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Research Article

SYNTHESIS OF SOME NOVEL 5- IMIDAZOLONES AND ITS ANTIMICROBIAL ACTIVITY

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ABSTRACT

Based on the importance of heterocyclic rings in the field of medicinal chemistry, a new series of 4-arylidene-1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methyleneamino)-2-phenyl-1*H*-imidazol-5(4*H*)-one **(3a-e)** was designed, synthesized and screened for antimicrobial activity. In present investigation, 5-imidazolones **(3a-e)** have been synthesized by the condensation of 1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methylene)hydrazine **(1)** with different 4-arylidene-2-phenyloxazol-5(4*H*)-ones **(2a-e),** in presence of dry pyridine as the solvent. Structure elucidation of the synthesized compounds was made on the basis of elemental analysis and spectral techniques such as IR, ^{1}HNMR, and further supported by Mass spectra. The title compounds were screened *in-vitro* for antibacterial and antifungal activity against different strains of bacteria and fungi. The result revealed that some of the title compounds exhibited significant antibacterial activity but were found to be inactive against the selected fungi.

Keywords: Quinoline, oxazolone, imidazolone, antimicrobial activity

INTRODUCTION

Heterocyclic rings are the gate way for medicinal science. Various compounds such as alkaloids, antibiotics, amino acids, vitamins, hemoglobin, hormones, many synthetic drugs and dyes contain heterocyclic system. Nitrogen containing compound basically DNA and RNA which contains purine and pyrimidine bases are the heterocyclic compound. They are used to optimize potency and selectivity through bioisosterism and pharmacokinetic and by adjust polarity, lipophilicity and solubility of target molecule[1]. Today's challenging problems is to decrease death rate over worldwide. Heterocyclic system containing quinoline ring is the biologically accepted pharmacophore found in many natural and synthetic products. Drugs such as Chloroquine, Primaquine containing quinoline nucleus were used for the treatment of malaria. Quinoline is the important structural unit[2] exhibiting broad range of biological activities such as anti-tubercular[3], anticancer[4], antifungal[5], antibacterial[6,7], anti-hyperglycaemic[8].

In the recent years, the synthesis of heterocyclic ring containing nitrogen is the basic need. 5-oxo imidazole is a five membered ring in which nitrogen is at 1, 3 position and carbonyl group at 5 position. The biological and chemical interest of 5-oxo imidazole ring is long as it is medicinally effective against pathogens. Number of drugs such as Albendazole, Thiabendazole, Omeprazole contain Benzimidazole as a pharmacophore. Imazaquin is a class of herbicide has a quinoline moiety along with Imidazolone. Rather than the major application of Imidazolone towards herbicide[9] these compound have been extensively explored for their pharmacological activities such antibacterial[10-12], antifungal[13-15], anticancer[16] and are potent against the cancer cell lines MCF-7 and HePG2[17], anticonvolsunt[18], anti-inflammatory[19], antioxidant[20]. The imidazolidinone derivatives are also studied for systematic evaluation of their metabolic profiles and toxicities on TAMH cells[21], inhibitory for kinase[22], as an antioxidant in lubricant oil[23]. Many researchers have focused on the biological activities of the new series of compounds containing both quinoline and imidazolinone moiety[24].

Due to wide range of applicability of quinoline nucleus towards the medicine, the present work attracted us to focus on the synthesis of some novel derivatives of quinoline. In the present research, a new series of compounds of 5-oxo-imidazole containing quinoline moiety are reported in order to evaluate how combined effect of both these moieties enhances the biological activities.

