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SOME 2-QUINOLONE ANALOGUES: SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL STUDY

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ABSTRACT

The present study is intended to the synthesis, characterization and study of antibacterial activity of various 2-quinolone analogues coupled with different amines. The derivatives were synthesized in a moderate to good yield. The structural characterizations were performed based on their analytical data, IR, ^{1}HNMR and Mass spectral studies. All the compounds were subjected for antibacterial evaluation, among them 3a, 3b and 3c showed good activity against the organisms used. The antibacterial study suggested that these derivatives may be modified for future drug development.

INTRODUCTION

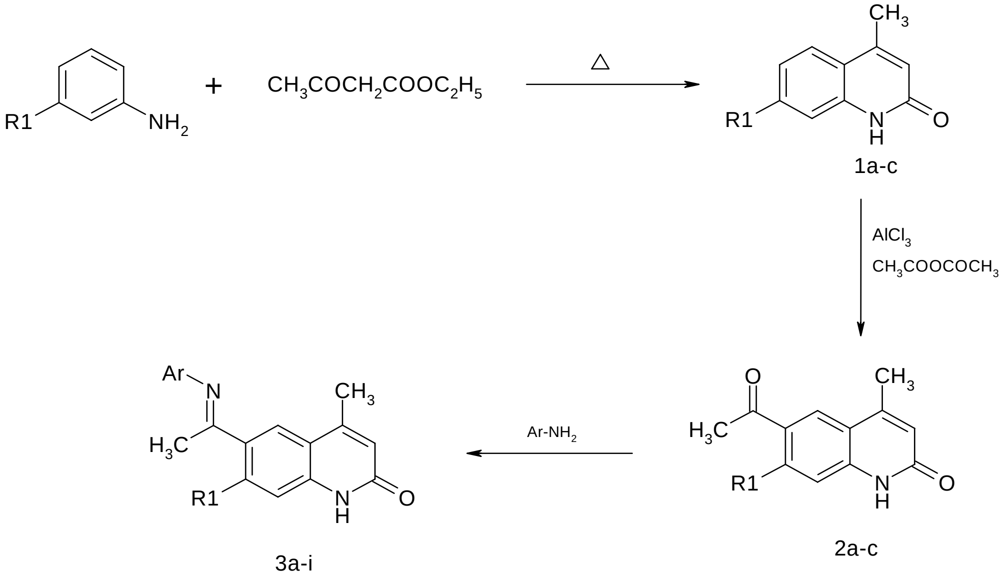
It is evident that many organic compounds used as drug do not have organic mechanism of action, some are activated or transformed biologically *in vivo*. Many drugs possess modified toxicological and pharmacological properties and probably Schiff bases are versatile enough possessing broad spectrum of biological activities. Schiff base are the compound containing azomethine group (N=CH). They are the products of condensations of carbonyl compounds (aldehydes or ketones) with primary amines. Formation of Schiff base generally takes place by using acid or base catalysts or by heating. Generally Schiff bases are crystalline solids, which are basic in nature. Schiff base are used as intermediates for the synthesis of amino acids or as ligands for preparation of metal complexes with or without a spacer. Schiff bases have a large number of synthetic uses in organic chemistry. Acylation of Schiff bases by acylating agents is initiated by the attack at nitrogen atom and ultimately results to a net addition of that reagent to the carbon-nitrogen double bond. Reactions of this type have been widely used to have a good and reasonable use in natural product synthesis. Schiff bases appear to be an important intermediate in a number of enzymatic reactions, as some enzymes are amphoteric in nature, involving interaction of an enzyme with an amino or a carbonyl group of the substrate.

