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Research Article

Synthesis of Some Quinoline Oximes by an Efficient Method and their Biological Screening

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ABSTRACT

Quinoline scaffolds have gained substantial interest in the modern era of medicinal chemistry due to their wide range of biological applications. The present work reported the synthesis of various oxime derivatives of quinolines by the reaction of substituted 2-chloro-3-formyl-quinolines with hydroxyl amine hydrochloride. The reaction was mediated by aqueous ethanol, whereas hexamine was used as an efficient, non-toxic and easily available basic organocatalyst. The developed protocol has various advantages, including operational ease, affordability, an eco-friendly approach, and short reaction time. Moreover, the synthesized compounds were subjected to *in-vitro* antimicrobial activities. The antimicrobial evaluation of almost all the compounds found to be potent and effective. Compounds 4c, 4d, and 4f showed a broad spectrum of inhibition and were more effective when tested against specific Gram (-) and Gram (+) bacteria. In *in-vitro* antifungal evaluation, all synthesized compounds (4a-4g) showed good sensitivity against the tested fungal cultures except *Aspergillus niger*.

Introduction

Oximes have attracted significant interest in recent years as they can be easily synthesized by the reaction of aldehydes or ketones with hydroxylamine hydrochloride and have several biological applications.[1-4] In the past two decades, oxime group containing organic molecules have been investigated for their significant function as acetylcholinesterase reactivators used as therapeutic medicines.[5-7] Oxime motif was discovered to demonstrate numerous additional pharmacological actions such as antimicrobial, anti-inflammatory, antioxidant, antituberculosis, anti-diabetes and anti-human immunodeficiency (HIV) agents due to inhibition of HIV protease.[8-15] The use of oxime derivatives in the treatment of cancer and neurological diseases has also been reported.[16-22] Oximes are usually prepared using traditional bases such as KOH, NaOH.[23-34] and pyridine.[25] Some other protocols have also been reported such as use of basic Al_2O_3,[26] Bi_2O_3,[27] hyamine,[28] pyrimidine[29] and oxalic acid.[30] However, some of the reported methods suffer from disadvantages, including poor yields, protracted reaction times and usage of hazardous solvents, catalyst, and reagents. Hence, there is a demand to develop an environmentally benign process for the preparation of oximes that can overcome these drawbacks. In the present study, we have synthesized some quinoline oxime derivatives by a new process involving the reaction of various synthesized quinoline aldehydes with hydroxyl amine hydrochloride using hexamine as an efficient organocatalyst. The scientific community has shown interest in organocatalysts for a number of reasons, including their low cost, large chiral pool, resistance to moisture and air, and non-hazardous nature. Herein, we explored for the first time the catalytic activity of hexamine in aqueous ethanol medium for the synthesis of oximes of 2-chloro-3-formyl-quinoline derivatives.

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Quinoline compounds represent an important class of heterocyclic nuclei and are useful intermediates for the synthesis of organic molecules of medicinal value. The medicinal properties of quinoline derivatives, such as antibacterial, antimalarial, anti-asthmatic, antifungal, anti-infammatory, antihypertensive and antiplatelet activity has continued to be of great interest.[31,32] They also have anti-tubercular and immuno-suppressing properties.[33] Some other quinoline scaffolds found to be more promising, like bulaquine quinine, mefloquine and amodiaquine as an antimalarial and anti-inflammatory agent.[34-36] The development, maintenance, and operation of the mammalian reproductive system as well as in non-sexual tissues are all significantly influenced by some 2-arylquinoline derivatives.[37] Numerous quinoline compounds have shown to be useful as agrochemicals.[38] Quinolines also have been utilized as ligands to prepare OLED phosphorescent complexes and as selective chemo-sensors for fluoride and metal ions using conjugated polymers.[39-41] Due to the alarming rise in bacterial infections and their resistance to the majority of first-line antibiotics, antibacterial therapy has been difficult.[42] This poses a significant risk to human health and urgently demand ongoing research to design new broad-spectrum drug agents with more potent antimicrobial activity. In this context, quinoline derivatives are among significant scaffolds that have previously been identified to exhibit a variety of biological functions.[43-44] As a result, adding various functional groups to the quinoline scaffold is a smart idea for the development of novel drugs.[45-46] In this view our focus in this work is to synergize the antimicrobial potential of quinoline motif with oxime group in an effort to obtain potent antimicrobial agent.

