_3$, $R_2$=$CH_3$, X=N–$CH_2CH_3$) | ++ | – | – | ++ | + |
| **6i** ($R_1$=$CH_3$, $R_2$=$CH_3$, X=N–$CH_3$) | ++ | + | + | +++ | ++ |
| **6j** ($R_1$=$CH_3$, $R_2$=Ph, X=O) | ++ | ++ | – | +++ | +++ |
| **6k** ($R_1$=$CH_3$, $R_2$=Ph, X=N–$CH_2CH_3$) | + | – | – | +++ | ++ |
| **6l** ($R_1$=$CH_3$, $R_2$=Ph, X=N–$CH_3$) | + | + | + | ++ | ++ |
| **6m** ($R_1$=$OCH_3$, $R_2$=$CH_3$, X=O) | + | + | – | +++ | +++ |
| **6n** ($R_1$=$OCH_3$, $R_2$=$CH_3$, X=N–$CH_2CH_3$) | + | – | – | +++ | ++ |
| **6o** ($R_1$=$OCH_3$, $R_2$=$CH_3$, X=N–$CH_3$) | ++ | – | – | +++ | ++ |
| **6p** ($R_1$=$OCH_3$, $R_2$=Ph, X=O) | ++ | – | – | +++ | +++ |
| **6q** ($R_1$=$OCH_3$, $R_2$=Ph, X=N–$CH_2CH_3$) | +++ | – | + | +++ | + |
| **6r** ($R_1$=$OCH_3$, $R_2$=Ph, X=N–$CH_3$) | ++ | – | – | +++ | ++ |
| **6s** ($R_1$=H, $R_2$=$CH_3$, X=–) | ++ | – | + | +++ | +++ |
| **6t** ($R_1$=H, $R_2$=Ph, X=–) | ++ | – | – | +++ | +++ |
| **6u** ($R_1$=$CH_3$, $R_2$=$CH_3$, X=–) | + | ++ | – | +++ | +++ |
| **6v** ($R_1$=$CH_3$, $R_2$=Ph, X=–) | + | + | – | ++ | +++ |
| **6w** ($R_1$=$OCH_3$, $R_2$=$CH_3$, X=–) | ++ | + | + | ++ | +++ |
| **6x** ($R_1$=$OCH_3$, $R_2$=Ph, X=–) | ++ | – | – | +++ | +++ |
| Ampicillin | +++ | +++ | +++ | NT | NT |
| Griseofulvin | NT | NT | NT | +++ | +++ |

(–) = inactive (inhibition zone <7 mm); (+) = slightly active (inhibition zone 8–10 mm); (++) = moderate activity (inhibition zone 11–13 mm); (+++) = good activity (inhibition zone ≥14 mm); NT = not tested. Control (DMF) (–) = no activity.

Antimicrobial study of all the title derivatives revealed good to moderate inhibition except compound **6q** ($R_1$=$OCH_3$, $R_2$=Ph, X=N–$CH_2CH_3$) found exceedingly potent against bacterial species *E. coli*. Whereas, all the compounds, against *B. subtilis* and *B. cereus*, found poorly active. In addition, all the synthesized compounds were screened for their antifungal activitiy against *A. parasiticus* and *S. rolfsii* and were found significantly active upon comparison with Griseofulvin.

The structure–activity relationship (SAR) study revealed that antifungal screening of compounds having substitution X=O displayed better activity and X=N–Et showed poor activity against Griseofulvin. Compounds containing X=O (**6a**, **6d**, **6g**, **6j**, **6m** and **6p**) were extremely active but, upon replacing with X=N–Et/N–Me (**6b**, **6c**, **6e**, **6f**, **6h**, **6i**, **6k**, **6l**, **6n**, **6o**, **6q** and **6r**) resulted in poor activity towards *S. rolfsii*. While, substitution X=N–Et (**6b**, **6e** and **6h)** derivatives have shown poor activity and upon replacing with X=N–Me (**6c**, **6f** and **6i)** enhanced potency against fungal pathogen *A. parasiticus*. Moreover, against *A. parasiticus*, $R_2$=Me derivative (**6w)** exhibited moderate activity, upon changing $R_2$=Ph (**6x)** resulted in increased inhibitory action.

Reviewing and comparing the activity data, it is worthy to mention that the compounds of this series possess better fungicidal activity as well as poor bactericidal activity and antimicrobial activity of the target compounds depends not only on the bicyclic heteroaromatic pharmacophore appended through aryl ring but also on the nature of the peripheral substituents and may also upon their spatial relationship and positional changes.

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