MATERIALS AND METHODS

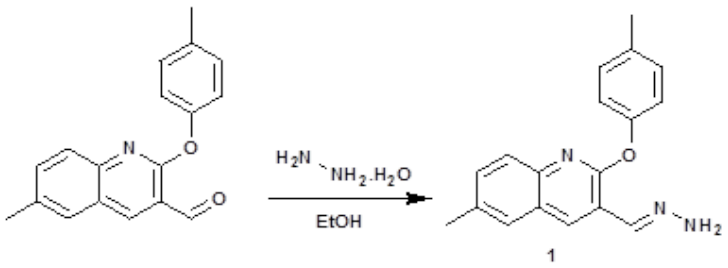
The melting points of all synthesized compounds were found in open capillary in paraffin oil bath and are found to be uncorrected. H^{1}NMR spectra recorded on Bruker AM 400 instrument using tetramethylsilane (TMS) as an internal reference and DMSO-d^6 as solvent. IR spectra were recorded on a Shimatzu-FT-IR 8400-Spectrophotometer; Frequency ranges from 4000-400 cm^{-1}. Elemental (C, H, N) analysis was done using Thermo Scientific ((Flash-2000) and results obtained are close to the calculated value. Mass spectra were obtained with a Waters Micro mass Q-TOF Micro, Mass Spectrophotometer. All the chemicals used were of AR grade of Merck S. D. Fine and Aldrich. The IR, ^{1}HNMR, Mass spectra and elemental analysis of **(1a)** was determined. Antibacterial and antifungal activities were carried out for **(1a)** at different concentration and for series (**1a-e**) at concentration of 1000µg/ml.

Experimental

General procedure for the synthesis of 1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methylene) hydrazine (1):

Equivalent amount of 7-methyl-2-(p-tolyloxy)quinoline-3-carbaldehyde (0.01M) and hydrazine hydrate (0.01M) in ethyl alcohol (15-20 mL) were refluxed for 2h. The reaction mixture was poured in ice cold water and neutralized by 1:1 HCl, filtered and further purified by recrystallization using 1,4-dioxane to give **1** (Scheme **I**).

Scheme-I



1

1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methylene)hydrazine (1)

Crystalline yellow colour solid; recrystallising solvent, DMF (dimethyl formamide); mp for $C_{18}H_{17}N_3O$, 307-310°C; yield 81%; IR (KBr v max in cm^{-1}): 3192, 3355 (-NH_2 stretch), 3030, 3066 (C– H aromatic str.), 1505,1602 (C = C str.), 2999, 2920 (C – H aliphatic asym. str.), 2866 (C–H aliphatic sym. str.), 1431(C – H aliphatic), 1126,1143 (C – N – C aliphatic asym. def.), 1350 (C – H aliphatic sym. def.), 1602,1680 (C = N str.), 1021,1059 (C = N str.), 1126, 1143 (C–N–C str.) 1203, 1248 (C–O–C) sym. str.), 1019 (C–O–C) asym. str.). ^{1}HNMR (DMSO-d_6) δ(ppm): 3.29(s, 3H, Ar-CH_3), 3.38(s,3H, CH_3Quinoline ring), 8.44(s,1H-C<u>H</u>=N-NH_2), 7.08-8.23(m, 10H, Ar + Quinoline ring + N<u>H</u>$_2$ Protons). Mass spectra: *m/z* 292 [M+H] $^+$, 293 [M+2] $^+$, 314 [M+Na] $^+$. Elemental Anal.Calcd: for $C_{18}H_{176}N_3O$; C, 74.20; H, 5.88; N, 14.42; Found: C, 74.31; H, 5.38; N, 14.36.