Materials and Methods

Chemicals were purchased from SD Fine Chemicals. A Bruker Advance DPX-250 was used to record NMR spectra. Mass spectra were recorded on the Waters GC-MS spectrophotometer. Silica gel TLC plates were used to monitor the reactions and the product's purity.

Typical Procedures

Preparation of acetanilide (N-phenylacetamide) (2a-g)[47]

In 20 mL of equal amount of glacial acetic acid and acetic anhydride was added to a 250 mL conical flask containings 10 mL (10.3 g) of aniline. The mixture was stirred for 10 minutes then poured into 200 mL cold water and stirred vigorously. The precipitated solid was filtered off and the crude was washed thoroughly with water. A mixture of water and acetic acid recrystallized the acetanilide derivatives.

Preparation of 2-chloro-3-formyl-quinoline (Vilsmeier-Haak Reaction)(3a-g)[48-49]

To the mixture of acetanilide (N-phenylacetamide) derivatives (5 mmol) in DMF (15 mmol) $POCl_3$ (60 mmols) was added drop wise with shaking at 0 to 5°C. After complete addition the mixture was stirred at 80 to 90°C for about 4-6 hours. After TLC monitored the reaction, the reaction mixture was poured into the beaker containing crushed ice and stirred for a few minutes. The precipitate was filtered off and washed with water and dried. Ethyl acetate was used to recrystallize the appropriate analogues of 2-chloroquinoline-3-carbaldehyde (3a-g) that were produced.

Preparations of 2-chloro-3-formyl-quinoline oximes derivatives (4a-g).

2-chloro-3-formyl-quinoline derivatives (1-mmol) and hydroxylamine hydrochloride (2 mmole) were added in 10 mL of water:ethanol (1:1) solvent. To this mixture hexamine (20 mol%) was added as a catalyst. The reaction mass was stirred at room temperature and monitored by TLC. After reaction completion the reaction mixture was poured in cold water and the precipitated solid was filtered and dried. The crude products were recrystallized by ethanol to obtained pure products.

Spectral Characterization

2-Chloro-quinoline-3-carbaldehyde oxime (4a)

^{1}H-NMR (500 MHz, DMSO-d_6): δ11.95 (1H, S, N-OH), 8.72(s, 1H, CH=N), 8.41(S, 1H, ArH), 8.10(d, 1H, ArH), 7.93(d, 1H, ArH), 7.81(t, 1H), 7.64 (t, 1H, ArH), ^{13}C-NMR (125MHz, DMSO-d_6) δ 147.85, 146.81, 143.94, 135.41, 131.32, 128.52, 127.57, 127.49, 126.66, 124.78, MS (m/z): 206.53,

2-Chloro-6-methyl-quinoline-3-carbaldehyde oxime (4b)

^{1}H-NMR (500 MHz, DMSO-d_6): δ11.90 (S, 1H,N-OH), 8.52 (s, 1H, CH=N), 8.36(S, 1H, ArH), (7.75, d, 2H, ArH), 7.56(m, 1H, ArH), 2.50 (S, 3H, CH_3), ^{13}C-NMR (125 MHz, DMSO-d_6) δ 146.89, 145.37, 143.93, 137.20, 134.51, 133.34, 127.14, 126.96, 126.94, 124.50, 20.94, MS (m/z): 220.61.

2-Chloro-6-ethyl-quinoline-3-carbaldehyde oxime (4c)

^{1}H-NMR (500 MHz, DMSO-d_6): δ11.91 (1H, S, N-OH), 8.63(s, 1H, CH=N), 8.39(S, 1H, ArH), 7.85-7.82(m, 2H, ArH), 7.68-7.66(m, 1H, ArH), 2.77 (q, 2H, CH_3), 1.25 (t, 3H, CH_2), ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.99, 145.63, 143.97, 143.32, 134.83, 132.42, 127.32, 126.69, 125.79, 124.62, 27.94,41.96, MS (m/z): 234.67.

2,6-Dichloro-quinoline-3-carbaldehyde oxime (4d)

^{1}H-NMR (500 MHz, DMSO-d_6): δ12.01 (1H, S, N-OH), 8.64(s, 1H, CH=N), 8.35(S, 1H, ArH), 8.16(d, 1H, ArH), 7.86 (d, 1H, ArH), 7.73 (t, 2H, ArH), ^{13}C-NMR (125 MHz, DMSO-d_6) δ148.28, 145.08, 143.60, 134.42, 131.89,131.55, 129.46, 127.35, 127.04, 125.70, MS (m/z): 240.68.

