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Schiff bases of Quinolin-2-ones: Synthesis, Characterization and Antibacterial activity

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ABSTRACT

The present study envisaged here involved the synthesis, characterization and evaluation of antibacterial activity of Schiff bases of quinolin-2-ones. The derivatives were synthesized in a good to moderate yields. The structural confirmations for the synthesized derivatives were carried out by their physical and analytical data as well as by IR, ^{1}HNMR and Mass spectral study. Further the compounds were screened for antibacterial activity by cup-plate method. Compounds 3c, 3d, 3e, 3h, 3i and 3j showed good antibacterial activity against the bacterial strains compared to the standard drug. In view of the antibacterial studies observed it can be concluded that these derivatives can be modified and investigated further for future development.

Keywords: *2-quinolones, Antibacterial activity, Condensation.*

INTRODUCTION

The research for an ideal quinolone antibacterial continues worldwide. Such a quinolone must be active enough biologically, that a large group of microorganisms including bacteria (gram positive and gram negative), aerobes and anaerobes should be susceptible to these compounds, and they must have side effects as minimum as possible with excellent solubility in water and acceptable oral bioavailability. The quinolone framework is composed of a pyridone moiety fused with a benzene ring. The quinolones, not substituted on ring nitrogen, exhibits aromaticity because of the tautomeric quinolinol structure, although *N*-substituted quinolones cannot tautomerize to the quinolinol form, they are slightly aromatic.

Antibiotics such as beta-lactams, macrolides, aminoglycosides and tetracyclines were discovered and introduced in a short period of time. These were obtained either by isolation from fungi or by chemically modifying the naturally isolated substances. These dominated the antimicrobial industry, while substances obtained synthetically played a minor role. The generations of quinolones have some common characteristics; a similar mechanism of action which involves the inhibition of the A subunit of DNA-gyrase, photo toxicity, cartilage toxicity, neurotoxicity etc. The antibacterial activity of quinolones is the result of the combination of two facts; the bacterial cell penetration and DNA gyrase inhibitory activity. The antibacterial property of quinolones depends not only on the bicyclic heteroaromatic system which combines the 1,4-dihydro-4-pyridine moiety and an aromatic ring, but on the nature of the substituents on both these two moieties and their spatial arrangements. These substituents exert their influence on antibacterial activity by modifying affinity for bacterial enzymes, increasing in cell penetration or altering the pharmacokinetic property. 2-Quinolones (carbostyrils) are isosteric with coumarins and isomeric to 4-quinolones could become the probable potential candidate for antibacterial activity [1, 2]. A wide variety of clinical indications have been approved for quinolones eradicating many infections commonly encountered in community practice such as upper and lower respiratory tract, gastrointestinal and gynecologic infections, sexually transmitted diseases and some skin, bone, and soft tissue infections. 2-Quinolone derivatives were found to be associated with various biological activities such as antitumor [3], anti-inflammatoryl [4], antiplatelet, antiulcer [5], antioxidant [6] and inhibit the synthesis of mitochondrial DNA [7]. Many substituted quinolin-2-one derivatives have recently earned great interest in chemotherapy as antitumor drugs too [8]. In this present study the synthesis of some 2-quinolone analogues has been undertaken and the derivatives were subjected for antibacterial screening.

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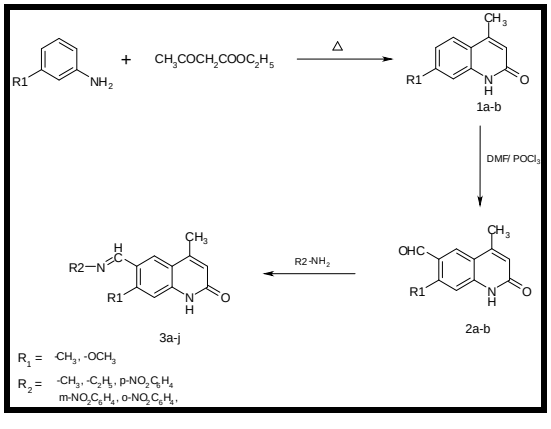
MATERIALS AND METHODS

All the chemicals utilized to synthesize the title compounds were of analytical grade. Open capillary tube method was used to determine the melting point and is uncorrected. Precoated Silica gel G plates were used for thin layer chromatographic studies to monitor the progress of reaction as well as to check the purity of the compounds; Benzene: Ethyl acetate-1:1 was used as mobile phase. The IR spectra were recorded (KBr discs) in the region of 5000-500 cm^{-1} in a Shimadzu 8400S Fourier Transform IR spectrophotometer. NMR spectra were obtained on a Brukar Spectrospin 200 spectrometer (TMS as internal standard). Mass spectra were obtained by using JEOL GC mate instrument.