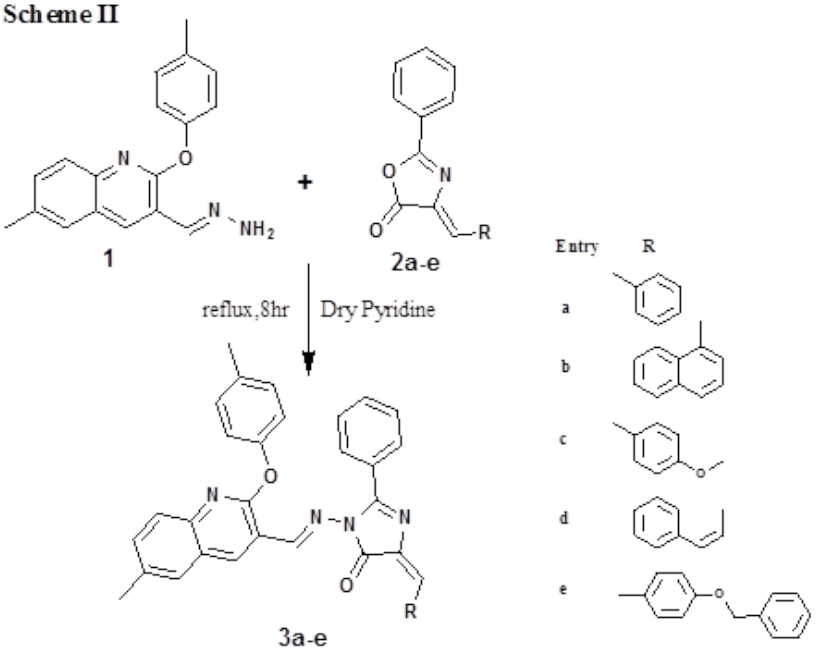
General procedure for the synthesis of different 4-benzylidene-2-phenyloxazol-5(4*H*)-ones (2a-e)

A mixture of different aromatic aldehydes (0.125M), benzoyl glycine (0.125M), acetic anhydride (0.75M) and freshly fused sodium acetate (0.125M) was heated on water bath with constant shaking for two hours. Ethanol (50mL) was slowly added to the mixture and kept overnight. The separated oxazole was filtered, washed with ice cold ethanol (20mL) and further purified by recrystallization with a suitable solvent to give **2a-e**.

General procedure for the synthesis of 4-arylidene-1-(6-methyl-2-(tolyloxy)quinolin-3-yl)methyleneamino)-2-phenyl-*1H*-imidazol-5(4*H*)-ones (3a-e)

A equimolar mixture of 4-benzylidene-2-phenyloxazol-5(4H)-ones **(2a-e)** and 1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methylene)hydrazine **(1)** were refluxed in dry pyridine (15mL) for 8h. The reaction content was cooled and poured on crushed ice and neutralized by 1:1HCl, the product obtained was filtered, washed and recrystallized from DMF to get **3a-e,** respectively.

Scheme II



4-benzylidene-1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methyleneamino)-2-phenyl-1*H*-imidazol-5(4*H*)-one, 3a
Yellow crystalline solid; Recrystallizing solvent DM), mp, for $C_{34}H_{26}O_2N_4$, 285-290°C; yield 80% IR (KBr v max in cm-1): 2919 (Aliphatic C–H asym. str.), 2860 (Aliphatic C–H sym. str.), 1429(Aliphatic C – H asym.def.), 1376 (Aliphatic C – H sym.def.), 3029, 3061(Aromatic C–H str.), 1503,1588 (C = C str.), 1059, 1103, 1129, (C–H. i.p.def), 820(C–H o.o.p.def.), 1608(C=N str. in quinoline ring), 1680,1724(C= O str.), 1608, 1588(C=N str. in imidazolinone ring.), 1129(C– N–C str. in Imidazolinone ring.), 1059(N-N str. in imidazolinone ring) 1204, 1247(C–O–C sym.str.).^{1}H NMR (DMSO-d_6) δ(ppm): 3.35(s, 3H Ar-CH_3), 3.47(s, 3H, quinoline ring -CH_3), 7.18-8.31(m, 20H, ArH). Mass spectra *m/z* 522[M]$^+$, 523[M+H]$^+$, 524[M+2]$^+$. Elemental analysis calculated for $C_{34}H_{26}N_4O_2$; C, 78.14; H, 5.01; N, 10.72; Found: C, 78.10; H, 4.89; N, 10.62.