2-Chloro-6-methoxy-quinoline-3-carbaldehyde oxime (4f)

^{1}H-NMR (500 MHz, DMSO-d_6): δ11.91 (1H, S, N-OH), 8.62 (s, 1H, CH=N), 8.39 (S, 1H, ArH), 7.82 (d, 1H, ArH), 7.45 (m, 2H, ArH), 3.89 (3H,S, OCH_3) ^{13}C-NMR (125 MHz, DMSO-

d_6) δ 157.86, 145.17, 144.01, 142.87, 134.04,128.90, 127.94, 124.78, 123.75, 106.17, 55.55, MS (m/z): 236.67.

Antimicrobial Activity

Antibacterial activity

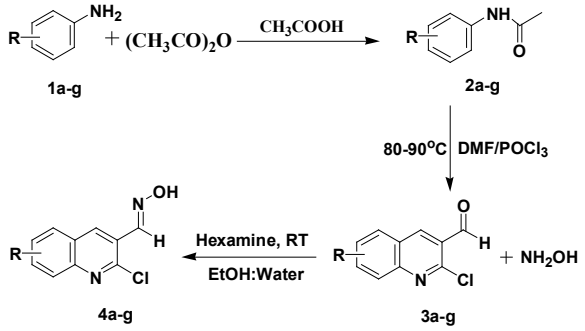
The agar plate method was utilized to test the synthesized compounds (4a-4g) for their antibacterial activity. The antibacterial screening used both gram-positive and gram-negative bacteria of various types. Dimethyl sulfoxide (DMSO) and standard streptomycin were used as positive and negative controls respectively. The experiment was done in triplicates and the zone of inhibition measured in mm was taken for the evaluation of antibacterial activity of the test compounds.

Antifungal activity

The synthesized compounds were also tested using agar plate method for their antifungal properties. The compounds' antifungal effects on *A. niger, T. rubrum, C. neoformans*, and *C. albicans* were assessed in triplicates during the experiment. The positive and negative controls used were DMSO and regular fluconazole. The inhibition zone measured in mm was taken for the evaluation of antifungal activity.

Results and Discussion

The targeted derivatives (4a-g) are synthesized by a new protocol as depicted in Scheme 1. The intermediates N-Phenyl-acetamide (2a-g) derived from substituted aromatic amines and 2-Chloro-quinoline-3-carbaldehydes (3a-g) were prepared according to previously reported procedures.[47-49] The N-Phenyl-acetamides (2a-g) were achieved via the addition of acetic anhydride to amines stirred in acetic acid at room temperature. This reaction proceeded via a nucleophilic acyl substitution mechanism. IR, NMR and mass confirmed the structures of the prepared compounds 2a-g. 2-Chloro-quinoline-3-carbaldehyde (3a-g) was prepared by heating the appropriate compounds 2a-g with $POCl_3$ in DMF at 80 to 90°C for about 4 to 6 hours. This reaction is proposed to proceed via Vilsmeir cyclization mechanism. The structure of the prepared compounds 3a-g was deduced from spectral data IR, Mass and NMR.



Scheme 1: Synthesis of quinoline-3-carbaldehyde oximes

Here we report for the first-time synthesis of quinoline-3-carbaldehyde oximes derivatives (4a-g) by the reaction of hydroxyl amine hydrochloride with 2-Chloro-quinoline-3-carbaldehydes (3a-g) using hexamine as an efficient basic catalyst in ethanol: water (1:1) at room temperature. Initially, a model reaction was set up with -2-Chloro-quinoline-3-carbaldehyde (3a), and hydroxylamine (Table 1). Different parameters such as solvent, catalyst concentrations and temperature were investigated (Table 1, entries 1-9). The focus for the reaction optimization was to develop convenient and green conditions for synthesizing quinoline oxime derivatives. After comprehensive investigation, it was observed that hexamine as a base catalyst has a unique potential to augment the rate of reaction in ethanol and water (1:1) at room temperature (Table 1, entry 6) whereas ethanol alone at room temperature gave almost same results (Table 1, entry 4). If the water ratio is doubled then the product yield decreases (Table 1, entries 5). In addition, other solvents like methanol, acetonitrile and water alone were also studied but gave lower product yield at room temperature (Table 1, entries 1-3). If the temperature of ethanol and water (1:1) mediated reaction is increased to 70°C then it was observed that there is no noticeable change in the efficacy of the reaction (Table 1, entry 9).