The 1-methylquinolin-2-one, one of the fundamental moieties and a partial structure, is found in the quinoline alkaloids in more than 300 quinoline derivatives and their isolation & structural characterization have been extensively studied in the recent past[1-4]. The naturally occurring quinolone derivatives are of significant interest because they show a wide range of pharmacological and biological activities such as antibacterial, antiparasitic, antiproliferative, cytotoxic, antitumor activities etc[-5-7]. The quinolone framework is composed of a pyridone moiety and a fused benzene moiety. The quinolone analogues unsubstituted on ring nitrogen exhibits aromaticity because of the tautomeric quinolinol structure. The quinolone ring system is often activated by an electron-donating group for introduction of a substituent at the suitable position and thereby may provide the opportunity for that particular group which further may condense with appropriately introduced substituent to form an additional ring fused to the quinolone ring[8-10]. Thus considering the probable significance of quinolone derivatives it was of our importance to have synthesized some Schiff bases of 2-quinolone and evaluated for antibacterial activity.

MATERIALS AND METHOD

All the research chemicals purchased were of analytical grade and was used as such for the reactions. Solvents were dried and purified, when necessary, according to the literature. Reactions were monitored by thin- layer chromatography (TLC) on pre-coated Silica gel G plates. Melting point of synthesized compounds were determined by capillary tube method and reported as uncorrected values. The IR spectra of the final derivatives were recorded on a Shimadzu 8400S Fourier Transform Infra Red spectrophotometer by using KBr pellets. The proton NMR spectra were recorded in a Brukar Spectrospin 200 spectrometer and Chemical shift are given in δ ppm units with respect to TMS as internal standard. Mass spectra were recorded and mass values are reported as M+1. The purity of the compound was examined by TLC on silica gal plate using chloroform, Methanol and ethyl acetate.

Scheme of synthesis:



R_1 = -OH, $-CH_3$, $-OCH_3$

Ar = $p\text{-}NO_2C_6H_4$, $m\text{-}NO_2C_6H_4$, $o\text{-}NO_2C_6H_4$,

Synthesis of 7-substituted-2-quinolone (1a):

m-aminophenol (0.15mol) and ethylacetoacetate (0.15mole) were taken in a flask, mixed together and heated at 150^0 C for 24 hours on an oil bath. Temperature of the bath was maintained with a careful observation. The flask was cooled to room temperature and 250ml of water was added. Then the contents were heated to boil for about 30 minutes. Then the mixture was kept overnight in cold condition. The next day it was filtered and the precipitate was collected and dried in air. The compound was recrystallised from methanol. Yield 63%. In a similar manner 1b and 1c were synthesized.

Synthesis of 6-acetyl-7-substituted-2-quinolone (2a)

7-hydroxy-4-methyl-2-quinolone (1a, 0.01 mol) was taken to a flask in 50 ml of nitrobenzene. To this acetic anhydride (0.02 mol) and freshly powdered 0.022 mol of anhydrous aluminium chloride were added and then the reaction mixture was heated at around 150^0C for about 5 hours. The reaction content was then set aside for another1 hour, cooled and to this added 75 gm of crushed ice and 10 ml of concentrated hydrochloric acid. The product was filtered and recrystallised from 95% ethanol. Yield 57%. Similarly compounds 2b and 2c were synthesized.

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

A solution of the suitable amine (0.01 mol) in 50ml of alcohol and about 5-6 drops of piperidine were added to 2a (0.01 mol) and heated under reflux for 5 hours. The reaction mixture was then allowed to cool to room temperature and poured into 150 ml of water mixed with ice. The product was filtered and washed repeatedly with cold water and dried. Recrystallization was accomplished from aqueous ethanol. In a similar manner compounds 3b-i were synthesized. The physical data are reported in table 2.

Antibacterial evaluation:

All the synthesized title compounds were screened in their DMF solution for antibacterial activity by cup plate Agar diffusion method. The bacterial strains used were *Staphylococcus aureus, Pseudomonus aeruginosa, Bacillus subtilis and Escherichia coli*. Agar plates were prepared by pouring melted agar media onto the petridishes and were allowed to solidify. Then the plates were inoculated over the surface of the media. The bores were then made and filled with the solution of suitable concentration of sample and standard and incubated (37^0C for 24 hours). The antimicrobial agents slowly spread around the cups and produce a particular zone of inhibition of the microbial growth which was then measured (Table 2). Under identical condition the control ($CHCl_3$) with solvent (DMF) did not show any activity. Ciprofloxacin was used as a standard.