1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methyleneamino)-4-(naphthalen-1-ylmethylene)-2-phenyl-1*H*-imidazol-5(4*H*)-one 3b
Yellow crystalline solid; Recrystallizing solvent DMF; mp, 206-210°C; yield, 94%; Elemental Analysis Calcd: for $C_{38}H_{28}N_4O_2$; C,79.70; H,4.93; N,9.78; and Found : C,79.30; H, 4.98; N,9.80.

4-(4-methoxybenzylidene)-1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methyleneamino)-2-phenyl-1*H*-imidazol-5(4*H*)-one 3c
Yellow crystalline solid; Recrystallizing solvent DMF; mp,158-162°C; yield, 82%. Elemental Analysis Calcd: for $C_{35}H_{28}N_4O_3$, C, 76.07; H, 5.11; N, 10.14; and Found: C, 76.01; H, 5.00; N, 10.16.

1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methyleneamino)-2-phenyl-4-(3-phenylallylidene)-1*H*-imidazol-5(4*H*)-one 3d
Yellow crystalline solid; Recrystallizing solvent DMF; mp, 236-240°C; yield, 83%. Elemental Analysis Calcd: for $C_{36}H_{28}N_4O_2$, C, 78.81; H, 5.14; N, 10.21; and Found: C, 78.72; H, 4.99; N, 10.11.

4-(4-(benzyloxy)benzylidene)-1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methyleneamino)-2-phenyl-1*H*-imidazol-5(4*H*)-one 3e Yellow crystalline solid; Recrystallizing solvent DMF; mp, 168-172°C; yield, 79%. Elemental Analysis Calcd: for $C_{41}H_{32}N_4O_3$, C, 78.32; H, 5.13; N, 8.91; and Found: C, 78.25; H, 5.15; N, 9.00.

Antimicrobial Activity

All the synthesized compounds were screened *in-vitro* for their antibacterial and antifungal activities.

General procedure for antimicrobial screening

The newly synthesized compounds were screened *in-vitro* for antimicrobial at different concentration ranging from 1000 to 63µg/mL using disc diffusion method. Initially the stock culture of *S. aureus* and *E. coli* were revived by inoculating in broth media at 37°C for 18h. The agar plate of nutrient agar media was prepared and sterilized. After the inoculation of bacterial cultural, the discs were dipped in the different concentration of the compound which was prepared in DMSO and placed on the surface of agar plate. All the plates were incubated for 37°C for 24h and diameter of the zone of inhibition were noted in mm. The results were compared with Chloramphenicol as the standard drug. Same procedure was applied for fungus *A. niger* and *C. albicans* and results were compared with Amphotericin as the standard drug.

RESULTS AND DISCUSSION

The reactions of the title compounds (**3a-e)** are mentioned in the above schemes **I** and **II**, their purity was checked by TLC. The structures of newly synthesized compounds have been confirmed with the help of elemental and spectral analysis such as IR, ^{1}HNMR, and Mass. The spectral and analytical data obtained confirms the structure of the synthesized product. 2-chloro quinoline-3-carbaldehyde was synthesized by Vilsmeier-Haack reaction[25], which on treatment with p-cresol gave 6-methyl-2-(p-tolyloxy) quinoline-3-carbaldehyde which on further reaction with hydrazine hydrate in ethanol yielded 1-((6-methyl-2-(p-tolyloxy)quinolin-3-yl)methylene)hydrazine (**1**).

The IR spectra of compound (**1),** showed characteristics bands at 3355, 3192 cm^{-1}due to -NH_2 stretch while all the bands due to different stretching appeared as per the expected regions supporting the formation of **(1). T**he ^{1}H NMR spectrum of **1** attribute a singlet at δ 3.29 ppm due to three protons of -CH_3 another singlet at δ 3.38 due to three protons of -CH_3 attached to the Quinoline moiety, a distinguished singlet was obtained at δ 8.44 ppm due to azomethine proton of -C<u>H</u>=N-, and multiplet exhibited in the range of δ 7.08-8.23 ppm due to ten aromatic protons including aromatic, Quinoline and -NH_2 group. Mass spectra gave different ion peaks at *m/z* 292 [M+H]$^+$, 293 [M+2]$^+$ and 314 [M+Na]$^+$ which further supported the formation of **1.** The elemental analysis of compound **1** showed % of C, H, and N to be 74.31, 5.38, 14.36 respectively, which is in agreement with the calculated value. Thus, these results described above confirm the formation of **1** having molecular formula $C_{18}ON_3H_{17}$.