Scheme of synthesis:



Synthesis of substituted 4-methyl-2-quinolone (1a):

m-Toluidine (0.1mol) and ethylacetoacetate (0.1mole) were mixed together and heated at 150^0 C for 24 hours on an oil bath. The temperature was maintained by careful observation. After that it was cooled to room temperature and was added around 225ml of water. Then the contents were heated to boil for about 15 minutes. Then the mixture was kept in cold condition overnight,

filtered and the precipitate was collected and dried in air. The compound was recrystallised from methanol. Yield 68%. In a similar manner 1b was synthesized.

Reaction of substituted 4-methyl-2-quinolone with DMF-$POCl_3$ (2a):

The substituted 4-methyl-2-quinolone (1a, 0.01mol) was added to the Vilsmier Haac reagent at 0^0C by cooling the reaction vessel in an ice bath and maintaining the temperature strictly. The reaction mixture was then stirred in intervals at room temperature for 2 hr. Then it was treated with sodium carbonate solution and heated to 90^0C. The solution was then repeatedly extracted with chloroform. The chloroform layer was dried over anhydrous calcium chloride. The combined extracts were evaporated to dryness and purified by recrystallization from rectified spirit. Yield 61%. Compound 2b was prepared similarly.

General procedure for the synthesis of title compounds (3a):

To a solution of the suitable amine (0.01 mol) in 50ml of absolute alcohol was added 2a (0.01 mol) and refluxed for 5 hours. The reaction mixture was allowed to cool to room temperature and then poured into 150 ml of ice cold water. The product was filtered and washed repeatedly with cold water, dried and recrystallised from aqueous ethanol. Similarly the compounds 3b-j were prepared. The physical data is reported in table 2.

3a-IR (KBr, cm^{-1}): 3041 C-H str aromatic, 2930 C-H str aliphatic, 1719 C=O str, 1681 C=N str, 1491 C=C str aromatic, 1341 C-H bending aliphatic, 1189 C-N str, 835 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.8 3H CH_3, 2.5 3H CH_3, 3.08 1H NH, 3.5 3H N-CH_3, 4.9 1H C-3 H, 5.67 1H s CH=N, 6.83 2H Ar H. Mass (M+H): 215

3b-IR (KBr, cm^{-1}): 3030 C-H str aromatic, 2928 C-H str aliphatic, 1731 C=O str, 1681 C=N str, 1484 C=C str aromatic, 1343 C-H bending aliphatic, 1194 C-N str, 848 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.6 3H CH_3, 1.8 3H CH_3, 2.5 3H CH_3, 3.01 1H NH, 3.49 2H N-CH_2, 4.87 1H C-3 H, 5.71 1H s CH=N, 6.85 2H Ar H. Mass (M+H): 229.

3c-IR (KBr, cm^{-1}): 3034 C-H str aromatic, 2937 C-H str aliphatic, 1724 C=O str, 1687 C=N str, 1498 NO_2 str, 1459 C=C str aromatic, 1349 C-H bending aliphatic, 1178 C-N str, 841 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 2.13 3H CH_3, 2.59 3H CH_3, 3.04 1H NH, 4.82 1H C-3 H, 5.73 1H s CH=N, 6.85 2H Ar H, 7.2-7.4 4H Ar H. Mass (M+H): 322.

3d-IR (KBr, cm^{-1}): 3042 C-H str aromatic, 2931 C-H str aliphatic, 1734 C=O str, 1681 C=N str, 1489 NO_2 str, 1459 C=C str aromatic, 1357 C-H bending aliphatic, 1180 C-N str, 858 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 2.18 3H CH_3, 2.52 3H CH_3, 3.14 1H NH, 4.79 1H C-3 H, 5.75 1H s CH=N, 6.91 2H Ar H, 7.22-7.47 4H Ar H. Mass (M+H): 322.