RESULTS AND DISCUSSION

Structural variations of some 2-quinolone analogues were carried out by the preparation of Schiff bases of 6-acetyl-7-substituted-4-methyl-2-quinolones with different amines. The derivatives were synthesized successfully in appreciable yields. The structures of the title compounds (3a-i) were confirmed by their physical and IR, ^{1}HNMR & Mass spectral analysis. The IR spectra of the synthesized title compounds shown the characteristic absorption band; around 3542-3580 cm^{-1} for O-H stretching (3a, 3b and 3c), 3028-3061 cm^{-1} for C-H stretching aromatic, 2934-2957 cm^{-1} for C-H stretching aliphatic, 1727-1752 cm^{-1} for C=O stretching, 1652-1699 cm^{-1} for C=N stretching, 1518-1548 cm^{-1} for NO_2 stretching, 1445-1469 cm^{-1} for C=C stretching aromatic etc. The ^{1}HNMR spectrum of 3a revealed two singlet peaks for alkyl protons; this was confirmed as the 3 protons each (total 6 protons) equivalent to two signals due to two methyl groups attached to the 4th position and the 6-acetyl side chain of the quinolone ring system. The NH proton of the quinoline ring appeared as around δ 3.08 in the NMR spectrum of 3a. The proton associated with 3rd position was a bit more deshielded and resonated at around δ 4.61-4.81, which is generally little higher value than the normal; the rationale behind it was that the 3rd position proton was associated with a π electron framework between 3rd and 4th carbon atom. Thus the presence of these doubly bonded electrons made this particular proton to be appeared at a greater δ value. It was also noticed by careful observations that the ^{1}HNMR spectra of 3a, 3b and 3c exhibited a sharp singlet at δ 10.64-10.76; this was later analyzed and confirmed as the proton associated with hydroxyl group which was directly attached to the aromatic ring. Being attached with electronegative oxygen as well as to the aromatic framework this proton appeared at such a higher δ value. The other aromatic protons associated with the quinolone ring and the amine moieties were observed in the aromatic region. The mass spectra of all the synthesized compounds gave the characteristic M+1 molecular ion peak from which the molecular weights of the analogues were confirmed.

The antibacterial study, performed by applying cup-plate method involving four different organism namely *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, revealed that, although not so active in general, but the derivatives like 3a, 3b and 3c were appreciably effective against the organisms used. Other compounds were either inactive or little active.

3a-IR (KBr, cm^{-1}): 3580 (O-H str), 3049 C-H str aromatic, 2934 C-H str aliphatic, 1729 C=O str, 1685 C=N str, 1518 NO_2 str, 1445 C=C str aromatic, 1341 C-H bending aliphatic, 1191 C-N str, 835 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.79 3H CH_3, 2.46 3H CH_3, 3.08 1H NH, 4.9 1H C-3 H, 6.43 4H Ar H, 6.91 2H Ar H, 10.7 1H OH. Mass (M+H): 338.39

3b-IR (KBr, cm^{-1}): 3542 (O-H str), 3028 C-H str aromatic, 2950 C-H str aliphatic, 1741 C=O str, 1659 C=N str, 1538 NO_2 str, 1461 C=C str aromatic, 1335 C-H bending aliphatic, 1181 C-N str, 839 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.92 3H CH_3, 2.54 3H CH_3, 3.12 1H NH, 4.87 1H C-3 H, 6.51 4H m Ar H, 6.97 2H Ar H, 10.76 1H OH. Mass (M+H): 338.53