After optimization of reaction conditions, the generality of the new developed protocol was examined by the reaction of various quinoline aldehydes with hydroxylamine hydrochloride (Table 2, entries 1-7).

Spectral data confirmed the structures of the synthesized 2-chloro-3-formyl-quinoline oximes. ^{1}H-NMR spectrum of compound 4a revealed the presence of a singlet signal at 11.95 ppm and a signal at 8.72 ppm attributed to oxime proton (N-OH) and CH=N proton of oxime group respectively. The remaining protons at 8.10 to 7.60 ppm attributed to aromatic protons. Moreover, the spectrum of compound 4c showed one quartet signal at 2.77 ppm and

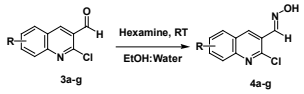
Table 1: Optimization of reaction conditions for the synthesis of quinoline-3- carbaldehyde oximes

3a 4a

Entry	*Solvents* [a]	*Hexamine*	*Temperature (°C)*	*Time (min)*	*Yield (%)*[a]
1	ACN	20 mole%	RT	30	52
2	MeOH	20 mole%	RT	25	65
3	H_2O	20 mole%	RT	30	70
4	EtOH	20 mole%	R.T	20	84
5	EtOH: H_2O (1:2)	20 mole%	R.T	25	78
6	EtOH: H_2O (1:1)	20 mole%	R.T	15	85
7	EtOH: H_2O (1:1)	10 mole%	R.T	30	72
8	EtOH: H_2O (1:1)	30 mole%	R.T	15	85
9	EtOH: H_2O (1:1)	20 mole%	70°C	15	86

[a] isolated yield

Table 2: Hexamine catalyzed synthesis of quinoline from 2-chloro-3-quinoline-carbaldehyde oximes



Sr. No	*Compound*	*R*	*Time (min)*	*Yield (%)*[a]	*M.P. (°C)*
1	4a	H	15	85	190–195
2	4b	6-CH_3	15	77	200–208
3	4c	6-C_2H_5	20	80	200–203
4	4d	6-Cl	25	76	115–120
5	4e	6-F	25	81	120–125
6	4f	6-OCH_3	20	70	200–210
7	4g	Benzene	30	72	213–216

[a]Isolated yield

one triplet signal at 1.25 ppm attributed to CH_2CH_3 protons of ethyl chain. Additionally, the presence of a singlet signal at 3.89 ppm was attributed to the OCH_3 protons of the methoxy moiety of compound 4f and singlet signal at 11.91 ppm and 8.62 attributed to N-OH and CH=N proton of oxime group in compound 4f. ^{13} CNMR of compound 3a revealed two signals at 147.85 ppm assigned to the oxime group carbon and the remaining signals attribute to aromatic carbons in compound 4a. The signal at 146.99 ppm attributed to the carbon of oxime group in 4c whereas signals at 27.94 and 41.96 ppm are assigned to the carbon atoms of ethyl group of compound 4c. Similarly, in ^{13}CNMR of compound 4f, the more deshielded carbon atom at 157.86 ppm attributed to carbon atom of oxime group and a signal in shielded region at 55.55 ppm assigned to OCH_3 carbon of methoxy group. Mass spectrum showed their corresponding molecular ion peaks.

Biological Evaluation

Antibacterial activity of compounds 4a-4g were tested towards gram (-) and gram (+) bacteria (Table 3). From the obtained results, it can be seen that all the synthesized compounds showed inhibiting effect against the selected pathogens as compared to standard drug Streptomycin (20 µg). A study of structure-activity relationships revealed that the variation in activity of compounds depends on the nature of the substituent in phenyl group at sixth position in the quinoline structure. Compounds 4a in which there is no any substituent at sixth position on quinoline ring and 6-methyl substituent on quinoline ring (4b) were less effective against *Proteus vulgaris*. Compounds 4c (6- ethyl substituent), 4d (6-chloro substituent) and 4f (6-methoxy substituent) found to