3e-IR (KBr, cm^{-1}): 3054 C-H str aromatic, 2947 C-H str aliphatic, 1727 C=O str, 1687 C=N str, 1494 NO_2 str, 1465 C=C str aromatic, 1361 C-H bending aliphatic, 1172 C-N str, 864 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 2.14 3H CH_3, 2.58 3H CH_3, 3.17 1H NH, 4.69 1H C-3 H, 5.71 1H s CH=N, 6.79 2H Ar H, 7.32-7.49 4H Ar H. Mass (M+H): 322.

3f-IR (KBr, cm^{-1}): 3048 C-H str aromatic, 2941 C-H str aliphatic, 1723 C=O str, 1681 C=N str, 1495 C=C str aromatic, 1338 C-H bending aliphatic, 1194 C-N str, 844 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 2.3 3H OCH_3, 2.72 3H CH_3, 3.11 1H NH, 3.57 3H N-CH_3, 4.9 1H C-3 H, 5.69 1H s CH=N, 6.87 2H Ar H. Mass (M+H): 231.

3g-IR (KBr, cm^{-1}): 3030 C-H str aromatic, 2939 C-H str aliphatic, 1719 C=O str, 1684 C=N str, 1487 C=C str aromatic, 1349 C-H bending aliphatic, 1192 C-N str, 840 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.65 3H CH_3, 2.1 3H CH_3, 2.47 3H OCH_3, 3.07 1H NH, 3.57 2H N-CH_2, 4.89 1H C-3 H, 5.71 1H s CH=N, 6.89 2H Ar H. Mass (M+H): 245.

3h-IR (KBr, cm^{-1}): 3042 C-H str aromatic, 2942 C-H str aliphatic, 1731 C=O str, 1674 C=N str, 1498 NO_2 str, 1463 C=C str aromatic, 1357 C-H bending aliphatic, 1170 C-N str, 847 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 2.13 3H CH_3, 2.57 3H OCH_3, 3.01 1H NH, 4.85 1H C-3 H, 5.77 1H s CH=N, 6.81 2H Ar H, 7.22-7.46 4H Ar H. Mass (M+H): 338.

3i-IR (KBr, cm^{-1}): 3038 C-H str aromatic, 2961 C-H str aliphatic, 1729 C=O str, 1659 C=N str, 1481 NO_2 str, 1451 C=C str aromatic, 1365 C-H bending aliphatic, 1177 C-N str, 853 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 2.17 3H CH_3, 2.61 3H OCH_3, 3.14 1H NH, 4.78 1H C-3 H, 5.69 1H s CH=N, 6.78 2H Ar H, 7.27-7.51 4H Ar H. Mass (M+H): 338.

3j-IR (KBr, cm^{-1}): 3044 C-H str aromatic, 2961 C-H str aliphatic, 1740 C=O str, 1647 C=N str, 1487 NO_2 str, 1457 C=C str aromatic, 1361 C-H bending aliphatic, 1163 C-N str, 857 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 2.14 3H CH_3, 2.58 3H OCH_3, 3.17 1H NH, 4.77 1H C-3 H, 5.65 1H s CH=N, 6.74 2H Ar H, 7.25-7.49 4H Ar H. Mass (M+H): 338.

Antibacterial screening:

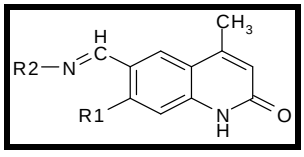
All the synthesized title compounds were screened for their antibacterial activity by cup plate Agar diffusion method. The organisms used were *Staphylococcus aureus, Pseudomonus aeruginosa, Bacillus subtilis and Escherichia coli*. Agar plates were prepared by pouring melted agar media onto the petridishes and allowed to solidify. Then it was inoculated over the surface of the media. Then the cups were made and filled with the solution of suitable concentration of sample and standard and incubated at 37^0C for 24 hours. The antimicrobial agents diffuse around the cups and produce a specific zone of inhibition of the microbial growth which was then measured (Table 3). Under identical condition the control ($CHCl_3$) with solvent (DMF) showed no activity. Ciprofloxacin was used as a standard.