3c-IR (KBr, cm^{-1}): 3551 (O-H str), 3031 C-H str aromatic, 2945 C-H str aliphatic, 1734 C=O str, 1652 C=N str, 1523 NO_2 str, 1469 C=C str aromatic, 1338 C-H bending aliphatic, 1175 C-N str, 841 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.85 3H CH_3, 2.59 3H CH_3, 3.17 1H NH, 4.83 1H C-3 H, 6.57 4H m Ar H, 6.92 2H Ar H, 10.64 1H OH. Mass (M+H): 338.43

3d-IR (KBr, cm^{-1}): 3037 C-H str aromatic, 2941 C-H str aliphatic, 1734 C=O str, 1673 C=N str, 1528 NO_2 str, 1447 C=C str aromatic, 1329 C-H bending aliphatic, 1173 C-N str, 847 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.49 3H s CH_3, 2.31 3H s CH_3, 2.86 3H CH_3, 3.04 1H NH, 4.83 1H s C-3 H, 6.43 4H Ar H, 6.91 2H Ar H. Mass (M+H): 336.39

3e-IR (KBr, cm^{-1}): 3042 C-H str aromatic, 2957 C-H str aliphatic, 1740 C=O str, 1689 C=N str, 1533 NO_2 str, 1436 C=C str aromatic, 1342 C-H bending aliphatic, 1151 C-N str, 834 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.52 3H s CH_3, 2.28 3H s CH_3, 2.96 3H CH_3, 3.08 1H NH, 4.76 1H s C-3 H, 6.49 4H Ar H, 6.82 2H Ar H. Mass (M+H): 336.46

3f-IR (KBr, cm^{-1}): 3061 C-H str aromatic, 2942 C-H str aliphatic, 1730 C=O str, 1681 C=N str, 1547 NO_2 str, 1439 C=C str aromatic, 1337 C-H bending aliphatic, 1159 C-N str, 841 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.46 3H s CH_3, 2.25 3H s CH_3, 2.91 3H CH_3, 3.04 1H NH, 4.71 1H s C-3 H, 6.53 4H Ar H, 6.87 2H Ar H. Mass (M+H): 336.41

3g-IR (KBr, cm^{-1}): 3046 C-H str aromatic, 2935 C-H str aliphatic, 1727 C=O str, 1691 C=N str, 1538 NO_2 str, 1448 C=C str aromatic, 1357 C-H bending aliphatic, 1167 C-N str, 851 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.52 3H s CH_3, 2.31 3H s CH_3, 2.97 3H OCH_3, 3.11 1H NH, 4.81 1H s C-3 H, 6.55 4H Ar H, 6.92 2H Ar H. Mass (M+H): 352.42

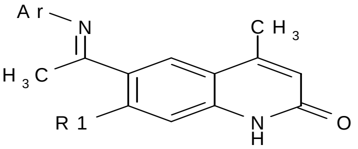
3h-IR (KBr, cm^{-1}): 3039 C-H str aromatic, 2943 C-H str aliphatic, 1748 C=O str, 1699 C=N str, 1542 NO_2 str, 1454 C=C str aromatic, 1367 C-H bending aliphatic, 1158 C-N str, 834 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.47 3H s CH_3, 2.38 3H s CH_3, 2.88 3H OCH_3, 3.07 1H NH, 4.64 1H s C-3 H, 6.58 4H Ar H, 6.97 2H Ar H. Mass (M+H): 352.48

3i-IR (KBr, cm^{-1}): 3042 C-H str aromatic, 2951 C-H str aliphatic, 1752 C=O str, 1684 C=N str, 1548 NO_2 str, 1447 C=C str aromatic, 1361 C-H bending aliphatic, 1143 C-N str, 827 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ ppm): 1.38 3H s CH_3, 2.34 3H s CH_3, 2.96 3H OCH_3, 3.03 1H NH, 4.61 1H s C-3 H, 6.52 4H Ar H, 6.97 2H Ar H. Mass (M+H): 352.45

CONCLUSION

It can be concluded that the some of the synthesized 2-quinolone analogues with different amines showed appreciable antibacterial activity against the organisms. Further study can be performed to modify these compounds for its optimal structural variations to derive more effective antibacterial agents.