Table 3: Antimicrobial activity test (Zone of inhibition in MM)

Test Compound	*GM + VE BACTERIA*				*GM - VE BACTERIA*			
	Staphylococcus aureus	*Streptococcus pneumoniae*	*Diplococcus sp*	*Bacillus sp*	*Proteus vulgaris*	*Escherichia coli*	*Pseudomonas fluorescens*	*Salmonella typhy*
4a	30 ± 0.25	31 ± 0.55	30 ± 0.24	32 ± 0.29	18 ± 0.25	28 ± 0.12	18 ± 0.40	30 ± 0.45
4b	32 ± 0.35	33 ± 0.23	33 ± 0.17	34 ± 0.37	23 ± 0.12	26 ± 0.61	22 ± 0.42	32 ± 0.85
4c	33 ± 0.74	34 ± 0.67	34 ± 0.16	35 ± 0.48	...	32 ± 0.34	16 ± 0.74	34 ± 0.79
4d	31 ± 0.63	36 ± 0.68	35 ± 0.14	30 ± 0.13	...	30 ± 0.18	14 ± 0.58	30± 0.68
4e	18 ± 0.72	22 ± 0.45	...	28 ± 0.29	22 ± 0.24	20 ± 0.14	18 ± 0.45	14 ± 0.48
4f	33 ± 0.15	40 ± 0.38	...	32 ± 0.82	33 ± 0.39	33 ± 0.19	16 ± 0.23	33 ± 0.21
4g	--	29 ± 0.12	...	26 ± 0.63	29 ± 0.67	29 ± 0.11	15 ± 0.49	15 ± 0.19
Streptomycin (20µg)	21 ± 0.24	20 ± 0.17	19 ± 0.27	29 ± 0.14	32 ± 0.36	24 ± 0.13	29 ± 0.63	26 ± 0.17

Data are given as mean S.D (n=3); S.D = Standard Deviation

Table 4: Antifungal activity test (Zone of inhibition in MM)

Test Compound	*Candida albicans*	*Aspergillus niger*	*Trichophyton rubrum*	*Cryptococcus neoformans*
4a	32 ± 0.48	**...**	34 ± 0.43	32 ± 0.68
4b	36 ± 0.19	**...**	36 ± 0.14	34 ± 0.72
4c	33 ± 0.17	**...**	32 ± 0.11	36 ± 0.43
4d	30 ± 0.63	...	22 ± 0.21	35 ± 0.12
4e	18 ± 0.60	...	30 ± 0.67	33 ± 0.11
4f	32 ± 0.74	...	32 ± 0.19	38 ± 0.23
4g	19 ± 0.38	...	36 ± 0.17	31 ± 0.22
Fluconazole (25 µg)	21 ± 0.13	17 ± 0.20	25 ± 0.12	27 ± 0.19

Data are given as mean S.D (n=3); S.D = Standard Deviation

show less effective against *Pseudomonas fluorescent* only. Compound 4e (6-fluoro substituent) was found to be more effective against *Streptococcus pneumonia* and *Escherichia coli*. Hence compound 4c, 4d and 4f exhibited broad spectrum of inhibition and found to be more potent. Almost all the compounds are found to be more effective against selected gram (-) and gram (+) bacteria.

The fungal cultures were found to be sensitive against all the tested compounds (4a-4g) except *A. niger (Table 4)*. A study of structure-activity relationships revealed that as in the case of antibacterial activity, antifungal activity also depends on the nature of the substituent in phenyl group at sixth postion in the quinoline structure and also presence of benzo group on quinoline structure. The compounds were found to be more potent than the controlled antibiotic fluconazole (25 µg). The compounds having 6-chloro substituent (4d), was found to be less inhibitory to *T. rubrum* and compounds having 6-fluoro substituent (4e) and benzoquinoline (4g) were found to be less inhibitory to *C. albicans*.

Conclusion

The synthesis of chloro-7-methoxy-quinoline-3-carbaldehyde oxime derivatives utilizing hexamine as a base catalyst at room temperature in ethanol/water medium would be a beneficial contribution to the method development in organic chemistry. The biological evaluation of the synthesized quinolione oximes was also performed to suppress a variety of Gram-positive and Gram-negative bacteria and some fungi. It has been found that many of the synthesized derivatives can successfully inhibit the growth of certain bacterial and fungal microorganisms.

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