RESULTS AND DISCUSSION

Substituted 4-methyl-2-quinolne was synthesized from aniline derivatives by the reaction with ethylacetoacetate. Introduction of an aldehydic group took place by the reaction of DMF/$POCl_3$ with the quinoline derivatives. The title compounds that are the Schiff bases of quinoline derivatives were then synthesized by condensing with different amines. The reactions proceeded via a moderate to good yield. The synthesized compounds were then characterized by their analytical and spectral data. The IR spectra of the title compounds shown characteristic absorption bands in the range of 3030-3054 cm^{-1}, 2930-2961 cm^{-1}, 1647-1687 cm^{-1}, 1451-1495 cm^{-1}, 1338-1365 cm^{-1}, 1163-1194 cm^{-1}, 835-864 cm^{-1} for C-H stretching aromatic, C-H stretching aliphatic, C=N stretching, C=C stretching aromatic, C-H bending, C-N stretching, C-H bending aromatic respectively. The NO_2 stretching was observed for compounds 3c, 3d, 3e, 3h, 3i and 3j in the range of 1481-1498 cm^{-1}. The ^{1}HNMR spectrum of 2a and 2b showed a characteristic proton signal around δ 9.8 as a sharp singlet. This was further analyzed to be the aldehydic proton, thus confirming the reaction of DMF/$POCl_3$ with 4-methyl-2-quinolne. The NMR spectrum of 3a exhibited resonances for protons at around δ 1.8, 2.5 and 3.5 which were ascertained as the protons associated with 4^{th} position methyl group, 7^{th} position methyl group and the substituent on nitrogen atom respectively. The -CH_3 protons attached directly with amino nitrogen was appeared at a little more downfield value due to the direct electronegative deshielding effect exerted by nitrogen. The C-3 proton being deshielded due to the presence of π electrons between C-3 and C-4 was resonated around δ 4.9, a much greater value than its normal. A careful observation of the NMR spectrum of 3a also revealed that the CH=N proton was appeared at δ 5.67; this particular proton was deshielded by the dual effect of π electrons associated with C=N and the nitrogen.

The *in vitro* antibacterial activity of the synthesized compounds was determined by using cup-plate method. The results of antibacterial study of newly synthesized derivatives were reported against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*. Compounds 3c, 3d, 3e, 3h, 3i and 3j showed good antibacterial activity against the bacterial strains compared to the standard drug ciprofloxacin. It was very interesting to note that the compounds containing nitro group was effective in a better manner than others. So presence of nitro group could have made the compounds 3c, 3d, 3e, 3h, 3I and 3j to be effective.

Table No. 1: Structures of Schiff bases of quinoline-2-ones



Compound code	R1	R2
3a	CH_3	CH_3
3b	CH_3	C_2H_5
3c	CH_3	p-$NO_2C_6H_6$
3d	CH_3	m-$NO_2C_6H_6$
3e	CH_3	o-$NO_2C_6H_4$
3f	OMe	CH_3
3g	OMe	C_2H_5
3h	OMe	p-$NO_2C_6H_4$
3i	OMe	m-$NO_2C_6H_4$
3j	OMe	o-$NO_2C_6H_4$

Table No. 2: Data of the synthesized derivatives

Compound code	Mol. Formula	Mol. Wt	Melting point (^{0}C)	R_f value	Yield (%)
3a	$C_{13}H_{14}N_2O$	214	251	0.64	49
3b	$C_{14}H_{16}N_2O$	228	239	0.59	55
3c	$C_{18}H_{15}N_3O_3$	321	245	0.51	56
3d	$C_{18}H_{15}N_3O_3$	321	264	0.56	54
3e	$C_{18}H_{15}N_3O_3$	321	227	0.61	50
3f	$C_{13}H_{14}N_2O_2$	230	234	0.58	53
3g	$C_{14}H_{16}N_2O_2$	244	285	0.62	57
3h	$C_{18}H_{15}N_3O_4$	337	262	0.55	47
3i	$C_{18}H_{15}N_3O_4$	337	272	0.64	51
3j	$C_{18}H_{15}N_3O_4$	337	259	0.59	48

Table No. 3: Antibacterial activity of the derivatives

Compound code	Zone of inhibition			
	S. aureus	*P. aeruginosa*	*B. subtilis*	*E. coli*
3a	-	-	+	-
3b	-	+	-	-
3c	++	+	++	+
3d	++	++	+	++
3e	+	++	+	+
3f	-	+	-	+
3g	-	-	-	+
3h	+	++	++	+
3i	++	+	+	++
3j	++	+	+	++

- = inactive, +++ = highly active (18-22 mm), ++ = moderately active (13-17 mm), + = weakly active (8-12 mm)

CONCLUSION

In view of the antibacterial study carried out it can be concluded that the some of the synthesized analogues showed good activity against the organisms. An in-detailed study may be a thought of interest to design these compounds further to derive more effective antibacterial agents.

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