Compound **1** on further condensation with different substituted 4-arylidene-2-phenyloxazol-5(4*H*)-ones **(2a-e)** in dry pyridine as a solvent resulted in the formation of five novel series of derivatives of **3a-e.** The percentage yields of the newly synthesized compounds were in the range of 80-85% and recrystallized from dimethyl formamide. The IR spectra of **3a** showed a absorption band at 1724 cm^{-1} due to -N-C=O which was absent in **1,** similarly, other IR peaks obtained in the expected regions supported the formation of **3a**. The ^{1}H NMR spectrum of **3a** showed two singlets' at δ 3.35 and 3.47 ppm due to three protons of each -CH_3 groups attached to benzene and quinoline ring respectively while other signals for aromatic protons appeared in expected region. Disappearance of signal in **3a** due to -NH_2 group present in **1a** also confirm its formation. The mass spectra of **3a** gives a molecular ion peak of [M+H]$^+$ at 523 and [M+2]$^+$ at 524, is in agreement with the molecular formula $C_{34}H_{26}O_2N_4$. Elemental analysis gave the % of C, H and N as 4.31, 5.38, and 14.36 respectively.

Antibacterial activity

The newly synthesized compound **3a** was screened *in-vitro* for antimicrobial activity at different concentration ranging from 1000 to 63µg/mL while remaining compounds **3b-e** were studied at 1000µg/mL (Table 1). According to the screening, **3a** showed good activity at concentration 1000 µg/mL against bacterial culture *S. aureus* and *E. coli.* The compound **3a** was found to be inactive against fungi *A. niger* and *C. albicans***.** (**3a-e**) were then tested at the same concentration of 1000 µg/mL (Table 2). All the series of compounds shows good activities towards selected bacteria *S. aureus* and *E. coli,* but zone of inhibition was found to be negative for fungi under consideration.

Table 1: Antibacterial activity of 3a against standard drug

Sr. No	Conc. in (µg/mL)	Zone of Inhibition in mm			
		Chloramphenicol		3a	
		Gram +ve *S. aureus*	Gram –ve *E. coli*	Gram +ve *S. aureus*	Gram -ve *E. coli*
1	1000	26	16	11	11
2	500	30	16	11	11
3	250	27	17	10	11
4	125	21	16	10	11
5	63	18	15	14	10

Table 2: Antibacterial activity of 3a-e against standard drug

		Zone of Inhibition in mm at 1000µg/mL	
Sr. No.	Entry	Gram +ve *S.aureus*	Gram –ve *E. coli*
1	3a	11	11
2	3b	10	10
3	3c	11	10
4	3d	11	11
5	3e	11	11
6	Chloramphenicol	18	15

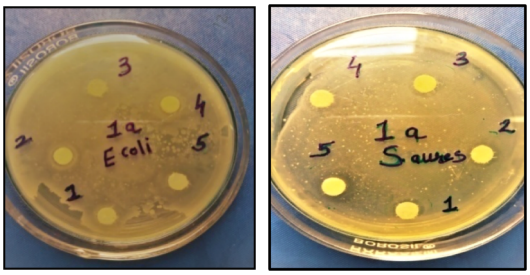


Figure 1 : Zone of inhibition of test compound 3a at different concentration for bacterial strain

CONCLUSION

A series of novel derivatives of 5-oxo-imidazoles cotaining quinoline moiety were successfuly synthesized in good yields. Physical and spectral data confirmed the structure of synthesized compounds. All the synthesized compounds possessed good activity against bacteria chosen for the study but were found to be inactive against the selected fungi.

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