Table- 1. Structures of synthesized 2-quinolone analogues:



Compound code	R1	Ar
3a	OH	p-$NO_2C_6H_4$
3b	OH	m-$NO_2C_6H_4$
3c	OH	o-$NO_2C_6H_4$
3d	CH_3	p-$NO_2C_6H_4$
3e	CH_3	m-$NO_2C_6H_4$
3f	CH_3	o-$NO_2C_6H_4$
3g	OMe	p-$NO_2C_6H_4$
3h	OMe	m-$NO_2C_6H_4$
3i	OMe	o-$NO_2C_6H_4$

Table- 2. Data of the synthesized derivatives:

Compound code	Mol. Formula	Mol. Wt	Melting point (^{0}C)	R_f value	Yield (%)
3a	$C_{18}H_{15}N_3O_4$	337.34	261	0.69	51
3b	$C_{18}H_{15}N_3O_4$	337.34	249	0.55	58
3c	$C_{18}H_{15}N_3O_4$	337.34	241	0.57	56
3d	$C_{19}H_{17}N_3O_3$	335.37	254	0.55	59
3e	$C_{19}H_{17}N_3O_3$	335.37	257	0.64	47
3f	$C_{19}H_{17}N_3O_3$	335.37	244	0.53	51
3g	$C_{19}H_{17}N_3O_4$	351.37	275	0.67	50
3h	$C_{19}H_{17}N_3O_4$	351.37	271	0.51	49
3i	$C_{19}H_{17}N_3O_4$	351.37	278	0.67	58

Table- 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	-	+	+	-

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

REFERENCES

1. Michael, J.P. Quinoline, quinazoline and acridone alkaloids. Natural Product Reports. 2008; 25: 166-187.
2. Michael, J.P. Quinoline, quinazoline and acridone alkaloids. Natural Products Reports. 2003; 20: 476-493.
3. Grundon, M.F. Quinoline, quinazoline and acridone alkaloids. Natural Products Reports. 1990; 7: 131-138.
4. Grundon, M.F. Quinolone Alkaloids Related to Anthranic Acid. In The Alkaloids. Brossi, A., Ed.;Academic Press: London: UK, 1988; 32: 341-439.
5. Chilin, A., Dodoni, G., Frezza, C., Guiotto, A., Barbieri, V., Di Lisa, F., Canton, M. 4-Hydroxymethyl-1,6,8-trimethylfuro[2,3-h]quinoline-2(1H)-one induces mitochondrial dysfunction and apoptosis upon its intracellular oxidation. Journal of Medicinal Chemistry. 2005; 48: 192-199.
6. Chilin, A., Marzano, C., Guiotto, A., Baccichetti, F., Carlassare, F., Bordin, F. Synthesis and biological evaluation of a new furo[2,3-h]quinoline-2(1H)-one. Journal of Medicinal Chemistry. 2002; 45:1146-1149.
7. McLaughlin, M.J., Hsung, R.P. Total syntheses of pyranoquinoline alkaloids: simulenoline, huajiaosimuline, and (±)-7-demethoxyzanthodioline. Journal of Organic Chemistry 2001; 66: 1049-1053
8. Thangavel, D.; Ravindran, S.; Gengan, R.M.; Mohan, S.P. Simple efficient synthesis of pyranoquinoline alkaloids: findersine, khaplofoline, haplamine and their analogues. Journal of Chemical Research. 2007; 124-126.
9. Abdel-Megid M., Abass M., Hassan M. Substituted quinolinones. Part 13. A convenient route to heterocyclization reactions with 3-substituted 4-hydroxyquinolin-2(1H)-one. Journal of Heterocyclic Chemistry. 2007; 44: 315-322.
10. Suresh T., Dhanabal T., Kumar R.N., Mohan P.S. Synthesis of pyranoquinoline alkaloids via (4+2) cycloaddition reaction. Heterocyclic Communication. 2005; 11: 79-84.